Title of the article: Risk Factors Contributing to Bacteraemia at a Tertiary Cancer Center in South Asia

Running title: Risk factors for Bacteraemia in Cancer Patients

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Title of the article: Risk factors contributing to bacteraemia at a tertiary cancer center in South Asia

Abstract:

Context: Cancer patients are immunocompromised due to their medical condition resulting in neutropenia, increased exposure to intravascular devices (IVDs) and prolonged hospital stays. These conditions are established risk factors in causing bacteraemia. Bateraemia is a contributing factor towards increased rates of morbidity and mortality in several countries including Sri Lanka.

Aims: The current study evaluates the risk factors such as demographic factors, neutrophil counts, presence of an IVD and length of hospitalization that would contribute to the development of bacteraemia among cancer patients at the Apeksha Hospital – Maharagama, Sri Lanka.

Results: A higher prevalence of bacteraemia compared to other countries (13.7%) was reported with the highest frequency identified from oncology wards. Patients above 60 years with carcinomas were revealed to be more susceptible. A length of hospital stay exceeding three days was a statistically significant factor in causing bacteraemia. Gram-negative organisms accounted for majority of the infections while *Acinetobacter* species were more frequently isolated from IVDs.

Conclusions: It could be suggested that additional care and sterility measures be taken when carrying out invasive procedures in such patients. Precautions could be taken in managing patients with a hospital stay exceeding 3 days as they have been identified as a risk group in acquiring nosocomial infections.

Key-words: Cancer, immunocompromised, bacteraemia, neutropenia

Introduction:

Bacteraemia or bloodstream infections (BSIs) being one of the prominent cause for complications in cancer patients, has become a contributing factor towards increased rates of morbidity and mortality worldwide [1,2,3]. It has been identified as one of the top seven causes of death in Europe and North America [1].

This study focused on cancer patients who were generally immunocompromised due to the underlying medical condition or treatment which includes surgery, chemotherapy and radiotherapy depending upon the type and severity or stage of cancer [4]. Previous studies had identified three major risk factors contributed to bacteraemia such as neutropenia [5,6,7], intravascular catheterization [8, 9, 10, 11,] and prolonged hospital stays [12,13,14].

Hence this study focused on evaluating the effect of three risk factors; neutropenia, intravascular catheterization and length of hospital stay towards contributing to the development of bacteraemia among cancer patients admitted to a tertiary care hospital in Sri Lanka.

Subjects and Methods:

Ethical approval for the study was obtained from the General Sir John Kotelawala Defence University Sri Lanka (KDU) Ethical Review Committee and the National Cancer Institute – Maharagama, Sri Lanka. Prior to recruitment, written consents were obtained from all participants. When recruiting children below 18 years of age, written consents were taken from the parent or guardian of child. This cross-sectional cohort study was conducted at a tertiary cancer care centre in Sri Lanka which treats only cancer patients.

Inclusion and Exclusion Criteria

All samples sent to the microbiology laboratory for blood culture, were retrospectively analyzed. Data were collected from a sample size of 205 cases during a two month period from 01st of July to the 31st of August, 2016.

Blood culture bottles which were refrigerated, subjected to leakage, broken, unlabelled or received without patient information and history were excluded from the study.

Data Collection

Patients' age, gender, hospital ward, usage of catheters, oncological diagnosis, the total white blood cell counts and neutrophil counts gathered from patients' reports and date of admission were recorded from the respective Bed Head Tickets.

Sample Collection and Processing

Two blood samples were collected into Blood culture bottles (BD Bactec Plus aerobic/F; Bactec Myco/F Lytic blood culture bottles and BD Bactec Ped Plus/F bottles-BD Diagnostic Systems 442192, USA) from patients with in-situ catheters; the first one through the catheter line and the second sample from a peripheral site collected at the same time [15]. All blood cultures were analyzed by the BD Bactec 9120 Automated Blood Culture System. A vial which did not provide positive results within 5 days were considered as negative for organisms [16]. Blood culture vials that were detected positive for organisms within 5 days were cultured on Blood agar, MacConkey agar and Chocolate agar [15] and incubated at 35ºC overnight. The Chocolate agar plates were incubated in 5% to 10% carbon dioxide. Organism identification was performed according to routine laboratory protocols stated in Sri Lankan College of Microbiologists' manual [15]. Clinical and Laboratory Standards Institute (CLSI) protocols were followed when performing antibiotic sensitivity testing [15].

