REPUBLIQUE DU CAMEROUN
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FACULTE DE MEDECINE ET DES SCIENCES BIOMEDICALES

REPUBLIC OF CAMEROON
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MINISTRY OF HIGHER EDUCATION
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THE UNIVERSITY OF YAOUNDE I
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FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

DEPARTMENT OF INTERNAL MEDICINE AND SPECIALTIES

SEPSIS HOSPITALIZATIONS IN TWO MEDICAL ONCOLOGY SERVICES IN YAOUNDE: PREVALENCE, CHARACTERISTICS AND OUTCOME

Dissertation submitted in partial fulfillment of the requirements for the award of a Specialist Diploma in Medical Oncology by:

Dr. AZEMAFAC Kareen ESENWOH

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Academic year 2023-2024

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Dr. AZEMAFAC Kareen Esenwoh

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Date of defense: 25/09/2024

Members of the jury:

President

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Moderator

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Members

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Supervision team:

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Co-supervisors

Dr. ATENGUENA OKOBALEMBA Etienne

Dr. ESSON MAPOKO Berthe

Academic year 2023-2024

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DEDICATION

To my late husband, FOZAO Raphael May God Almighty grant him eternal rest.

ACKNOWLEDGEMENTS

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SUMMARY

Introduction and objectives: Sepsis is a life threatening organ dysfunction caused by dysregulated host immune response to infection. It is the leading cause of morbidity and mortality worldwide with an estimated 49 million cases and 11 million deaths annually. In cancer patients, sepsis is the first cause of death globally and in Cameroon accounting for 37.8% to 47 % of deaths. Sepsis in cancer patients poses a diagnostic and treatment challenge especially in resource limited settings. Information about clinical features and factors associated with increased risk of death in these patients is necessary to help physicians recognize those patients more predisposed to having sepsis and those at higher risk of death. This would permit early identification and prompt management and hence improve outcomes. This study aims to investigate the prevalence, socio-demographic, clinical, therapeutic characteristics and outcomes of sepsis-related hospitalizations in two Medical Oncology Services in Yaounde.

Methods: We conducted a descriptive cross sectional study with retrospective data collection at two cancer treatment sites (YCH and YGH) from 1st June 2024 to 31st August 2024. Adult patients (≥18 years) with confirmed solid cancer diagnoses admitted to the oncology ward for sepsis between 1st January 2023 and 31st July 2024 were included. Data on patient demographics, cancer and sepsis characteristics, treatment and outcomes were collected and analyzed. Multivariable logistic regression was used to identify independent risk factors for mortality following a sepsis related hospitalization.

Results: Among 685 cancer related hospitalizations that occurred during the study period, 205(29.9%) were diagnosed with sepsis. The mean age was 51.88± 14.46years. The most common cancer sites observed were urogenital, breast and thoracic at 33.60%, 18.54% and 16.10% respectively. On cancer diagnosis, 49.76% of participants were metastatic and at time of sepsis, 42% of our study population was experiencing active relapse/progression of their cancer. In 64% of our study population, sepsis occurred within 12 months of cancer diagnosis and the predominant foci of infection were the urogenital tract, the skin and pulmonary site in 29%, 21% and 18% respectively. The in hospital mortality rate after a sepsis hospitalization was 34.15 %. Receiving one to three cycles of chemotherapy was associated with decreased risk of mortality (p=0.02). Factors independently associated with increased risk of in hospital mortality were being female (p=0.03), qSOFA ≥2 (p<0.01), presence of an indwelling urinary catheter (p=0.02), and nosocomial infections (p<0.01).

Conclusion In our study, Sepsis remains a significant cause of morbidity and mortality among cancer patients in Yaoundé. Our findings highlight the need for enhanced sepsis prevention strategies, early detection protocols, and prompt treatment initiation in cancer care settings. Further research is needed to develop context-specific interventions to reduce sepsis burden in Oncology centers in Cameroon.

Keywords: sepsis; cancer; solid tumors; prevalence; outcomes; Cameroon;

RESUME

Introduction et objectifs : Le sepsis est un dysfonctionnement organique potentiellement mortel causé par une réponse immunitaire dérégulée de l'hôte à une infection. C'est la principale cause de morbidité et de mortalité dans le monde, avec environ 49 millions de cas et 11 millions de décès par an. Chez les patients cancéreux, la septicémie est la première cause de décès au niveau mondial et au Cameroun, représentant 37,8% à 47% des décès. La septicémie pose un défi diagnostique et thérapeutique, particulièrement dans les milieux aux ressources limitées. Des informations sur les caractéristiques cliniques et les facteurs associés à un risque accru de décès chez ces patients sont nécessaires pour aider les médecins à reconnaître les patients les plus prédisposés à souffrir d'une septicémie et ceux dont le risque de décès est le plus élevé. Cela permettrait une identification précoce et une prise en charge rapide, et donc une amélioration de leur devenir. Cette étude vise à examiner la prévalence, les caractéristiques sociodémographiques, cliniques et thérapeutiques, ainsi que le devenir des hospitalisations liées à la septicémie dans deux services d'oncologie médicale à Yaoundé.

Méthodes : Nous avons mené une étude descriptive transversale avec collecte rétrospective de données dans deux sites de traitement du cancer (HCY et HGY) du 1er Juin 2024 au 31 août 2024. Les patients adultes avec un diagnostic confirmé de cancer solide, admis dans le service d'oncologie pour septicémie entre le 1er janvier 2023 et le 31 juillet 2024, ont été inclus. Les données sur les caractéristiques démographiques des patients, les types de cancer, les diagnostics de septicémie, le traitement et le devenir ont été collectées et analysées. Une régression logistique multivariée a été utilisée pour identifier les facteurs de risque indépendants de mortalité suite à une hospitalisation liée à la septicémie

Résultats : Parmi les 685 hospitalisations liées au cancer survenues pendant la période d'étude, 205 (29,90%) ont été diagnostiquées avec une septicémie. L'âge moyen était de 51,88 ± 14,46 ans. Les sites de cancer les plus fréquents observés étaient urogénital, mammaire et thoracique, représentant respectivement 33,60%, 18,54% et 16,10%. Au moment du diagnostic de cancer, 49,76% des participants étaient métastatiques et au moment de la septicémie, 42% de notre population d'étude connaissait une rechute/progression active de leur cancer. Chez 64% de notre population d'étude, la septicémie est survenue dans les 12 mois suivant le diagnostic de cancer et les sources prédominantes d'infection étaient le tractus urogénital, la peau et le site pulmonaire, représentant respectivement 29%, 21% et 18%. Le taux de mortalité hospitalière après une hospitalisation pour septicémie était de 34,15%. Le fait de recevoir un à trois cycles de chimiothérapie était associé à un risque réduit de mortalité (p=0,02). Les facteurs indépendamment associés à un risque accru de mortalité hospitalière étaient le d'être une femme (p=0,03), un qSOFA ≥2 (p<0,01), la présence d'une sonde urinaire à demeure (p=0,02) et les infections nosocomiales (p<0,01).

Conclusion : Dans notre étude, la septicémie demeure une cause importante de morbidité et de mortalité chez les patients atteints de cancer à Yaoundé. Nos résultats soulignent la nécessité de stratégies améliorées de prévention de la septicémie, de protocoles de détection précoce et d'initiation rapide du traitement dans les contextes de soins oncologiques. Des recherches supplémentaires sont nécessaires pour développer des interventions spécifiques au contexte afin de réduire le fardeau de la septicémie dans les centres d'oncologie au Cameroun.

Mots-clés : septicémie ; cancer ; tumeurs solides ; prévalence ; résultats ; Cameroun ;

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ABBREVIATIONS

Abbreviation	:	Meaning
AJCC	:	American Joint Committee for Cancer
BSI	:	Blood Stream Infection
CLABSI	:	Central Line Associated Blood Stream Infection
CMV	:	Cytomegalovirus
CNS	:	Central Nervous System
CoNS	:	Coagulase Negative Staphylococci
EBV	:	Ebstein Barr Virus
ENT	:	Ear Nose and Throat
GCSF	:	Granulocyte Colony-Stimulating Factor
GIT	:	Gastrointestinal Tract
HIV	:	Human Immune Virus
HM	:	Hematologic Malignancy
HSV	:	Herpes Simples Virus
ICD	:	International Classification of Diseases
ICU	:	Intensive Care Unit
MAP	:	Mean Arterial Pressure
MDR	:	Multi Drug Resistant
MRSA	:	Methicillin Resistant Staphylococcus Aureus
MSSA	:	Methicillin Susceptible Staphylococcus Aureus
qSOFA	:	Quick Sequential Organ Failure Assesment
RECIST	:	Response Evaluation Criteria In Solid Tumors
SIRS	:	Systemic Inflammatory Response Syndrome
SOFA	:	Sequential (sepsis related) Organ Failure Assesment
STN	:	Solid Tumor Neoplasia
TNM	:	Tumor Node Metastasis
UICC	:	Union International For Cancer Control
VZV	:	Varicella Zoster Virus
YCH	:	Yaounde Central Hospital
YGH	:	Yaounde General Hospital

STANDARD UNITS OF MEASUREMENTS

mg/L	Milligrams per Liter
mm Hg	Millimeters of Mercury
kPa	Kilopascal
mg/dL	Milligrams per Deciliter
mL/d	Milliliters per Day
mm3	Cubic millimeters
ºC	Degrees Celsius

CHAPTER 1
INTRODUCTION

1.1. Background and problem statement

Cancer, characterized by uncontrolled cell growth and spread, is a major global health issue[1]. In 2022, there were approximately 19.96 million new cases and 9.7 million deaths worldwide, making it the second leading cause of death globally[2]. Sub-Saharan Africa has seen cancer incidence double in 30 years, with deaths projected to reach 1 million by 2030 without intervention[3,4]. Cameroon reported 19,564 new cases and 12,798 deaths in 2022, with a 65% mortality-to-incidence ratio[2]. While advances in cancer treatments have Sepsis contributes significantly to morbidity and mortality among cancer patients[5–7].

Cancer patients have an estimated 4-10 fold risk of sepsis [8] and this is highest within the first year of cancer diagnosis with an estimated sepsis incidence of 6.4% in the U.S[9,10]. Also, cancer survivors have more than a 2.5-fold increased risk of sepsis[11]. Over 20% of global sepsis hospitalizations are cancer related amongst which 63.4% of patients had a solid tumor [12,13].

Sepsis hospitalizations in cancer patients are often transient in nature, but can have consequences like extended length of hospital stay, cancer treatment delay, increased health care costs, higher rates of nosocomial infections(11.5 versus 7.6% per admission) [14], higher rates of 30 day readmission following a cancer related sepsis hospitalizations (23.2% versus 20.1%) and death[12,15]. Sepsis is the primary cause of death among cancer patients, accounting for 37.8 to 47% of deaths[1,16,17], with 14.1% mortality within one month of emergency presentation [18].

Despite therapeutic advancements, sepsis mortality remains high in cancer patients due to severe immunosuppression and emerging antibiotic-resistant pathogens[19]. In Greece, 72% of cancer patients presented with multi-drug resistant bacterial infections, resulting in a 32% mortality rate[20].

In a survey of 196 consecutive adult medical admissions in Cameroon, 33% had sepsis and 21% had septic shock[8]. Metogo et al showed that 8.3% of patients admitted to an ICU for septic shock had an active cancer[21]. Also, Okobalemba et al had sepsis accounting for 45% of deaths among patients who died 30 days after receiving Systemic anti-cancer treatment(SACT) hence the first cause of death[16].

Cancer patients are particularly predisposed to sepsis and it’s the first cause of mortality in this group of patients accounting for 37.8 to 47% of deaths[16,17,22].Improving the understanding of the characteristics and outcome of sepsis in this population can lead to early

identification of sepsis and timely management including early ICU transfer and swift initiation of appropriate antimicrobial treatment. This would help to reduce sepsis morbidity and mortality.

1.2. Research question

What is the prevalence, Socio- demographic, clinical and therapeutic characteristics and outcome of sepsis hospitalizations in two oncology centers in Yaounde?

1.4. Objectives

2.1.3. Mechanism of infections in patients with solid cancers.

The relationship between infections and cancer is complex. Some infections increase a persons' chance of developing cancer. Conversely, immunocompromised cancer patients are more susceptible to contracting certain infections. The infections most commonly seen in cancer patients are changing with evolving treatment modalities[23].

Solid tumor malignancies increase the risk of developing an infection via fistula formation or obstruction of a biologic passageway. Solid tumors have the capacity to introduce pathologic organisms by way of broncho-pleural, tracheo-esophageal, vesico-vaginal or recto-vaginal fistulas. Tumors also have the ability to obstruct essential body passages. For example, expanding tumors that impede airway function may facilitate post-obstructive pneumonia. Post-obstructive pneumonia may either overlap with bacterial community-acquired pneumonia or present as a unique entity, limiting the ability to make a clinical distinction at the time of admission. Solid tumor obstructions of the biliary tract, urethra, and bowel also increase the risk of infection in cancer patients.

Medical procedures combined with the increasing use of inpatient medical devices directly increase a patient's risk of acquiring a nosocomial infection. Conventional chemotherapy and radiation therapy damage mucosal surfaces and increase the likelihood of microbial colonization and subsequent mucositis[24]. Patients with tumors of the central nervous system, either primary or metastatic, are at risk for a unique set of infections based on the associated neurological deficit.

In solid tumors, notwithstanding issues such as immunosenescence, comorbidities, poor nutrition, smoking, and anatomical obstruction, it is usually only in the very advanced stages of these malignancies that serious, generalized immunosuppression develops. In this latter scenario, intense secondary cancer-related immunosuppression spreads systemically from the

primary tumor site. Importantly, tumor-related immune dysfunction in the context of both hematological and solid malignancies is exacerbated by the superimposition of the immunosuppressive effects of anti-neoplastic therapy[25].

1.4.1. General objective

To describe the prevalence, Socio-demographic, clinical and therapeutic characteristics and outcome of sepsis hospitalizations in two medical Oncology Centers in Yaoundé.

1.4.2. Specific objectives

1. Determine the prevalence of sepsis hospitalizations
2. Outline the socio-demographic, clinical and therapeutic characteristics of cancer patients hospitalized with sepsis.
3. Recount the characteristics and outcome of sepsis hospitalizations.
4. To explore factors associated with death as an outcome following a sepsis hospitalization

1.3. Research hypothesis

Sepsis is common among cancer patients and is associated with a high mortality rate

1.5. Operational definition of terms

Sepsis; was defined by a proven or clinically suspected infection with presence of ≥2signs of systemic inflammation in response to infection[26].

SIRS; Systemic inflammatory response syndrome including ≥2 of the following criteria, temperature of <36ºc or >38ºc, tachycardia >90bpm, tachypnea >20cycles/min, and hyperleucocytosis >12000/mm3 or leucopenia <4000/mm^3[26].

Infection; was defined as the presence of a pathogenic microorganism in a sterile site (such as blood, cerebrospinal fluid, or ascites) or a clinical suspicion of invasion of the body by germs that needed administration of antimicrobials [27]. The categories are as defined below

- **Probable or clinically documented infection**; presence of a clinical focus of infection without any microbiologic documentation regardless of the reason for no documentation.
- **Possible infection or isolated fever;** recent and isolated fever without clinical focus and without microbiologic documentation**.**

- **Proven or microbiologically confirmed infection;** causative germ was identified.

Cancer; A clinical suspicion of malignancy with a proven histologic report.

Hospitalization; hospital stay for greater than 24hours.

Adult patient; all patients greater than or equal to 18years.

Clinical Outcome; clinical and biologic recovery or death during hospitalization.

Nosocomial infection; infection that starts after 48hours of hospitalization[28].

No treatment was defined as cancer patients who were naïve to all treatment modalities.

Community acquired infection; infection that starts in the outpatient setting or within less than 48hours of hospitalization.

Status of cancer; most would be attributed based on RECIST Criteria as seen below

- **Newly diagnosed** all cancer patients diagnosed within the last 03 months whether on treatment or not.
- **Remission** reduction of at least 30% of all target lesions and not in complete remission or absence of evidence of presence of disease.
- **Stable disease** reduction of less than 30% of all target lesions and no new lesions.
- **Progressive disease** presence of new lesions or increased size of old lesions both in patients on treatment and patients not on treatment diagnosed more than 03months prior.
- **Relapse** reappearance and progression of lesions in a patient who was disease free.

CHAPTER 2
LITERATURE REVIEW

2.1. Knowledge recall on cancer and sepsis

2.1.1. Definition and recall on cancer

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs[8]. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or 1 in 6 deaths. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women[8].

Classification of solid cancers

Cancers are classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body where the cancer first developed. The international standard for the classification and nomenclature of histologies is the International Classification of Diseases (ICD) for Oncology. This section introduces you to the first method: cancer classification based on histological type. These cancers can be grouped into six major categories based on the histologic subtype Carcinoma, Sarcoma, Lymphoma, Myeloma, Leukemia and Other mixed types.

The TNM Classification is the system primarily used in solid tumors and can be used to assist in prognostic cancer staging. The system has its basis on assessing the tumor, regional lymph nodes, and distant metastasis.

T - Tumor. Used to describe the size of the primary tumor and its' invasion into adjacent tissues. T0 indicates that no evidence of tumor is present, while T1-T4 are used to identify the size and extension of the tumor, with progressive enlargement and invasiveness from T1 to T4

N - Nodes. Used to describe regional lymph node involvement of the tumor. Lymph nodes function as biological filters, as fluid from body tissues is absorbed into lymphatic capillaries and flows to the lymph nodes. N0 indicates no regional nodal spread, while N1-N3 indicates some degree of nodal spread, with a progressively distal spread from N1 to N3.

