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PREVALENCE, CLINICAL PROFILE AND RESISTANCE PATTERNS OF KLEBSIELLA PNEUMONIAE NOSOCOMIAL INFECTIONS IN PAEDIATRIC CARDIAC INTENSIVE CARE UNIT HOSPITAL SERDANG

GROUP 31

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ABSTRACT

Background: Nosocomial infections known as healthcare-associated infections (HAI), are infection(s) acquired during the process of obtaining health care that was not present during the admission. Looking at children with heart conditions, the majority of them rely on cardiac surgery as the transition into adulthood is impeded as many develop complications. In paediatric intensive care units (PICU), NI constitutes complications following cardiac surgery. Multiple surgical wounds and the use of invasive equipment after surgery are the major causes of NI in these individuals. Bloodstream infections are the most common in PICUs, as opposed to adults, where ventilator-associated pneumonia is the most common. *Escherichia coli* and *Klebsiella pneumoniae* are two prevalent pathogens that cause NI, with *K. pneumoniae* being the second most frequent Gram-negative aerobic bacteria. These infections are common in hospitalised patients, and they are frequently treated with β-lactams and other antibiotics. Antibiotic-resistant *K. pneumoniae* strains, on the other hand, have emerged independently all over the world. In this study, we hope to investigate the prevalence, clinical profiles, and resistance patterns of *K. pneumoniae* infection in children admitted to PCICU Hospital Serdang.

Materials & Methods: A retrospective cross-sectional study was conducted in 2 months among PCICU patients in Hospital Serdang from June 2018 to December 2020. Descriptive analysis and non-parametric analysis were used to present the data and establish any association of statistical significance between independent and dependent variables.

Results: Only 49 out of 903 patients in PCICU Hospital Serdang developed nosocomial *Klebsiella pneumoniae* infection from June 2018 to December 2020. Thus, the prevalence is 5.43%. There were significant associations found between few sociodemographic factors, patient factors and medical interventional factors with the outcome of the infection. The association between gender and respiratory sequelae was significant, where it was more prevalent among males (86.4%, p-value=0.004) than females (45.5%, p-value=0.004). Besides that, infection of *K. pneumoniae* within the bloodstream has shown to be significantly higher (42.9%) to be associated with death rather than *K. pneumoniae* infections outside of the bloodstream (8.1%). Another association found was that the use of chest drain showed a significantly lower occurrence at 0% when compared to using other invasive procedures (32.4%) resulting in sepsis and infections. As for the resistance patterns of *K. pneumoniae,* the majority of PCICU patients were infected with ESBLs (75.5%), followed by non-resistant strains (22.4%). Only 1 patient had an infection of Carbapenem Resistant Klebsiella pneumoniae (CRKP) strains (2.0%).

Conclusion: The prevalence of *K. pneumoniae* nosocomial infection in PCICU Hospital Serdang from 2018 to 2020 is 5.43%. This study showed that there was no significant association between most of the sociodemographic factors, patient factors and medical interventional factors with the outcome of *K. pneumoniae* nosocomial infections in the PCICU. However, there were significant associations between gender and respiratory sequelae, bloodstream infections and death, and chest drain and sepsis and infections sequelae of *K. pneumoniae* nosocomial infections. In our findings, the majority of the *K. pneumoniae* strains were ESBLs followed by non-resistant strains and CRKPs.

Keywords: *Klebsiella pneumoniae*, nosocomial infection, PCICU

APPROVAL

The dissertation proposal had been submitted and approved by the Medical Research Ethics Committee (MREC) and the Ethics Committee for Research of Universiti Putra Malaysia (JKEUPM).

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CHAPTER 1
INTRODUCTION

1.1 Background

Paediatric cardiovascular disease describes heart conditions that are congenital or acquired, affecting children until adulthood. Recent advances in medical and surgical care seem promising. However, the transition into adulthood is impeded as many develop complications before, after or even during surgical corrections. Mortality and morbidity of these children are not only dependent on the complexity of the type of cardiac surgery but other associated factors such as premorbid conditions and post operative complication.

Nosocomial infections (NI) represent a major complication in paediatric intensive care (PICU) patients undergoing cardiac surgery. The main causes of NI in these patients are the presence of multiple surgical wounds and postoperative utilization of invasive devices. Nosocomial infections are defined as those that occur within 48 hours after admission to the hospital, 3 days after discharge, or 30 days after surgery (Louis V., et al, 1995). Studies based on Paediatric Cardiac ICU (PCICU) report incidences between 6.1 - 15.1% (Urrea M., et al, 2003; Richards MJ., et al, 1999) whilst a cross-sectional study found a prevalence of 11.9% (Sohn, A. H et al., 2001).

Several studies have established that there is a difference between nosocomial infections in children and adults. PICUs have the most widespread Bloodstream (BSI) infections (28-52%) contrasting from adult intensive care where ventilator associated pneumonia (VAP) is most prevalent. In children, BSI is followed by pneumonia (including VAP) and urinary tract infection (UTI), enteric, surgical site and skin infections come next respectively. Common organisms that cause NI are *Escherichia coli* and *Klebsiella pneumoniae* where *K. pneumoniae* is the second most common Gram-negative aerobic bacteria (N. Shinagawa., et al, 2014). In hospitalised or otherwise immunocompromised patients, these infections typically occur and are regularly treated with β-lactams and other antibiotics that are selective against

Enterobacteriaceae. Antibiotic-resistant strains of *K. pneumoniae* and hypervirulent strains of *K. pneumoniae* have, however, developed independently across the globe. Moreover, recent advancements in molecular capabilities have shown that other Klebsiella species are currently a proportion of clinical isolates known as *K. pneumoniae* (Martin, R. M., & Bachman, M. A., 2018). By understanding this information, we aim to identify the clinical profile, associated factors and resistance patterns of *Klebsiella pneumoniae* infection in children admitted to PCICU Hospital Serdang in this study.

1.2 Problem Statement

Klebsiella pneumoniae is one of the commonest organisms causing nosocomial infections in post-cardiac paediatric patients. In Malaysia, paediatric cardiac intensive care is very limited. There are only four paediatric cardiac centres providing surgical intervention in Malaysia, out of those only one centre is fully government funded which is Hospital Serdang. Data available on nosocomial infections are limited to the adult population due to this factor. To our knowledge, there is no published data on *K. pneumoniae* infections among children undergoing cardiac surgery in Malaysia. Hospital Serdang infectious disease surveillance data also found *K. pneumoniae* infection highest among children admitted to PCICU Hospital Serdang.

1.3 Significance of Study

The purpose of this study is to determine the prevalence, clinical profile and antibiotic resistance of *Klebsiella pneumoniae* nosocomial infections among children admitted to paediatric cardiac intensive care units. By understanding the current resistance pattern in PCICU Hospital Serdang, we hope to provide information for better selection of antibiotics in the future so that it can shorten duration of treatment in hospitals and maximise the therapeutic potential as well as decrease health care costs. This study also serves as baseline data for the future establishment of antibiotic stewardship in the new upcoming cardiac centre in Hospital Serdang.

1.4 Research question

1. What is the prevalence and clinical profile of *K. Pneumoniae* nosocomial infection in PCICU Hospital Serdang?
2. Are there any associated factors for *K. Pneumoniae* nosocomial infections in PCICU Hospital Serdang?
3. What is the antibiotic resistance pattern in children with *K. Pneumoniae* nosocomial infections in PCICU Hospital Serdang?

1.5 Objectives

1.5.1 General Objective

1. To study prevalence, clinical profile and antibiotic resistance of *Klebsiella Pneumoniae* nosocomial infection in paediatric cardiac intensive care unit Hospital Serdang.

1.5.2 Specific Objective

1. To determine the prevalence of *Klebsiella pneumoniae* nosocomial infections in a PCICU.

2. To determine association between the clinical profile (sociodemographic factors, patient factors, medical intervention factors) and outcome of *Klebsiella pneumoniae* nosocomial infections in a PCICU.

3. To determine the antimicrobial resistance patterns of *Klebsiella pneumoniae* in a PCICU.

1.6 Hypothesis

Null hypothesis

1. There is no significant association between the sociodemographic factors and outcome of *Klebsiella Pneumoniae* nosocomial infections in PCICU Hospital Serdang.
2. There is no significant association between the patient factors and outcome of *Klebsiella Pneumoniae* nosocomial infections in PCICU Hospital Serdang.
3. There is no significant association between the medical interventional factors and outcome of *Klebsiella Pneumoniae* nosocomial infections in PCICU Hospital Serdang.

CHAPTER 2
LITERATURE REVIEW

2.1 Overview

The genus *Klebsiella* belongs to the Klebsiella tribe, a member of the Enterobacteriaceae family. *Klebsiella* is named after a 19th century German microbiologist, Edwin Klebs. *Klebsiella* is categorised as a nonmotile, rod-shaped, gram-negative bacteria with a prominent polysaccharide capsule. *Klebsiella* can be found in soil and water and on plants, and several strains are part of the normal flora of the human gastrointestinal tract.

Carl Friedlander, a German Microbiologist and pathologist first described *Klebsiella pneumoniae* in 1882. It is a well known opportunistic pathogen that causes serious diseases such as septicemia, pneumonia, urinary tract infections (UTIs), chronic lung disorders, and nosocomial infections in immunocompromised patients. Once this bacterium infects the human body, it can exhibit elevated levels of virulence and resistance towards antibiotics. The arising of bacteria producing extended-spectrum beta-lactamase (ESBL) especially in *klebsiella pneumoniae* is becoming a major issue for the production of antibiotics.

The defense of the host from bacterial invasion relies mostly on two things: polymorphonuclear granulocytes, which phagocytose bacteria, and bactericidal serum complement proteins. In the case of *Klebsiella pneumoniae* infection, the alternative mechanism of complement activation is predominant. Neutrophil myeloperoxidase and lipopolysaccharide-binding protein are facilitated to protect against *Klebsiella pneumoniae* infection.

Bacteria have polysaccharide capsules that consist of complex acidic polysaccharides that will affect its pathogenicity. The capsule prevents bacteria from serum bactericidal proteins and phagocytosis. With both fimbrial and non-fimbrial adhesions, it adheres to host cells, and this is crucial to the infectious process.

2.2 Background of study population

Based on Population Distribution and Basic Demographic Characteristic Report 2010, Malaysia in general has a total population about 28.3 million of which 91.8% were Malaysian citizens which consists of Malay ethnic predominantly, followed by Chinese and Indians. Statistics by Statista (2020) summarised that approximately 24% of the Malaysia population in 2019 is children. According to the World Health Organisation, the Malaysian proportional fatality rate of cardiovascular diseases (CVDs) stood at 36% in 2014. In 2015, around 17.7 million people died from CVDs worldwide, representing 31% of all global deaths.

According to Health Indicator 2007 by the Malaysian Department of Statistics, the prevalence of Congenital Heart Diseases (CHD) among Malaysian children is about 8 to 10 per 1,000 live births. The number of children born with CHD is around 5,000 a year with an average of 500,000 deliveries a year. Two-thirds of the children with CHD will require surgical intervention. Thus, the number of children requiring surgery annually is about 2,000 to 3,000. Presently, only the National Heart Institute, Hospital Serdang and 2 other private hospitals are operating complex paediatric cardiothoracic surgeries.

2.3 Heart disease in children

Heart disease is defined as any condition affecting only the heart. In children, there are two types of heart problems which are congenital and acquired. Children's Hospital of Pittsburgh (2020) stated that children's heart disease is diverse from coronary artery disease in adults and normally does not result in heart attacks.

Congenital heart defects develop in intrauterine life during the development of the fetal heart. Mild defects usually do not require treatment. In contrast, moderate and severe defects are essential to be treated.

In acquired heart disease,the problem appears after birth as a consequence of damage done to the heart by a disease or pathogens. In some children with acquired heart disease, a cause cannot be found.

2.3.1 Acquired heart disease in children

Acquired heart diseases are the consequences of conditions that develop during lifetime due to infections and inflammations that may injure the heart. According to Malaysia Healthcare (2020), acquired heart disease is much less frequent in children compared to adults with the two most common; rheumatic heart disease and Kawasaki disease.

Rheumatic heart disease is the complication of rheumatic fever caused by streptococcal bacteria. Rheumatic fever is an inflammatory disease that is caused by streptococcus pharyngitis. It can affect connective tissue of the body, especially in the heart, joints, skin and brain. Hung and Nadia (2016) stated that in Malaysia's paediatric population, the highest group of age for rheumatic heart disease is the school age children with clinical presentation of fever and joint pain. Rheumatic fever has the ability to scar the heart valves until it loses its function.

An article, Kawasaki disease (2019) made by UCSF Benioff Children's Hospital emphasizes that Kawasaki disease is described by inflammation of blood vessels all over the body, principally the coronary arteries. Children under 5 years old are commonly infected and occur more frequently in boys. Malik (n.d.) reported that over a period of 8 years, seven cases of Kawasaki disease were reported admitted to Hospital Universiti Sains Malaysia with the average age at the time of admission was less than 30 months and four of the children were boys.

2.3.2 Congenital heart defects

According to the Oxford dictionary, the term congenital is the condition that is present from birth either a disease or physical abnormalities resulting from malformation. The NHS website (2018) stated that congenital heart defects (CHD) is a prevailing term for a variety of birth deformities that influence the natural heart functions. Worldwide, there are around 0.8% to 1.2% of CHD predominant live births. Statistics recorded by CDC (2020) finalised that almost 1% or about 40000 births annually in the United States are affected by CHD and the predominance of mild type is rising and the others remain constant. In fact, around 25% of the babies born with CHD showed a serious CHD and demanded surgery or other treatments.

In another population based study at Johor, Malaysia, Bah et al. (2018) concluded that the birth predominance of CHD was 67 of 10000 live births (LB) and around 40% of these were very serious and the rest were mild and moderate. From 2006 to 2015, there was a serious increment in the birth predominance of CHD from 51 per 10000 LB to 78 per 10000 LB. Two out of five of the birth predominances of CHD were severe and approximately presented with syndrome and extracardiac problems. In recent years, there was an approximate increment in detection of more serious lesions that increased the overwhelm on resources that are already restricted in the intermediate-income country.

2.3.2.1 Cyanotic heart defects

Healthwise (2019) reported that in cyanotic heart defects, there is poor oxygenated blood reaching the tissues of the body, especially the distal part of the body. This results in the development of a bluish tint (cyanosis) to the parts of body and clinically manifested with bluish skin, lips, and nail beds. In paediatric, there are a lot of cyanotic heart defects due to congenital malformation such as tetralogy of fallot, transposition of great vessels, pulmonary atresia, total anomalous pulmonary venous return, truncus arteriosus, hypoplastic left heart syndrome and tricuspid valve abnormalities.

Tetralogy of Fallot is a combination of four congenital abnormalities which are generally presented as heart boot shape. The characteristics are overriding aorta, ventricular septal defect (VSD), pulmonary stenosis and right ventricular hypertrophy. With an overriding aorta, the aorta receives oxygenated and deoxygenated blood from both ventricles of the heart. This allows the mixing of oxygenated and deoxygenated blood, granting a high percentage of oxygen-poor blood to distribute to the body. There is also a very large opening in the ventricular wall that gives rise to a high degree of ventricular septal defect. In the tetralogy of Fallot, the narrow valve of pulmonary vessels due to the pulmonary stenosis allows less blood flow through the pulmonary artery to the lungs to become oxygenated. As a result, stronger contractions of the right heart needed for the blood to be pumped out of the right ventricle of the heart thus thicken the right ventricle.

In the transposition of great vessels, the aorta receives deoxygenated blood from the right side of the heart instead of carrying oxygen-rich blood from the left side of the heart to the body normally. Meanwhile, the pulmonary artery, which normally carries deoxygenated blood from the right side of the heart to the lungs, instead receives oxygenated blood from the left side of the heart. In this condition, the right ventricle of the heart is responsible for pumping blood to the rest of the body. However, due to the physicality of the right ventricle which histologically represents only one-third of myocardium thickness compared to the left ventricle, the right side of the heart is normally inadequate to pump blood effectively to the whole body. As a result, this will cause incremental workload on the right side of the heart thus can lead to a weakened heart.