Determining Source of Bacteraemia

The source of bacteraemia was determined as per standard protocols stated in the Sri Lankan College of Microbiologists' manual [15]. If blood cultures taken through the catheter becomes positive two or more hours prior to the peripheral blood culture with the same organism, it was reported as intravascular catheter associated blood stream infection (CRBSI). If the blood culture through the line was positive but the peripheral blood was negative the source of

bacteraemia was determined as intravascular catheter colonization and if both the blood cultures through the catheter and the peripheral blood becomes positive with the same organism but the time gap is less than two hours or the peripheral blood culture becomes positive first, it was reported as bacteraemia not associated with intravascular catheters.

Determining Neutropenia

Absolute Neutrophils Counts (ANCs) less than 500 cells/µl were considered as neutropenia [5, 7] and ANCs more than 500 cells/µl were considered as non-neutropenia[6,7].

Determining Length of Hospital Stay

The length of hospital stay (LOS) was calculated by reducing the date of admission from the day the blood culture was detected as positive. Infections that occurred after 72 hours of hospital admittance were considered as nosocomial infections in accordance with the studies conducted by Weinstein et al. [17]and Laupland and Church [18].

Data Entry and Statistical Analysis

Statistical Package for Social Sciences (IBM® SPSS® version 16.0) software was used in interpreting statistical data. The incidence of bacteraemia was analysed in terms of frequency. Two-way frequency table, cross tabulation and Chi-squared test and the odds ratio were carried out to identify whether neutropenia, intravascular catheterization and LOS contributes to the development of bacteraemia. A 95% confidence interval (95% CI) was used in all statistical analysis.

Results:

Study Population and Demographic Characteristics

The current study identified 120 positive bacteraemic cases among 210 cancer patients over a period of 2 months from 1st July 2016 to 31st August 2016. The bacteraemic population of the current study consisted of 74 (35.2%) males and 46 (21.9%) females. Age was categorized based on the United Nations Provisional Guidelines, 1982[19]. Accordingly, age groups were

included in the study were Infants (0-1 year), Pre-school (2-5 years), Schooling (6-19), Working (20-60 years) and Seniors (>60 years). The overall study population consisted of 104 (49.5%) paediatric patients of which 53 (25.2%) had bacteraemia and a total of 106 (50.5%) adult patients of which 67 (31.9%) had bacteraemia. The mean age of the bacteraemic populations was 30 years. A markedly high prevalence of BSIs was recorded from the Senior category which consisted of patients aged above 60 years (Table 01). Though age was not a statistically significant factor in causing bacteraemia within a confidence interval of 95% (*P*= 0.053), it was observed that the age was a significant causative factor at 90% CI.

Table 01: The distribution of bacteraemia within the age groups categorized according to the United Nations Provisional Guidelines, 1982

			Incidence of bacteraemia		**Total**
			No Bacteraemia	**Bacteraemia**	
Age	**Infants** (0 to 1 years)	**Count**	10	14	24
		% within Age	41.7%	58.3%	100.0%
		% of Total	4.8%	6.7%	11.4%
	Pre school (2-5 years)	**Count**	24	18	42
		% within Age	57.1%	42.9%	100.0%
		% of Total	11.4%	8.6%	20.0%
	Schooling (6-19 years)	**Count**	19	23	42
		% within Age	45.2%	54.8%	100.0%
		% of Total	9.0%	11.0%	20.0%
	Working (20 – 60 years)	**Count**	30	40	70
		% within Age	42.9%	57.1%	100.0%
		% of Total	14.3%	19.0%	33.3%
	Seniors (> 60 years)	**Count**	7	25	32
		% within Age	21.9%	78.1%	100.0%
		% of Total	3.3%	11.9%	15.2%
Total		**Count**	90	120	210
		% within Age	42.9%	57.1%	100.0%
		% of Total	42.9%	57.1%	100.0%

Hospital wards and the prevalence of bacteraemia

Data were collected from 27 wards which were categorized into four main groups based on the type of patients; Paediatric, Intensive Care Units (ICUs), Surgical and Oncological. Our study

identified a higher prevalence of bacteraemia in the Oncology wards (68.4%) followed by Intensive Care Units (57.9%) (Table 2).