M - Metastasis. Used to identify the presence of distant metastases of the primary tumor. Metastasis is when the tumor spreads beyond regional lymph nodes. A tumor is classified as M0 if no distant metastasis is present and M1 if there is evidence of distant metastasis.

The TNM system helps to establish the anatomic extent of the disease, and the combination of the three factors can serve to define the overall stage of the tumor. TNM classification is summarized by the American Joint Cancer Committee (AJCC) and the Union for International Cancer Control (UICC) into 5 stages.

Stage 0 - Carcinoma in situ. Tis, N0, M0.

Stage I - Localized cancer. T1-T2, N0, M0.

Stage II - Locally advanced cancer, early stages. T2-T4, N0, M0.

Stage III - Locally advanced cancer, late stages. T1-T4, N1-N3, M0.

Stage IV - Metastatic cancer. T1-T4, N1-N3, M1

2.1.2. Definitions and recall on sepsis in cancer patients

Infection is a condition in which pathogenic germs that cause disease have entered the body bacteria, viruses, fungi)[27].

Sepsis is life threatening organ dysfunction caused by dysregulated host response to infection as determined by a change in the sequential sepsis related organ failure score (SOFA score) of 2 or more [8]. This is the sepsis-3 definition put in 2016 by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) [26]. It is frequently a final common pathway for many infectious diseases and a common cause of morbidity and mortality[8,29]. The definition of sepsis has evolved over the years. In 1991, Sepsis-1 was defined as infection or suspected infection leading to the onset of SIRS. 10years later the definition changed to Sepsis-2 which was not very different from sepsis-1. Sepsis-2 defined, as with Sepsis-1, an individual must have at least 2 SIRS criteria and a confirmed or suspected infection [26].

Based on the current sepsis-3 definition, the authors recommended use of SOFA scoring (Table I) to assess the severity of organ dysfunction in a potentially septic patient. However, the complexity of the method, the lack of requisite data for many patients, and due to concerns that it may result in late identification relative to other methods raise the possibility that its use according to the Sepsis-3 method may prove impractical in clinical practice. Recognizing these practical limitations, the 2016 SCCM/ESICM task force described a simplified method termed “quick SOFA” to facilitate easier identification of patients potentially at risk of dying from sepsis. This score is a modified version of the Sequential (Sepsis-related) Organ Failure

Assessment score (SOFA). qSOFA consists of only three components that are each allocated one point as seen in table II. A qSOFA score of ≥2 points indicates organ dysfunction[26].

Table I: Summary of the SOFA criteria

Organ system	**SOFA score**				
	0	**1**	**2**	**3**	**4**
Respiratory, PO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory
Coagulation, Platelets, $\times 10^3/mm^3$	≥150	<150	<100	<50	<20
Liver, Bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system, Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal, Creatinine, mg/dL. Urine output, mL/d	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5.0 <200

PO2 - Partial Pressure of Oxygen, FiO2 - Fraction of Inspired Oxygen

Table II: quick sequential organ failure assessment.

qSOFA (Quick SOFA) Criteria	**Points**
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

2.1.4. Risk factors for infection

Several factors have been shown to play a role promoting infections in cancer patients. These factors are divided into those that are host associated and those that are treatment associated (Table III). In practice, multiple deficiencies are usually encountered simultaneously[13].

Table III: factors predisposing cancer patients to infections

Host factors
Disrupted anatomical barriers
Humoral immunodeficiencies
Cell mediated immunodeficiencies
Organ dysfunction
Concurrent illness and past infection
Psychological stress
Nutritional status
Treatment associated factors
Surgery
Radiation therapy
Immunosuppressant therapies
Chemotherapy
Biologic response modifiers
Antimicrobial use
Diagnostic and invasive procedures
Central venous catheters
Urinary catheters
Tracheostomies
Blood transfusions

2.1.4.1. Host associated risk factors

Immune deficiencies -Deficiencies in innate immunity

The innate immune system is not antigen specific and comprised of anatomical barriers, humoral factors that aid in the inflammatory response, and cellular components that facilitate phagocytosis. In cancer patients, these barriers can be compromised by malignant invasion,

mechanical obstruction, or treatments such as radiation and cytotoxic chemotherapy. Radiation combined with chemotherapy further increases the risk of skin and mucosal toxicity. Tumors of the oral cavity and nasopharynx damage the mucosa, resulting in local infection of the ENT Sphere. Occasionally, these infections can spread to the meninges causing meningitis or locally invade the sinuses, resulting in osteomyelitis with or without subsequent cerebral abscess.

Tumors of the GI tract can invade the mucosa, causing local abscess formation, bacteremia, or perforation and resulting peritonitis. Gynecological malignancies disrupt barriers in the female genitourinary (GU) tract predisposing to infection with enterococci, enteric aerobic and anaerobic gram-negative bacilli, and Clostridium spp.

Neutrophils are the single most important cells for defense against bacterial infection in cancer patients. Neutropenia, commonly defined as an absolute neutrophil count (ANC) lower than 1,000 or 500 cells/mm3. Solid organ tumors can infiltrate the bone marrow and result in neutropenia. The absolute neutrophil count, the rapidity in the decline of the neutrophil count, the duration of neutropenia, and whether the count is rising or falling are all important determinants of infection risk.

Whether due to the invasion and progression of the malignancy itself or to the treatments directed against it, destruction of anatomical barriers and deficits in non-specific humoral and cellular immunity diminish the host's frontline, rapid response to infection[30].

Immune Deficiencies - Adaptive Immunity

The adaptive immune system is antigen specific and exhibits immunological memory; thus, it requires time to react but can mobilize more rapidly, on repeat exposure to the same organism. Adaptive immunity is comprised of both humoral and cellular components mediated through B and T lymphocytes, respectively.

Impairment of cell-mediated immunity can occur with most cancers, including acute and chronic leukemia; solid organ tumors such as breast, lung, brain, GI tract, and GU tract; and following HSCT. Additionally, irradiation and medications such as azathioprine, cyclosporine, and corticosteroids can result in cellular immunodeficiency. Several predominantly intracellular pathogens are associated with deficiencies of cell-mediated immunity[30].

Organ Dysfunction

In addition, risk of infection is also increased due to organ compromise through tumor invasion, mechanical obstruction, and surgical resection.

Asplenia

The spleen, the largest reticuloendothelial organ in the body, contains monocytes, macrophages, dendritic cells, natural killer cells, T and B cells. Cancer patients who have undergone splenectomy have approximately a 5 % risk of developing overwhelming sepsis, usually with S. pneumoniae, at some time during their lifetime. They should receive education regarding the need for early administration of oral antibiotic therapy for fevers; some authorities recommend lifelong prophylactic antibiotics for all immunosuppressed patients after splenectomy. Asplenic patients should undergo immunization with pneumococcal, H. influenzae, meningococcal, and influenza vaccines, in addition to other vaccinations according to routine immunization schedules[30].

Other Organ Dysfunction

Patients with primary or metastatic tumors of the central nervous system (CNS) are predisposed to a variety of infections. Those with either a partial or complete loss of the gag reflex are at increased risk for aspiration pneumonia. Patients with CNS tumors also frequently suffer from impaired micturition, leading to urinary retention and recurrent urinary tract infections, and from impaired mobility predisposing to skin breakdown with resulting decubitus ulcers and osteomyelitis. Interestingly, meningitis, encephalitis, and brain abscesses are uncommon in patients with CNS tumors unless related to problems of surgery.

Patients with primary or metastatic lung tumors are particularly susceptible to recurrent pneumonia and to lung abscess formation due to decreased mucociliary clearance, bronchial obstruction, and post obstructive atelectasis. Local invasion of other malignancies such as those of the head and neck, breast, gastrointestinal and genitourinary tracts also predisposes to infection with the flora residing in these sites. In addition, malignancies such as lymphoma and carcinoma of the prostate, ovary, cervix, and rectum commonly obstruct the urinary tract, leading to urinary retention and recurrent urinary tract infections. Obstruction of the biliary tract by lymphoma, cholangiocarcinoma, or pancreatic cancer predisposes to ascending cholangitis. Tumors obstructing blood vessels and lymph nodes can cause septic thrombophlebitis, ischemia, and lymphedema, predisposing to infection. Importantly, when obstruction occurs as a result of tumor, eradication of the infection without relief of the obstruction is usually unsuccessful [30].

Concurrent Illnesses and Past Infections

Increased infection risk has been noted in cancer patients with certain chronic illnesses like diabetes, Obesity and especially those undergoing oncologic surgery.

Cancer patients previously infected with certain organisms are at increased risk of infection reactivation, especially when undergoing immunosuppressive therapies. Organisms of concern include Mycobacterium tuberculosis; viruses such as HSV, and hepatitis B; fungi such as Aspergillus spp, Pneumocystis jirovecii; and parasites such as Toxoplasma gondii. Clinicians should be aware of past infection and colonization status with drug-resistant pathogens to help facilitate empiric antimicrobial choices when infections arise[30].

Nutritional Status

Nutritional status is often jeopardized by the natural progression of neoplastic diseases. Many factors lead to denutrition, including anorexia, nausea, vomiting, diarrhea, constipation, stomatitis, mucositis, dysphagia, alterations in taste and smell, pain, depression, and anxiety. Anorexia and cancer cachexia is a complex process that is thought to result from the actions of both host- and tumor-derived factors. These nutritional deficiencies are associated with increased risk of infection, increased antimicrobial use, increased hospital stay, decreased quality of life, and increased mortality. Because poor nutritional status is so prevalent and portends worse outcomes, early detection of risks for malnutrition and ongoing nutritional assessments should be a standard part of the quality of care in oncology practices[30].

Psychological Stress

Psychological stress plays a role in susceptibility and response to certain infections. Acute and chronic stress can alter the immune response to viral challenges, vaccine response, and wound healing. Stress activates the major neural pathways of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system to release mediators that can in turn induce pronounced changes in the immune system. Chronic high-level stress, as experienced by many cancer patients, is thought to be detrimental[30].

2.1.4.2. Treatment-Associated Factors

Although essential to patient care, no procedure or treatment is without risk. The following treatment-associated factors have all been shown to predispose patients with underlying malignancies to an increased risk of infection.

Surgery

Extensive surgery, especially in the maxillofacial, gastrointestinal, or pelvic regions, increases the risk of infection in cancer patients. Extensive procedures are often necessary, especially for advanced invasive tumors, but they remove large areas of otherwise protective tissue and disrupt anatomical barriers. Postoperative infections have been shown in one series to be twice as common in cancer versus non-cancer patients. Intra-abdominal procedures which involve diverting colostomy, are frequently complicated by infection in patients with underlying malignancies[30].

Radiation Therapy

Infection is the most common complication in patients who receive preoperative irradiation prior to oncologic surgery of the upper respiratory or gastrointestinal tract. This is predominantly due to fistula formation or impaired wound healing and has been well described in patients receiving radiation therapy for rectal cancer. In addition to causing local tissue damage, radiation can result in stenosing lesions, leading to obstruction. Some studies have reported genital condyloma, following pelvic irradiation therapy. Opportunistic infections such as P. jirovecii, Aspergillus terreus, and CMV have been reported following the use of radiation in combination with temozolomide, in the treatment for glioblastoma. Radiation of the spleen or lymph nodes can depress cell-mediated immunity and antibody production. Total body irradiation predictably results in substantial depression of cellular immune function for months to years and can result in prolonged marrow depression and neutropenia. Radiation reactions such as radiation enhancement and radiation recall predispose to infection due to local tissue inflammation and breakdown. These reactions frequently result in localized skin erythema but can progress to ulceration and necrosis[30].

Chemotherapy

Chemotherapeutic agents predispose to infection in a variety of ways. Many of these agents damage the body’s anatomical barriers. Most notably, they can cause ulceration of the gastrointestinal tract, allowing for erosion and invasion by endogenous microorganisms. Other agents such as bleomycin and methotrexate are associated with skin lesions that can predispose to bacteremia with staphylococci and other skin flora. Agents such as doxorubicin, cytarabine, and duanorubicin irritate veins, increasing the risk of phlebitis and subsequent bacteremia. Many chemotherapeutic agents cause bone marrow suppression and neutropenia in a dose related fashion. Some of these drugs can also inhibit neutrophilic migration and chemotaxis.

Regimens that include corticosteroids inhibit the bactericidal activity of neutrophils all of these place patients at an increased risk for developing complications secondary to infections[23]. In order to reduce infectious complications, various societies have put forth recommendations for antibacterial, antifungal, and antiviral prophylaxis[23].

Antimicrobial Use

A patient's intact normal flora protects the surfaces of the skin and mucous membranes by competing with non-indigenous organisms for binding sites and by producing substances that inhibit or kill these microorganisms. The use of antimicrobial agents can radically alter host flora, predisposing to infection. Patients who have lost their normal flora, such as those receiving broad-spectrum antibiotics, are at greater risk of colonization and infection with these more invasive organisms[6]. Dramatic changes in microbial flora can also occur in debilitated patients. Severity of illness and antibiotics, not hospitalization per se, is associated with changes in endogenous flora. Although necessary for both infection prophylaxis and treatment, antimicrobial agents can cause rapid and radical alterations in endogenous flora. In addition to altering the type of microflora, antimicrobial use selects for resistant organisms. Fluoroquinolone use in neutropenic cancer patients is associated with an increase in infections with resistant staphylococci, streptococci, and anaerobes, as well as increased fluoroquinolone resistance in gram-negative bacilli. Likewise, incidence of antimicrobial-resistant fungal infections is related to prophylaxis and treatment. Fluconazole prophylaxis has resulted in the development of resistant strains of C. albicans and non-albicans Candida spp .and to outbreaks of inherently fluconazole-resistant Candida krusei. Antibiotic use in cancer patients is essential in many situations, the emergence of resistant organisms is dramatically increasing, can be directly linked to antibiotic selective pressure, and poses a major health threat to all patients, especially to those who are immunocompromised[30].

Diagnostic and Invasive Procedures

Any procedure that breaks the natural protective barrier between the internal environment and external environment can allow entry of microorganisms and predispose to infection. Biopsies, bone marrow aspirations, endoscopy, and indwelling vascular and urinary catheters are but a few examples. Strict attention to sterile technique, when applicable, can decrease but cannot completely eliminate the infectious risk associated with these procedures [30].

Central Venous Catheters and peripheral catheters

Although indwelling venous access devices are commonly required in cancer patients, infection is a common and often severe complication. The risk of infection varies with the device used, duration of placement, and extent of the patient's immunosuppression. In general, the risk of infection is the greatest for non-tunneled catheters, followed by peripherally inserted central catheters (PICCs), tunneled catheters, and implanted ports. Multilumen catheters may increase the risk of infection[7].

Clinical diagnosis of infection can be difficult as local signs and symptoms are inconsistent and, even if present, can be unreliable indicators of catheter. The evolution of these signs over time, however, is suggestive of infection. Venous access device infections are categorized as entry site infections, tunnel or pocket infections, and catheter-associated bloodstream infections. Entry site infections can often be treated effectively with appropriate antimicrobial therapy, without the need for catheter removal. Tunnel and pocket infections necessitate catheter removal as well as immediate initiation of an empirical antimicrobial therapy that includes vancomycin to cover methicillin resistant S. aureus until culture results are available.

It is often especially difficult to determine whether a bloodstream infection is related to the venous access device because frequently, no evidence of local catheter inflammation is seen. Recently, however, the concept of differential time to positivity has been used to distinguish venous-access-device-related infections from other types of infection, as follows: If the times at which blood cultures become positive (by machine detection in the clinical microbiology laboratory) are more than 2 h apart for simultaneously obtained catheter and peripheral vein blood cultures, the catheter is then strongly implicated as the source of the infection. Although this differential may help determine whether a catheter can be retained or must be removed, most indwelling catheter-related infections will respond to antimicrobial therapy alone, without catheter removal; however, some authors suggest that catheter salvage should be attempted cautiously for neutropenic cancer patients with gram-negative bacteremia. Certain exceptions are notable: Catheter removal is advisable for patients with bloodstream infections caused by fungi and non-tuberculous mycobacteria. For other bacteria, the decision concerning the need for catheter removal will depend on the severity of the clinical picture, the degree of immunosuppression, and the availability of an alternative vascular access site in a given patient. S. aureus may cause endocarditis, and the value of transesophageal echocardiography in the setting of any S. aureus bloodstream infections has been well

demonstrated to determine the duration of therapy. In general, if blood cultures remain positive despite appropriate antimicrobial therapy for more than 48 h, or if the patient is clinically unstable, the catheter should be removed independent of etiology.

Other invasive procedures, such as placement of urinary catheters or tracheostomies, can also alter normal flora. Urinary catheters can become colonized with organisms that track along the catheter and colonize these normally sterile body sites. Patients with tracheostomies generally become colonized with gram-negative bacteria within a few days following placement. If pneumonia develops, it is usually due to these same bacterial pathogens with which the patient is colonized. Indeed, the majority of patients are infected with the organisms with which they are colonized; however, 50 % of these organisms are acquired after hospitalization.

Blood Transfusions

Nosocomial infections from blood transfusions occur despite modern blood banking techniques designed to prevent this complication. Cancer patients often require several blood transfusions during the course of the illness. Contamination of blood products can occur during processing and storage, but most commonly occurs through collection of blood from infected donors. Viruses are the most frequently encountered pathogens associated with blood transfusions. These include hepatitis viruses, HIV, EBV, and CMV. Although most of these are detected by present screening procedures, CMV remains a significant risk for cancer patient. Protozoal diseases, such as leishmaniasis, trypanosomiasis, are acquired through transfusion in developing countries.