Pulmonary atresia is a type of congenital heart defect in which the opening between the pulmonary artery and the right ventricle is blocked. This can result in an enlarged heart, problems with the right ventricle and reduced blood vessel function in the lungs thus less poor-oxygen blood reaches the lungs capillary to become oxygenated.

With total anomalous pulmonary venous return, all the pulmonary veins from the lungs do not attach with the left atrium as normally should. Instead, they attach to veins or structures that drain into the right atrium. As a consequence, the oxygenated blood flows back into the right side of the heart. However, the left side of the heart which pumps to the rest of the body get some oxygenated blood due to other defects that are normally present together, including atrial septal defect (ASD) and patent foramen ovale, which is the opening between the two atria of the heart that remains open after birth. Both associated defects help in distribution of oxygen to the body part.

Truncus arteriosus is a rare type of heart defect in which a baby is born with only one large blood vessel emerging from the ventricles instead of two vessels which is the pulmonary artery and aorta. This single blood vessel mixes oxygenated blood with deoxygenated blood and distributes the mixed blood to the lungs and the rest of the body at high pressure. Babies who are born with this defect may suffer difficulty in breathing due to excess pulmonary blood circulation that may cause extra fluid build up in the lungs. The babies also may die of heart failure unless they have treatment soon after birth.

In hypoplastic left heart syndrome, the left side of the heart and aorta are very small in size or underdeveloped during pregnancy. The small left ventricle cannot produce a normal strong force to pump the blood to the rest of the body. Hence, it makes the right ventricle responsible for pumping blood to the lungs and body which will cause overwork. Over time, only a small volume of blood may be pumped to the rest of the body, leading to heart failure.

In tricuspid valve abnormalities, the valve may not form correctly or not form at all during fetal growth in pregnancy. These abnormalities can interfere with normal blood flow because the right ventricle and right atrium cannot function properly. There are several types of tricuspid valve disease such as tricuspid atresia, tricuspid valve stenosis, tricuspid valve regurgitation and Ebstein's anomaly. Some babies who are born with an abnormal tricuspid valve have other heart defects that help him or her to survive.

2.3.2.2 Acyanotic Heart Defects

Healthwise (2019) reported that acyanotic heart defects are heart problems that develop before or at birth but do not usually interfere with the amount of oxygen or blood that reaches the body tissue. Although a cyanotic, bluish tint of the skin probably occurs, it is not frequent in babies with acyanotic heart defects. If a cyanotic occurs, it is usually during activities when the baby is demanding for oxygen supply for example when crying and feeding. In paediatric, there are a lot of acyanotic heart defects due to congenital malformation such as ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defect, patent ductus arteriosus (PDA), pulmonary valve stenosis, aortic valve stenosis and coarctation of aorta. In acyanotic heart defects, all of the defects depend on the degree of mixing of blood which is still not too high to cause cyanosis.

Ventricular septal defect (VSD) is an abnormal opening in the heart that forms between the ventricles of the heart. Reller et al. (2008) stated that VSD occurs during intrauterine life if the ventricular wall that forms between the left and right ventricle does not fully develop, leaving a hole. Most ventricular septal defects are small and do not cause a problem. The opening of the VSD can be as small as a pinhole which lowers the degree of mixing of blood, or the wall between the heart chambers may be totally absent which may cause cyanosis. This defect is normally detected when a baby is 7 to 28 days old. In addition, atrial septal defect (ASD) is also an abnormal opening in the heart that forms between the atria of the heart. Following the combination of both defects forming atrioventricular septal defect may also categorise as acyanotic heart defects if the degree of abnormal opening does not cause too much mixing of the oxygenated and deoxygenated blood.

A patent ductus arteriosus (PDA) allows small amounts of oxygenated blood to flow from the aorta back into the pulmonary artery and to the lungs instead of to the rest of the body. Because some of the oxygenated blood proposed for the body tissue returns to the lungs, the left ventricle has to pump harder to ensure enough blood supply to the body. As a result, this can enlarge and weaken the heart. Some babies do not show any symptoms other than poor feeding and shortness of breath from a patent ductus arteriosus. An older child may establish heart failure or an infection of the inner lining of the heart, infective endocarditis. The severity of the symptoms and whether the consequences develop depend on the volume of blood flowing through the ductus arteriosus.

In pulmonary valve stenosis, there is a deformity on or near the pulmonary valve which narrows the pulmonary valve opening and slows the blood flow to the lung. Because the valve is narrow, the heart needs to pump harder to ensure enough blood to pass through it. The narrower the valve, the more symptoms the baby will have. If the degree of narrowing is not too high, this defect will not result in cyanosis.

In aortic valve stenosis, the heart's aortic valve narrows which limit the valve from opening fully. It decreases or prevents blood flow from your heart into the aorta and to the rest of the body. A narrowed aortic valve forces the left ventricle to pump harder to permit enough blood through the valve. In addition, aortic valve stenosis can be induced by a structural defect called bicuspid aortic valve, which congenitally develops before a baby is born. In these cases, the valve has only two leaflets, instead of the normal three leaflets. As a person ages, aortic valve stenosis also can occur due to the calcium build up at the leaflets which harden and thicken the leaflets.

Coarctation of aorta is a birth defect in which a part of the aorta is narrower than normal aorta. As a result, the left heart needs to pump harder to overcome the resistance. Over time, this can cause hypertension, heart failure, or other complications.

2.4 Surgical Interventions in Paediatric Heart Disease

Heart defects, specifically congenital heart defects often need surgical interventions to correct the problems and improve the symptoms presented. Jenkins et al. (2002) have developed a consensus-based method of risk adjustment for congenital heart disease (RACHS-1) for hospital acquired mortality among children younger than 18 years after cardiac surgery. The congenital cardiac surgical interventions are classified into six risk categories and the risk of mortality is proportionate with the categories.

Atrial septal defect (ASD) surgery is one of the cardiac surgical interventions that is classified under the first category of RACHS. Based on the medical encyclopedia of the U.S. national library of medicine, ASD can be closed with or without open-heart surgery. In the absence of open heart-heart surgery, the surgeon makes a tiny cut in the groin to insert a wire into a blood vessel that continues to the heart. Then, two small umbrella-shaped "clamshell" devices are placed on both sides of the septum so that they are attached to each other to close the hole in the heart. If an open-heart surgery is needed, the surgeon stitches the septum or covers the hole with a patch.

In ventricular septal defect (VSD), normally small VSD close by itself at 1 years old. However, larger VSD that cause heart failure or endocarditis, need open-heart surgery to close the hole in the septum with a patch.

Patent Ductus Arteriosus (PDA) can be corrected by a ligation procedure which is called PDA ligation. This procedure is normally considered after failure in medicine used to close the PDA. In this procedure, the surgeon makes a tiny cut in the groin to insert a wire and tube called a catheter into an artery in the leg and passes it up to the heart. Next, a small metal coil or another device is passed through the catheter into the infant's ductus arteriosus artery to block the blood flow.

To repair coarctation of aorta, a cut is most often made in between the ribs on the left side of the chest. There are five ways to repair coarctation of the aorta including surgery and non-surgery procedure. The commonest way to repair it is to cut the narrow section and make it bigger with a patch of synthetic material, made of Gore-tex. In older children, this defect usually is repaired by removing the narrow section of the aorta and stitching the remains together. Another way to repair this defect is called a subclavian flap which enlarges the narrow section of aorta by taking a patch originating from the left subclavian artery into a cut that is made in the narrow part of the aorta. A fourth way to repair the defect is to connect a tube to the normal sections of the aorta, on either side of the narrow section to bypass the narrow section. A newer method (non-surgery) to repair the defect is by placing a stent or small tube with a small balloon in the narrow section to open up the narrow area. This procedure only requires a small incision.

In the tetralogy of Fallot, there are several surgical procedures involved to correct the defect. First, the surgeon closed the VSD with a patch. Then, the pulmonary valve is opened and the thickened muscle that causes stenosis is removed. After that, a patch is placed on the right ventricle and main pulmonary artery to recover the blood flow to the lungs. If the open-heart surgery needs to be delayed, the child may have a shunt procedure first to move the blood into a correct vessel.

Correcting transposition of the great vessels also requires open-heart surgery soon after birth if possible. The commonest repair is called an arterial switch which divides the aorta and pulmonary. The pulmonary artery and the aorta are connected to their normal ventricle, specifically the pulmonary artery is connected to the right ventricle and the aorta is connected to the left ventricle.

To repair the truncus arteriosus, the pulmonary arteries are separated from the aortic trunk, and any defects presented are patched. To repair the tricuspid atresia, a series of shunts and surgeries may be needed to allow blood flow into the lungs. The surgeon may have to undergo valve repair or valve replacement or put in a shunt so that blood can get to the lungs.

Although acquired heart disease is rare compared to congenital heart disease in paediatrics, there are surgical interventions to treat the underlying conditions. In rheumatic heart disease, surgical intervention that is usually done to repair this defect caused by underlying pathogens is valve repair. Gerding (2011) stated in his journal of paediatric health care that after recovery from acute Kawasaki disease, a cardiac catheterization with coronary angiography should be performed if noninvasive tests or clinical or laboratory results are suggesting ischemia.

2.5 Nosocomial Infection in Children

The prevalence of NIs in the general children's ward in Europe is 1% and 23.6% in the neonatal intensive care units have been recorded. Childrens' NI frequency appears to be smaller and is negatively associated with age, varying from 7% to 9% for babies younger than 1 year of age to 1.5% to 4% for hospitalized 10-year-old children (Raymond J et al., 2000). Bloodstream infections, pneumonia (ventilator-associated VAP), urinary tract infections (UTI), skin and surgical site infections are the most common types of NI in children (Becerra MR., 2010). The key causes of NIs are species like gram-negative bacilli, coagulase-negative staphylococci, coagulase-positive staphylococci, pseudomonas spp, and streptococcus.

According to Vincent JL et al in 1995, the high NI occurrence (23.6%) in PICUs was close to that recorded in the European Prevalence of Infection in Intensive Care Sample for adult ICUs (20.6 %). The form of NI was based on the illness and the unit's specialization. According to the Ford-Jones report in 1989, the prevalence of bacteremia in neonatal units (71%) and gastrointestinal infections in general paediatric units was similar. The prevalence of NI differs greatly according to the facilities. In PICUs, hematology units, oncology units, special units, and neonatal units, it is highest: patients are severely compromised in these areas and are exposed to extended stays and multiple diagnostic and therapeutic procedures (M. Campins et al., 1993).

2.6 Epidemiology of *Klebsiella pneumoniae*

For *Klebsiella pneumoniae*, humans act as the main reservoir. 5-38% of people in the general population bear the organism in their stools and 1-6% in the nasopharynx. The urinary tract of the patient and the hands of hospital staff are the major sources of infection and this can lead to nosocomial infection. In hospitalized patients, the carrier prevalence for *Klebsiella pneumoniae* is much higher than that seen in the population. Walter et al. reported, in the stools of those hospitalized, carrier rates as high as 77% can be found and are felt to be linked to the amount of antibiotics being given (Ashurst & Dawson, 2020).

Although a reasonably frequent diagnosis is community-acquired pneumonia, infection with *Klebsiella pneumoniae* is very unusual. In the western culture, it is believed that approximately 3-5% of all community-acquired pneumonia is due to an infection caused by *Klebsiella pneumoniae*, although in developing countries such as Africa, it can account for approximately 15% of all cases of pneumonia. About 8-12% of patients that develop pneumonia while on a ventilator are caused by *Klebsiella pneumoniae*, while in patients who are not ventilated the occurrence is 7%. In total, *Klebsiella pneumoniae* responsibles for 11.8% of all hospital-acquired pneumonia in the world (Ashurst & Dawson, 2020).

In a 8-year long study by Jarvis, W et al., (1985), they characterised the epidemiology of epidemic *K. pneumoniae* outbreaks. Infections of the bloodstream or urinary tract were responsible for 80% of the outbreaks. The most prevalent route of transmission was person-to-person, and approximately half of the outbreaks occurred in neonatal critical care units. There was no clear winner among the serotypes, and there was no link between serotype and infection location or antimicrobial susceptibility pattern. The case-fatality ratio for nosocomial K pneumoniae was 1.1% during the 8-year period, with higher ratios in paediatrics (5%).

2.7 Site of *Klebsiella pneumoniae* Nosocomial Infection

The human mucosal surfaces, either as colonization or an infection, serve as a reservoir for the human acquisition of *K. pneumoniae.* (Bagley, 1985). The most prevalent cases recorded were central-line associated bloodstream infection and ventilator-associated infection (52.4%), followed by bloodstream infection (42.9%), catheter-based urinary tract infection, and urinary tract infection with respect to the form of nosocomial infection in PICU (21.4%). *K. pneumoniae* was reported to be the highest at 34.3% (Almasadi, M. M. et al., 2020). However, owing to transmission from an established source into the bloodstream, BSI is also a secondary infection. The urinary tract, the gastrointestinal tract, intravenous or urinary catheters, and respiratory sites are important causes of secondary BSI. (Montgomerie and Ota, 1980).

The urinary tract is the most common site of infection by *K. pneumoniae* (Podschun and Ullmann, 1998). Another infection caused by *K. pneumoniae* is catheter-associated UTIs (CAUTIs). It is believed that the ability to form biofilms and bind to catheters enhances these infections. (Schroll C et al., 2010). Klebsiella also plays a role in wound/surgical site infections. This site represents 13% of all infections caused by Klebsiella species (Podschun and Ullmann, 1998; Magill et al., 2014). Altogether, *K. pneumoniae* infections at both of these locations of the body constitute an endemic opportunistic pathogen that is a major healthcare burden.

2.8 Socio-demographics

There are a lot of sociodemographic factors that are related to this study. Pillai et al. (2016) in their studies concluded that among the total paediatric cardiothoracic patients, male patients have higher prevalence (53.9%) compared to females (46.1%) with the difference 7.8%. Following the age groups, younger children with the age range between 1 to 4 years old predominate by 57.8%. The second group of age which records the second highest prevalence is children with age between 5 - 9 years old with 17.0%. Majority of the paediatric patients are Malays (61.7%), followed by the other mixed minority ethnicities (14.8%), and the least ethnic was Chinese (10.4%).

86.5% of the patients' parents had ended their studies in primary education only. The highest education background of the patients' parents is only tertiary education with prevalence as low as 2.2% only (Pillai et al., 2016).

In previous study, Unit, P. I. C. (1999) states that amongst all underlying diseases of the paediatric intensive care unit patients, respiratory disease has the highest predominance (32%) followed by neurology (22%), haematology-oncology (18%), sepsis (11%) and others.

2.9 Risk Factors of Nosocomial Infection

For the implementation of effective prevention steps, the detection of risk factors for nosocomial infections are very crucial (Abdel-Hady et al., 2008). Determining the risk factors for nosocomial infection will help minimize the occurrence of infections and decrease the cost of health care (Aktar et al., 2016).

In a previous study that was conducted in Turkey, Aktar et al. (2016) found that long-term surveillance, invasive procedures, total parenteral nutrition and the use of high-spectrum antibiotics are factors that increase the risk of infection among patients treated and monitored in paediatric hospitals, especially in paediatric intensive care units (PICUs) and in paediatric hematology clinics.

Prior hospital stay of more than 7 days, chest drain, more than 14 days central venous catheter (CVC) indwelling period , mechanical ventilation duration that is more than 7 days, more than 5 number of transfusions , and re-interventions (cardiac surgery) were found as important risk factors in the univariate study associated with postoperative nosocomial infections in newborns that underwent cardiac surgery. While in the multivariate study, the separate risk factors of nosocomial infection were used of mechanical ventilation more than 7 days, CVC indwelling time more than 14 days and number of transfusions (Garcìa et al., 2017).