Bacteraemia among Different Oncologic Conditions

During the study period, 27 different types of oncologic conditions were identified. These were categorised into three main groups as Haematological malignancies, Sarcoma and Carcinoma [20]. The highest frequency of BSIs were reported in patients with carcinomas or solid tumours, (78/120 positive incidences, 65%) despite haematological malignancies being the highest reported cancer type (64.8% of all cancer types). Oncology wards consisted of 28 patients with haematological malignancies and 23 patients with carcinomas all positive for bacteraemia. All positive incidences in ICUs reported 10 of the total 12 incidences to be solid tumours while surgical wards consisted of solely patients with solid tumours and was identified as the third highest ward with positive BSIs. The lowest reported incidence of bacteraemia was from the paediatric wards which had only 4 incidences with solid tumours.

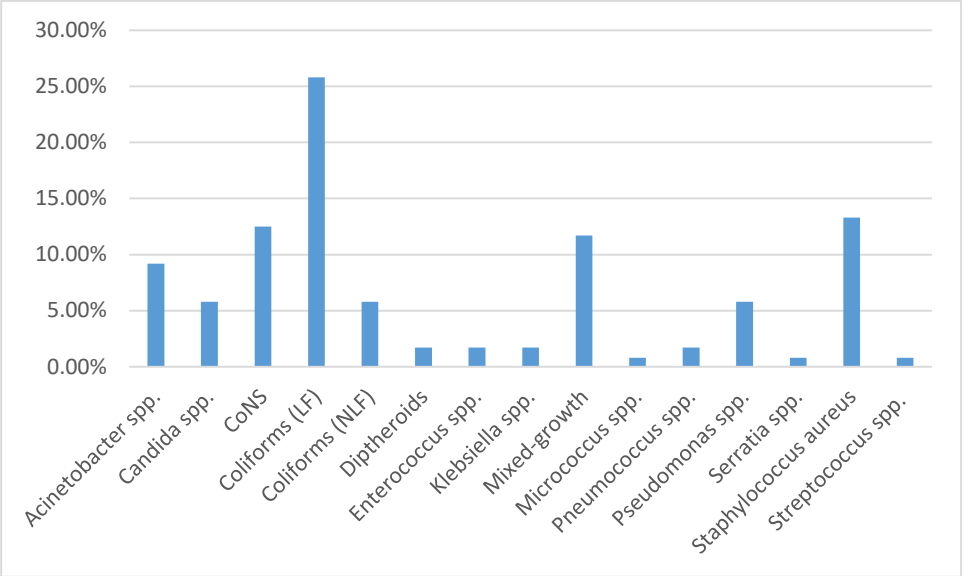
Table 02: The distribution of bacteraemia among the wards

			Incidence of bacteraemia		**Total**
			No Bacteraemia	**Bacteraemia**	
Wards	**Paediatric**	Count	47	42	89
		% of Total	22.4%	20.0%	42.4%
	ICU	Count	16	22	38
		% of Total	7.6%	10.5%	18.1%
	Surgical	Count	3	4	7
		% of Total	1.4%	1.9%	3.3%
	Oncological	Count	24	52	76
		% of Total	11.4%	24.8%	36.2%
Total		Count	90	120	210
		% of Total	42.9%	57.1%	100.0%