Neutropenia

Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/mm^3. The most frequent cause of neutropenia is antineoplastic chemotherapy and may result in periods of neutropenia for 7–10 days or more and occasionally after extensive infiltration of the bone marrow by advanced spreading tumor. Most patients with solid tumors have normally functioning neutrophils and conventional chemotherapy rarely produces severe neutropenia lasting longer than 7 days. Consequently, the “at risk” period is generally short and many solid tumor patients who develop neutropenic fever are considered low risk[31]. Table IV below summarises the common risk factors for infections in cancer patients [32].

Table IV: Common risk factors for infections in cancer patients

Infection	Common risk factors[b]	Immune dysfunction	Common pathogen(s)	Comments
Bacterial	Neutropenia, broad-spectrum antibiotics, central venous catheter	Mucosal barrier, cellular immunity, humoral immunity	CoNS, Enterococcus spp., viridans streptococci, Gram-negative bacteria, Legionella species, C. difficile	Duration and severity of neutropenia is longer for HM/HSCT than ST
Viral	Lymphopenia, GVHD, high corticosteroids, immunosuppressants, D^+/R^- serostatus, monoclonal antibodies, HLA mismatch donor, cord blood, T-cell depletion, myeloablative conditioning	Cellular immunity	CMV, HSV, EBV, HHV-6, adenovirus, norovirus	Highest risk of CMV or HSV disease in D^+/R^- seropositive
Fungal	Neutropenia, GI mucositis, GVHD, broad-spectrum antibiotics, CMV disease, central venous catheter and port-A catheter, severe neutropenia, corticosteroid, iron overload, T-cell depletion	Mucosal barrier, cellular immunity	Candida, Aspergillus	Non-Aspergillus and PCP are less common but significant causes of high mortality
Parasitic	Corticosteroid, HTLV-1	Cellular immunity, eosinopenia	Toxoplasma, Strongyloides	Rare, travel history important

[a] Allo, allogeneic; HSCT, hematopoietic stem cell transplantation; HM, hematologic malignancies; auto, autologous; ST, solid tumor.[b] Neutropenia defined as absolute neutrophil

count (ANC) of ≤500 cells/µl; profound neutropenia defined as ANC of ≤100 cells/µl; D^+, donor serostatus positive; HLA, human leukocyte antigen; HTLV-1, human T-cell lymphotropic virus-1; ST has overall low risk.

2.1.5. Clinical aspects of infections during cancers

Infections in cancer patients can manifest in several ways and even same infection can manifest differently in different patients depending on the individuals immune system (Table V) [31].

Table V: Common sites of infection in patients with solid tumors

Infection site	Comments
Bloodstream	Often associated with vascular access catheters and neutropenia. Changing epidemiology, with resistant Gram-negative organisms emerging
Breast	Generally related to breast cancer surgery, including reconstruction and implants. Changing epidemiology with MRSA and Gram-negative organisms common
Bone, cartilage, joints	Often surgery- or prosthetic device-related. May require device removal and/or long-term suppressive therapy
Central nervous system	Including ventriculitis, meningitis, shunt-related infections, and post-surgical infections
Skin and skin structure	Most often related to surgery, including invasive diagnostic procedures. May be chronic or persistent in irradiated areas. Poly-microbial infections are common
Respiratory tract	Aspiration pneumonia in patients with loss of gag reflex or ciliary function. Post-obstructive pneumonia (with empyema or fistula formation with progressive disease)
Hepato-biliary pancreatic	Ascending cholangitis (±bacteremia); local abscess formation, reactivation of viral infections (HBV, HCV, CMV)
Upper gastro-intestinal	Tracheo-esophageal fistula; percutaneous endoscopic gastrostomy (PEG)-tube-related infection, gastric perforation with abscess formation or peritonitis
Lower gastro-intestinal, pelvic	Bowel perforation with peritonitis or abscess formation, neutropenic enterocolitis, Clostridium difficile- or CMV-associated colitis; perirectal/peri-anal infection
Genitourinary tract and prostate	Complicated urinary tract infections; obstructive uropathy; prostatitis; abdominal and/or pelvic abscesses

2.1.5.1. Isolated fever

Fevers are not caused only by infection but can be due to other factors such as the administration of medications or blood transfusions, atelectasis, or the malignant process itself.

The management of fever in cancer patients depends upon the characteristics of each patient, the duration of fever, and the physical signs and symptoms. Patients can be divided into four general categories: those with no obvious predisposing causes, those with local predisposing factors, those with impaired host defense mechanisms other than neutropenia and those with neutropenia[33]**.**

2.1.5.2. Respiratory affection

A study by Hensley and colleagues revealed the most common site of infection in cancer patients to be respiratory accounting for 37.7%[12]. Pneumonia in patients with solid tumors is usually a consequence of primary or metastatic tumor invading the lung or tracheobronchial tree. Surgical procedures, tracheostomies and aspiration are also associated with pneumonia. The majority of infections in these patients probably result from the inhalation of organisms. The majority of cases of pneumonia occurring in patients receiving cancer chemotherapy are caused by Gram-negative bacilli which may cause extensive necrosis and have a high fatality rate. Pneumonia is a major problem in patients with neutropenia. Since neutropenic patients are incapable of producing an adequate inflammatory response, pulmonary infection may spread rapidly and extensively. Due to the lack of inflammatory response, these patients may fail to develop the characteristic signs of pneumonia [34].

2.1.5.3. Skin

Skin infections are common in cancer patients for several reasons. Some patients remain bedridden for long periods and develop decubitus ulcers. Anti-tumor agents such as vincristine and adriamycin cause local necrosis when infiltrated subcutaneously and can lead to extensive tissue damage with superinfection. Some of the commonly used antibiotics, such as amphotericin B cause thrombophlebitis. Often, cancer patients require prolonged intravenous infusions and the sites of infusion frequently serve as a portal of entry for infection. The majority of cases of cellulitis involve the extremities because they are associated with venipunctures and other procedures. Facial cellulitis is especially distressing because it may lead to disfigurement. Fungi such as Aspergillus spp. and Mucor spp. may cause periorbital or paranasal sinus infections which extend to the face, and cause widespread destruction. Herpes simplex infections of the lip often become superinfected with mixed bacterial and fungal organisms, resulting in extensive cellulitis. Often, it is difficult to identify the organism causing cellulitis. Aspiration of the infected site seldom is productive. Even tissue biopsy and culture infrequently leads to isolation of the etiologic agent[34].

2.1.5.4. Genitourinary tract

Recurrent urinary tract infections are a frequent cause of morbidity in patients with genitourinary cancer. Often these patients require prolonged urethral catheterization because of tumor obstruction which cannot be removed. Some patients require ileal conduits to replace bladders extensively involved with tumor and these may be the harbinger of recurrent infection. Although antibiotic therapy is usually successful in treating the acute systemic symptoms of infection, they seldom eliminate the organism from the urinary tract. The most serious consequences of this problem are the emergence of antibiotic resistance in those organisms which persist or the replacement of sensitive organisms with multiple antibiotic-resistant strains. These organisms may then serve as a reservoir which colonizes the hospital environment and other patients. The use of closed drainage systems has reduced the frequency of bladder colonization. Bladder rinses with antibiotic solutions also reduce the frequency of infection in patients requiring prolonged catheterization. Catheterization should be avoided in the neutropenic patient whenever possible because bladder colonization often leads to septicemia[34].

2.1.5.5. Gastrointestinal tract

The gastrointestinal tract is often the portal of systemic infection in the cancer patient, especially during periods of neutropenia. Localized tumors may become ulcerated or necrotic and then infected. Many antitumor agents cause both myelosuppression and gastrointestinal ulceration, making the patient susceptible to bloodstream invasion by enteric organisms which include bacteria and candida. Tumors located in the gastrointestinal tract may be destroyed rapidly by chemotherapeutic agents, resulting in severe mucosal damage hence perforation and peritonitis. This is most likely to occur with lymphomas[5,34].

Pseudomembranous or necrotizing enterocolitis is a serious complication in neutropenic patients. The lesions may be diffuse, extending from esophagus to rectum. When localized, they usually involve the terminal ileum, appendix and ascending colon. The involved surfaces are covered by a shaggy gray or greenish pseudomembrane. There is necrosis of the mucosa, underlying tissues and blood vessels. Myriads of organisms invade the wall of the gut with little inflammatory response. Pseudomonas aeruginosa has a propensity for causing this type of infection, but other Gram-negative bacilli and fungi also may be responsible. Clinically, the patient with necrotizing enterocolitis presents with hectic fever, cramping abdominal pain and bloody diarrhea. Therapeutic measures are seldom effective.

Perianal infections occur in a few patients and the Infection often arises at the site of a hemorrhoid. The lesion is often painful, indurated and erythematous, but seldom is fluctuant[5,34].

2.1.5.6. Central nervous system

Central nervous system infections appear to be increasing in frequency among cancer patients. During a 15-year period, these infections increased from 0.03 to 0.2% of admissions in one cancer hospital. Most infections occur in patients who have undergone surgery for tumors involving the head and spine. Meningitis accounts for 75% of these infections and 30% of these infections are caused by fungi, primarily Cryptococcus neoformans. Gram-negative bacilli were responsible for 40% of meningeal infections. The majority of patients with meningitis have fever, headache, altered consciousness and nuccal rigidity. Meningitis is easily overlooked in patients with neutropenia because the only signs may be fever and lethargy. Pleocytosis may not be present in the cerebrospinal fluid, but the glucose concentration is decreased and the protein concentration in increased [34].

2.1.5.7. Blood stream infections

Septicemia is more common among cancer patients than among a general hospital population. The frequency of septicemia per 100 hospital admissions is two episodes for patients with solid tumors. In a general hospital there is about one episode of septicemia per 100 hospital admissions. Gram positive cocci account for less than 15% of cases of septicemia in cancer patients. Escherichia coli, klebsiella pneumoniae and P. aeruginosa account for most of the Gram-negative bacillary infections [34].

2.1.6. Clinical workup for sepsis

Comprehensive history and examination remain the fundamental cornerstone in the workup of suspected sepsis. The history element, in particular, needs to elicit any symptoms suggestive of a focal site for infection, establishing any recent infective contacts, clarifying the chemotherapy regimen and confirmation of antimicrobial and G-CSF prophylaxis[25].

Initial biochemical investigations for patients presenting with suspected neutropenic sepsis include complete blood count, urea and electrolytes, liver function tests (including serum albumin), coagulation screen, CRP, lactate, and performance of blood cultures. At least two sets of blood cultures should be performed from separate venepuncture sites. If the patient has a central line, paired blood cultures should be obtained from each lumen of the line and

peripherally. Further cultures should be guided by the clinical history and examination. Sputum cultures should be obtained in those who are expectorating. A chest X-ray should be performed in all patients with respiratory symptoms and there should be a low threshold for performing this investigation in all patients, especially in those with a previous history of respiratory infections [25] .

Assessment for upper respiratory viral pathogens, including SARS-CoV-2, may be useful in determining the etiology of the fever. Stool cultures should be sent in the case of patients with diarrhea and include analysis for Clostridium difficile toxin and common viral pathogens. Urine culture should be obtained in those with urinary symptoms or a positive urinalysis. Cerebrospinal fluid (CSF) should be analyzed in those with symptoms suggestive of central nervous system infection, ensuring that any coagulopathy or thrombocytopenia are appropriately corrected prior to performing a lumbar puncture. Obtaining cultures should not delay the initiation of antibiotic therapy [25].

2.1.7. Paraclinical aspects

The causative germ of Infections in cancer patients differ by anatomical location, source, and duration of cancer treatment. Patients with solid tumors commonly harbor infections caused by organisms that mirror the individual's resident microflora at the specific site of infection. The incidence of some infections in cancer patients closely mirrors that of seasonal incidence in the general population. Other organisms are opportunistic, infecting patients with weakened immune defenses as a result of cytotoxic chemotherapies[24].Acquisition of nosocomial or healthcare-associated pathogens generally occurs several days after hospitalization and in out-patient oncology centers. Prolonged or multiple antibiotic exposure, which often occurs in solid tumor patients, leads to the selection of resistant organisms[31]. Bacteria account for the majority of infections in cancer patients. At the present time, bacteria account for about 75% to 90% of fatal infections in patients with solid tumors, followed by fungal disease (11%), viral illness (8%), and opportunistic organisms (6%)[30] .

2.1.7.1. Bacterial infections

Gram positive bacteria

Gram-positive bacteria are responsible for at least 50% of infections acquired by cancer patients. Nearly 80% of catheter-related infections are caused by gram-positive organisms. Staphylococci, streptococci, and enterococci carry the greatest burden of disease. *Staphylococcus aureus* infections are generally classified as being caused by methicillin-

resistant *S. aureus* (MRSA) or methicillin-susceptible *S. aureus* (MSSA). It has also been demonstrated that both MSSA and MRSA infections in non-neutropenic, cancer patients are serious clinical conditions frequently associated with the placement of a central venous catheter or an indwelling urinary catheter. Enterococci infections are disproportionately found in cancer patients and are challenging to treat and have been linked to nosocomial infection onset, prior antibiotic exposure, and prolonged neutropenia [23].

Gram negative bacteria

Gram-negative bloodstream infections are more common than gram-positive bloodstream infections in cancer patients with solid tumors. The most commonly isolated gram-negative organisms include: Escherichia coli, Klebsiella species, and Pseudomonas aeruginosa. These organisms commonly colonize the urinary tract following urinary stasis and can lead to the development of complicated urinary tract infections, urosepsis, or bacteremia. Escherichia coli has historically been the most common gram-negative species to cause infection in neutropenic cancer patients. One study of bacteremia in cancer patients described nearly 21% of gram-negative bacteremia cases were attributed to E. coli infection, with associated mortality of 17%. Klebsiella species are prevalent pathogens in healthcare-associated infections, and multidrug resistant strains pose a challenge to cancer patients with neutropenia. Most infections associated with Klebsiella species are urinary tract infections or primary blood stream infections while all Klebsiella species infections in cancer patients are associated with high mortality related to acute infection[35].

2.1.7.2. Infections associated with targeted therapies

Many novel agents have either stimulatory or no effect on host immune function, including immune checkpoint inhibitors and novel cellular therapies. However, novel combination therapies, including chemotherapy and immune therapies, may produce complex effects on immune function and susceptibility to microbial infection. Further, as with many cellular therapies (such as CAR-T), the novel agent may be given following myelosuppressive chemotherapy and produce symptoms that are clinically indistinguishable from infection (including cytokine release syndrome). Thus, while overall rates of infection may decrease with novel therapies, the complexity of identifying and managing diverse infections may grow over time [25].

The concern surrounding ICIs relates to treatment for immune-related toxicities. The mainstay of therapy, high-dose corticosteroids, may produce risks for opportunistic infections.

While the usual 4-6-week steroid taper is not associated with substantial infectious risks, many patients require more prolonged dosing or additional immunosuppressive agents. In these patients, a variety of opportunistic infections have been reported like occasional cases of P. jirovecii pneumonia and invasive fungal infections in patients treated with corticosteroids ± infliximab after treatment with combination of anti-PD-1 and ipilimumab [25].

2.1.8. Diagnosis of sepsis

The patient with suspected sepsis requires a head-to-toe physical examination focusing on high-risk sites of infection, such as the oral cavity and skin and organ-specific signs and symptoms of infection. The diagnosis of sepsis is based on clinical indicators, laboratory tests, and other diagnostic methods, such as radiology or sonography, that provide characteristic clues in certain infections. The most important and sensitive of these diagnostic tests is the culture and sensitivity of body fluids and surfaces. Unfortunately, 40% to 70% of febrile episodes do not yield a positive culture for any organism, yet are treated as infection. One study has shown that blood cultures drawn from an infected central line became culture positive an average of 6 hours sooner than peripheral cultures in the same patient. This information may be used to identify patients more likely to have line-related sepsis than bacteremia from other causes, allowing the removal of infected lines sooner. Dry sites should not be cultured with dry swabs, but should be first wet with culture media or preservative-free sterile water. febrile episodes result in a screening chest x-ray, yet research demonstrates that they are rarely abnormal In addition, some blood culture media produce a less optimal culture yield when the patient has been receiving antibiotics. The use of complementary diagnostic tools will vary with infection site, organism, and patient population; however, the use of radiology for diagnosis of pneumonia is well established. Almost all in the absence of respiratory symptoms [6].

The differential diagnosis of the acute febrile illness in Africa must include consideration of malaria and tuberculosis[8].

2.1.9. Biomarkers used in sepsis

Several studies in the general population have demonstrated that the Sequential Organ Failure Assessment (SOFA) score better predicts hospital mortality for ICU patients with infection compared with the systemic inflammatory response syndrome. In 2016, new definition of sepsis and septic shock was adopted which can be reliably applied to both the general population and to cancer patients. The SOFA and qSOFA scores are therefore useful

tools to identify and predict complications and mortality in these patients, and as such, should be applied to all cancer patients with suspected infection.

Several biomarkers are being evaluated for the diagnosis and prognosis of sepsis but so far none has proven to be sufficiently specific or sensitive clinically. Procalcitonin (PCT) and C-reactive protein (CRP) are the most commonly used but they can't reliably distinguish sepsis from other inflammatory conditions and they have not also shown a prognostic value. However, PCT has shown better accuracy than CRP in differentiating infectious from non-infectious causes of fever, and in predicting bacteremia in cancer patients with and without neutropenia. Elevated serum lactate is being investigated as a biomarker for the diagnosis of septic shock and there is need for other biomarkers to serve as diagnostic, prognostic, and theragnostic markers in febrile cancer patients, particularly those with FN [10].