Abdel-Hady et al. (2008) reported that risk factors of nosocomial infections by extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumoniae* in neonatal intensive care units (NICUs) are mechanical ventilation, duration of hospitalization more than 15 days, total parenteral nutrition and previous use of oxyimino-antibiotics. In our study, we are going to focus on ESBL *Klebsiella pneumoniae* nosocomial infections in paediatric cardiac intensive care units (PCICUs).

2.10 Laboratory Investigations of *Klebsiella pneumoniae*

Children with bacterial pneumonia cannot be precisely distinguished on the basis of any single criterion from those with viral disease such as clinical, laboratory or chest radiograph results. Invasive procedures, such as biopsy or lung tissue needle aspiration, are rarely performed in children, particularly with acute pneumonia (CPG-RAUP). Thus, the non-invasive gold standard for evaluating the exact aetiology of pneumonia remains the blood culture. The sensitivity of this test is very limited, however. Positive blood cultures are only present in 10% to 30% of pneumonia patients. (Donowitz GR, Mandell GL., 1990).

In the setting of infection with *K. pneumoniae,* it is confirmed by either blood culture analysis or sputum test, especially if the patient is presented with pneumonia (Ergul AB et al., 2017). "Currant jelly" sputum is referred to as a hallmark of *K. pneumoniae* infection with sputum culture. As *K. pneumoniae* results in substantial inflammation and necrosis of the underlying tissue, this is apparent. (John V. Ashurst; Adam Dawson., 2020). However, young children seldom produce a sputum specimen that is sufficient for examination. Respiratory tract specimens included nasopharyngeal swab. In addition, swabs from heart surgical wounds, broncho-alveolar lavage (BAL), central venous catheter (CVC), aspiration catheter, tracheostomy, pleural cavity, peritoneal fluid are some forms of specimens collected from patients (Bissenova, N et al., 2017). Tracheal aspirates have similar details as BAL in intubated children. However, for children with rapidly progressing lower respiratory tract disease, BAL is more fitting (Jarvis, W. R., 2000).

Antimicrobial susceptibility testing (AST) is a laboratory procedure performed by clinical laboratory scientists to identify which antimicrobial regimen is particularly effective for individual patients (Marlon L. Bayot; Bradley N. Bragg., 2020). Accurate diagnostic methods for their identification have been required by the growing significance of ESBL-producing species. ESBL development of *K. pneumoniae*, as suggested by the Clinical and Laboratory Standards Institute (CLSI), is calculated by disk diffusion using both cefotaxime and ceftazidime alone and in conjunction with clavulanic acid. Another test is the E-test screen, which uses third-generation cephalosporins with and without a beta-lactamase inhibitor. The most popular test, the Vitek ESBL, which is an automated broth microdilution test, uses cefotaxime and ceftazidime alone and in combination with clavulanic acid.

A reliable method for screening might include a cefpodoxime screen followed by confirmatory disk diffusion for screen-positive isolates. Since the Vitek test has a specificity of 100% and also sensitivity of at least 99.5%, it is known to be a reliable single-test alternative. (Miftode E et al., 2008)

2.11 Treatment and Antibiotic resistance of *Klebsiella pneumoniae*

The choice of the most fitting regimen remains subject to discussion, but there are no standards for paediatric patients undergoing heart surgery. (Amine Cheikh et al., 2017). The initial step would be cardiovascular support and supportive measures to improve haemodynamics and oxygenation, which are critical to overcoming a severe infection, followed by antibiotics (Iregui, M et al., 2002). The use of broad-spectrum antibiotics can be readily narrowed based on microbiologic knowledge wherever possible. In this way, whenever resistant infections are involved, initial use of narrow-spectrum antibiotics will increase the risk of death due to insufficient treatment. The overuse of antibiotics, however, is linked to the development of a pattern of resistance (Hoffken, G et al., 2002).

K. pneumoniae is one of a number of bacteria that have undergone a significant rise in resistance to antibiotics in recent decades. *K. pneumoniae* includes many antibiotic resistance pathways, with resistance to b-lactams having the largest influence on drug therapy. ESBLs, such as third-generation cephalosporins and aztreonam, are able to hydrolyze oxyimino-cephalosporins but are inhibited by clavulanic acid. (Bush et al., 1995). Carbapenems have typically been the drug of choice to treat severe infections caused by ESBL-producing bacteria.

Carbapenem resistance may have arisen due to the extreme use of carbapenem in the treatment of ESBL infections, and *K. pneumoniae* is the most widespread Enterobacteriaceae immune to carbapenem (CRE). Colistin is one of the antibiotic polymyxin groups used to treat Gram-negative infections, but has been discontinued due to renal and neurotoxicity. (Jerke et al., 2016). However, the recent emergence of CRE has made it necessary to return to colistin as a drug of last resort.

Combination therapy with beta-lactam and aminoglycoside may be an effective technique to improve resistance to empirical antibiotics and to reduce empirical therapy with carbapenem compared with beta-lactam monotherapy. Although carbapenems also demonstrated the highest degree of susceptibility, carbapenem-resistant *K. pneumoniae* can surface. Therefore, carbapenem use should be limited as much as possible (Han S. B. et al., 2014).

To simplify it, ESBLs can be resistant to third generation cephalosporins such as cefotaxime, ceftriaxone and ceftazidime, as well as aztreonam (Philippon A et al., 1989). Not only that, it also has resistance towards all Beta lactams, and many other classes of antibiotics, including aminoglycosides, trimethoprim, sulphonamides, tetracyclines and chloramphenicol (Paterson D.L. et al., 2000; Livermore DM et al., 2006). Either cephamycins (cefoxitin, cefotetan and cefmetazole) or the carbapenems (imipenem and meropenem) should be used because they are not hydrolyzed by the ESBLs (Philippon A et al., 1989). Whereas, infectious disease consultation can be sought to guide management when CRE is diagnosed. CRE is typically immune to almost all the antimicrobial agents present. Several antibiotic treatment choices for CRE include polymyxin class, tigecycline, fosfomycin, aminoglycosides, or carbapenem dual therapy antibiotics. As described earlier, combined therapy with two or more agents will decrease mortality relative to monotherapy alone. (John V. Ashurst; Adam Dawson., 2020).

2.12 Outcome of *Klebsiella pneumoniae* Nosocomial Infections

Most admitted children have significant underlying diseases in the paediatric ICU, such as: liver disease, chronic pulmonary disease, renal failure and primary or secondary immunodeficiency, in addition to post-operative complications, particularly after cardiac and neurosurgical procedures. (Abramczyk, M. L. et al., 2003)

In 75% of the cases, bacteremia due to *K. pneumonia* was a nosocomially acquired infection, compared to the 77% (Garcia TM et al. 1985) and 84% (Kreger BE et al., 1980) rates of nosocomially acquired adult pneumoniae bacteremia. The research carried out by Kim et al (2002) shows that a higher mortality risk is associated with bacteremia caused by ESBLs. They also note that the use and early administration of antimicrobials with carbapenem can reduce the mortality rate among patients with ESBL-producing organism infections. A less desirable prognosis for antibiotic regimens containing extended-spectrum cephalosporins with or without aminoglycosides has been linked with infections with these strains.

In critically ill children, sepsis and septic shock are a key cause of morbidity and death, with about 2% of all hospitalized patients developing sepsis. The finding is determined by the causative agents, with gram-negative rod infections having a slightly higher mortality (25%) than gram-positive bacteria (10%) (Oda & Matsuo, 2000). Young age and immunological immaturity may also contribute to the delayed diagnosis of sepsis (Clapp DW, 2006).

Other neonatal infections include brain abscess, childhood gastroenteritis meningitis, conjunctivitis, necrotizing enterocolitis, endocarditis, necrotizing fasciitis, arthritis, and osteomyelitis (Long, S. S et al., 2017). In the literature by Carrie, C et al. (2019), it is stated that all the meningitis-causing *K. pneumoniae* strains found in children under the age of 1 year were ESBL-producing, which is why it mainly affects children in the 1st year of life, a key period for brain development.

In a study conducted by Sahu et al (2016), it is stated that in the cardiac surgical ICU, the overall incidence of NI was 4.6% with a high mortality among the infected patients. For paediatric post-cardiac surgery HAIs, the case-fatality rate (CFR) was 19.2%, although the total mortality rate was just 6.0% (Grisaru-Soen et al., 2009). In addition to this, Kim et al (2002) reported higher mortality for infections caused by ESBL producers in hospitalized children relative to non-ESBL producers, while Zaoutis et al (2005) reported an insignificant association between ESBL producers and mortality. *K. pneumoniae* in particular has arisen as a significant cause of HAIs and mortality rates, particularly among patients in the NICU, which can be as high as 70% (Morgan ME et al., 1984). Children under 12 months of age with afebria accounted for more than half of all fatalities due to *K. pneumoniae* bacteremia. Perhaps the failure of the infected, young child with systemic infection to mount a fever is an index of insufficient host response and poor outlook (Bonadio, W.A., 1989).

2.13 Conceptual Framework

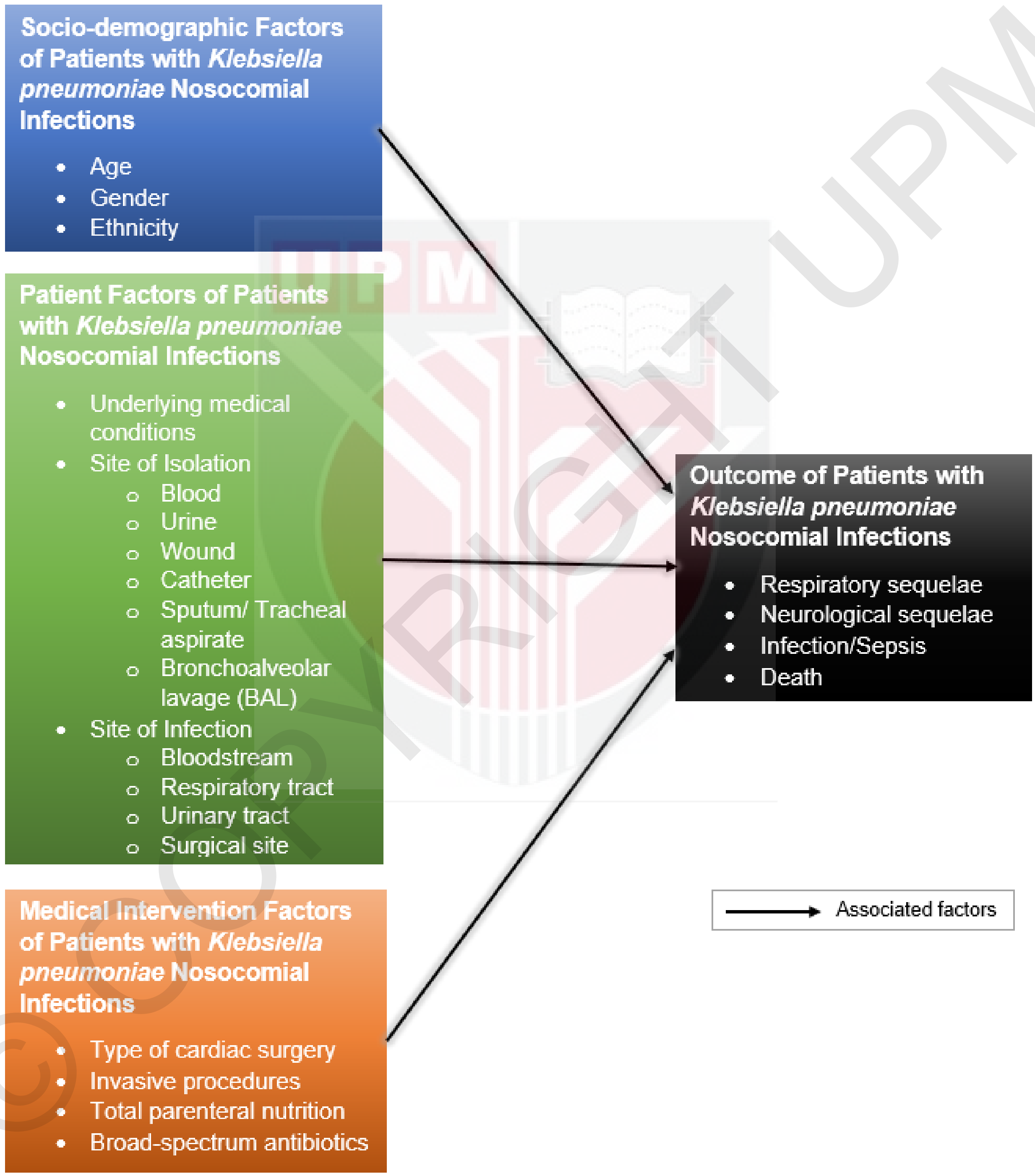

Figure 2.13: Conceptual Framework

CHAPTER 3

METHODOLOGY

3.1 Study Location

This study was conducted at the Paediatric Cardiac Intensive Care Unit (PCICU) in Hospital Serdang, Selangor.

3.2 Study Design

This research was a retrospective cross-sectional study.

3.3 Study Duration

This research was conducted from December 2020 to July 2021.

3.4 Sampling

3.4.1 Study Population

All children who were admitted to the paediatric cardiac intensive care unit (PCICU) at Hospital Serdang, Selangor from June 2018 until December 2020.

3.4.2 Sampling Population

3.4.2.1 Inclusion Criteria

1. Patients aged 12 years old and below who were admitted in the PCICU because the age limit is only up until 12 years old in PCICU.
2. Patients who acquired nosocomial infection while admitted in PCICU.

3.4.2.2 Exclusion Criteria

1. Patients with mixed growth of *K. pneumoniae* with concomitant isolation of other bacterial organisms were excluded from the study.

3.4.3 Sampling Frame

List of children aged 12 years and below who acquired nosocomial infection while admitted to paediatric cardiac intensive care unit (PCICU) at Hospital Serdang, Selangor from June 2018 to December 2020.

3.4.4 Sampling Unit

A child aged 12 years old or below who acquired nosocomial infection while admitted to paediatric cardiac intensive care unit (PCICU) at Hospital Serdang, Selangor.

3.4.5 Sample Size Estimation

Objective 1: To determine the prevalence of *Klebsiella pneumoniae* nosocomial infections in PCICU.

$$n = \frac{z^2_{1-\propto/2}}{d^2} P\,(1-P)$$

N = Sample size

Z = Confidence interval (95%, 1.96)

P = Expected value from previous research, 0.153 (Radji et al., 2011)

d = Acceptable margin of error for proportion (5%=0.05)

$$N = \frac{(1.96)^2 \times (0.153) \times (1\text{-}0.153)}{(0.05)^2}$$

$$= \frac{3.8416 \times 0.1296}{0.0025}$$

$$= 199$$

Since this was a retrospective analysis, there might be incomplete data collection, so 10% of data had to be added so, (1.1 × 199 = 219)

Total sample size will be N = 219

<u>Objective 2: To determine the clinical profile (sociodemographic factors, patient factors, medical intervention factors) of *Klebsiella pneumoniae* nosocomial infections in a PCICU.</u>

$$n = \frac{z_{1-\alpha/2}^{2}}{d^{2}} P\,(1-P)$$

N = Sample size
Z = Confidence interval (95%, 1.96)

P = Expected value from previous research, 0.515 (Low et al., 2017)

d = Acceptable margin of error for proportion (5%=0.05)

$$N = \frac{(1.96)^2 \times (0.515) \times (1-0.515)}{(0.05)^2}$$

$$= \frac{3.8416 \times 0.2498}{0.0025}$$

$$= 384$$

Since this was a retrospective analysis, there might be incomplete data collection, so 10% of data had to be added so, (1.1 × 384 = 422)

Total sample size will be N = 422

<u>Objective 3 : To determine the antimicrobial resistance patterns of *Klebsiella pneumoniae* in a PCICU.</u>

$$n = \frac{z_{1-\alpha/2}^{2}}{d^{2}} P\,(1-P)$$

N = Sample size

Z = Confidence interval (95%, 1.96)

P = Expected value from previous research, 0.09 (Cheikh et al., 2017)

d = Acceptable margin of error for proportion (5%=0.05)

$$N = \frac{(1.96)^2 \times (0.09) \times (1-0.09)}{(0.05)^2}$$

$$= \frac{3.8416 \times 0.0819}{0.0025}$$

$$= 126$$

Since this was a retrospective analysis, there might be incomplete data collection, so 10% of data had to be added so, (1.1 × 126 = 139)

Total sample size will be N = 139

3.4.6 Sampling Method

This study involved the medical records of all children aged 12 years and below who acquired nosocomial infections admitted to the paediatric cardiac intensive care unit (PCICU) at Hospital Serdang, Selangor from June 2018 to December 2020.