Spectrum of Causative Organisms

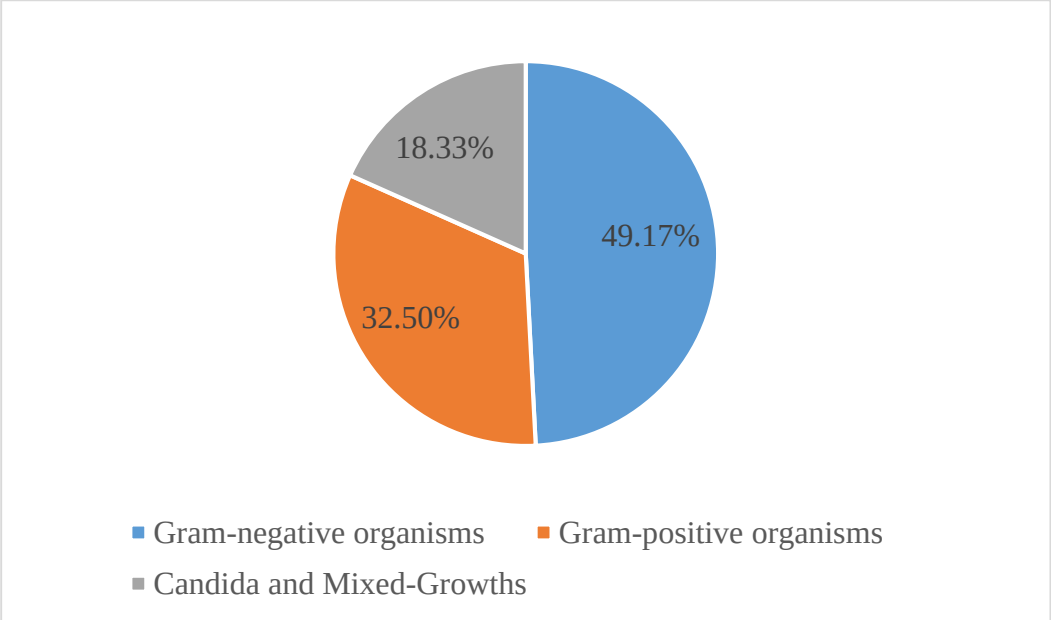
Out of the 120 positive bacteraemic cases identified, 31 (25.8%) incidences were caused by lactose fermenting coliforms (Coliforms LF) and *Staphylococcus aureus* following up as the second most highly isolated pathogen attributing for 16 cases (13.3%) (Figure 01).

Figure 01: Prevalence bacteraemia causing organisms



But overall, Gram-negative pathogens accounted for the majority of the infections (49.17%) (Figure 02).

Figure 02: Spectrum of causative organisms



The Association between Intravascular Devices and Bacteraemia

Several studies describe, normal flora at the insertion site or contamination of the catheter through direct contact during placement, and contamination of infusate as methods in which

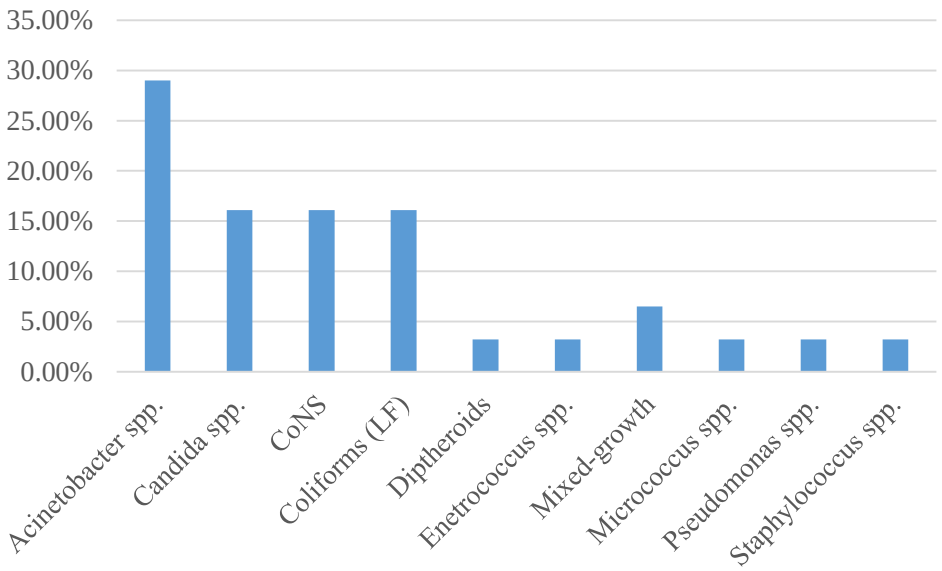
organisms could enter the blood stream of a patient with IVDs. Our study identified that 73.8% of the population did not have IVDs with majority of them being bacteraemic (57.4%). Thus, the presence of an IVD was not a statistically significant factor contributing to the development of bacteraemia (*P*= 0.892).

Spectrum of Microorganisms in Intravascular Devices (IVDs)

Multidrug-resistant (MDR) *Acinetobacter* specices were isolated from 29.0% (9/31) of the population studied with IVDs (Figure 05). MDR *Acinetobacter* species is defined as organisms displaying resistance to at least three classes of antibiotics including penicillins, cephalosporins, fluoroquinolones and aminoglycosides[22]. It is noteworthy that *Acinetobacter* species were not isolated from patients without IVDs which means the organism was only prevalent among IVD users. Furthermore, *Acinetobacter* species displayed the highest resistance for antibiotics with sensitivity only to Polymixin B (Sensitivity of 93.3%). *Candida* species was reported as the second predominant organism isolated from IVDs (5/31 incidences, 16.1%) with majority of the patients being non neutropenic.