Tableau I: laboratory testing and challenges for infections in cancer patients **[32]**

Infection	**Diagnostic method**	**Commercial molecular methods**	**Challenges**
Bacterial	Bacterial culture, urinary antigens, molecular methods	FilmArray blood culture, PNA-FISH (Gram positive, Gram negative), Verigene Gram positive, Verigene Gram negative, MALDI-TOF MS, C. difficile	Time to bacterial growth, no standard tests for direct from specimen detection, differentiation between infection and disease
Viral	Viral culture, DFA/IFA, molecular methods	FilmArray respiratory panel, FilmArray gastrointestinal panel, Luminex gastrointestinal panel, Xpert Norovirus, HSV 1/2 (lesions),[c] Simplexa HSV 1&2 (CSF)	Variability in quantitative PCR assays for herpesviruses, differentiation between infection and disease
Fungi	Fungal culture, β-d-glucans, Aspergillus galactomannan, molecular methods	PNA-FISH (yeast), T2 Biosystems, MALDI-TOF MS	No standardized molecular assays, specificity of fungal antigens

[a] DFA, direct fluorescent-antibody assay.

[b] IS, international standards.

[c] Includes several IVD-cleared commercial assays. MALDI-TOF MS, matrix-assisted laser desorption ionization–time of flight mass spectrometry; PNA-FISH, peptide nucleic acid fluorescence in situ hybridization.

2.1.10. Treatment of sepsis

2.1.10.1. Maintenance of Hemodynamic Stability

The septic patient will present with either vasodilation and relative vascular volume deficiency or vasoconstriction and myocardial depression. The choice of treatment for hemodynamic instability will depend largely on the clinical presentation. The reader is referred to critical care references that provide suggestions for the management of septic shock [36].

2.1.10.2. Antimicrobial Therapy

The most important management strategy of suspected sepsis in the patient with cancer is prompt initiation of antimicrobial therapy. The initial therapy should provide broad-spectrum antibacterial coverage[10]. However, early, frequent or inconsiderate use of antibiotics can lead to microbial resistance. Unless patients exhibit signs or symptoms of impending shock, the antimicrobial regimen is usually not changed for 72 hours. The ideal agent or combination is less clear and depends on several parameters [36].

2.1.10.3. Neutropenic patients

Risk assessment in neutropenic patients with persistent unexplained fever is difficult. Fever can be associated with non-infectious processes including administration of blood products, the underlying cancer, chemotherapeutic agents, antimicrobial agents, and inflammatory processes such as thrombophlebitis or haematomas. Therefore, broadening the antibacterial coverage is of limited value in most cases, whereas the identification of patients likely to benefit from antifungal therapy is of paramount importance. No globally or even nationally applicable guidelines for antibacterial therapy in febrile patients receiving chemotherapy can be developed, because the local frequencies of various pathogens vary and the local and regional susceptibility and resistance patterns also differ. Moreover, both patterns of infections and resistance patterns change over time [36].

Whatever the initial regimen chosen, there are no reasons to change from one antibiotic regimen to another every other day, changes in antibiotic regimens should not be carried out during the first 5 days of therapy unless the patient’s clinical condition deteriorates

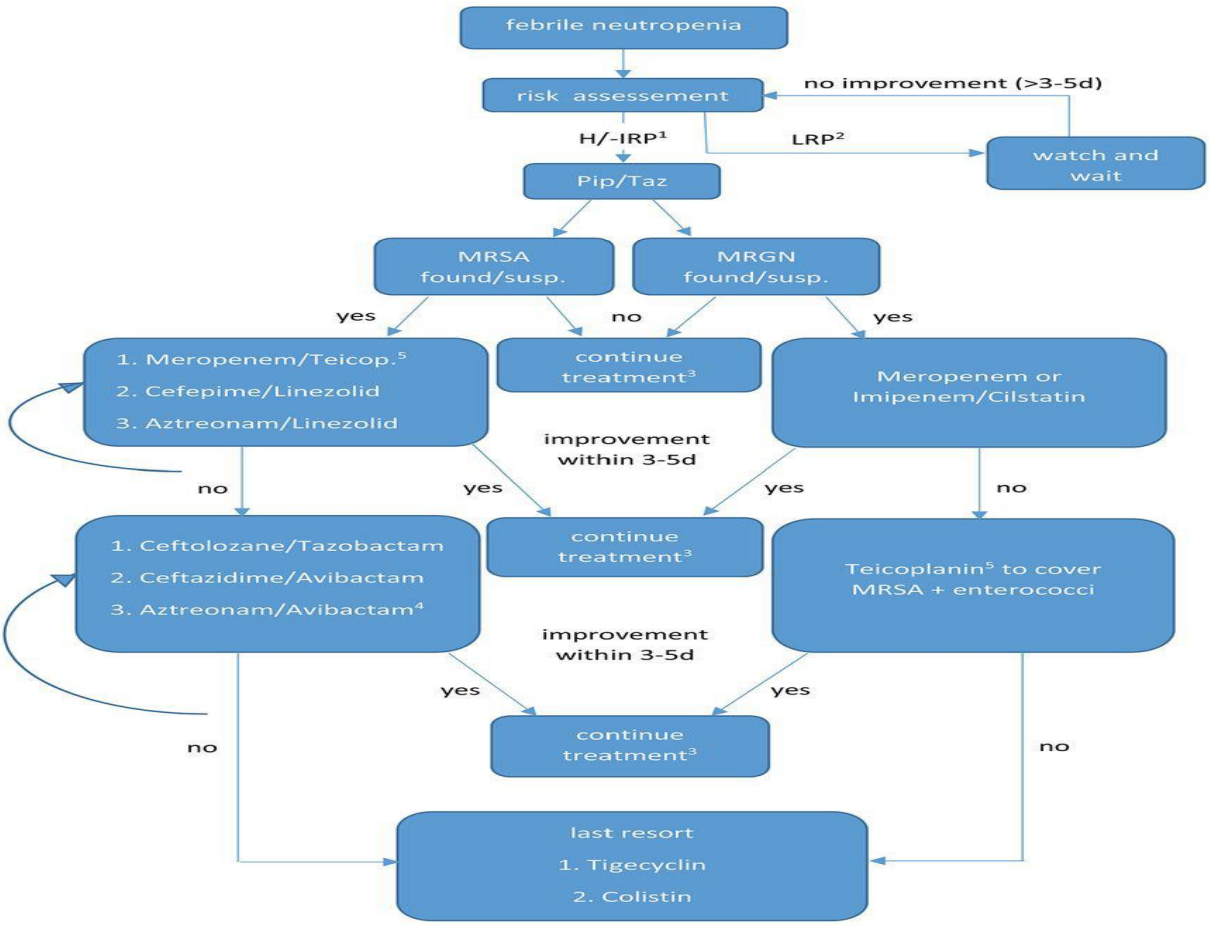
substantially. The observations of Elting and colleagues, that the median time to clinical response of febrile neutropenia due to bacterial infections was 5–7 days after introduction of antibiotics, must be always kept in mind.

Most patients with febrile neutropenia do not have a microbiological documentation of infection, so decisions on the duration of treatment cannot be made on the basis of sterilisation of cultures or the presence of a specific organism. Pizzo and colleagues suggested that therapy should be continued until neutropenia resolves (neutrophilia >500cells /mm3) but a shorter duration would lower the risks of development of fungal infections, antibiotic resistance, and drug-related toxic effects. Decisions have to be taken case by case, considering the condition of the patient (stable or deteriorating), characteristics of the mucous membranes and skin (intact or not), and the prospect of further cycles of chemotherapy or invasive procedures [36].

If the patient is febrile after 5 days of empirical antibiotic therapy, and especially if there is evidence of progressive disease, addition of vancomycin, amphotericin, or both is reasonable, and treatment should be continued for at least 2 weeks if a clinical response is obtained. Vancomycin should be used in the initial antimicrobial regimen only if the patient shows clinically suspected serious catheter-related infections (eg, bacteraemia, cellulitis), known colonisation with pneumococci resistant to penicillin and cephalosporins or MRSA, positive results of blood culture for Gram-positive bacteria before final identification and susceptibility testing,hypotension or other evidence of cardiovascular impairment [36].

2.1.10.4. Host-directed therapies

Targeting the causative pathogen(s) with broad anti-infective therapies has been the primary focus in managing infections with little emphasis on efforts to restore the failing immune responses that permit uncontrolled pathogen replication or on attempts to curtail exaggerated immune activity and inflammatory responses at sites of pathology. Recently, host-directed therapies have emerged as potential adjunctive strategies against infection. Host-directed therapies have traditionally used granulocyte infusions and colony-stimulating factors to correct neutropenia; however, this approach has limited utility in patients with established infection. More novel approaches include the use of recombinant cytokines to manipulate existing leukocytes, manipulation of host cell factors that are required by a pathogen for replication, augmentation of the antimicrobial activities of phagocytes through the activation of cytokines, or modulation of inflammation by manipulating cytokine signaling pathways. These novel strategies are still investigational but very promising and personalized[25].



[1]High/intermediate risk, [2]low risk, [3]continue treatment, [4]currently under development, [5]use therapeutic drug monitoring, target values 40–60 mg/L. MRGN, multidrug-resistant Gram negative; MRSA, methicillin-resistant Staphylococcus aureus[37].

Figure 1: therapeutic escalation approach in septic neutropenic patients.

2.2. Current state of knowledge on the subject

In America, a systematic review and meta-analysis was done on All-cause mortality in cancer patients treated for sepsis in intensive care units with the aim of summarizing the existing evidence on mortality rates in this patient population [38]. They included all prospective and retrospective observational studies evaluating ill adult cancer patients with sepsis, severe sepsis, and/or septic shock that reported at least one mortality outcome. Three of these studies used the Sepsis -2 criteria to define sepsis. 10 studies including 6605 patients met the inclusion criteria. The mean patient age ranged from 51.4 to 64.9 years and the pooled hospital mortality rate was 62%. In conclusion, these studies showed that cancer patients with sepsis had poor survival, with a hospital mortality rate of about two-thirds [38].

In Australia, valentine et al found the prevalence of sepsis among hospitalized cancer patients to be 29% [39]. A single center retrospective cohort study done in India by Beniwal *et al*. where they defined sepsis using the sepsis-3 criteria had a sepsis prevalence 36.1% [40]. In 2015, a study carried out in Brazilian hospitals entitled sepsis outcomes in patients with malignancies revealed a prevalence of 37% [27]. Contrary to the above findings, a study in the USA entitled the Epidemiology and Outcomes of Cancer-Related versus Non-Cancer-Related Sepsis Hospitalizations used the International Classification of Diseases,9^{th} version (ICD) codes to identify sepsis hospitalizations from the National Readmissions Database (NRD) and they had a lower sepsis prevalence of 5.7% [41]. Silva et al in 2021, at an oncology hospital had a sepsis prevalence of 19.2% and in their study the criteria used to define sepsis was not specified [42].

Bou Chebl *et al*. conducted a single-centre retrospective cohort study entitled Sepsis in patients with haematological versus solid cancer using the Sepsis-3 definition, documented with a SOFA score of 2 points or greater. 69% of their study population had a solid tumor and the mean age at presentation was 67.92 ±13.32years. Among patients with solid malignancies, lung cancer was the most common source 15.6%. During their hospital stay, 51.8% patients with a solid malignancy died. There was no statistically significant association between cancer type and hospital mortality [43].

Valentine et al had as predominant primitive sites of cancer to be thoracic, bone and articular cartilage of limbs and Kaposi sarcoma [39]. In Brazil a multicenter prospective cohort study in 28 ICUs by Torres et al had a median SOFA score of 9 (7-12) points. The most frequent sites of infection were the lungs (48%), intra-abdominal region (25%), bloodstream as primary infection (19%), and urinary tract (17%) [27]. Similarly, Lopez et al had as source of infection mainly the pulmonary or digestive systems [44]Half of the patients had microbiologically proven infections, and Gram-negative bacteria were the most common pathogens causing sepsis (31%). In hospital mortality rate was 56%. The number of acute organ dysfunctions, performance status 2-4 and polymicrobial infections were all factors associated with hospital mortality [27].

Williams *et al.* carried out a study to evaluate the incidence and mortality due to sepsis in Hospitalized cancer patients in the USA where they had an in hospital mortality 37.8% [22]. In mexico, Munoz *et al*. looked at risk factors associated with mortality in cancer patients with BSI. They observed progression or relapse of the oncologic disease, inappropriate antimicrobial treatment, and having resistant bacteria to be independently associated with 30-

day mortality[45]. In their study, Gram-negative were the most frequent bacteria (72.8%), with Escherichia coli occupying the first place 42.3%, 48% were (ESBL) producers, and 1.8% were resistant to carbapenems [45]. A study in Korea to delineate the characteristics and outcomes of BSI in adult cancer patients showed that Staphylococcus aureus bacteremia, nosocomial infection and pneumonia were all independently associated with death[46].

A study on the Clinical course and prognostic factors of critically ill patients with cancer and sepsis revealed a mean age of 59.2 ± 17.8years and 54% of the study population was male. Over 78% of their participants had a loco regional and metastatic solid tumor, 18% were in active recurrence /progression, 36% in active newly diagnosed cancer and 49% in remission. With regards to proof of infection, 68% were microbiologically proven and 60% were nosocomial infections. The most common foci of infection were the lungs 44%, abdomen 31%, urinary tract 8% and skin 6%. Independent factors found to be associated with mortality were medical admissions, having an active newly diagnosed cancer, a cancer in active relapse/ progression, SIRS criteria 3 or 4 and presence of organ dysfunction [47].

In a survey of 196 consecutive adult medical admissions in Cameroon, 33% had sepsis and 21% had septic shock [10]. Also, Metogo Mbengono *et al*. carried out a retrospetive cross sectional study at the ICU on patients with septic shock using the Sepsis -3 criteria.8.3% of the study population had an active cancer, the most frequent foci of infection experienced were pulmonary 45.7%, intra-abdominal 31.4%, cutaneous 11.4 and urinary 11.4% and an in-hospital mortality of 39% [21].

CHAPTER 3
METHODOLOGY

3.1. Study design

We carried out a descriptive cross-sectional study with retrospective data collection.

3.2. Study site

This study was carried out at two oncology treatment centers in Cameroon: Yaounde General Hospital (YGH) and the Yaounde Central Hospital (YCH). Both are referral hospitals in Cameroon, located in the administrative capital and serve as teaching hospitals.

The YGH was created in 1987 and is a first category health service in the health Pyramid of Cameroon. It is found in a quarter called Ngousso which is at the north-east of Yaounde. The YGH is bordered to the North by 'la pharmacie bleue', and the Mvog Ebanda quarter, to the south by Ngousso Government primary school, to the east by HGOPY and to the west by CHRACERH. The YGH has several health departments which are internal medicine and specialties, gynecology, surgery and specialties, pediatrics, radiology, intensive care and radiotherapy. The Internal medicine department has several services: medical oncology, infectious diseases, hepato-gastroenterology, cardiology, neurology, endocrinology, rheumatology, dermatology and nephrology. The radiotherapy service has not been functional for several years. The hospital has a capacity of 302 beds.

The oncology unit was created in 1997 and runs services from screening to diagnosis, management, and surveillance. It is the first oncology service in the country and one of the reference centers in Cameroon for the management of cancers. It's comprised of a team of 03 medical oncologists, 01 radiation oncologist, 21 residents, a general practitioner, two Majors (conventional hospitalization unit and the day hospital), certified nurses, state registered nurses, nurse aids, auxiliary staff and a secretary. The service is very well structured with a big office shared by the head nurse and the resident doctors, a nurse's station, a kitchen and 08 wards of 03 different categories each with a restroom. There are 05 general wards with 06 beds per ward, 01 semi private ward with 03 beds and 02 private wards with 01 bed each, making a total of 35 hospital beds. The first general ward is designated as the hospitalization day hospital and set aside for chemotherapy sessions that warrant an overnight stay at the hospital, when it's the very first cycle of treatment or the first time a patient receives a new protocol. There is a day hospital with 11beds for patients whose chemotherapy sessions last just for few hours and they return home. The beds in both the day hospital and conventional hospitalization are fully occupied 80% of the time. The service has 02 functional computers and a printer to enable patients to have personalized and typed chemotherapy prescriptions and protocols, transfer

letters, medical certificates and other documents like estimated cost of treatment when the need arises.

The team runs a daily out-patient department (OPD) consultation clinic which has a patient turnover of about 120 patients a week and averagely 700 new patients yearly. In 2022, the service realized a total of 6824 consultations and 4570 chemotherapy sessions. Cytotoxic preparations and administration of cancer related treatment is carried out by nurses. The radiotherapy unit is non-functional since 2012.

The YCH equally serves as a teaching hospital. It was created in 1993 and initially intended for daycare. Over the years it has undergone several changes and is now considered a second category hospital with good quality technical facilities. It has several health departments among which is the internal medicine and specialties department with 152 hospital beds. This department includes the following specialties gastroenterology, cardiology, hematology, nephrology, neurology, endocrinology, infectious diseases, dermatology, rheumatology, geriatrics and oncology. The oncology service is newly created. There is 01 medical oncologist, 01 oncologic surgeon, a head nurse who also serves as the head nurse for gastroenterology and hematology services as all three services share same space, several state registered nurses and nurse assistants. OPD consultations are done on Tuesdays and Thursdays with a patient turnover of about 35patients weekly. Chemotherapy sessions are prepared and administered by the nurses daily.

These two centers have an experienced health care team that provides comprehensive cancer care. The centers also have a high volume of diverse cancer patients with an acceptable medical record system. For these reasons, these two treatment centers were chosen as our study site to maximize and diversify the number of cases received and to improve on generalizability.

3.3. Study period and study duration

This study was carried out during a period of 18 months from 1st January 2023 to 31st July 2024. This period was chosen in order to provide recent data allowing for an up to date understanding of sepsis in cancer patients and to provide a sufficient sample size for meaningful analysis and generalizability of results. Data was collected during 03 months 1st June to 31st August 2024 from the files of cancer patients.