3.5 Instrument

Data from the medical registry of PCICU was used to collect patients' registry numbers. Then, we looked into each patient's medical record in the database. A proforma sheet was then used to retrieve information on the prevalence, clinical profiles, resistance patterns and outcome of children who acquired *K. pneumoniae* nosocomial infection after staying in the PCICU.

3.6 Data analysis

The data were analyzed using IBM SPSS version 26.0. The normality of the continuous data was tested statistically by using Kolmogorov-Smirnov and Shapiro-Wilk statistics and graphically by histograms, stem-and-leaf plots, normal probability plots and detrended normal plots. Descriptive analysis was reported as the mean+standard deviation (SD) for continuous and normally distributed data or median with interquartile range (IQR) if it was not normally distributed. Categorical data were presented as number (n) and percentage (%). All hypothesis testing was applied as the two-sided test with a level of significance (α) fixed at 0.05. Chi-square test was used to analyze the association between the socio-demographic factors, patient factors and medical interventional factors with prevalence and resistance patterns of *Klebsiella pneumoniae* nosocomial infections in PCICU Hospital Serdang. When more than 20% of the cells have a frequency less than 5, Fisher exact test was used instead.

3.7 Study ethics

Ethical clearance from the National Medical Research Register was before commencement of the study. Ethical approval was obtained from the Ethics Committee For Research Involving Human Subject of Universiti Putra Malaysia (JKEUPM) prior commencement of the study.

3.8 Variables

3.8.1 Dependent variables

Children with *K. pneumoniae* infections admitted to PCICU in Hospital Serdang and the outcome, which include:

Outcome

- Respiratory sequelae
- Neurological sequelae
- Infection/Sepsis
- Death

3.8.2 Independent variables

Sociodemographics

- Age
- Gender
- Ethnicity

Patient factors

- Underlying medical conditions
- Site of infection
  - Respiratory tract
  - Bloodstream
  - Urinary tract
  - Surgical site
- Site of isolation
  - Blood
  - Urine
  - Wound
  - Catheter
  - Sputum or tracheal aspirate
  - Bronchoalveolar lavage (BAL)

Medical intervention factors

- Type of cardiac surgical procedure
- Invasive procedures
- Total parenteral nutrition
- Broad-spectrum antibiotics
- Long-term surveillance

3.9 Definition of variables

There are two definitions for each variable, which are (a) conceptual definition and (b) operational definition. For the operational definition of dependent variables, the data was categorized as ‘yes’ or ‘no’, instead of using numbers.

I. The prevalence

(a) The proportion of the population with the disease at the specified time.

(b) The prevalence was calculated by using this formula :

Prevalence = The number of new and existing cases of *K. pneumoniae* nosocomial infection in PCICU in every year / The number of persons at risk for the *K. pneumoniae* in every year from 2018 to 2020.

II. Age

(a) The amount of time during which a person has lived.

(b) Age was defined and calculated based on the formula below:

Age= date of surgery – date of birth as stated in the medical record and round off to nearest years.

III. Gender

(a) The state of being male or female

(b) Gender was either male or female as stated in the medical record.

IV. Underlying medical conditions

(a) A chronic or long-term illness, which in turn weakened the immune system and required long term treatment.

(b) The diseases or defects presented in the PCICU patients before undergoing cardiac surgery.

V. Site of infection

(a) A constellation of signs, symptoms, and systemic responses caused by a wide range of microorganisms that may eventuate into septic shock.

(b) The origin of Klebsiella *pneumoniae* nosocomial infections as stated in medical records.

VI. Site of isolation

(a) The spread of an infectious agent from an infected or colonized patient to susceptible persons.

(b) The site of *Klebsiella pneumoniae* nosocomial infection which was obtained in the PCICU patient using diagnostic methods.

VII. Type of cardiac surgical procedure

(a) A category of surgery on the heart or great vessels performed by cardiac surgeons.

(b) The cardiac surgery undergone by PCICU patients to correct the cardiac disease or defects as stated in medical records.

VIII. Invasive procedures

(a) A medical procedure that invades (enters) the body, usually by cutting or puncturing the skin or by inserting instruments into the body.

(b) The instrumentation that was used by the PCICU patients as stated in medical records.

IX. Complete parenteral nutrition

(a) A method of complete feeding that bypasses the gastrointestinal tract.

(b) Use of parenteral nutrition throughout PCICU stay by PCICU patients as stated in medical records.

X. Extended spectrum antibiotics

(a) A group of antibiotics that had the widest antibacterial spectrum of all penicillins.

(b) The type of antibiotics that were prescribed prior to *Klebsiella pneumoniae* infections as stated in medical records.

XI. Long term surveillance

(a) Range of time for monitoring of behavior, activities, or information for the purpose of information gathering, influencing, managing or directing.

(b) Long term surveillance was defined and calculated based on the formula below:

Long term surveillance = date of discharge – date of admission in PCICU in days as stated in the medical records.

XII. Respiratory sequelae

(a) A pathological condition of the respiratory system resulting from a prior disease, injury, or attack.

(b) Complications that were related to the respiratory tract due to *Klebsiella pneumonia* nosocomial infections in PCICU patients as stated in medical records.

XIII. Neurological sequelae

(a) A pathological condition of the neurological system resulting from a prior disease, injury, or attack.

(b) Complications that were related to the neurological system due to *Klebsiella pneumoniae* nosocomial infections in PCICU patients as stated in medical records.

XIV. Infections/sepsis

(a) The invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that were not normally present within the body.

(b) Complications that were related to invasive or surgical procedures due to *Klebsiella pneumoniae* nosocomial infections in PCICU patients as stated in medical records.

XV. Death

(a) The end of the life of a person or organism.

(b) The mortality of the PCICU patients and the underlying causes.

CHAPTER 4
RESULTS

4.1 Response Rate

From June of 2018 until December 2020, a total of 903 cardiac patients were admitted to the paediatric cardiac ICU. These case notes were reviewed from the hospital data. Sample size calculated for this study was 422. However, the number of cases that were identified to PCICU with *Klebsiella pneumoniae* nosocomial infection was only 49 cases. 5 cases were excluded due to patients being transferred out. Therefore, only 44 cases at PCICU were eligible for our study when associated with the outcome of *K. pneumoniae* nosocomial infection.

4.2 Descriptive Data
4.2.1 Prevalence of Nosocomial Infection of *Klebsiella pneumoniae* in PCICU

Based on the data collected from June 2018 to December 2020 in PCICU of Hospital Serdang, a total of 903 patients were admitted. Out of the 903 patients, only 49 patients had nosocomial *Klebsiella pneumoniae* infection in the PCICU. By calculation, it was known that the prevalence of *K. pneumoniae* nosocomial infection in PCICU Hospital Serdang from June 2018 to December 2020 was 5.43%.

Table 4.1: The prevalence of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang from June 2018 - December 2020

Year	Number of admission	Number of *K. pneumoniae* nosocomial infections	Prevalence (%)

2018 (From June)	192	7	3.65
2019	348	19	5.46
2020	363	23	6.34
Total	903	49	5.43

4.2.2 Sociodemographic

Figure 4.1 showed the distribution of patients according to sociodemographic factors. Majority of the PCICU patients were from an age group of less than 12 months (77.6%) with slightly female predominant (53.1%). Most of the PCICU patients were Malay with 37 out of 49 patients (75.5%).

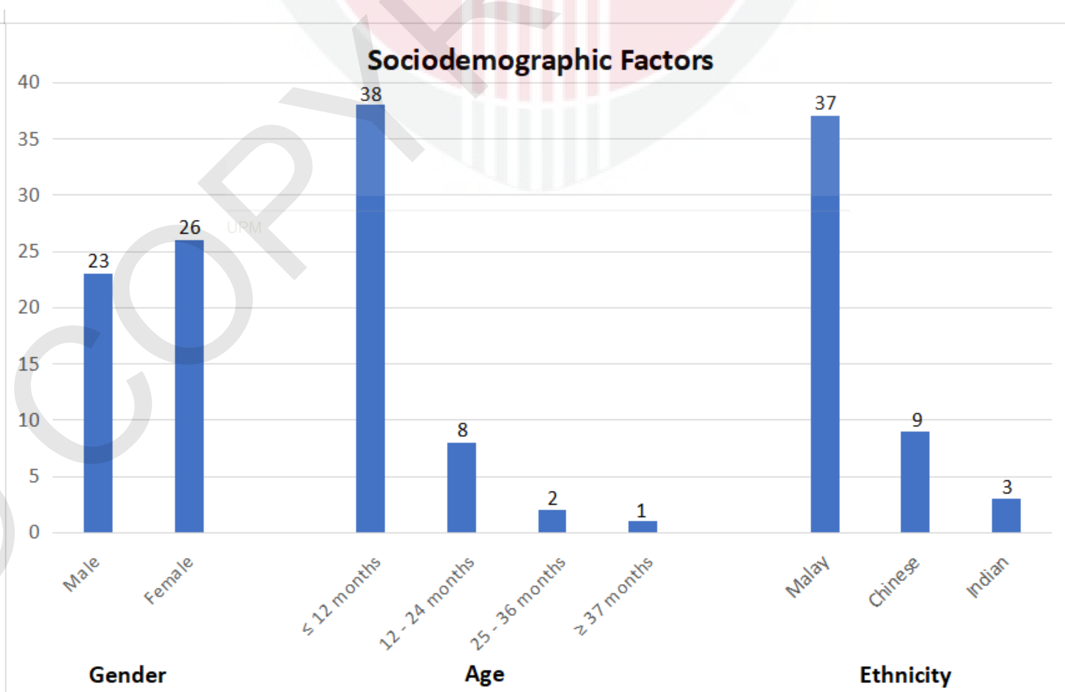

Figure 4.1 : Distribution of PCICU patients in Hospital Serdang infected with *Klebsiella pneumoniae* nosocomial infections according to sociodemographic factors

4.2.3 Risk factors

The risk factors identified in this study were the types of cardiac surgery, invasive procedures, complete parenteral nutrition and broad spectrum antibiotics usage.

Figure 4.2.1 until figure 4.2.4 showed the risk factors of developing *Klebsiella pneumoniae* nosocomial infection in paediatric patients. Most patients had undergone multiple types of surgery in an operation. Among all types of cardiac surgery, the majority of the patients had undergone PDA ligation with 30 out of 49 patients (61.2%) followed by VSD closure (32.7%) and ASD Closure (26.5%). Total anomalous Pulmonary Venous Drainage Repair (TAPVD Repair) shows only 6.1% among all patients in PCICU with only 3 out of 49 patients. Both Valve Replacement and Partial Anomalous Pulmonary Venous Drainage Repair (PAPVD Repair) show the least frequency among all patients in PCICU with only 2 out of 49 patients (4.1%). Other types of cardiac surgery which include right glenn shunt, MPA transection, atrial septectomy, IAA repair, repair of arch of aorta, main pulmonary arterio-plasty, balloon atrial septostomy, coronary translocation, truncus arteriosus repair and total Tetralogy of Fallot repair were rarely seen in those PCICU patients thus classified under group of others.

Most PCICU patients had undergone multiple invasive procedures with the highest 4 combinations of invasive procedures including mechanical ventilator, chest drain, central venous catheter (CVC) and blood transfusion. Among all five types of invasive procedures, almost all patients have been using mechanical ventilators with 48 out of 49 patients (98.0%). The second highest invasive procedure that has been used was blood transfusion with 19 out of 49 patients (38.8%) followed by CVC with 15 out of 49 patients (30.6%). However, there was no patient reported using the urinary catheter.

The total number of patients with complete data on complete parenteral nutrition was only 48 patients. Among all the 48 patients, the number of patients that required complete parenteral nutrition (37.5%) was lesser than the number of patients that did not require complete parenteral nutrition (62.5%) with a difference of 25%.

The majority of the PCICU patients did not require broad-spectrum antibiotics (51.0%). 20 out of 49 patients in PCICU (40.8%) used cephalosporin as broad-spectrum antibiotics. There were no PCICU patients using Sulphonamide, Tetracycline, Chloramphenicol and Trimethoprim. The lowest frequency of broad-spectrum antibiotics was Augmentin which was only in 1 out of 49 patients (2.0%).

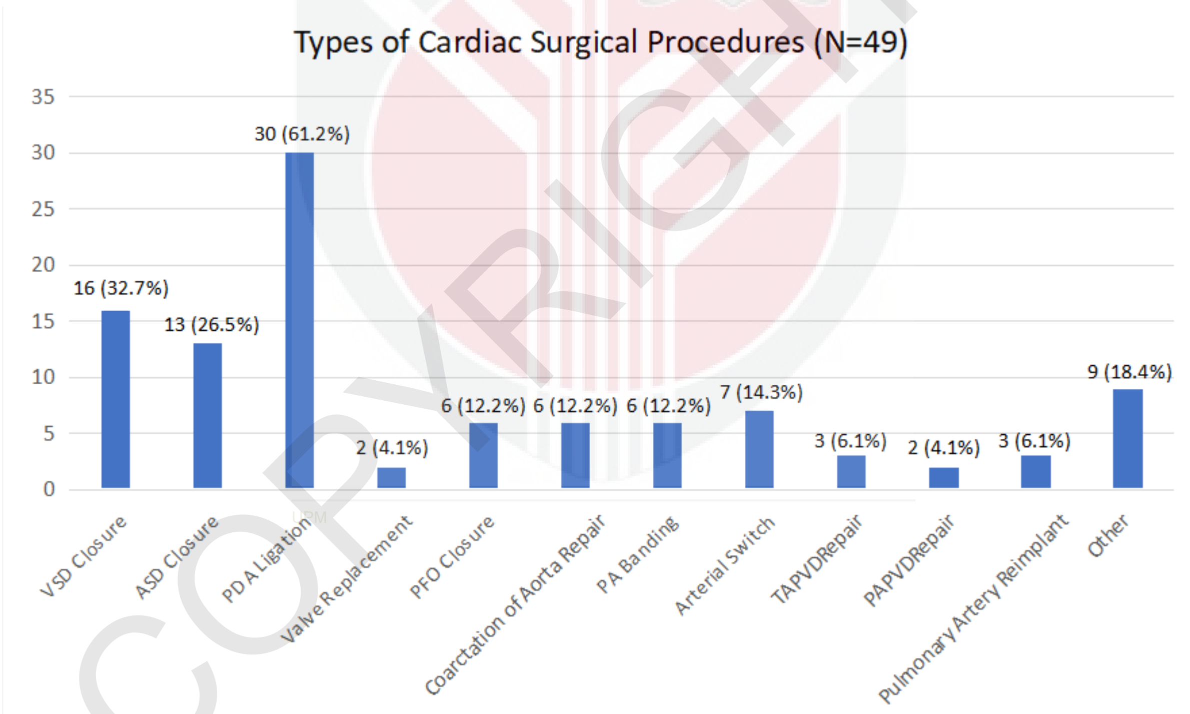

Figure 4.2.1: Types of cardiac surgical procedures in PCICU Hospital Serdang from June 2018 - December 2020. (N=49)