Our study reported only 8 Catheter Related Blood Stream Infections (CRBSIs) from 120 positive cases (6.7%) and majority of CRBSIs (3/8, 37.5%) were caused by *Acinetobacter* species.

Figure 03: Distribution of organisms isolated from intravascular devices



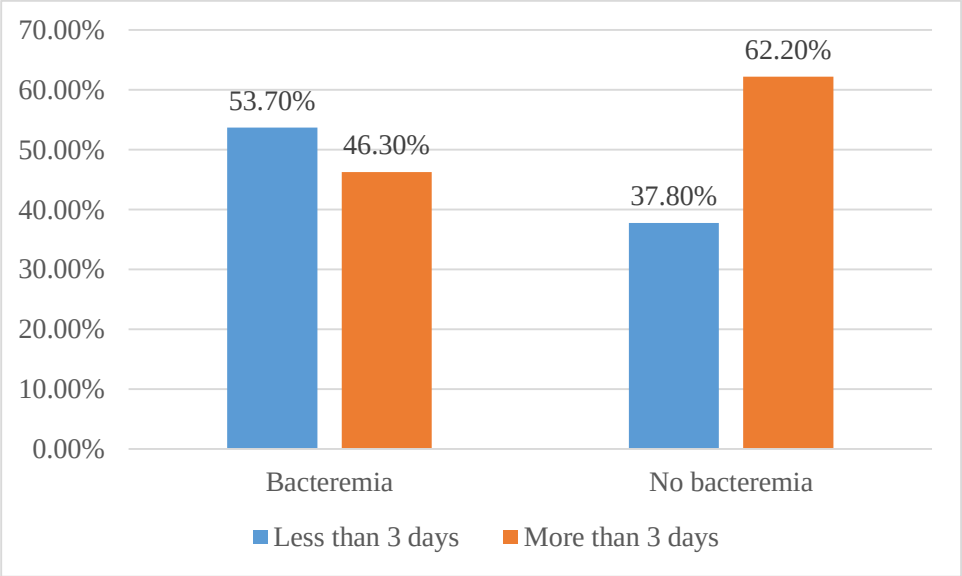
The Association between Neutropenia and Bacteraemia

Cancer patients are inevitably exposed to chemotherapy, corticosteroid drugs, stem cell transplantations and radiotherapy as part of their treatment regimen which result in neutropenia [7, 23].The current study identified majority of the cancer population to be non neutropenic (154/210, 73.3%) with a minority reporting positive to BSIs. Only 56 neutropenic incidences were reported of which 24.2% had bacteraemia while majority of the non neutropenic population had BSIs (59.1%). It was identified that neutropenia was not statistically significant in causing bacteraemia among cancer patients (*P*= 0.344) at this cancer hospital in South Asia.

The Associations between Length of Hospital Stay and Bacteraemia

The Length of Stay (LOS) of cancer patients are affected by demographic factors, type of malignancy, the treatment regimen and infections caused by antibiotic resistant organisms[24, 25, 26, 27]. The present study identified LOS as a statistically significant factor contributing to the development of bacteraemia (*P*= 0.029, 95% CI), which supports the findings of the studies conducted previously.

Figure 04: Distribution of bacteraemia based on the hospital duration



Discussion:

The frequency of bacteraemia incidences per year in hospitals of different countries showed variable results. An Indian cancer center reported 10% of positive blood stream infections in the year 2007[28] while a study conducted at a tertiary cancer care center in Bangalore reported 14.7% positive bacteraemic incidences over a period of 5 months from July 2011 to December 2011[29]. A study conducted at a West African Hospital with cancer patients reported 19.4% positive episodes in 2010, 31.1% in 2011 and 33.3% in 2012[30]. While our study identified 17.1% positive BSIs in 2015 and 13.7% within the first 10 months of 2016; which shows no significantly high incidence of blood stream infections (BSIs) in the present setting.

Patients aged above 60 years were revealed to be at a greater risk in acquiring BSIs which was in accordance with that of several other similar studies. Nielson [35] observed that elderly patients aged more than 65 years were at a greater risk in developing BSIs while Lenz et al. [36]and Al-Rawajfah, Stetzer and Beauchamp Hewitt [37] also reported similar findings in their studies which identifying elderly patients as a risk group in developing bacteraemia.