3.4. Study population and sampling

3.4.1. Source of participants

The files of all cancer patients hospitalized during the study period.

3.4.2. Target population

The target population was all cancer patients**.**

3.4.3. Inclusion criteria

All files of adult cancer patients (≥18years) with a proven histologic report and a diagnosis of sepsis (proven or clinical suspicion of infection and ≥2 SIRS criteria) either on hospital admission or during their hospital stay within the study period were included.

3.4.4. Exclusion criteria

Patient files with sepsis 2 criteria but resolution of SIRS following malaria treatment and no antibiotics and also patients whose files were incomplete such that we weren't able to discriminate if the hospitalization was due to sepsis or another cause.

3.4.5. Sample size calculation

Patients were recruited using the non-probability and exhaustive sampling method.

The Schwartz formula was used for sample size calculation

$$\mathbf{N= z^2 [p\ (1-p)]/E^2}$$

Whereby

N= estimated number of participants

Z= 95% confidence interval used 1.96

P= prevalence from a previous study done in Brazil was at 37%[27].

E= estimated error margin considered 5% (standard value 0.05)

$N= (1.96)^2 [0.29(1-0.29)] \div (0.05)^2 = 359$ (minimum sample size)

We therefore had a minimum sample size of 359 participants/ hospitalizations

3.5. Study procedure

- The research protocol was validated by the supervisors then we went on to obtain ethical approval from the institutional review board of the university and authorizations to collect data at the study sites were equally obtained.
- Our study design was with retrospective data collection hence we set out to study patient files.
- We extracted the names of all hospitalized patients in the medical oncology service from August 1st 2023 to July 31st 2024 from the hospitalization register of the medical oncology service of YCH and YGH. These names were typed and arranged in alphabetical order to ease the search for the patient files from the archives.
- The files of all hospitalized patients were studied. The patients hospitalized for sepsis had their files exploited and the data collection form (appendix 1) was filled. Files with non-sepsis related hospitalizations were also exploited, the reason for their hospitalization was noted beside their name but the data collection form was not filled. This enabled us to calculate the prevalence of sepsis hospitalizations.
- The data collection form was structured into four parts which were socio-demographic characteristics, clinical characteristics, oncologic history and history of the infection episode and clinical outcome. All missing or unspecified data in the files was noted as unknown or unspecified.
- The variables assessed in part one (socio demographic characteristics) were
    - Age
    - Sex
    - Civil status
    - Occupation
    - Educational level
    - Residence
- The clinical characteristics assessed were
    - Obesity
    - Hypertension
    - Heart failure

- Kidney disease
- Dialysis
- Diabetes
- Chronic liver disease
- HIV/AIDS
- Alcohol consumption
- Cigarette smoking

❖ The variables assessed in the oncologic history were:

- Primitive site of the cancer,
- Histological type.
- The date of diagnosis
- The stage of the cancer at diagnosis (the AJCC classification was used for most solid cancers, FIGO classification for gynecologic cancers and the Ann Arbor classification for lymphomas.
- The cancer treatment history without dose precision
  - Chemotherapy with precision of the protocol, number of cycles received and date of last treatment.
  - Radiotherapy
  - Combined chemo radiation
  - Surgery
  - Hormone therapy
  - Targeted therapy
  - Immunotherapy

❖ **In part 4, we assessed Characteristics of the sepsis episode.**

- Number of sepsis episodes per patient within the study period
- Place of sepsis onset
- Time of onset with respect to cancer diagnosis
- Time of onset with respect to last chemotherapy
- The kind of infection (probable, proven or possible)
- Presence of a clinical point of entry/ site of infection
- Presence of any indwelling devices(port a cath, urinary catheter and stoma) in the patient's body

- Status of cancer at time of infection(newly diagnosed, stable disease, remission progression or relapse)
- Site of sample collection
- The first neutrophil count done at onset of infection
- Results of microbiologic analyses germ identified and antibiotic profile.
- Duration of hospitalization
- Clinical outcome of infection (recovery, death)

The above data was collected by means of a pretested data collection form. We were able to bring out the socio demographic, clinical and therapeutic characteristics of sepsis hospitalizations and to assess factors associated with death as an outcome.

- **The quick sequential (sepsis related) organ failure assessment (qSOFA)** is a prompt bedside tool for risk of poor outcome. Assessed by evaluating 03 elements
  - Respiratory rate >22 cycles /min
  - Systolic Blood pressure <100mmHg
  - Altered consciousness as assessed by a GCS <15.

Each element had a score of 1 and it was considered positive if the score was 2 or 3

- **Systemic inflammatory response syndrome (SIRS**) an over whelming body response to a stressor. its positive when ≥2 of the following criteria are present
  - temperature of <36ºc or >38ºc,
  - tachycardia >90bpm,
  - tachypnea >20cycles/min, and
  - hyperleucocytosis >12000/mm3 or leucopenia <4000/mm^3

3.6. Data Analysis

All data was typed into an excel spreadsheet. Descriptive statistics were computed for all study variables. The socio-demographic, clinical and therapeutic characteristics of the sample were described using measures of central tendency. For quantitative variables we used the mean for normal distribution for dispersion we used standard deviation. We then transformed them into qualitative variables and presented in ranges. For qualitative variables, frequency and percentages were calculated and tables used to display results. The outcome (In hospital mortality or recovery) was described in percentage.

To determine the Association between socio-demographic, clinical, therapeutic and sepsis episode characteristics and in hospital mortality, we used the homogenous chi square test and the fisher exact test for frequencies <3. The level of statistical significance was set at $p< 0.05$. Finally, to determine the level of association between independent variables and in hospital mortality, we calculated the crude OR after bivariate analysis. Finally, to eliminate cofounders we did multiple logistic regression where we calculated the Adjusted Odds ratio.

To achieve all these we used Excel 2013 to type our data, to draw the figures and do the tables. Microsoft word was used to type the results. EPI Info version 7.2 was used for statistical analysis.

3.7. Ethical Considerations

An ethical clearance was obtained from the Institutional Review Board of the Faculty of Medicine and Biomedical Sciences, The University of Yaoundé I. Administrative authorization was obtained from the Directors of the Yaounde General and Central Hospitals. All records were kept confidential, accessible only to members of the immediate study team. Only the principal investigator and other members of the research team had access to information concerning participants. Codes were used in questionnaires to represent the patients rather than names.

We strived to adhere to the principles of the Helsinki Declaration of 1964, as revised in October 2013, namely the principles of beneficience, non maleficience, confidentiality, and of justice. The results will be used for scientific purposes.

CHAPTER 4

RESULTS

A total of **684** participants were involved in our study among which **205** had sepsis

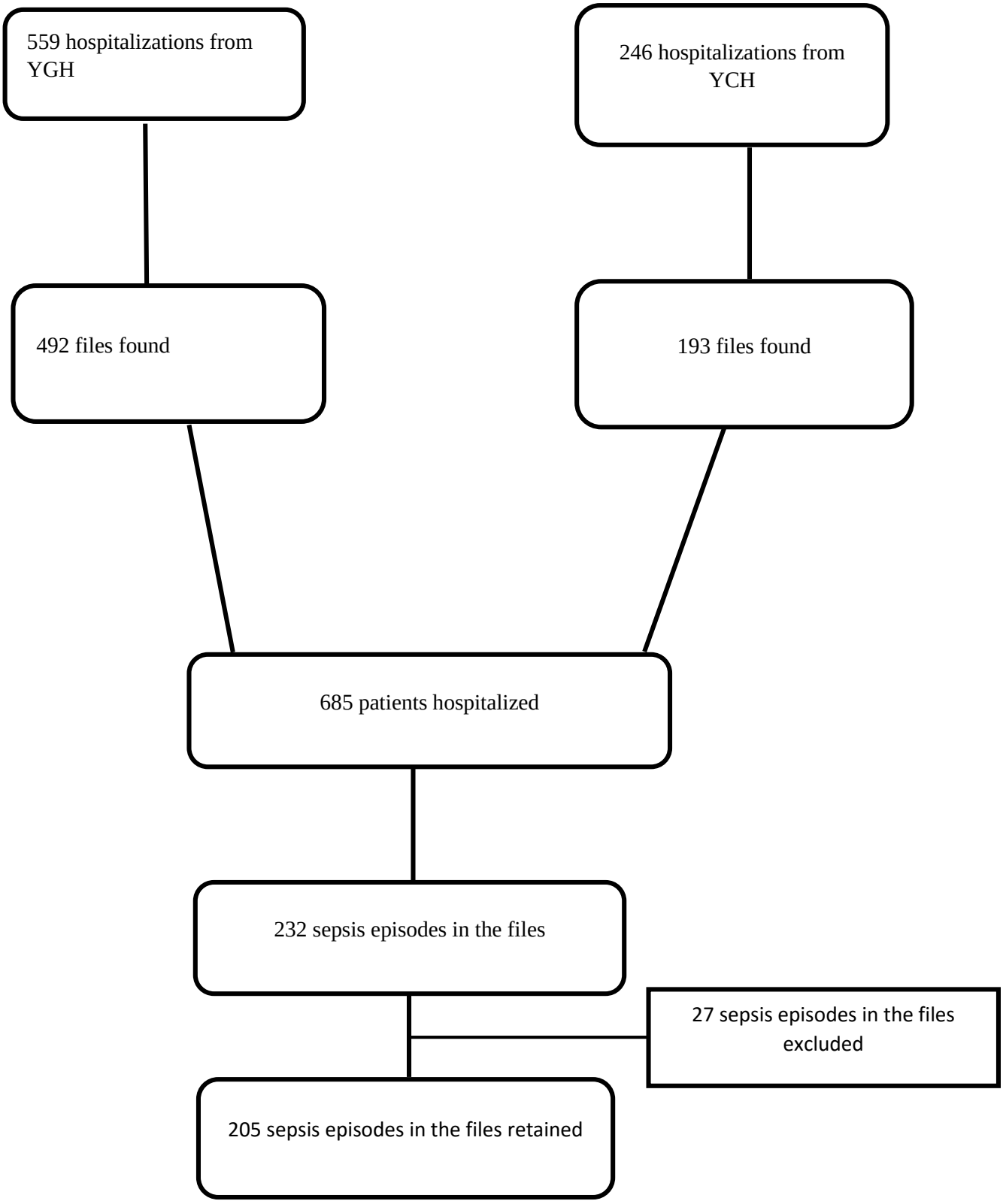


Figure 2: flow chart showing recruitment procedure

4.1. Prevalence of sepsis hospitalizations

A total of 685 patient hospitalizations occurred in the oncology service during the study period. There were 205 sepsis related hospitalizations. Hence the prevalence of sepsis hospitalizations was calculated to be 29.9 %.

4.2. Socio-demographic, clinical and therapeutic characteristics of the study population hospitalized for sepsis

4.2.1. Socio-demographic characteristics of hospitalized adult solid cancer patients with sepsis

As seen on table VI, most of our study participants were female 69.27 % (142/205) and the mean age we had was 51, 88± 14,46years with the 50-59years range being the most represented.

Table VI: distribution of sepsis hospitalizations with by socio-demographic characteristics of the patients involved

Variable N= 205	**Frequency(n)**	**Percentage (%)**
Sex		
Female	142	69.27
Male	63	30.73
Age(years) Mean : 51.88± 14.46 MIN-MAX : 19-83		
19-29	18	8.78
30-39	23	11.22
40-49	40	19.51
50-59	56	27.32
60-69	37	18.05
≥70	31	15.12
Residence		
Urban zone	110	53.66
Rural zone	26	12.68
Residence not specified	69	33.66
Marital status		
Married	86	41.95
Single	60	29.27

Widow(er)	10	4.88
Divorced	1	0.49
Unknown	48	23.41
Level of education		
Primary	24	19.35
Secondary	60	48.39
Higher education	40	32.26
Profession		
Employed	64	31.22
Student/unemployed	61	29.75
Employment status not specified	80	39.02

4.2.2. Clinical characteristic of the study population

As seen on table VII below are the varied comorbidities presented by our study population.

Table VII: distribution of hospitalized adult solid cancer patients with sepsis by comorbidities

Variable N=205	**Frequency (n)**	**Percentage (%)**
Alcohol	52	25.37
Hypertension	47	22.93
Obesity	41	20
Tobacco smoking	27	13.18
HIV	24	11.71
Diabetes	20	9.76
Kidney disease	18	8.78
Chronic Liver Disease	11	5.37
Dialysis	3	1.46
Heart failure	2	0.98

- **Primitive site of cancer (insert vertical axis**

The most frequent primitive cancer location was Genitourinary in 33.66% (52/205) participants and closely followed by breast cancer in 18.5 % (8/205) of the study population (figure 3).

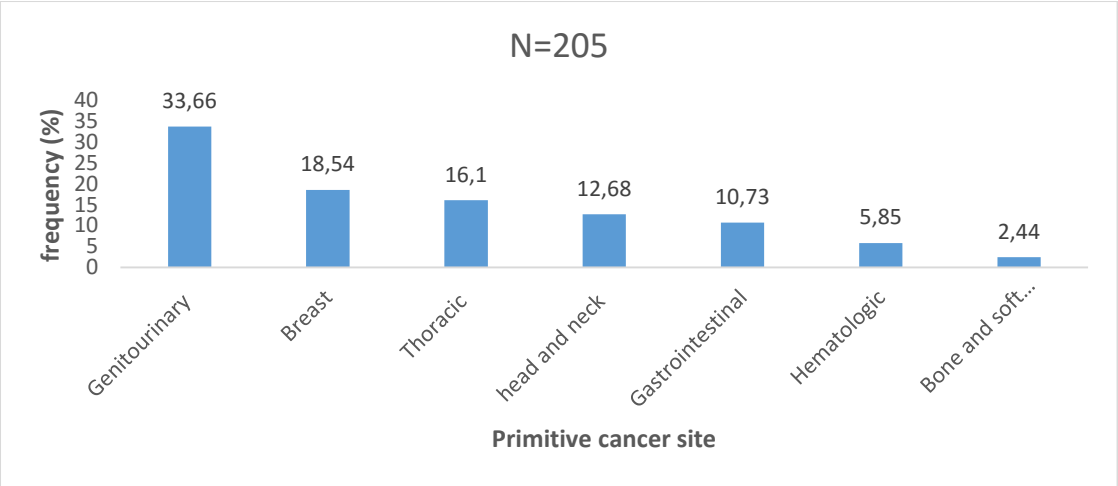


Figure 3: distribution of sepsis hospitalizations by primitive site of cancer

- **Stage at diagnosis and histological subtypes of cancers**

The predominant stage of presentation at time of diagnosis was stage IV 49.76% (102/205) as seen on table VIII. The most common histologic type found was adenocarcinoma 45.37 % (93/205).

Table VIII: distribution of sepsis hospitalizations by stage of cancer at diagnosis and histological type

Variable N=205	Frequency (n)	Percentage (%)
Stage at diagnosis		
Stage I	22	10.73
Stage II	25	12.19
Stage III	56	27.32
Stage IV	102	49.76
Histological type		
Adenocarcinoma	93	45.37
Squamous cell carcinoma	58	28.29
Sarcoma	18	8.78
Lymphoma	17	8.29
Other histologic subtypes*	19	9.27

* Neuroendocrine tumors, Melanoma and Germinal tumors.

- **Cancer status at time of infection**

At the time of infection, (figure 4) most of our study population had a cancer that was in progression 42 % (86/205).

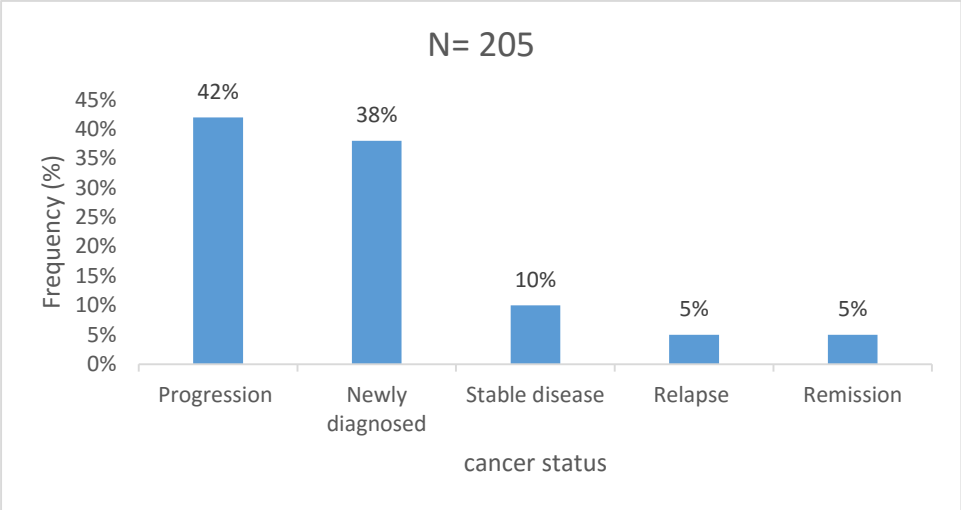


Figure 4: distribution of sepsis hospitalizations by cancer status at time of sepsis

4.2.3. Therapeutic characteristics of study population at time of sepsis

- **Cancer treatment status and treatment modality received**

At the time of sepsis, most of the patients had received at least one treatment modality with a frequency of 124(60.49%) as seen in table IX and half of the study population had received chemotherapy.

Table IX: distribution of sepsis hospitalizations by cancer treatment status and treatment modality received.