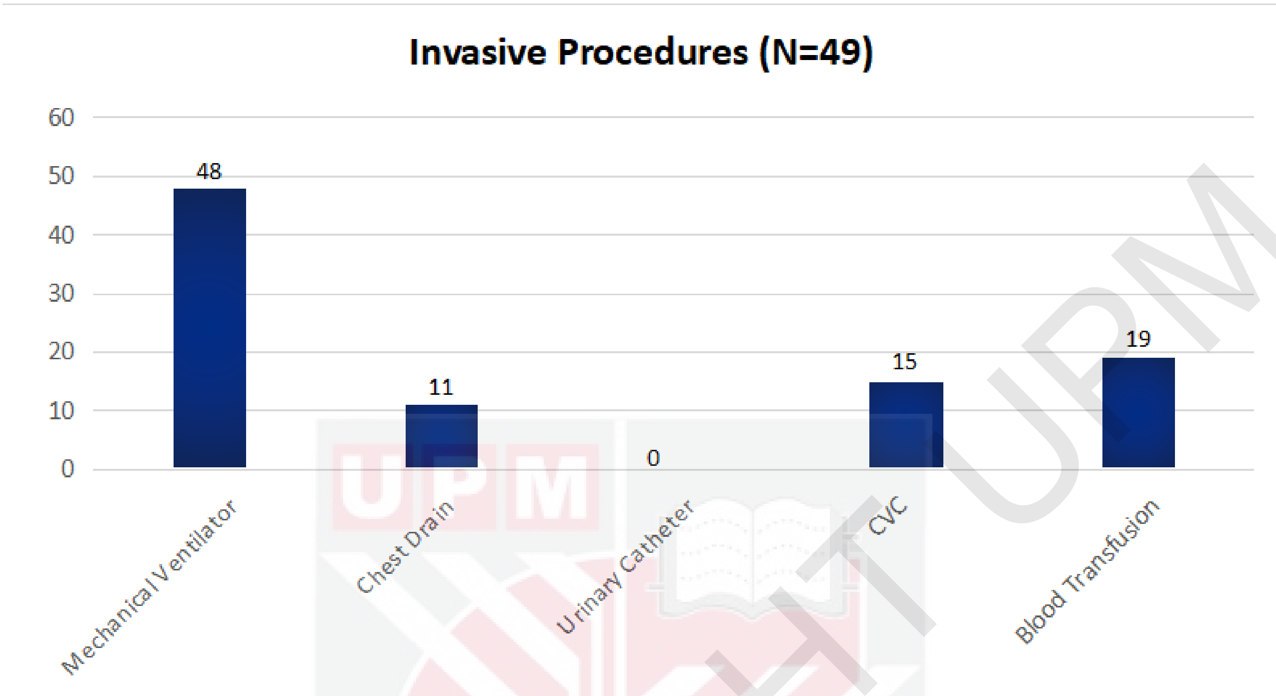

Figure 4.2.2: Invasive procedures in PCICU Hospital Serdang from June 2018 - December 2020. (N=49)

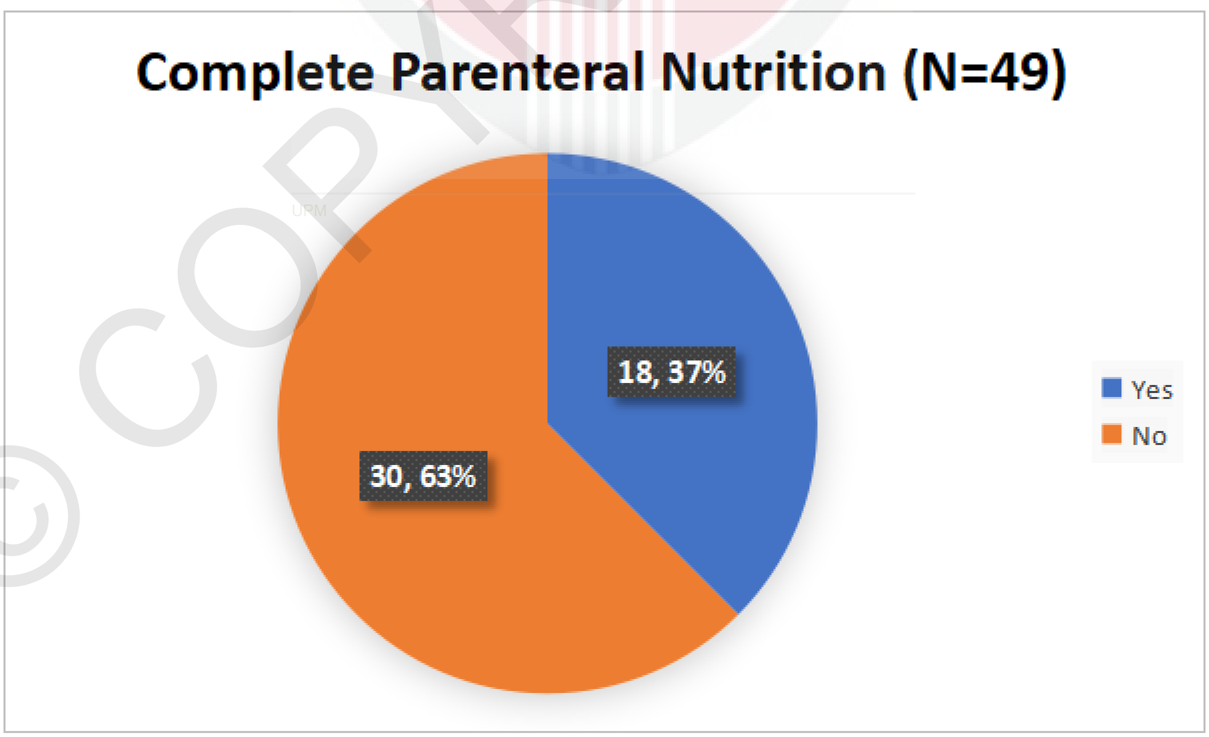

Figure 4.2.3: Complete parenteral nutrition in PCICU Hospital Serdang from June 2018 - December 2020. (N=49)

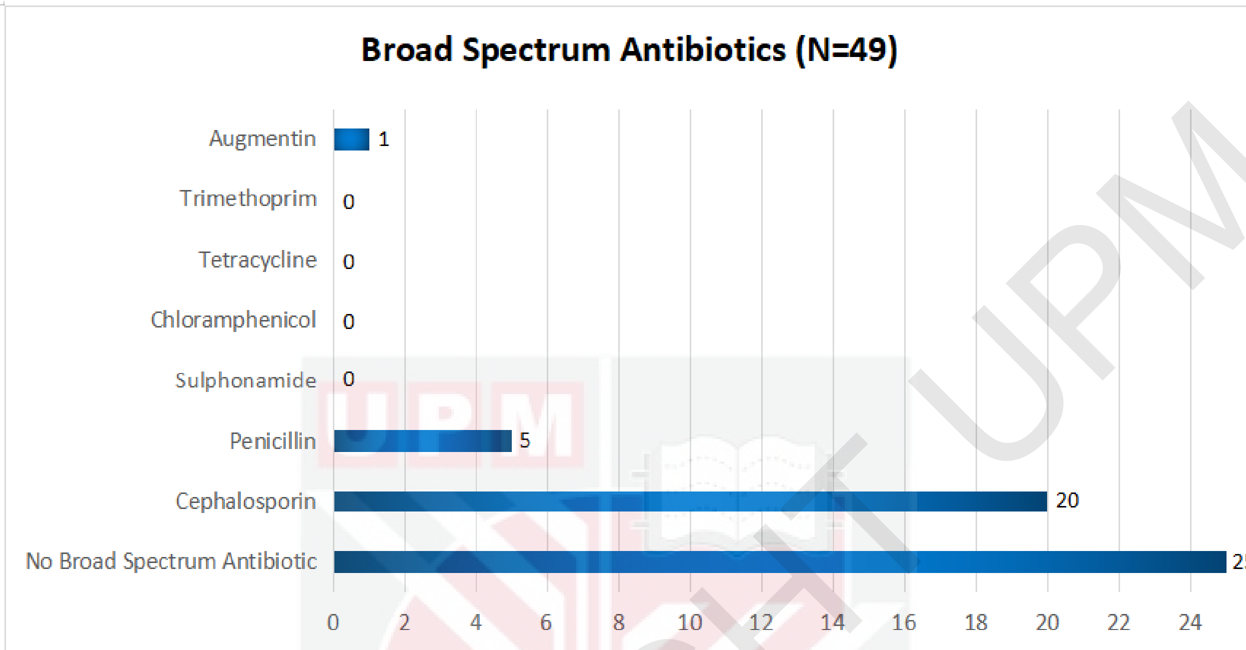

Figure 4.2.4: Use of broad-spectrum antibiotics in PCICU Hospital Serdang from June 2018 - December 2020. (N=49)

4.2.4 Sites of infection

Figure 4.2.5 showed the profile of *Klebsiella pneumoniae* nosocomial infection in PCICU. 13 PCICU patients did not show any site of infections. Among 36 patients, the highest site of infection in PCICU patients was at the respiratory tract (66.7%) followed by bloodstream infections (22.2%). 6 out of 36 patients (16.7%) were found to have infections at eye, rectum and wound thus classified under others. There were no patients infected with *Klebsiella pneumoniae* in the urinary tract.

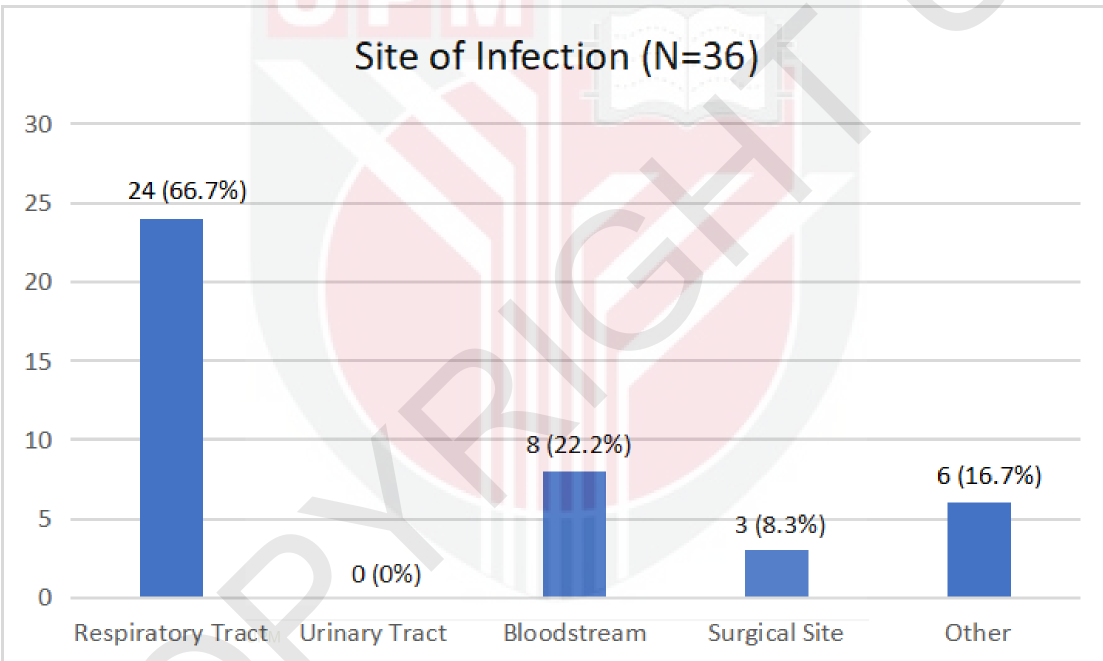

Figure 4.2.5: Sites of infection of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang from 2018 - 2020. (N=36)

4.2.5 Sites of isolation

A total of 48 PCICU patients have shown *Klebsiella pneumoniae* isolated in various sites. Some of the patients showed multiple sites of isolation. The highest site of isolation was tracheal aspirate (45.8%), followed by rectum (33.3%) and blood (16.7%). Wound isolation and nasopharynx isolation showed 6.3% and 8.3% respectively. There were 0 isolation at urine isolation, catheter and bronchoalveolar lavage isolation. 6.3% of PCICU patients showed isolation at eyes and nasal cavity, thus grouped together under others.

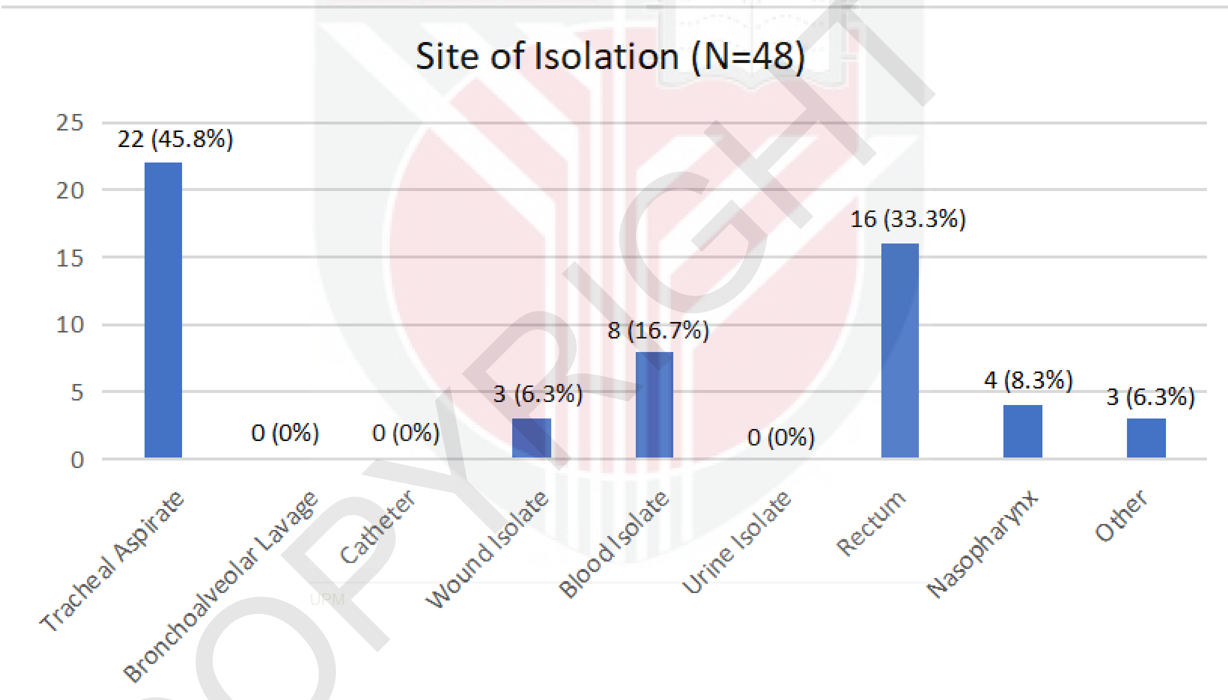

Figure 4.2.6: Sites of isolation of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang from June 2018 - December 2020. (N=48)

4.2.6 Blood parameters

Table 4.2 shows the blood parameters of *Klebsiella pneumoniae* nosocomial infection in PCICU. As per data analysis done on 49 patients for the Full Blood Count (FBC), C-Reactive Protein (CRP), Liver Function Tests (LFT) & Renal profile, some of the data was incomplete as well as data for majority of the lab values being skewed (not normally distributed).

There was only one Lab Value that revealed a normal distribution. The total White Blood Cells (WBC) indicated a mean of 12.82 x 10^9/L with a Standard Deviation (SD) of 5.59.

Table 4.2: Blood parameters of patients with *K. pneumoniae* infection in PCICU Hospital Serdang from 2018 - 2020.