Zembower[38] stated that the patients with solid tumours were at a greater risk of infection due to invasion of the carcinoma, mechanical obstruction and surgery. It is known that patients with solid tumours undergo extensive surgery [39] which could result in disruption of anatomical barriers and exposing internal organs and blood to normal flora of non-sterile regions and has more medical co-morbidities [40] which could explain the higher incidence of BSIs being reported among patients with solid tumours compared to haematological malignancies. Zembower[38] also stated that radiotherapy given prior to surgery in patients with breast cancer showed a twofold increase in infections. All these factors could play an important role contributing to the development of bacteraemia among carcinoma patients and the wards they are housed in.

Our study found that BSIs were more prevalent among the patients with no intravascular device (IVD) which contradicted the findings of many studies which considered IVDs as a risk factor for BSIs [41, 42, 43, 44]. This could be a result of complications such as surgeries, immunosuppression and the underlying malignancies itself which would result in bacteraemia independent of the presence of an IVD.

Acinetobacter was the most common species isolated from IVDs which was also observed by Chanock and Pizzo[45] and Aktaş et al.[46]. In their study, Fukuta et al. [47] state that the underlying malignancy does not contribute to infections by Multidrug-resistant (MDR) *Acinetobacter baumanni*, but rather acquired as a nosocomial infection. Kim et al. [48] describes a similar outcome and reveals that longer stays in the ICUs, increased the risk of acquiring MDR *A. baumanni* among cancer patients. Accordingly, our study identified all *Acinetobacter* related BSIs inpatients with a hospital stay exceeding 3 days. Candida was the second most common isolate identified with a higher prevalence among non-neutropenic patients. Candidaemia is less prevalent among neutropenic populations as indicated in previous studies[49, 50] with a greater incidence among patients with solid tumours. Rolston [51] has described the reason for this as the increased exposure of patients with solid tumours, to medical interventions such as catheterization and surgical procedures. Nonetheless, our study did not show a difference between patients with haematological malignancies and solid tumours since each reported two cases of candidaemia. According to Walsh and Rex [52] candidaemia is ranked as the 3rd to 4th most common nosocomial BSI. This becomes factual with the present study where 3 out of the 5 candidaemic incidences were in patients with a Length of Stay (LOS) exceeding 3 days which means the infections are acquired from the hospital setting.

Several studies have revealed neutropenia and the degree of neutropenia as risk factors for bacteraemia [53, 54, 55]. Majority of the cancer population to be non neutropenic (154/220 cases, 73.3%) with ANCs exceeding 500 cells/ µL with a majority reporting positive to BSIs (91/120

positive incidences, 75.8%). Yet, our study identified BSIs to be more prevalent among the non neutropenic population, which is an indication that neutropenia is not a risk factor in causing bacteraemia in the present population. Our study recorded 136 haematological malignancies of which 52 (57.1%) are non neutropenic yet the neutrophil function was not assessed thus the qualitative nature of neutrophils and its affect in increasing the risk of BSIs could not be determined.

Prolonged length of hospital stay (LOS) was identified as a risk factor for acquiring nosocomial infections with 74.2% of positive cases having a hospital stay exceeding 3 days. Similar findings were also reported in literature [56,57]. Majority of the incidences reporting a LOS exceeding 3 days were patients with Acute Lymphoid Leukaemia (ALL) and Acute Myeloid Leukaemia (AML) (68.6% and 72.9% respectively). Similarly several studies had observed a 3 fold greater risk of extended LOS from patients with AML[52][61] while Kumari, Mishra and Mohan[14] revealed ALL patients to have the highest hospital duration. Thus, patients with AML and ALL are at a greater risk in acquiring BSIs due to the lengthy hospital stays associated with the underlying malignancies.

In conclusion, bacteraemia was more prevalent in old age, especially exceeding 60 years and was more frequently observed in patients with solid tumour carcinomas. Accordingly, the oncology wards, consisting a majority of patients diagnosed with carcinomas, reported the highest incidence of BSIs. Thus, demographic factors that would increase the risk of bacteraemia were identified to be, old age and wards with patients diagnosed with solid tumours. A hospital stay exceeding three days was a risk factor contributing to the development of bacteraemia while neutropenia and the presence of an intravascular device were identified to have no impact on the risk in causing BSIs. Gram-negative organisms were identified as the most frequently isolated pathogen among patients with BSIs (49.17%).

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