Treatment status N=205	Frequency(n)	Percentage (%)
No treatment	81	39.51
Chemotherapy	105	51.21
Surgery	41	20
Hormone therapy	18	8.78
Radiotherapy	16	7.80
Combined chemoradiation	9	4.39
Targeted therapy	8	3.90
More than 01 treatment modality	53	25.85

- **Lines of treatment**

Amongst the study participants who received chemotherapy, the majority received 01 line of chemotherapy with a frequency of 74/99(74.75%) (Figure 5).

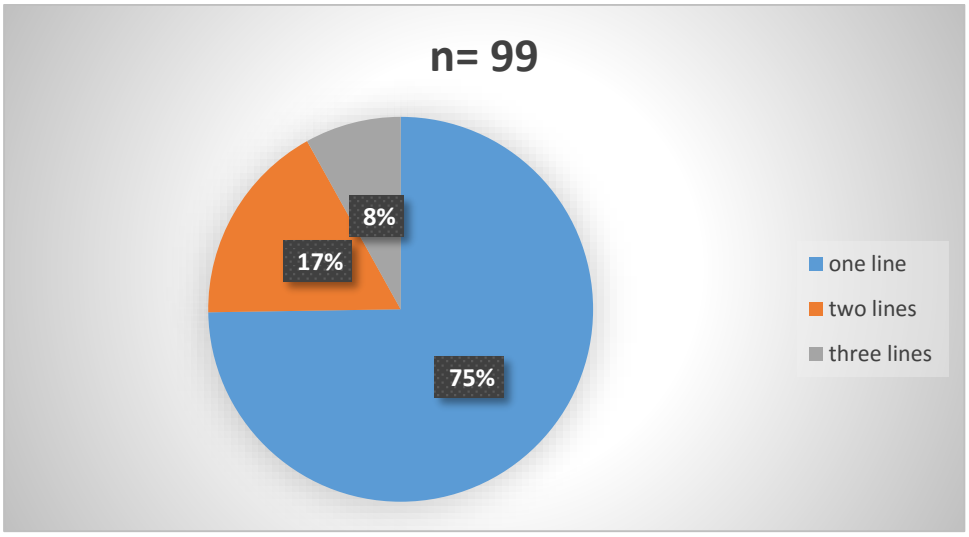


Figure 5: distribution of sepsis hospitalizations by number of lines of chemotherapy received

- **Cycles of treatment**

Amongst those who received chemotherapy, 41% (39/98) had received 1-3 cycles of chemotherapy. The mean number of chemotherapy cycle received was 5.25 ±4.00 cycles with a range of 1 to 18 cycles as illustrated on figure 6.

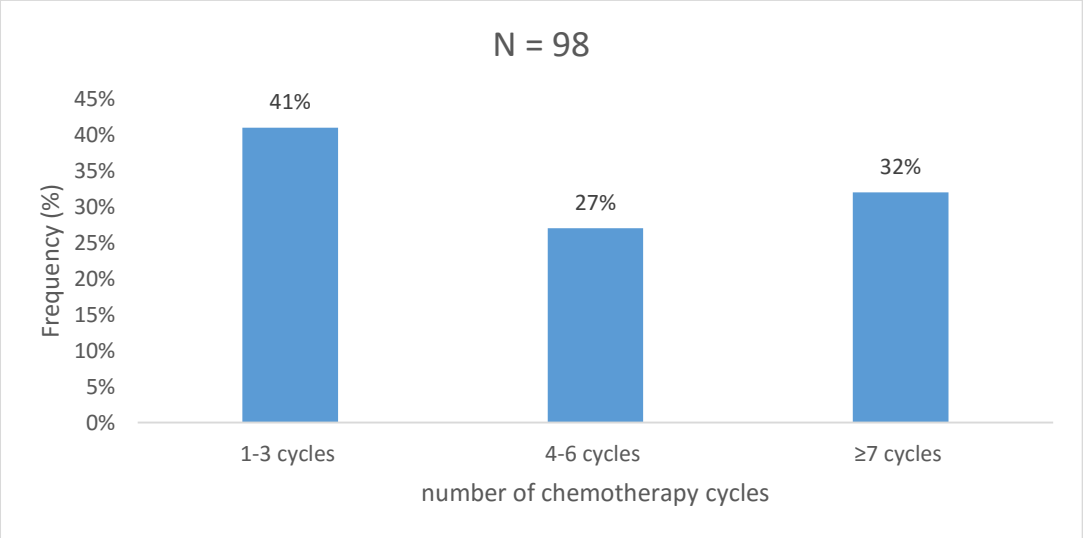


Figure 6: distribution of sepsis hospitalizations by number of chemotherapy cycles received

4.3. Characteristics of the sepsis episodes among hospitalized adult cancer patients

- **Number of sepsis episodes, place of sepsis onset and category of infection**

As seen on table X below, 87.8 % (180/205) of our study participants experienced 01 episode of sepsis, had community acquired infections and these were mostly probable infections.

Table X: distribution of sepsis hospitalizations by the number of sepsis episodes, place of sepsis onset and category of infection

Variable N= 205	Frequency (n)	Percentage (%)
Number of sepsis episodes		
01 episode	180	87.80
≥2 episodes	25	12.20
Place of sepsis onset		
Out of hospital	156	76.10
In hospital	49	23.90
Category of infection		
Probable	145	70.7
Proven	42	20.5
Possible	18	8.8

- **Presenting symptoms and signs**

The participants in our study population presented with different signs and symptoms on diagnosis of sepsis. Table XI summarizes the most common symptoms and signs we encountered

Table XI: distribution of sepsis hospitalizations with respect to symptoms and signs at presentation

Variable N=205	Frequency(n)	Percentage (%)
Symptoms		
Altered consciousness	20	9.76
Purulent discharge	42	20.49
Other symptoms *	45	35.43
Signs		
Tachycardia	193	94.15
Tachypnoea	71	34.63
Hypotension	40	19.51
Altered neurological status	25	12.20
In dwelling devices(catheter, stoma)	66	32.20

*physical asthenia, abdominal pain, vomiting, diarrhea, headache, dysuria, cough,

- **Biomarkers for diagnosis and prognosis of sepsis episodes**

As shown on table XII, most (88.24%) of our study participants had a qSOFA score of 1 a SIRS score of 2 (45.37%).

Table XII: distribution of sepsis hospitalizations by sepsis biomarkers

Biomarker N=205	frequency	Percentage (%)
qSOFA assessment		
≤1	169	82.4
2	29	14.2
3	7	3.4
SIRS assessment		
2	93	45.37
3	92	44.88
4	20	9.75

- **Clinical sites of infection**

In our study, the most common site of infection was urogenital in 29% (Table XIII).

Table XIII : distribution of sepsis hospitalizations according to specific site of infection

Site	Specific infection	Frequency n=205	Percentage (%)
Pulmonary		**37**	**18.05**
	Pneumonia	28	
	Empyema	4	
	Bronchitis	1	
	Bronchopneumonia	4	
ENT		**08**	**4.00**
	Pharyngitis	2	
	Tracheostomy	2	
	Sinusitis	1	
	Infected tumor	3	
Ocular	Purulent eye discharge	1	0.5
Gastrointestinal		**33**	**16.00**
	Stomatitis	2	
	Gastroenteritis	12	
	Enterocolitis	10	
	Infected ascitic fluid and cholangitis	9	
Urogenital system		**60**	**29.00**
	Uretritis	3	
	Cystitis	9	
	Pyelonephritis	34	
	Prostatitis	2	
	PID/Abscess	1	
	Infected tumor	11	
Skin and appendages		**43**	**21.00**
	Abscess	5	
	Ulcers	2	
	Superinfected wounds/ stoma	35	
	Cellulitis	1	
Central Nervous system		**08**	**4.00**
	Encephalitis	1	
	Meningitis	6	
Unknown site		**16**	**8.00**

- **Para-clinical work ups**

A sample for culture and antibiotic sensitivity was provided by 43.4 % (89/205) of our study population. Of these, 47.1% (41/89) had a germ identified. In all 41 patients, one or more bacteria were isolated and in 2.4% (1/41), a fungi isolated (table XIV).

Table XIV: distribution of sepsis hospitalisations by microorganism identified

Micro organism	Frequency n= 53	Percentage (%)
Gram positive bacteria	**8**	**15.1**
Staphylococcus aureus	3	
Staphylococcus epidermidis	2	
Streptococcus agalactiae	1	
Peptoriphilus assacharolyticus	1	
Clostridium ramosum	1	
Gram negative bacteria	**43**	**81.1%**
Klebsiella Sp	15	
Escherichia coli	10	
Acinetobacter baumanii	2	
Citrobacter freundi	1	
Pseudomonas aeruginosa	3	
Proteus mirabilis	3	
Enterobacter cloacae	2	
Providencia stuartii	2	
Salmonella sp	1	
Serratia marcescens	2	
Shigella dysenteriae	1	
Morgagnella morgagni	1	
Mycobacterium	**1**	**1.87**
Mycobacterium TB		
Fungi	**1**	**1.87**
Candida albicans		

- **Timing of sepsis episode with respect to cancer diagnosis and last chemotherapy session**

Over 60% (123/205) of our participants were cancer diagnosed within the preceding year (Table XV) and 56.59 % (100/205) were not yet on chemotherapy at the time of sepsis occurrence.

Table XV: distribution of sepsis hospitalizations by timing of sepsis episode with respect to cancer diagnosis and last chemotherapy session.

Variables N=205	Frequency (n)	Percentage (%)
Duration in months from cancer diagnosis to sepsis episode		
<12 months	123	60
>12 months	62	30.2
Undefined	20	9.8
Duration in months from last chemotherapy session to sepsis		
≤1 month	51	24.9
] 1-3]	13	6.3
] 3-6]	17	8.3
>6	24	11.7
Not yet on chemo	100	48.8

- **Length of hospital stay**

The mean duration of hospitalization of our study participants was 11.68±8,32days with a range of 2 to 62days. Most of our study participants were hospitalized for ≥5days 144/202(71.29%) and 58/202(28.71%) were hospitalized for <5 days.

- **Neutrophil count**

Most 49.27% (101/205) of our study participants had a neutrophilia >7000/mm3 seen in figure 7.

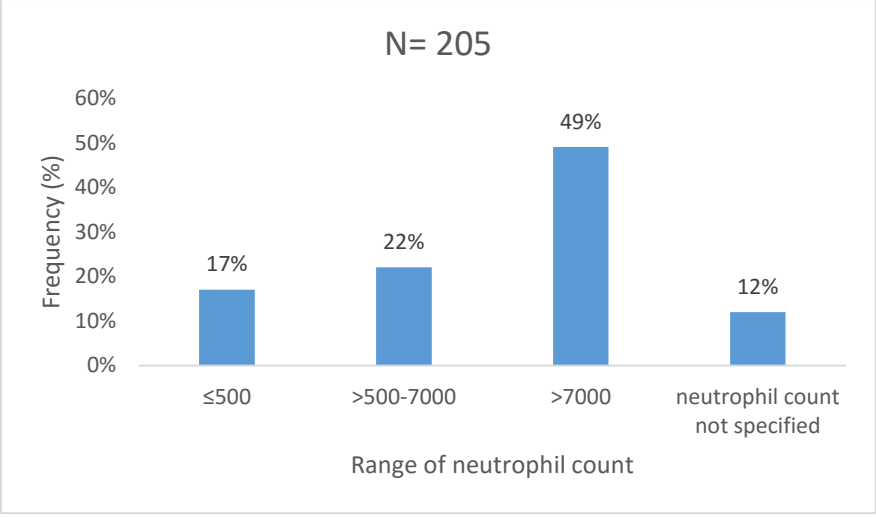


Figure 7: distribution of sepsis hospitalizations by range of neutrophil count.

- **Antibiotics used by hospitalized cancer patients with sepsis**

Table XVI outlines the various antibiotics that were prescribed during the episodes of sepsis hospitalization.

Table XVI: distribution of sepsis hospitalisations by antibiotics used

Antibiotic	Frequency
Amoxicillin clavulanic acid	46
Metronidazole	52
Piperacillin tazobactam	5
Ceftriaxone	39
Ofloxacin	40
Gentamicin	6
Imipenem	11
Meropenem	7
Fliucloxacillin	1
Ciprofloxacin	7
Ornidazole	2
Azithromycin	6
Amikacin	19
Vancomycin	2
Spiramycin	3
Ampicillin	1
Cotrimoxazole	1
Levofloxacin	1
Ceftazidime	1
Cefotaxime	1
Cefuroxime	1
Pyostacine	1

- **Clinical outcome of patients following an episode of sepsis**

Most of our study participants 66% (135/205) recovered after an episode of hospitalization with sepsis (figure 8).

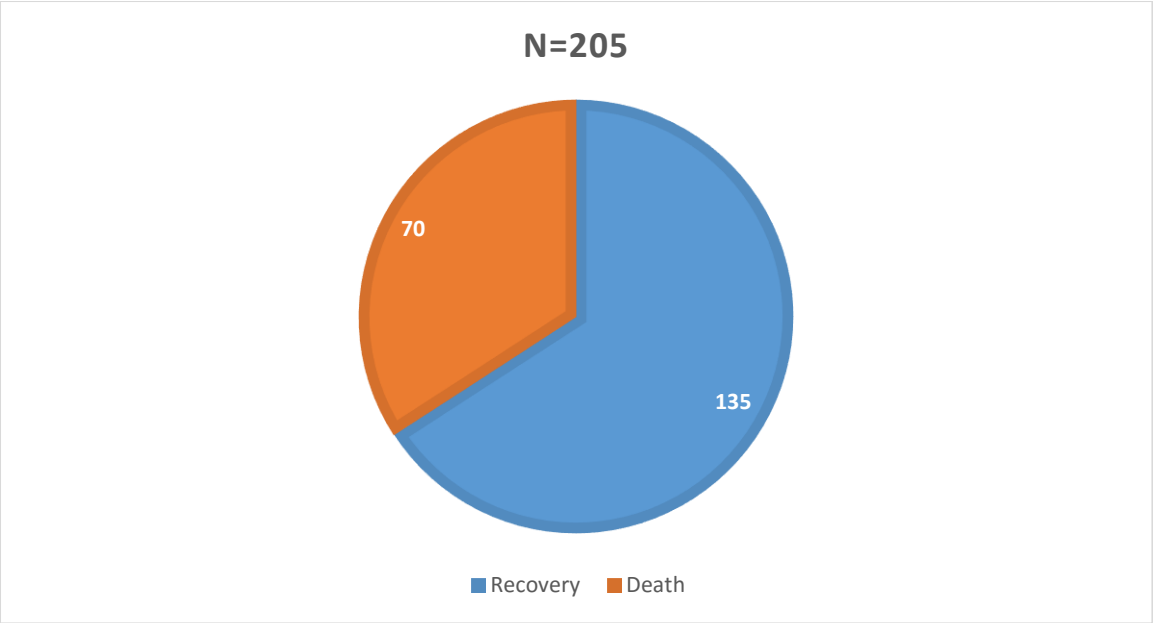


Figure 8: distribution of sepsis hospitalizations by clinical outcome of sepsis

4.4. Factors associated with death as an outcome following a hospitalization for sepsis

4.4.1. Socio-demographic characteristics associated with occurrence of death following sepsis

Socio demographic factors associated with death in our study population included being female and being a student or unemployed (OR<1; p<0.05) (Table XVII).

Table XVII: socio-demographic factors associated with death among hospitalized cancer patients with sepsis

Variable	**Total**	**Outcome**		**OR**	**95% CI**	**P value**
		Death	Recovery			
Sex						
Male	63(30.73)	14(19.72)	49(36.57)	1		
Female	**142(69.27)**	**57(80.28)**	**85(63.43)**	**2.35**	**(1.19-4.64)**	**0.01**
Employment status						
Employed	64(31.22)	15(21.13)	49(36.57)	**1**		
Student/unemployed	**61(29.75)**	**29(40.84)**	**32(23.88)**	**2.96**	**(1.37-6.37)**	**0.00**
Employment status not specified	80(39.02)	27(38.03)	53(39.55)	1.66	(0.79-3.49)	0.17

4.4.2. Clinical and therapeutic factors associated with death among hospitalized cancer patients with sepsis

In our study, having an adenocarcinoma and presence of indwelling urinary catheter were associated with a higher risk of death Receiving 01 line and 1-3 cycles of chemotherapy was associated with a lower risk of death (table XVIII). There was no association between the cancer status at time of sepsis and death following a sepsis episode.

Table XVIII: clinical and therapeutic factors associated with death among hospitalized cancer patients with sepsis

Variable	Total	Outcome		OR	95% CI	P value
		Death	Recovery			
Histologic subtypes						
Adenocarcinoma	**10(45.37)**	**49(56.34)**	**53(39.55)**	**4.31**	**(1.17-15.92)**	**0.04**
Squamous cell carcinoma	58(28.29)	19(26.76)	39(29.10)	2.27	(0.58-8.88)	0.37
Sarcoma	18(8.78)	5(7.04)	13(9.70)	1,79	(0.35-9.05)	0.76
Lymphoma	17(8.29)	3(4.23)	14(10.45)	1		
Other histologic subtypes*	19(9.27)	4(5.63)	15(11.20)	NA		1.00
Number of lines of Chemotherapy						
None	106(51.71)	46(64.79)	60(44.78)	1		0.00
One line	**74(74.75)**	**15(60.00)**	**59(79.73)**	**0.33**	**(0.17-0.66)**	**0.00**
Two lines	17(17.17)	4(16.00)	13(17.57)	0.40	(0.12-1.31)	0.20
Three lines	8(8.08)	6(24.00)	2(2.70)	3.91	(0.75-20.29)	0.17
Number of cycles of Chemotherapy						
None	107(52.20)	47(66.20)	60(44.78)	1		
1-3	**39(19.02)**	**4(5.63)**	**35(26.12)**	**0.15**	**(0.05-0.44)**	**0.00**
4-6	26(12.68)	9(12.68)	17(12.69)	0.68	(0.28-1.65)	0.39
7-18	33(16.10)	11(15.49)	22(16.42)	0.64		0.28
Cancer status						
Newly diagnosed	78(38.05)	25(35.21)	53(39.55)	2.36	(0.28-1.45)	0.46
Stable disease	21(10.24)	5(7.04)	16(11.94)	1.56	(0.25-9.64)	0.97
Progression	86(41.95)	37(52.11)	49(36.67)	3.77	(0.78-18.28)	0.15
Relapse	12(5.85)	2(2.82)	6(4.48)	1.67	(0.18-15.13)	1.00
Remission	12(5.85)	2(2.82)	10(7.46)	1		
Indwelling Catheter	**66(32.20)**	**37(52.11)**	**29(21.64)**	**3.94**	**(2.12-7.33)**	**0.01**

*****melanoma, germinal tumors, neuroendocrine tumors

4.4.3. Sepsis factors associated with death among hospitalized cancer patients with sepsis

Nosocomial infection, SIRS≥3, qSOFA ≥2, CNS as foci of infection and neutrophilia >7000 cells/mm3 were associated with a higher risk of death following a sepsis episode (OR >1; p <0.05) (Table XIX).