Lab Investigation	Median	Interquartile range (IQR)
Full Blood Count (N=44)		
Absolute Neutrophil	6.08 x 10^3/μL	4.22 - 10.7 x 10^3/μL
Platelet	308 x 10^9/L	192 - 397 x 10^9/L
Haemoglobin	12.2 g/dL	10.8 - 13.7 g/dL
C-Reactive Protein (N=14)	16.56 mg/L	9.19 -93.00 mg/L
Liver Function Test (N=41)		
ALP	177 U/L	95 - 271 U/L

AST	41 U/L	26 - 68 U/L
ALT	24 U/L	19 - 36 U/L
Total Bilirubin	15.2 mg/dL	5.8 - 26.2 mg/dL
Renal Profile (N=43)		
Creatinine	40 μmol/L	37 - 49 μmol/L
Urea	3.95 mg/dL	2.80 - 6.10 mg/dL
Potassium	4 μmol/L	3.2 - 4.6 μmol/L
Sodium	137 μmol/L	135 - 142 μmol/L
Chloride	99 μmol/L	94 - 104 μmol/L

4.2.7 Treatment and Resistance patterns

There were only 47 PCICU patients treated with antibiotics. Some of the patients were also treated with multiple antibiotics. Among these 47 PCICU patients, carbapenem (63.8%) was the majority choice of antibiotics to treat the infections, followed by cephalosporin (34.0%) and penicillin (21.3%). Aminoglycoside and Vancomycin were introduced in 6.4% and 8.5% of PCICU patients respectively. Polymyxin was not introduced to any of these patients.

The majority of PCICU patients were infected with extended spectrum β-Lactamase (ESBL) with 37 out of 49 patients (75.5%). Only 1 patient had a strain of Carbapenem Resistant *Klebsiella pneumoniae* (CRKP) strains (2.0%). 22.4% of the PCICU patients did not show any antibiotic resistance.

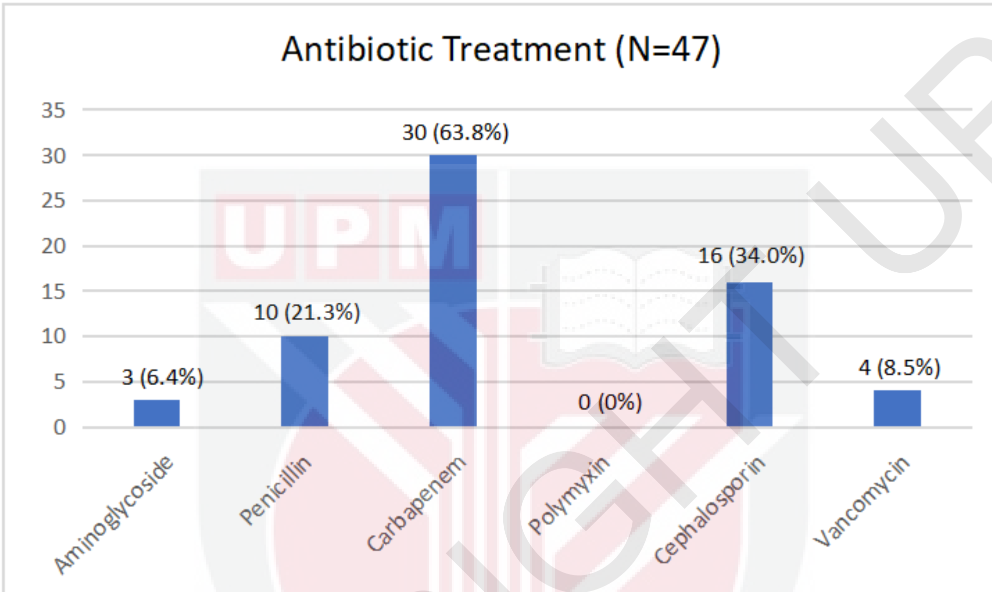

Figure 4.2.7: Treatment of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang. (N=47)

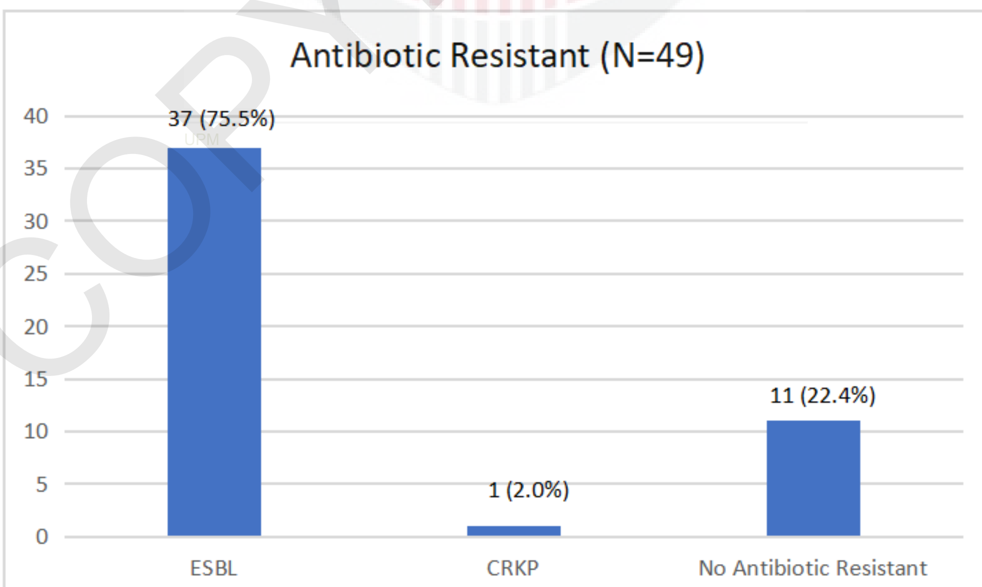

Figure 4.2.8: Resistance pattern of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang

4.2.8 Outcome

Table 4.3 showed the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. There were 30 patients having respiratory sequelae. Among these 30 patients, some of the patients developed multiple respiratory complications. Those who developed pneumonia were noted with 23 out of 30 patients (76.7%). The second highest complication was chronic lung disease (13.3%) followed by bronchospasm (10.0%). The lowest frequency of respiratory sequelae were pulmonary oedema and pneumothorax with 3.3% each.

There were 12 PCICU patients who developed severe infection or sepsis after being infected with the *K. pneumoniae.* Among these 12 patients, the majority of them developed sepsis (41.7%) followed by bloodstream infection or bacteremia (33.3%) and others (16.7%). The others group consisted of septic ileus and thrombocytopenia with leukopenia. The lowest frequency of this complication was surgical site infection with only 1 out of 12 patients (8.3%).

There were no PCICU patients who developed complications of the neurological system reported. There were 6 out of 49 PCICU patients (12.2%) resulting in death.

Table 4.3: The Outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang from June 2018 - December 2020

Case Characteristics	Frequency (n)	Percentage (%)
Respiratory Sequelae (N=30)		
Pneumoniae	23	76.7
Chronic Lung Disease	4	13.3
Bronchomalacia	2	6.7

RDS	2	6.7
Lung Collapse	2	6.7
Pleural Effusion	2	6.7
Pneumothorax	1	3.3
Bronchospasm	3	10.0
Pulmonary Oedema	1	3.3
Neurological Sequelae (N=0)		
Neurological Sequelae	0	0
Sepsis / Infection (N=12)		
Bloodstream Infection (BSI)	4	33.3
Surgical Site Infection (SSI)	1	8.3
Sepsis	5	41.7
Others	2	16.7
Death (N=49)		
Death	6	12.2

4.3 Analysis

4.3.1 Association between sociodemographic factors and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

4.3.1.1 Gender and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.4: Association between the gender and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Gender					0.004
Male	19	3	86.4	13.6	
Female	10	12	45.5	54.5	
Sepsis and Infection					
Gender					
Male	5	17	22.7	77.3	0.728
Female	6	16	27.3	72.7	
Death					
Gender					
Male	4	18	18.2	81.8	0.664
Female	2	20	9.1	90.9	

There was significant association between respiratory sequelae and gender ($P<0.05$). The percentage of having respiratory sequelae was significantly higher among males than females.

Based on Table 4.4, Chi-square test was performed to test the association between respiratory sequelae and gender. There were 2 categories of gender, and it was found that 19 out of 22 (86.4%) male PCICU patient have respiratory sequelae as a complication of *Klebsiella Pneumoniae* nosocomial infections and 10 out of 22 (45.5%) female PCICU patients develop respiratory sequelae as well. All genders had significant p-values ($p=0.004$). Therefore, males had significant association with respiratory sequelae. The null hypothesis was rejected.

Based on Table 4.4, a Chi-square test was also performed to test the association between gender and sepsis and infection. It was found that 5 out of 22 (22.7%) male PCICU patients have sepsis and infection and 6 out of 22 (27.3%) female PCICU patients develop sepsis and infection. However, all genders do not have significant p-values ($P=0.728$). Therefore, we failed to reject the null hypothesis. Hence, there was no significant association between gender and sepsis and infection.

Based on Table 4.4, Fisher's exact test was also performed to test the association between gender and death. It was found that the overall mortality rate was 12.2% with 4 out of 49 (8.16%) were male PCICU patients and 2 out of 49 (4.08%) were female PCICU patients. All genders did not have significant p-values ($P=0.664$). Therefore, null hypothesis was accepted. Hence, there was no significant association between gender and death.

4.3.1.2 Age and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.5: Association between the age and the outcome of Klebsiella pneumoniae nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Age					
≤ 12 months	24	11	68.6	31.4	0.464
13 - 24 months	3	3	50.0	50.0	0.394
25 - 36 months	2	0	100.0	0	0.540
≥ 37 months	0	1	0	100.0	0.341
Sepsis and Infection					
Age					
≤ 12 months	10	25	28.6	71.4	0.411
13 - 24 months	1	5	16.7	83.3	1
25 - 36 months	0	2	0	100.0	1
≥ 37 months	0	1	0	100.0	1
Death					
Age					
≤ 12 months	5	30	14.3	85.7	1
13 - 24 months	0	6	0	100.0	0.573
25 - 36 months	1	1	50.0	50.0	0.257
≥ 37 months	0	1	0	100.0	1

Based on Table 4.5, a Fisher's exact test was performed to test the association between the age and the respiratory sequelae. It was found that there were 4 categories of age in PCICU Hospital Serdang and it was found that 24 out of 35 (68.6%) of patient who were below 12 months old developed respiratory sequelae and 3 out of 6 (50.0%) of patient from 13 to 24 months old developed respiratory sequelae. Both patients (100%) in 25 to 36 months old groups developed respiratory sequelae and there were no patients (0%) from group age more than 37 months who developed respiratory sequelae. However, all groups of ages did not have significant p-value (P=0.464, P=0.394, P=540, P=0.341). Therefore, null hypothesis was not rejected. There was no association between age and respiratory sequelae.

Based on Table 4.5, Fisher's exact test was also performed on the association between the age and sepsis and infection. Within the 4 age groups in PCICU Hospital Serdang, it was noted that 10 out of 25 patients (28.6%) developed sepsis and infection in the less than 12 months old age group, followed by 1 out of 6 (16.7%) in the 13 to 24 months old group. It was also shown that there were no patients who developed sepsis and infection starting from the 25 to 36 month age group up until the age group of above 37 months old. However, all groups of ages did not have significant p-value (P=0.411, P=1, P=1, P=1). Therefore, null hypothesis was not rejected. There was no association between age and sepsis and infection.

Looking at Table 4.5, Fisher's exact test was also carried out to understand the association between age and death. It was observed that the age group less than 12 months old had the highest death count at 5 out of 35 patients (14.3%), followed by one death (50%) out of two patients in the 25 to 36 months old age range. There seemed to be zero deaths within both the 13 to 24 month group as well as above 37 month olds. Nonetheless, all groups of ages did not have significant p-value (P=1, P=0.573, P=0.257, P=1). Therefore, null hypothesis was accepted. There was no association between age and death.

4.3.1.3 Ethnicity and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.6: Association between the ethnicity and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Ethnicity					
Malay	20	14	58.8	41.2	0.249
Chinese	7	1	87.5	12.5	
Indian	2	0	100.0	0	
Sepsis and Infection					
Ethnicity					
Malay	10	24	29.4	70.6	0.809
Chinese	1	7	12.5	87.5	
Indian	0	2	0	100.0	
Death					
Ethnicity					
Malay	5	29	14.7	85.3	1
Chinese	1	7	12.5	87.5	
Indian	0	2	0	100.0	

Based on table 4.6, Fisher's exact test was executed to find the association between ethnicity and respiratory sequelae. As per our findings, the Malay group had the highest count at 20 out of 34 patients (58.8%), followed by the Chinese group with 7 out of 8 patients (87.5%) and two patients (100%) in the Indian group. Although, all three ethnicities did not have a significant p-value (P=0.249). Therefore, the null hypothesis was not rejected. There was no association between ethnicity and respiratory sequelae.

Fisher's exact test was also run based on table 4.6 to observe the association between ethnicity and sepsis and infection. The Malay group noted to have the both the highest count and percentage at 10 out of 34 patients (29.4%), followed by 1 out of 8 patients (12.5%) in the Chinese group. The Indian group noted to have zero sepsis and infection among 2 patients. Still, none of the ethnicities had a significant p-value (P=0.809). Thus, we failed to reject the null hypothesis. There was no significant association between ethnicity and sepsis and infection.

We also ran another Fisher's exact test based on table 4.6 to determine the association between ethnicity and death. The Malay group reported to have both the highest death count as well as in percentage at 5 out of 34 patients (14.7%), followed by the Chinese group with 1 out of 8 patients (12.5%). The Indian group had zero deaths out of two patients. Even so, the ethnicities did not have a significant p-value (P=1). Therefore, null hypothesis was not rejected. There was no association between ethnicity and death.

4.3.2 Association between patient factors and the outcome

4.3.2.1 Underlying medical conditions and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

A total of 36 out of 44 children were found to have underlying medical conditions. The most common underlying medical condition was that 12 of the patients had a history of pneumonia. Besides that, 8 of the patients reported to have Gastroesophageal reflux disease (GERD) and pulmonary hypertension. Hypothyroidism and a history of sepsis were reported in 7 patients. Besides that, 6 patients were noted to have chronic lung diseases, prematurity between 31 to 35 weeks as well as Down's syndrome. 5 patients also had bronchial issues such as bronchomalacia and bronchiolitis as well as failure to thrive. Conditions such as dysmorphism and respiratory distress syndrome were noted in 4 patients. DiGeorge syndrome, laryngomalacia and G6PD deficiency were also noted in 3 of the patients. Other underlying medical conditions include Turner's syndrome, inguinal hernia, hypoparathyroidism, seborrheic dermatitis, anaemia, hirschsprung disease, vocal cord palsy, TRO charge syndrome, cleft palates, uropathy, femoral vein aneurysm, pneumothorax, as well as esophageal conditions.

Table 4.7: Association between underlying medical conditions and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Underlying Medical Condition					
Yes	24	12	66.7	33.3	1
No	5	3	62.5	37.5	

Sepsis and Infection					
Underlying Medical Condition					
Yes	9	27	25.0	75.0	1
No	2	6	25.0	75.0	
Death					
Underlying Medical Condition					
Yes	4	32	11.1	88.9	0.297
No	2	6	25.0	75.0	

Based on table 4.7, Fisher exact test was used to determine the association between underlying medical conditions in PCICU patients and the outcome of *Klebsiella pneumoniae* infections. As per our findings, respiratory sequelae was noted to be the highest where 24 out of 36 patients (66.7%) with underlying conditions developed respiratory sequelae whereas 5 out of 8 (62.5%) patients without underlying conditions had respiratory sequelae. Even so, the underlying medical conditions did not have a significant p-value (P=1). Thus, the null hypothesis was not rejected. There was no significant association between underlying medical condition and respiratory sequelae.

We ran another Fisher's exact test to observe the association between underlying medical conditions and the sepsis and infection among the patients. We observed that the test yielded the same percentage of 25% even though there were more patients with underlying medical conditions who had sepsis and infection. 9 out of 36 patients with underlying medical conditions developed sepsis and infection whereas 2 out of 8 patients without underlying medical conditions had sepsis and infection. Still, the underlying medical conditions did not have a significant p-value (P=1). Therefore, we did not reject the null hypothesis. There was no significant association between underlying medical condition and sepsis and infection.

Another Fisher's exact test was also carried out based on table 4.7 to see the association between underlying medical conditions and death. It was seen that death prevalence was lower where it was reported that 4 out of 36 patients (11.1%) with underlying medical conditions had mortality while 2 out of 8 patients (25%) without underlying medical condition faced death. Although, underlying medical conditions did not show a significant p-value (P=0.297). Thus, the null hypothesis was not rejected. There was no significant association between underlying medical conditions and death.

4.3.2.2 Site of infection and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.8: Association between site of infection and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Respiratory Tract (N=44)					
Yes	16	6	72.7	27.3	0.340
No	13	9	59.1	40.9	
Bloodstream (N=44)					
Yes	6	1	85.7	14.3	0.393
No	23	14	62.2	37.8	
Surgical Site (N=44)					
Yes	1	2	33.3	66.7	0.264
No	28	13	68.3	31.7	
Others (N=44)					

Yes	4	1	80.0	20.0	0.647
No	25	14	64.1	35.9	
Sepsis and Infection					
Respiratory Tract (N=44)					
Yes	8	14	36.4	63.6	0.082
No	3	19	13.6	86.4	
Bloodstream (N=44)					
Yes	2	5	28.6	71.4	1
No	9	28	24.3	75.7	
Surgical Site (N=44)					
Yes	1	2	33.3	66.7	1
No	10	31	24.4	75.6	
Others (N=44)					
Yes	2	3	40.0	60.0	0.586
No	9	30	23.1	76.9	
Death					
Respiratory Tract (N=44)					
Yes	3	19	13.6	86.4	1
No	3	19	13.6	86.4	
Bloodstream (N=44)					
Yes	3	4	42.9	57.1	0.042
No	3	34	8.1	91.9	
Surgical Site (N=44)					

Yes	0	3	0	100.0	1
No	6	35	14.6	85.4	
Others (N=44)					
Yes	0	5	0	100.0	1
No	6	33	15.4	84.6	

Based on table 4.8, both Fisher's exact test and Chi-square test were performed to determine the association between site of infections and respiratory sequelae. It was noted that patients with bloodstream infection showed the highest prevalence of developing respiratory sequelae with 6 out of 7 patients (85.7%) whereas 23 out of 37 patients (62.2%) without bloodstream infection had also developed respiratory sequelae. Patients with the lowest prevalence of respiratory sequelae had surgical site infection with 1 out of 3 patients (33.3%) whereas those who did not have surgical site infection was higher with 28 out of 41 patients (68.3%). It was also noted that 16 out of 24 patients (72.2%) with respiratory tract infection had respiratory sequelae while 13 out of 22 patients (59.1%) without respiratory tract infection had respiratory sequelae. Other sites of infection were listed under others and those include eye, rectum and wound. Respiratory sequelae was found in 4 out of 5 patients (80%) who had these other sites of infection whereas it was also found in 25 out of 39 patients (64.1%) without infection of these other sites. Chi-square test was done on the respiratory tract and it yielded a p-value of 0.340. Fisher's exact test was used on bloodstream, surgical site and others and they showed p-values of 0.393, 0.264 and 0.647 respectively. For all these, the site of infections did not show a significant p-value. As such, the null hypothesis was not rejected. There was no significant association between site of infection and respiratory sequelae.

Similarly, both Fisher's exact test and Chi-square test were run on table 4.8 to determine the association between site of infection and sepsis and infection. It was understood that other sites of infection had the highest prevalence with 2 out of 5 patients (40%) whereas sepsis and infection was also found in 9 out of 39 patients

(23.1%) without the other site of infections. Those without respiratory site infection seemed to have the lowest prevalence of infection and sepsis with only 3 out of 22 patients (13.6%) whereas those with respiratory site infection were 8 out of 22 patients (36.4%). Patients with bloodstream infection who had sepsis and infection reported to be 2 out of 7 patients (28.6%) and those without bloodstream infection who had sepsis and infection at 9 out of 37 patients (24.3%). Sepsis and infection was also found in 1 out of 3 patients (33.3%) who had surgical site infection and 10 out of 41 patients (24.4%) in those without surgical site infection. In this outcome, Chi-square test was only done for the respiratory site which showed a p-value of 0.082. Fisher's exact test was done on bloodstream, surgical site and others which showed p-values of 1, 1 and 0.586 respectively. For all these, the site of infections did not show a significant p-value. As such, the null hypothesis was not rejected. There was no significant association between site of infection and sepsis and infection.

As for death associated with the sites of infection, we only used Fisher's exact test based on table 4.8. Death was reported to be of highest prevalence in bloodstream infections with 3 out of 7 patients (42.9%) whereas only in 3 out of 37 patients (8.1%) without bloodstream infection. The lowest prevalence was recorded to be with both surgical site and other sites which were zero out of 3 and 5 patients respectively. On the other hand, death was noted in 6 out of 41 patients (14.6%) without surgical site infection and in 6 out of 39 patients (15.4%) without other sites of infection. Respiratory site infection noted to have both similar results in prevalence associated with death together without respiratory site of infection where both were 3 out of 22 patients (13.6%). The p-values for each site of infection were 0.042 for bloodstream infection and 1 for the rest. Hence, the p-value was only significant in death associated with bloodstream infection. Therefore, the null hypothesis was rejected only for bloodstream infection and accepted for the rest. There was significant association between bloodstream site of infection and death whereas no significant association between respiratory tract, surgical site and other sites of infection and death. The bloodstream *K. pneumoniae* infection showed to be significantly higher in causing death than *K. pneumoniae* infection outside of the bloodstream.

4.3.2.3 Site of isolation and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.9: Association between site of isolation and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Tracheal Aspirate					
Yes	14	7	66.7	33.3	0.919
No	15	8	65.2	34.8	
Wound					
Yes	2	1	66.7	33.3	1
No	27	14	65.9	34.1	
Blood					
Yes	5	2	71.4	28.6	1
No	24	13	64.9	35.1	
Rectum					
Yes	7	6	53.8	46.2	0.313
No	22	9	71.0	29.0	
Nasopharynx					
Yes	4	0	100.0	0	0.282
No	25	15	62.5	37.5	
Sepsis and Infection					
Tracheal Aspirate					

Yes	8	13	38.1	61.9	0.055
No	3	20	13.0	87.0	
Wound					
Yes	0	3	0	100.0	0.561
No	11	30	26.8	73.2	
Blood					
Yes	2	5	28.6	71.4	1
No	9	28	24.3	75.7	
Rectum					
Yes	4	9	30.8	69.2	0.706
No	7	24	22.6	77.4	
Nasopharynx					
Yes	1	3	25.0	75.0	1
No	10	30	25.0	75.0	
			Death		
Tracheal Aspirate					
Yes	3	18	14.3	85.7	1
No	3	20	13.0	87.0	
Wound					
Yes	1	2	33.3	66.7	0.363
No	5	36	12.2	87.8	
Blood					
Yes	2	5	28.6	71.4	0.238

No	4	33	10.8	89.2	
Rectum					
Yes	0	13	0	100.0	0.157
No	6	25	19.4	80.6	
Nasopharynx					
Yes	0	4	0	100.0	1
No	6	34	15.0	85.0	

On the data from table 4.9, Fisher's exact test and Chi-square test were carried out on the sites of isolation and the outcomes of *K. pneumoniae* nosocomial infections in PCICU. As per Fisher's exact test run on the sites of isolation and respiratory sequelae and Chi-square test only run on tracheal aspirate, the highest prevalence was noted to be from nasopharynx with 4 patients (100%) and those without nasopharynx isolate at 25 out of 40 patients (62.5%). The lowest prevalence with respiratory sequelae on the other hand was with rectal isolate at 7 out of 13 patients (53.8%) whereas those without rectal isolate were more at 22 out of 31 patients (71%). Respiratory sequelae was seen in 66.7% with tracheal aspirate and wound isolates at 14 out of 21 patients and 2 out of 3 patients respectively. Respiratory sequelae developed in 15 out of 23 patients (65.2%) and 27 out of 41 patients (65.9%) in those without tracheal aspirate and wound isolate respectively. 5 out of 7 patients (71.4%) with blood isolate also reported to have developed respiratory sequelae whereas 24 out of 37 patients (64.9%) in those without blood isolate. The p-values determined for tracheal aspirate, wound, blood, rectum, nasopharynx were 0.919, 1, 1, 0.313 and 0.282 respectively. As such, none of the sites of isolation showed significant p-value. Thus, the null hypothesis was accepted. There was no significant association between sites of isolation and respiratory sequelae.

When looking into sepsis and infection based on table 4.9, we used both Chi-square test and Fisher's exact test as well to determine the association with sites of infection. Based on Chi-square test, infection/sepsis was the most prevalent in tracheal aspirate in 8 out of 21 patients (38.1%) and only found in 3 out of 23 patients (13%) without tracheal aspirate. Fisher's exact test was run for the other sites of isolation. The lowest prevalence of infection/sepsis however was noted to come from wound isolate in zero out of 3 patients (0%) whereas it was also prevalent in 11 out of 41 patients (26.8%) without wound isolate. Infection/sepsis was also present in 2 out of 7 patients (28.6%) with blood isolate and in 9 out of 37 patients (24.3%) without blood isolate. For rectal isolate, infection/sepsis was noted in 4 out of 13 patients (30.8%) and also in 7 out of 31 patients (22.6%) without rectal isolate. Infection/sepsis in patients with and without nasopharyngeal isolate yielded similar results of 25% where it was found in 1 out of 4 patients with the isolate and 10 out of 40 patients without the isolate. As such, p-values from the tests were 0.055 for tracheal aspirate, 0.561 for wound, 1 for blood, 0.706 for rectum and 1 for nasopharynx. None of the sites of infection showed significant p-value. The null hypothesis was not rejected. Therefore, there was no association between sites of infection and sepsis and infection.

Fisher's exact test was used to determine the association between sites of isolation and death based on table 4.9 also. As noted, death was most prevalent in patients with positive wound isolate at 1 out of 3 patients (33.3%) and 5 out of 41 patients (12.2%) in those without wound isolate. Meanwhile, mortality was lowest in prevalence in both rectal and nasopharyngeal isolates with zero patients (0%) out of 13 and 4 patients respectively. On the other hand, death was noted in 6 out of 31 patients (19.4%) without rectal isolate and also in 6 out of 34 patients (15%) without nasopharyngeal isolate). Tracheal aspirate was observed with 3 out of 22 patients (14.3%) and in 3 out of 23 patients (13%) without the isolate, both had mortalities. Death was also found in 2 out 7 patients (28.6%) with blood isolate and in 4 out of 37 patients (10.8%) without blood isolate. Fisher's exact tests came out with p-values of 1 for both tracheal aspirate & nasopharynx, 0.363 for wound, 0.238 for blood and 0.157 for rectum. Based on these values, none of the sites of isolation had significant p-values. Thus, the null hypothesis was accepted. There was no significant association between sites of infection and death.

4.3.3 Association between medical intervention factors and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

4.3.3.1 Cardiac surgical procedures and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.10: Association between cardiac surgical procedures and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Cardiac Surgery					
No Surgery	3	0	100.0	0	0.312
1 Surgery	5	4	55.6	44.4	
2 - 3 Surgery	17	11	60.7	39.3	
≥ 4 Surgery	4	0	100.0	0	
Sepsis and Infection					
Cardiac Surgery					
No Surgery	0	3	0	100.0	0.092
1 Surgery	0	9	0	100.0	
2 - 3 Surgery	9	19	32.1	67.9	
≥ 4 Surgery	2	2	50.0	50.0	
Death					
Cardiac Surgery					
No Surgery	0	3	0	100.0	0.465
1 Surgery	0	9	0	100.0	

2 - 3 Surgery	6	22	21.4	78.6
≥ 4 Surgery	0	4	0	100.0

Based on table 4.10, Fisher's exact test was executed to find the association between cardiac surgical procedure and outcome of *Klebsiella pneumoniae* nosocomial infections. 5 out of 9 (55.6%) PCICU patients who undergone only one cardiac surgery develop respiratory sequelae. Majority of PCICU patients (60.7%) who underwent 2 to 3 types of cardiac surgery had developed respiratory sequelae. In addition, all patients (100%) that did not undergo any surgery and who had undergone 4 or more types of cardiac surgery had developed respiratory sequelae. Although, all four groups of cardiac surgery did not have a significant p-value (P=0.312). Therefore, the null hypothesis was not rejected. There was no association between cardiac surgical procedure and respiratory sequelae.

9 out of 19 (32.1%) PCICU patients who underwent 2 to 3 types of cardiac surgery had developed sepsis and infection. Half of patients (50%) who underwent 4 or more types of cardiac surgery had also developed sepsis and infection. For patients that did not undergo any surgery and who underwent only one cardiac surgery, none (0%) of them developed sepsis and infection. However, all four groups of cardiac surgery did not have a significant p-value (P=0.092). Therefore, the null hypothesis was not rejected. There was no association between cardiac surgical procedure and sepsis and infection.

6 out of 28 (21.4%) PCICU patients who underwent 2 to 3 types of cardiac surgery had faced mortality. For other groups of cardiac surgery, none of them (0%) were found to have mortality. Even so, all four groups of cardiac surgery did not have a significant p-value (P=0.465). Therefore, the null hypothesis was not rejected. There was no association between cardiac surgical procedure and death.

4.3.3.2 Invasive procedures and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.11: Association between Invasive procedures and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Mechanical Ventilator					
Yes	28	15	65.1	34.9	1
No	1	0	100.0	0	
Chest Drain					
Yes	6	4	60.0	40.0	0.714
No	23	11	67.6	32.4	
CVC					
Yes	7	6	53.8	46.2	0.313
No	22	9	71.0	29.0	
Blood Transfusion					
Yes	10	8	55.6	44.4	0.228
No	19	7	73.1	26.9	
Sepsis and Infection					
Mechanical Ventilator					
Yes	11	32	25.6	74.4	1
No	0	1	0	100.0	

Chest Drain					
Yes	0	10	0	100.0	0.046
No	11	23	32.4	67.6	
CVC					
Yes	5	8	38.5	61.5	0.256
No	6	25	19.4	80.6	
Blood Transfusion					
Yes	5	13	27.8	72.2	0.738
No	6	20	23.1	76.9	

		Death			
Mechanical Ventilator					
Yes	6	37	14.0	86.0	1
No	0	1	0	100.0	
Chest Drain					
Yes	2	8	20.0	80.0	0.606
No	4	30	11.8	88.2	
CVC					
Yes	3	10	23.1	76.9	0.339
No	3	28	9.7	90.3	
Blood Transfusion					
Yes	3	15	16.7	83.3	0.676
No	3	23	11.5	88.5	

Based on table 4.11, Fisher's exact test was performed to elicit the association between mechanical ventilator and outcome of *Klebsiella pneumoniae* nosocomial infections. 28 out of 43 (65.1%) PCICU patients developed respiratory sequelae. There was only one patient (100%) who did not require mechanical ventilators and had developed respiratory sequelae. Although, mechanical ventilators as invasive procedures did not have a significant p-value (P=1). Therefore, the null hypothesis was not rejected. There was no association between mechanical ventilators and respiratory sequelae. 11 out of 43 (25.6%) PCICU patients developed sepsis and infection. Although, mechanical ventilators as invasive procedures still did not have a significant p-value (P=1). Therefore, the null hypothesis was not rejected. There was no association between mechanical ventilators and sepsis and infection. 6 out of 43 (14.0%) who required mechanical ventilators had faced mortality. However, mechanical ventilators did not have a significant p-value (P=1). Therefore, the null hypothesis was not rejected. There was no association between mechanical ventilators and death.