Table XIX: association between characteristics of sepsis episode and occurrence of death following sepsis

Variable	Total	Outcome		OR	95% CI	P value
		Death	Recovery			
Place of sepsis onset						
Out of hospital	156(76.10)	47(66.20)	109(81.34)	1		0.01
In hospital	**49(23.90)**	**24(33.80)**	**25(18.66)**	**2.23**	**(1.15-4.29)**	**0.01**
SIRS						
2	93(45.37)	18(25.35)	75(55.97)	1		
3	**92(44.88)**	**42(59.15)**	**50(37.31)**	**3.50**	**(1.81-6.76)**	**0.00**
4	**20(9.75)**	**11(15.54)**	**9(6.71)**	**5.95**	**(1.99-17.78)**	**000**
qSOFA						
0	99(48.3)	19(27.3)	80(59.7)	1		
1	70(34.15)	22(30.99)	48(35.82)	1.96	(0.95-4.03)	0.07
2	**29(14.15)**	**24(33.80)**	**5(3.73)**	**20.53**	**(6.89-61.17)**	**0.00**
3	**7(3.41)**	**6(8.45)**	**1(0.75)**	**25.67**	**(2.91-226.68)**	**0.00**
Foci of infection						
CNS*	7(3.41)	6(8.45)	1(0.75)	**12.27**	**(1.45-104.11)**	**0.01**
Neutrophil count						
<500	34(16.59)	5(7.04)	29(21.64)	1		
500 to 7000	47(22.93)	15(21.13)	32(23.88)	2.72	(0.88-8.42)	0.07
>7000	**101(49.27)**	**40(56.34)**	**61(45.52)**	**3.80**	**(1.36-10.65)**	**0.00**
Neutrophil count not specified	23(11.22)	11(15.49)	12(8.96)	**5.31**	**(1.52-18.61)**	**0.00**

***central nervous system

- **Multivariable analysis of factors associated with death**

After multivariable analysis, factors found to be independently associated with death as seen on table XX, were being female, nosocomial infection, presence of an indwelling urinary catheter and a qSOFA of ≥2.

Table XX: multivariate analysis of factors associated with death

Variable N=205	**aOR**	**(95% CI)**	**P value**
Sex			
Male	1		
Female	**3.30**	**(1.13-9.63)**	**0.03**
Number of cycles			
None	1		
1-3	**0.14**	**(0.03-0.73)**	**0,02**
4-6	1.09	(0.33-3.61)	0,87
7-18	0.79	(0.25-2.52)	0,70
Onset			
In hospital	**3.94**	**(1.46-10.65)**	**<0.01**
Out of hospital	1		
qSOFA			
0	1		
1	3.17	(1.26-7.97)	0,11
2	**65.79**	**(13.27-326.14)**	**< 0,01**
3	**59.28**	**(4.77-736.93)**	**< 0,01**
Indwelling Catheter	**3.08**	**(1.21-7.85)**	**0.02**

aor; adjusted odd ratio

CHAPTER 5
DISCUSSION

Our work was on the prevalence, socio demographic, clinical and therapeutic characteristics and outcome of sepsis hospitalizations in two Oncology centers in Yaounde. We also set out to determine factors associated with higher risk of death.To achieve this objective, we carried out a descriptive cross-sectional study with retrospective data collection at two cancer treatment centers in Yaounde: YGH and YCH which permitted us to have a sample size of 685 adult cancer patient hospitalizations.

The prevalence of sepsis hospitalization was 29.9%. Over 33.6% had a cancer of the urogenital tract and 42% of our study population was experiencing active relapse/progression of their cancer.23% of the sepsis episodes were secondary to nosocomial infections, the predominant foci of infection was urogenital in 29% and just 20% of our study population had a microbiologic confirmation of sepsis. The in-hospital mortality was 34.1%**.** Factors associated with increased risk of death were being female, presence of an indwelling urinary catheter, nosocomial infection, and qSOFA ≥2.

Study Limitations

The principal limitation of our study is its retrospective nature which had an impact on the completeness of our data as not all the clinical characteristics were noted. Hence we had a real data problem and this had a great impact on the search for factors associated with death as outcome of sepsis episode. Also, a good number of patient files couldn't be found.

Secondly for this study, we used the sepsis-2 definition to recruit our participants. The most recent sepsis-3 definition couldn't be applied to our context due to the intensive care parameters involved hence a possible risk of overestimating the prevalence of sepsis.

5.1. Prevalence of sepsis hospitalizations among all cancer patient hospitalizations

Sepsis accounted for 29.9% of medical oncology hospitalizations hence every 2 in 7 hospitalizations among cancer patients is for sepsis. This brings out the significant burden of sepsis among oncology hospitalizations. Similar to our results are those of Valentine *et al*. in their study on burden and clinical outcomes of sepsis among patients with cancer in Australia in 2020 had a prevalence of 29% in their study population[35] and Silva *et al*. in 2021 done at an oncology hospital had a prevalence of 19.2%[42]. In 2023, Beniwal *et al.* had a sepsis prevalence of 36.1% in their study on clinical course and outcomes of cancer patients admitted with sepsis in the ICU [40]. Torres *et al*. had a prevalence of 37% in Brazilian hospitals in 2015 in a study entitled sepsis associated outcomes in critically ill patients with malignancies [27]. These two studies were done in the ICU hence the higher value they had. Contrary to our

results, Hensley *et al.* had a lower prevalence of 5.7% in the USA[41]. The difference can be explained by the definition they used to identify sepsis cases which is different from that of our study. The high prevalence of sepsis in our study can be explained to be due to the fact that we used the older sepsis-2 definition for sepsis and not the recent sepsis-3 criteria probably accounting for the high number of sepsis hospitalizations. Also, most of our patients come at an already advanced stage of cancer diagnosis which already predisposes them to immune dysfunction hence greater susceptibility to sepsis secondary to immunosuppressive treatments, as well as to the underlying pathology itself. Patients with cancer have a higher risk of sepsis due to quantitative defects in neutrophil chemotaxis, phagocytosis problems and reduced bactericidal capacity, which generates impaired immune responses to the infectious agent [42]. Also, in our setting we are known to have a higher burden of infectious diseases and inadequate infection control measures[8]. All these increase the risk of sepsis in cancer patients hence the need to improve on sanitation to reduce the problem of sepsis.

5.2. Characteristics of cancer patients hospitalized for sepsis

5.2.1. Socio-demographic characteristics

Our study population was made up of 69.27% females, giving a female to male ratio of 2.2; which is compatible with Globocan 2022 statistics for Cameroon [2]. The mean age in our study was 51.88±14,46years and the most represented age group was 50-59years accounting for 27.32% of our study population. Our results corroborate those of Awad *et al.* in 2021 where they had a mean age of 56.8 ± 16.1 years [48]. Torres *et al.* also had a mean age of 63.1±15.0years and 47% of their study population was made up of males [27]. Silva *et al*. had a predominance of females in their study with ages ranging from 19-91years [42]. The predominant age group represented is due to the fact that most cancers in Cameroon are diagnosed around that age and the recent cancer statistics are in favor of more females being affected with the first 02 most prevalent cancers in Cameroon being female cancers[4,49–52]

5.2.2. Clinical characteristics

In our study, the most frequent primitive cancer sites were Genitourinary (33.66%), breast (18.54%), thoracic (16.1%) head and neck (12.6%) and gastrointestinal (10.73%). According to Globocan 2022 statistics, the first 03 cancers in Cameroon are breast, cervix and prostate cancers [2]. Cervical and prostate cancers being linked to the urogenital system often present late with locally advanced/metastatic disease. This leads to stasis in the urogenital tract hence predisposing to sepsis. These cancers as well often metastasize to bone leading to

metastatic spinal cord compression hence patients are bedridden with all the associated complications among which is sepsis from stasis and superinfected bed sores. Similar to our results, another study had Prostate cancer as the most common cancer associated with sepsis, followed by breast cancer and Kaposi sarcoma [53]. However, a study in brazil showed that gastrointestinal (25%), urogenital (15%), lung (9%), the most common primitive cancer sites in their patient population [27].

Most of our patients were diagnosed at stage IV 49.76% closely followed by 27.32% who were diagnosed at stage III hence a cumulative percentage of 77%. At advanced cancer stages, there is a state of chronic inflammation leading to dysregulated immune response and the cancer leads to dysfunction of several organs hence predisposing the patients to complications like sepsis. Also, the growing tumor mass has areas of necrosis that serve as a nidus for infection. Similar to our results, Lopez *et al*. in 2021 in their study on outcomes of sepsis in cancer patients had 84% of their patients having stage 3 and 4 cancers at diagnosis [44]. Also, Torres *et al.* didn't have any patients with early stage of solid cancer in their study[27]. In Cameroon, cancer patients are diagnosed late due to several reasons like insufficient screening programs and lack of public awareness on cancer symptoms and finally limited access to health care [51,54]. Our results therefore reflect the current cancer epidemiology in Cameroon

In our study, 45.85% of our participants were experiencing a progression or relapse of the cancer. This was closely followed by 38.5% of patients who had newly diagnosed active cancer and 16.9%were in remission or stable disease. Similar results were obtained in 2024 by Ture *et al.* in their study on epidemiology and sepsis in cancer patients whereby 40.8% were in relapse and progression, closely followed by 33.8% and 25.4% who were newly diagnosed and in remission respectively [55]. Also, Torres *et al*. had 35%, 54% and 11% for patients who were experiencing active recurrence and or progression, newly diagnosed and stable disease or remission respectively [27]. Their study, just like ours showed no association between cancer status and outcome of sepsis but Rosolem *et al.* showed that newly diagnosed active cancer and active recurrence/progressive cancer were both associated with mortality in cancer patients who had sepsis [47]. The reason for such a distribution of cancer status at time of infection can be due to the fact in Cameroon most patients are diagnosed at advanced stages as already seen and those who present with a relapse or progressive disease are already at a very advanced disease. This weakens the immune system, making it less effective at fighting off infections. Also, growing tumors create areas of necrosis that are favorable breeding grounds for bacteria

and can obstruct organs or ducts, leading to stasis hence infections. Advanced cancer often requires more frequent biopsies, surgeries, or placement of medical devices (e.g., central lines, feeding tubes), all of which increase infection risk. However, it's a bidirectional relationship because sepsis also creates a pro inflammatory environment which facilitates cancer growth and invasion in addition sepsis leads to interruption of cancer treatments for sepsis to get controlled.

5.3. Characteristics of sepsis episode

The most common foci of sepsis was Urogenital (31.01%), followed by the skin, pulmonary, gastrointestinal and other sites (23 %, 19.78 %, 17.65% and 8.56% respectively). Lopez *et al.* in their study on outcomes of sepsis among cancer patients showed the most common point of entry was digestive followed by the pulmonary, others and genitourinary[44]. Bou Chebl *et al*. had the lung 44.1%, urinary tract 22.1%, and the gastrointestinal tract 20.1% as the most common sites of infection in their study[43]. A study in brazil revealed Pneumonia was the most frequent site of infection (48%), followed by intra-abdominal, primary bloodstream, and urinary tract infections (25%, 19%, and 17%, respectively) [27]. Hensley *et al.* had the most common sites of infection being respiratory (37.7%), genitourinary (26.5%), and gastrointestinal (10.5%)[12]. The foci of sepsis in our study looks as such because amongst the 03 most prevalent cancers in Cameroon is cervix and prostate cancers. These patients present often with sepsis with point of entry being urogenital. Also, most patients with breast and prostate cancer present late with metastatic spinal cord compression making them bed ridden hence predisposed to pressure ulcers. Most patients with cervical cancer are locally advanced with complications such as lymphedema hence they also are often bed ridden and have pressure ulcers, hence putting them at higher risk of infection.

The majority of the patients had community acquired infections (CAI) at 76.10% and 23.90% had nosocomial infections. This in contrary to the findings we saw in 02 other studies whereby, over 68% and 60% of their study populations had nosocomial infections [27,47]. The high rate of CAI found in our study can be explained by the low level of sanitation and hygiene in our environments which increase the risk of CAI and in addition, since cancer patients frequently visit the hospital, these may as well be nosocomial which are being misclassified as CAIs.

A probable infection which was defined as patients with a suspected clinical point of entry but no microbiological confirmation regardless of the reason for no confirmation, was

found in 71%% of our study participants. Only 20.5% of our patients had a microbiologically proven infection and 8.8% had a possible infection which was defined as clinical suspicion of sepsis with no evident point of entry and no microbiological confirmation. The group of patients with a possible infection was made up of most patients with a febrile neutropenia. Our findings are contrary to those of Rosolem *et al*. and Torres *et al*. as 68% and 50.3% respectively of their study populations had a microbiologically proven infection. Rosolem *et al*. had just 32% of infections being clinically suspected [27,47]. The difference can be explained by the fact that their studies were done in ICU of developed countries, while ours was done in the medical oncology service of a limited resource country. The low percentage of microbiologically proven infections can be due to several reasons. The first is due to the fact that just 43.41% of our patients provided a sample for culture. Amongst those who provided samples for culture 47.19% were positive which is similar to another study whereby microbiological documentation of sepsis was obtained for 50% of their patients [27].The low level of positive cultures can be explained by the fact that these patients have access to OTC antibiotics which affects culture results. Also, the limited availability of expertise and techniques like PCR and Elisa to carry out cultures in our setting and many patients are unable to afford the cost of culture exams.

In our study, most of the participants with sepsis had been diagnosed with cancer within the preceding year at 60 % and 30.2 % of our participants had their cancer diagnosed more than one year prior to the sepsis episode. Our findings are in line with those of Te Marvelde *et al.* who showed that the rate of admission for sepsis was highest in the year following cancer diagnosis [9]. A peak of sepsis admissions around time of diagnosis is consistent with septic complications of a cancer leading to the initial detection of cancer and the combination of treatments in the months following diagnosis (surgery, chemotherapy, radiotherapy, invasive lines) predisposing cancer patients to infection and sepsis[9]. Also, in Cameroon over 50% of patients die within one year of cancer diagnosis[49] hence it explains our findings because the majority of our population was in their first year of cancer diagnosis

In hospital mortality in our study was 34.63%.This implies that every 1 in 3 sepsis hospitalizations would die. In 2019 Hensley *et al.* had an in hospital mortality of 27.9% in their study on outcomes of cancer related versus non cancer related sepsis hospitalizations [41]. Williams *et al.* in their study on hospitalized cancer patients with sepsis had a hospital mortality of 37.8% for severe sepsis and 7.2% for non-severe sepsis [22]. Beniwal *et al*. had an ICU mortality of 73.9% for patients hospitalized with sepsis [40] and in brazil, Torres *et al*. had an

in hospital mortality of 56% [27],we think the high mortality is because most of their study participants had nosocomial infections which were shown to be associated with a higher in hospital mortality. Even though its 34%, we think the mortality rate observed in our study was high. This is due to limited resources in our setting to adequately manage sepsis and also, it's usually challenging to sterilize the foci of infection since most of the patients are often in very advanced stages of cancer with huge tumors that obstruct passages and lead to organ dysfunction. This finding is a call to action for clinical researchers to expand on research in this population to provide a better understanding of sepsis outcomes in cancer patients and to identify strategies that may improve these outcomes.

5.4. Factors associated with death as outcome

5.4.1. Socio-demographic factors associated with death

After univariable and multivariable analysis, compared to males with cancer, being female was associated with 3.3times higher risk of death following an episode of sepsis (3.30; CI: 1.13-9.63; $p < 0.05$). This can be explained by the current cancer statistics of Cameroon where more females are being affected and the first 02 cancers are female cancers [4]. Also, among our study participants, being a student or unemployed was associated with 2.96 times higher risk of death following sepsis (OR >1; $p < 0.05$) compared with those who were employed however this did not persist on multivariable analysis. Lack of employment translates to lower health care purchasing capacity in our context whereby 38% of the population lives below the poverty line [56]. Therefore, these patients have the tendency of presenting to the hospital with more severe sepsis after haven tried OTC Antibiotics [57] without improvement and during hospitalization they are unable to respect the prescribed tests and treatments leading to poor infection control hence increased risk of death.

5.4.2.2. Clinical factors associated with death

Patients with an indwelling urinary catheter are 3.94 times more at risk of dying from an episode of sepsis compared to those without a catheter and this persisted on multivariable analysis (3.08; CI: 1.21-7.85; $p < 0.05$). The presence of urinary catheters have been shown to convey a 4.7-fold risk of sepsis [55] hence should only be used when very necessary and removed as soon as possible. Urethral catheters inoculate germs into the bladder and promote colonization by providing a surface for bacterial adhesion and causing mucosal irritation [58] hence risk of persistent sepsis and death. Stomas also breech the skin barrier hence providing a favorable site for dissemination of skin organisms. To better prevent these of urinary tract

infections, emphasis should be placed on use of aseptic technique in the insertion of the urinary bladder catheter ; keeping the urine bag below the level of the bladder and with less than three quarters of the filled capacity, or drain the collector every eight hours or when it reaches 50% of the container and keep urinary flow unobstructed and the drainage system closed [42].

Our study did not find any association between the cancer being in relapse/progression and death. These findings are similar to those of Torres *et al.* [59]. However, the study entitled critically ill patients with cancer and sepsis: clinical course and prognostic factors showed that cancer that was in active recurrence or progression or active and newly diagnosed were associated with a higher risk in in hospital death on multivariate analysis [47]. The difference in results can be attributed to the study design whereby they did a prospective study and our study as well as that of Torres were both retrospective studies.

As concerns chemotherapy, receiving 01 line or 1-3 cycles of chemotherapy were associated with a lower risk of death (OR<1; $p < 0.05$) after an episode of sepsis. This finding is similar to a recent study which also concluded that recent exposure to anticancer treatments, is no longer a major determinant of short-term mortality in critically ill patients with cancer [47].

5.4.2.3. Sepsis factors associated with death

The odds of death were 4 times higher in patients with sepsis as a result of a nosocomial infection when compared to those with a CAI (3.94; CI: 1.46-10.65; $p< 0.05$). In 2015 in brazil, nosocomial infections were also shown to be associated with risk of in hospital mortality[27]. After univariable analysis, Rosolem *et al.* [47] had nosocomial infections being associated with higher risk of death but contrary to our study, this did not persist in their study after multivariate analysis. A recent study had shown the crude mortality rate associated with HAI to vary from 12 to 80%, depending on the definition and populations under study [28]. Nosocomial infections convey a higher risk of death because they are often polymicrobial, occur in debilitated patients and are due to multi drug resistant germs[28].

A SIRS score ≥3 was observed in 53.17% of our study population and was associated with a higher risk of death (OR>1: $p< 0.05$) on univariable analysis but not on multivariable analysis. Our findings are similar to that of Rosolem *et al.* showed that a SIRS score ≥3 conveyed a higher risk of death on univariable analysis [47]. SIRS is a life threatening situation resulting from the body's response to infection and the more severe the infection the more

threatening the response. Therefore, the more severe the infection, the higher the SIRS score and the higher the risk of death.

In our study, compared to patients with a negative Qsofa, patients with a qSOFA score of 2 and 3 had a higher risk of death from an episode of sepsis on univariable and multivariable analysis. Our findings are in line with those of Olvera et al done in 2024 entitled Usefulness of the qSOFA score for predicting hospital mortality in cancer patients. Their study revealed that the risk of in-hospital mortality increased as the qSOFA score did: it was higher than 50% in the group with qSOFA scores of 2 and 3 points [60]. A higher qSOFA score translates to a more severe infection associated with several organ dysfunctions hence higher risk of death[27,61]. Qsofa being a simple and quick bedside test should be added to the daily routine evaluation of patients in order to promptly identify those at higher risk of death and tailor the appropriate measures like transfer to the ICU.

Participants who presented with a Neutrophilia of >7000/mm3 had a higher risk of death when compared to those with neutrophils <7000/mm3 (OR>1; $p < 0.05$). This can be explained by the fact that a higher level of neutrophils imply severity of the infectious process.

Patients who had the central nervous system as the foci of infection were at higher risk of death on Univariate analysis (OR>1; $p < 0.05$). Having the CNS as point of entry in sepsis is already in favor of a severe infection. Patients who present with such clinical foci are often those who have secondary meningeal or brain metastasis hence implied advanced disease. Therefore this explains why the site of infection being the CNS puts these patients at higher risk of death.

CONCLUSION

The main objective of our study was to evaluate the prevalence of sepsis hospitalizations, describe the socio-demographic, clinical and therapeutic characteristics and outcome of sepsis hospitalizations. At the end of our study, we noted the prevalence of sepsis hospitalizations in our study population to be 29.9 %. Hence every 2 in 7 hospitalizations in oncology are sepsis related.

The mean age of our study population was 51, 88± 14,46years with extremes of 19 and 83years and the age group 50 to 59years was predominantly represented. Females made up 69.27% of the study population. Cancers of the Urogenital tract were the most common cancer types found in our population and 49.8% of our study population had a metastatic cancer on diagnosis. At time of sepsis, most participants had received at least 01 treatment modality 60.49%, and half of the participants had received chemotherapy. At occurrence of sepsis, 48% of our participants were experiencing active relapse and progression of the underlying cancer. At time of sepsis, 64% of our participants had been diagnosed with cancer within the previous 12months and half of our study population had not yet received chemotherapy.

Most of our study population 87.8% had 01 episode of sepsis and this was mostly due to community acquired infections in 76% of the study population. The majority of our study population had a negative qSOFA score and a SIRS score of 2 and 3. The majority, 70% had a probable infection and among those who provided samples for culture, half were positive. The most frequent point of entry for infections was the urogenital tract in 31% of participants. Most of our study participants recovered from the episode of sepsis but the mortality rate was as high as 34.6% hence 1 in 3 sepsis hospitalizations will die.

Factors we identified to be independently associated with a higher risk of death following a hospitalization for sepsis were female sex, presence of an indwelling urinary catheter, nosocomial infections and patients with a positive qSOFA. Our results are a call to action to identify strategies that improve outcomes for cancer patients with sepsis.

There was no increased risk of death in those with active relapse and progressing cancer and among those who received chemotherapy receiving <4 cures was associated with a lower risk of death.

RECOMMENDATIONS

At the end of our study, we can suggest the following recommendations

- **To the treatment centers administration**

Organize continuous developmental training of both oncologists and infectious disease specialists on how to prevent, diagnose and manage sepsis in cancer patients, in view of reducing the associated morbidity and mortality due to sepsis.

- **To all those involved in cancer care management**

Adequate hygiene practices when working on patients to reduce transmitting germs from one patient to another.

Prompt transfer of patients with sepsis to the ICU

Proper counseling to cancer patients on symptoms of infection during their regular follow ups.

Carry out regular assessments of hospitalized cancer patients with sepsis to identify patients at higher risk of death and adjust their care accordingly to improve on their survival.

- **To all those suffering from cancer**

Promptly report to their treating oncologist or treatment center in case of any new symptoms they experience.

- **To the scientific committee**

Carry out prospective studies to determine more specifically using sepsis 3 criteria, the burden and understand the outcome of sepsis in cancer patients, assess other outcome measures that impact this patient population and eventually to identify strategies that may improve these outcomes.

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APPENDICES

Appendix 1: Data collection form

SEPSIS IN HOSPITALISED ADULT SOLID CANCER PATIENTS: PREVALENCE, CLINICAL CHARACTERISTICS AND OUTCOME.

SECTION I: SOCIODEMOGRAPHIC CHARACTERISTICS AND OTHER COMOBIDITIES

	PAT _ID	**Patient code**		
I.1	**DATE**			
I.2	**SEX**	What is your sex ?	1. Male □ 2. Female □	
I.3	**DAT_BIR**	Date of birth (or age)	_ _ _ /_ _ _ /_ _ _ _ _ _ (…… yrs)	
I.4	**RESID**	Category of area of residence	1. Urban □ 2. Rural □	
I.5	**MAT STA**	1=Married 2=single 3=Divorced 4=widow (er) 5=Concubinage		
I.6	**ED_LEV**	Highest level of education	1. None □ 2. Primary □ 3. Secondary □ 4. Higher education□	
I.7	**TYPE_PRO**	What is your profession?	Office worker= 1 business=2 teacher=3 student =4 unemployed=5 others=6 Precise	
PAST HISTORY AND COMORBIDITIES				
I.8	**OBE**	Obesity	. 1 yes □ 0. No□	
I.9	**HTN**	Do you have hypertension ?	1. yes □ 0. No □	
I.10	**HEA_FAI**	Do you have heart failure ?	1. yes □ 0. No□	
I.11	**KID_DIS**	Do you have kidney disease ?	1. yes □ 0. No□	
I.12	**DIALYSE**	Are you on dialysis	1. yes □ 0. No□	
I.13	**DIABET**	Do you have diabetes?	1. yes □ 0. No□	
I.14	**HEPATOP**	Do you have CLD	1. yes □ 0. No□	
I.15	**HIV**	Do you have HIV?	1. yes □ 0. No□	
I.16	**ALCOHOL**	Category of alcohol consumption	1. Non consumer □ 2. Previous consumer □ 3. Active consumer □	
I.17	**CIGAR**	Category of cigarette smoking	1. Non smoker □ 2. Ancient smoker □ 3. Active smoker □ 4. Passive smoker □	

SECTION II: ONCOLOGIC HISTORY

2.1	Primitive site of cancer	head and neck=1 esophagus=2 stomach =3 Colon and rectum =4 liver=5 Pancreas=6 Lungs=7 Prostate=8 kidney=9 Bladder=10 Ovary=11 Endometrium =12 cervix=13 breast=14 Lymph nodes, blood and bone marrow =15 skin=16 bone and soft tissue=17 Others=18 specify	☐
2.2	Histologic type of cancer:	Adenocarcinoma=1 Squamous cell carcinoma =2 Sarcoma =3 Lymphoma =4 Melanoma =5 germinal tumor=5 others =6 …… (precise)	☐
2.3	Date of diagnosis	DD/MM/YY…../……./……..	
2.4	stage of cancer upon diagnosis:	stage 1=1 stage 2=2 stage 3 =3 stage 4= 4	☐
2.5	Treatments received:	Chemotherapy=1 Surgery =2 Radiotherapy=3 Concomitant chemo r Radiotherapy =4 Hormone therapy=5 Immuno therapy=6 Targeted therapy=7	☐ Other than chemotherapy, precise name of other therapy received. Type of surgery
2.6	If chemotherapy precise number of lines	L1 Protocol……. Number of cycles…… L2 protocol……. Number of cycles……. L3 protocol…… Number of cycles …… Date of last treatment …/…./……	
2.7	Status of cancer	Newly diagnosed =1 Stable disease=2 Progression=3 Relapse =4 Remission =5	

SECTION III : INFECTION HISTORY

Number of episodes	…….

INFECTIOUS EPISODE Nº

Date of Onset	.....
Onset	Out of hospital In hospital …. No of days after hospitalization
Presenting symptoms	Fever Altered consciousness Purulent discharge Other , specify
Signs	Fever Tachycardia Tachypnea Hypotension Neurologic status
QSOFA	
Type of infection	Probable Infection …….. ….. yes □ . No□ Proven Infection …….. yes □ . No□ Possible Infection …….. yes□ . No□
Hospitalisation	Duration (in days)……
Indwelling catheter or stoma	Yes ▭ No ▭
Neutrophil count	

CLINICAL

Site of infection	Pulmonary	.yes □ . No □
	Pneumonia Pleuresy/ empyema Bronchitis Bronchopneumonia	
	ENT	yes□ . No □
	pharyngitis Otitis Sinusiis	
	Ocular	yes □ . No□
	Conjonctivitis Keratitis others	
	Digestive	yes □ . No□
	Stomatitis Gastroenteritis Enterocolitis Cholecystitis / cholangitis Infection of ascitic fluid	
	Cardiovascular	Yes □ . No□
	Pericarditis Endocarditis Myocarditis	
	Urogenital	Yes □ . No□
	Uretritis Cystitis Pyelonephritis Prostatitis PID Cervicitis	
	Skin and appendages	Yes □ . No□
	Abcess Ulcers Superinfected wounds / stoma Cellulitis	

	others Central Nervous system Encephaliis Méningitis Cérébral abscess Other Osteo-Articular Osteitis/osteomyelitis Arthritis Spondylodiscitis Others……..	Yes□ . No□ Yes □ . No□

PARACLINICAL WORKUPS

Samples collected	**1.Yes □ 0. No□**	
If yes, which	sputum	
	Urine	
	Pus	
	Pleural fluid	
	Joint fluid	
	Ascitic fluid	
	Cerebrospinal fluid	
	Stool	
	Blood	
	Others	
Germ identified	**Yes □ . No□**	
Type of germ	**Bacteria** Yes□ . No□ **Virus** Yes □ . No□ **Fungi** Yes □ . No□ **Parasite** yes □ . No□	
Specify		
Antibiogram	**Sensitive antibiotics …….** **Resistant antibiotics**	

Evolution during hospitalisation

Recovery **Death**

Appendix 2: Ethical clearance from the ethical review board

REPUBLIQUE DU CAMEROUN
PAIX – TRAVAIL – PATRIE
****
UNIVERSITE DE YAOUNDE I
****
FACULTE DE MEDECINE ET DES SCIENCES BIOMEDICALES

DEPARTEMENT DE MEDECINE INTERNE ET SPECIALITES
****

REPUBLIC OF CAMEROON
PEACE – WORK – FATHERLAND
****
THE UNIVERSITY OF YAOUNDE I
****
FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES
****
DEPARTMENT OF INTERNAL MEDICINE AND SPECIALITIES
****

DEPARTMENT OF INTERNAL MEDICINE AND SPECIALITIES

FACTORS ASSOCIATED WITH INFECTIOUS EPISODES AMONG HOSPITALIZED ADULT PATIENTS WITH SOLID CANCERS IN YAOUNDE

Dissertation proposal in view of a diploma of specialised studies in madical oncology

Submitted by

AZEMAFAC Kareen ESENWOH

Matricule : 20S1967

Supervisor :

Pr. NDOM Paul

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Oncologue Médical / HGY
ONMC: 4497

Académic year 2023 – 2024

Appendix 3: Research authorization from General Hospital Yaounde

REPUBLIQUE DU CAMEROUN
Paix - Travail - Patrie

MINISTERE DE LA SANTE PUBLIQUE

HOPITAL GENERAL DE YAOUNDE

DIRECTION GENERALE

BP 5408 YAOUNDÉ - CAMEROUN
TÉL : (237) 22 21 31 81
FAX : (237) 22 21 20 15.

REPUBLIC OF CAMEROON
Peace - Work - Fatherland

MINISTRY OF PUBLIC HEALTH

YAOUNDE GENERAL HOSPITAL

GENERAL MANAGEMENT DEPARTMENT

N/Réf : 452-24 /HGY/DG/DPM/APM-TR.

Yaoundé, le 24 MAI 2024

Le Directeur Général

A/to

Docteur AZEMAFAC Kareen Esenwoh
Résident niveau 4 en Oncologie Médicale
Matricule : 20S1967
FMSB – UNIVERSITE YAOUNDE I

Objet/subject :
V/demande d'autorisation de recherches.

Docteur,

Nous accusons réception de votre courrier du 15 mai 2024 dont l'objet est repris en marge.

Y faisant suite, nous marquons un avis favorable pour que vous effectuiez vos travaux de recherches au Service ONCOLOGIE dans le cadre de votre étude dont le thème s'intitule : « ***factors associated with infectious episodes among hospitalized adult patients with solid cancer in Yaounde***».

Cette étude sera supervisée par le Docteur ATENGUENA, Oncologue médical.

Pendant la durée des recherches, vous observerez le règlement intérieur de l'établissement. Toutefois, les publications se rapportant à ce travail devraient inclure les médecins de l'Hôpital Général de Yaoundé.

Recevez, Docteur, nos salutations distinguées. /-

HOPITAL GENERAL YAOUNDE
H.G.Y
Le Directeur Général Adjoint
YAOUNDE GENERAL HOSPITAL

Le Directeur Général,

Prof. EYENGA Victor

Ampliations :
- *DPM*
- *Chef service Oncologie*
- *Chrono/archives.*

Appendix 4: Research authorization from Central Hospital Yaounde

REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
****
MINISTERE DE LA SANTE PUBLIQUE
****
SECRETARIAT GENERAL
****
DIRECTION DE L' HOPITAL CENTRAL DE YAOUNDE
****
SECRETARIAT MEDICAL

N° 251/24 / AP/MINSANTE/SG/DHCY/CM/SM

REPUBLIC OF CAMEROUN
Peace-Work-Fatherland
****
MINISTRY OF PUBLIC HEALTH
*** *****
GENERAL SECRETARY
****
DIRECTORATE OF CENTRAL HOSPITAL OF YAOUNDE
****
MEDICAL SECRETARY

Yaoundé, le 23 MAI 2024

ACCORD DE PRINCIPE

Je soussigné **Professeur FOUDA Pierre Joseph**, Directeur de l'Hôpital Central de Yaoundé, marque mon Accord de principe à Monsieur/Madame **AZEMAFAC Kareen ESENWOH** , Résident de 4ème année d'Oncologie Médicale à la Faculté de Médecine et des Sciences Biomédicales de l'Université de Yaoundé I , sous le thème « FACTORS ASSOCIATED WITH INFECTIOUS EPISODES AMONG HOSPITALIZED ADULT PATIENTS WITH SOLID CANCERS IN YAOUNDE » à l'Hôpital Central de Yaoundé, sous la co-supervision du docteur ESSON MAPOKO Berthe Sabine .

Pour Le Directeur et par ordre
Le Conseiller Médical,

REPUBLIQUE DU CAMEROUN HOPITAL CENTRAL DE YAOUNDE Le Conseiller Médical MINISTERE DE LA SANTE PUBLIQUE

Ampliations :

- Conseiller Médical ;
- Chef service concerné ;
- Intéressé/e ;
- Archives /Chrono.