A Fisher's exact test was also performed to test the association between chest drain and outcome of *Klebsiella pneumoniae* nosocomial infections. The majority of the PCICU patients (60.0%) who required chest drain had developed respiratory sequelae while 23 out of 34 (67.6%) PCICU patients that did not require chest drain had also developed respiratory sequelae. Although, chest drain as invasive procedures did not have a significant p-value (P=0.714). Therefore, the null hypothesis was not rejected. There was no association between chest drain and respiratory sequelae. None of the patients (0%) who required chest drain had developed sepsis and infection while 11 out of 34 (32.4%) PCICU patients who did not require chest drain had developed sepsis and infections. However, we have found that chest drain as invasive procedures have a significant p-value (P=0.046). Therefore, the null hypothesis was rejected. There was an association between chest drain and sepsis and infection. One out of five (20%) PCICU patients who require chest drain have faced mortality while 4 out of 34 (11.8%) PCICU patients who did not require chest drain were also faced mortality. Although, chest drain as invasive procedures did not have a significant p-value (P=0.606). Therefore, the null hypothesis was not rejected. There was no association between chest drain and death.

We also ran Fisher's exact test to test the association between the central venous catheter (CVC) and outcome of *Klebsiella pneumoniae* nosocomial infections. 7 out of 13 (53.8%) PCICU patients who require CVC developed respiratory sequelae while the majority (71.0%) of PCICU patients who did not require CVC have developed respiratory sequelae. Although, CVC as invasive procedures did not have a significant p-value (P=0.313). Therefore, the null hypothesis was not rejected. There was no association between CVC and respiratory sequelae. 5 out of 13 (38.5%) PCICU patients who required CVC had developed sepsis and infection while 6 out of 31 (19.4%) PCICU patients who did not require CVC have developed sepsis and infection. However, CVC as invasive procedures did not have a significant p-value (P=0.256). Therefore, the null hypothesis was not rejected. There was no association between CVC and sepsis and infection. 3 out of 13 (23.1%) PCICU patients who require CVC have faced mortality while 3 out of 31 (9.7%) PCICU patients who did not require CVC have also faced mortality. Although, CVC as invasive procedures did not have a significant p-value (P=0.339). Therefore, the null hypothesis was not rejected. There was no association between CVC and death.

A Pearson Chi-Square test was performed to elicit the association of blood transfusion and respiratory sequelae. Among 18 PCICU patients who require blood transfusion, 10 of them (55.6%) had developed respiratory sequelae while the majority (73.1%) of PCICU patients who did not require blood transfusion had also developed respiratory sequelae. Although, blood transfusion as invasive procedures did not have a significant p-value (P=0.228). Therefore, the null hypothesis was not rejected. There was no association between blood transfusion and respiratory sequelae. Fisher's exact test was also performed to test the association between the blood transfusion and the remaining outcome which was sepsis and infection and death. 5 out of 18 (27.8%) PCICU patients who require blood transfusion had developed sepsis and infection while 6 out of 26 (23.1%) PCICU patients who did not require blood transfusion had developed sepsis and infection as well. However, blood transfusions as invasive procedures did not have a significant p-value (P=0.738). Therefore, the null hypothesis was not rejected. There was no association between blood transfusion and sepsis and infection. 3 out of 18 (16.7%) PCICU patients who require blood transfusion had faced mortality while 3 out of 26 (11.5%) PCICU patients who did not require blood transfusion had also faced mortality. Although, blood transfusions as invasive procedures did not have a significant p-value (P=0.676). Therefore, the null hypothesis was not rejected. There was no association between blood transfusion and death.

4.3.3.3 Total parenteral nutrition and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.12: Association between total parenteral nutrition and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Total Parenteral Nutrition					
Yes	13	3	81.3	18.7	0.087
No	15	12	55.6	44.4	
Sepsis and Infection					
Total Parenteral Nutrition					
Yes	2	14	12.5	87.5	0.166
No	9	18	33.3	66.7	
Death					
Total Parenteral Nutrition					
Yes	4	12	25.0	75.0	0.174
No	2	25	7.4	92.6	

Based on table 4.12, Pearson Chi-Square test was performed to test the association between total parenteral nutrition and respiratory sequelae. It was found that the majority (81.3%) PCICU patients who were on total parenteral nutrition had developed respiratory sequelae while the 15 out of 27 (55.6%) PCICU patients who were not on total parenteral nutrition had developed respiratory sequelae. Although, uses of total parenteral nutrition in both groups did not have a significant p-value (P=0.087). Therefore, the null hypothesis was not rejected. There was no association between total parenteral nutrition and respiratory sequelae.

A Fisher's exact test was performed to find the association between uses of broad spectrum antibiotic and sepsis and infection. It was found that out of 16 PCICU patients who use total parenteral nutrition, only 2 of them (12.5%) had developed sepsis and infection while 9 out of 27 (33.3%) patients who did not use total parenteral nutrition had also developed sepsis and infection. However, both groups of total parenteral nutrition usage did not have a significant p-value (P=0.166). Therefore, the null hypothesis was not rejected. There was no association between total parenteral nutrition and sepsis and infection.

Fisher's exact test was also performed to find the association between total parenteral nutrition and death. It was found that one out of four (25.0%) PCICU patients who use total parenteral nutrition had faced mortality while among 27 PCICU patients who did not use total parenteral nutrition, only 2 of them (7.4%) were also found to have mortality. Even so, both groups of total parenteral nutrition usage did not have a significant p-value (P=0.174). Therefore, the null hypothesis was not rejected. There was no association between total parenteral nutrition and death.

4.3.3.4 Use of broad-spectrum antibiotics and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.13: Association between Use of broad-spectrum antibiotics and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU. (N=44)

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Broad Spectrum Antibiotic					
Yes	14	11	56.0	44.0	0.112
No	15	4	78.9	21.1	
Sepsis and Infection					
Broad Spectrum Antibiotic					
Yes	6	19	24.0	76.0	1
No	5	14	26.3	73.7	
Death					
Broad Spectrum Antibiotic					
Yes	1	24	4.0	96.0	0.070
No	5	14	26.3	73.7	

Based on table 4.13, Pearson Chi-Square test was executed to find the association between use of broad spectrum antibiotic and respiratory sequelae. It was found that 14 out of 25 (56.0%) PCICU patients who used broad spectrum antibiotics had developed respiratory sequelae while the majority of PCICU patients (78.9%) who did not use broad spectrum antibiotics had developed respiratory sequelae. Although, uses of broad spectrum antibiotics in both groups did not have a significant p-value (P=0.112). Therefore, the null hypothesis was not rejected. There was no association between uses of broad spectrum antibiotic and respiratory sequelae.

Fisher's exact test was performed to find the association between uses of broad spectrum antibiotics and sepsis and infection. It was found that out of 25 PCICU patients who used broad spectrum antibiotics, 6 of them had developed sepsis and infection (24.0%) while 5 out of 19 (26.3%) patients who did not use broad spectrum antibiotics had also developed sepsis and infection. However, both groups of broad spectrum antibiotics usage did not have a significant p-value (P=1). Therefore, the null hypothesis was not rejected. There was no association between uses of broad spectrum antibiotics and sepsis and infection.

Fisher's exact test was performed to find the association between use of broad spectrum antibiotics and death. It was found that only 1 out of 25 (4.0%) PCICU patients who used broad spectrum antibiotics had faced mortality while among 19 PCICU patients who did not use broad spectrum antibiotics, only 5 of them (26.3%) were also found to have mortality. Even so, both groups of broad spectrum antibiotics usage did not have a significant p-value (P=0.070). Therefore, the null hypothesis was not rejected. There was no association between uses of broad spectrum antibiotics and death.

4.3.3.5 Duration of PCICU stay and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Table 4.14: Association between duration of PCICU stay and the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU

Case Characteristics	Frequency (n)		Percentage (%)		P-Value
	Yes	No	Yes	No	
Respiratory Sequelae					
Duration of PCICU stay					
≤ 15 Days	8	6	57.1	42.9	0.501
> 15 Days	21	9	70.0	30.0	
Sepsis and Infection					
Duration of PCICU stay					
≤ 15 Days	2	12	14.3	85.7	0.456
> 15 Days	9	21	30.0	70.0	
Death					
Duration of PCICU stay					
≤ 15 Days	2	12	14.3	85.7	1
> 15 Days	4	26	13.3	86.7	

Based on table 4.14, Fisher's exact test was executed to find the association between duration of PCICU stay and outcome of *Klebsiella pneumoniae* nosocomial infections. 8 out of 14 (57.1%) PCICU patients who stayed within 15 days in PCICU had developed respiratory sequelae while the majority of PCICU patients (70.0%) who stayed more than 15 days in PCICU had developed respiratory sequelae. Although, both groups of duration of PCICU stay did not have a significant p-value (P=0.501). Therefore, the null hypothesis was not rejected. There was no association between duration of PCICU stay and respiratory sequelae.

One per seven (14.3%) PCICU patients who stayed within 15 days in PCICU had developed sepsis and infection while 9 out of 30 (30.0%) patients who stayed more than 15 days had also developed sepsis and infection. However, both groups of duration of PCICU stay did not have a significant p-value (P=0.456). Therefore, the null hypothesis was not rejected. There was no association between duration of PCICU stay and sepsis and infection.

2 out of 14 (14.3%) PCICU patients who stayed within 15 days in PCICU had faced mortality while 4 out of 30 (13.3%) PCICU patients who stayed more than 15 days were also found to have mortality. Even so, both groups of duration of PCICU stay did not have a significant p-value (P=1). Therefore, the null hypothesis was not rejected. There was no association between duration of PCICU stay and death.

CHAPTER 5
DISCUSSION

5.1 Descriptive Analysis

In our data collected, only 49 out of 903 patients developed *K. pneumoniae* nosocomial infection in PCICU of Hospital Serdang from June 2018 to December 2020. This showed a prevalence of 5.43%. Our findings reported a prevalence of roughly half in comparison to what is stated by Ashurst & Dawson (2020) in which they reported it to be 11.8% worldwide.

Based on the age distribution pattern of the *K. pneumoniae* nosocomial infection in PCICU, it was noted to be negatively-associated with age exactly as mentioned by Raymond J. et al (2000). The highest occurrence of cases involved infants under or equal to the age of 12 months old which made up 77.6% of the total cases involved in the study and the only 2% of the cases involved children above or equal to 37 months old at time of admission.

One of the major risk factors of the *K. pneumoniae* infection that was looked into was the cardiac surgical procedures carried out on the patients. It was difficult to bring to light on which cardiac procedure specifically could have been a risk factor as most patients underwent multiple cardiac surgeries at a given time. Although, it can be noted that the majority of patients that had the NI had undergone PDA ligation (61.2%), VSD closure (32.7%) and ASD closure (26.5%). There were also some rare surgeries that were involved which include Interrupted Aortic Arch (IAA) repair, Glenn shunts, Truncus arteriosus repair, Tetralogy of Fallot repair and others as stated in the descriptive analysis.

When we look into the invasive procedures that were performed, it was shown that almost all (98%) of the patients who had the NI were either on mechanical ventilators or had a previous history of long term ventilation. However, the number of patients reported having a urinary catheter was nil. The use of broad-spectrum antibiotics, mainly Cephalosporin (40.8%) & Penicillin (10.2%) however could be debatable in increasing the susceptibility of the patients of being infected by *K. pneumoniae* as they were also one of the treatment choices for the infection.

As expected of the resistance pattern of *K. pneumoniae*, ESBL was noted to be the most frequent at 75.5% while CRKP being only 2%. Although as stated by Hoffken, G et al. (2002), the overuse of antibiotics is linked to the development of a pattern of resistance, the consistent use of Carbapenem (63.8%) as a definitive antibiotic in this particular PCICU did not seem to flourish the CRKP strains. Polymyxin class antibiotics were also not used as a last resort drug, indicating that the infections were under control.

There was some skeptical data in the record on both the site of infection as well as isolation. There were two instances of both the infection and isolate being at the eye. The site of isolation coming from rectal swab was also surprising at 33.3%. Although, we were unable to determine if the rectal swabs were reliable as many of them had multiple organisms present such as *E. coli.* Urine was not reported to be a site of infection nor isolated based on our findings, most likely as the use of urinary catheter was nil.

As expected of the *K. pneumoniae* outcome, 76.7% of patients with respiratory sequelae had pneumonia and 41.7% of patients with infections progressed to sepsis. The remarkable finding in this was having zero patients who developed neurological sequelae. It seems to be a mismatch from Carrie, C et al. (2019), who stated that *K. pneumoniae* strains found in children under the age of 1 year that were ESBL-producing, mainly affects children in the 1st year of life which can lead to meningitis.

5.2 Analytical Analysis

First and foremost would be to address that most of the analysis turned out to be accepting the null hypothesis as the p-values indicated insignificant. This was likely due to the smaller sample size that we achieved. This study has tried to determine the association between sociodemographic factors, patient factors as well as medical interventional factors with the outcome of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang. As per our findings on the sociodemographic factors, only the association between gender and respiratory sequelae turned out to be significant, where it was more prevalent among males (86.4%) than females (45.5%). This was an interesting finding as we expected the females to be more prevalent as the number of female patients was much higher.

Another significant finding was the association between *K. pneumoniae* infection in the bloodstream with mortality of the PCICU patients. It seems that infection of *K. pneumoniae* within the bloodstream has shown to be significantly higher (42.9%) to be associated with death rather than *K. pneumoniae* infections outside of the bloodstream (8.1%).

Besides that, looking into invasive procedures being a risk factor for *K. pneumoniae* nosocomial infections, only one of the procedures had an association with the outcome. It was noted that chest drain had a significant association with sepsis and infection. The use of chest drain showed a significantly lower prevalence at 0% when compared to not using a chest drain (32.4%) in being associated with sepsis and infections. This was a remarkable finding as we expected the use of such an invasive procedure to increase the chances of *K. pneumoniae* nosocomial infection.

CHAPTER 6
CONCLUSION

6.1 CONCLUSION

From this study, we were able to state the prevalence, clinical profile of nosocomial infections of *Klebsiella pneumoniae* as well as the resistance patterns in PCICU of Hospital Serdang from June 2018 to December 2020. We have also included the significant associations between the clinical profiles and the outcome of the infection.

Prevalence of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang from June 2018 to December 2020 was 5.43%. It was noted that 49 out of 903 PCICU patients had developed *K. pneumoniae* nosocomial infections.

As for the clinical profiles, only three factors seemed to be significantly associated with the outcome of *K. pneumoniae* nosocomial infections. The first one was sociodemographic factors where gender was significantly associated with the respiratory sequelae. The male patients who developed respiratory sequelae were significantly higher than females. Furthermore, sites of infection also had a significant association with the outcome when looking into bloodstream infection together with mortality. The patients with bloodstream infection of *K. pneumoniae* reported significantly higher mortality than those without the bloodstream infection. The final association was found in invasive procedures along with the outcome. Surprisingly, the use of chest drain showed a significantly lower number in sepsis and infections.

The *K. pneumoniae* strains that were mainly found in this study were ESBLs, followed by non-resistant strains and only one CRKP strain. Considering the consistent use of carbapenems in treating the ESBLs, the CRKP strains were reported to be much lower than expected.

6.2 LIMITATIONS

First and foremost would be the event of COVID-19 pandemic. Our data collection date was delayed for a month, as such the duration of data collection was significantly reduced. We also had to carry out the data collection in between classes to compensate for the delay. Furthermore, restrictive measures were taken during the data retrieval by only allowing one of us to collect data at a given time. Conditional Movement Control Order (CMCO) further restricted our movement to collect the data at the hospital thus slashing the data collection efficiency. The PCICU only has 2 computers available for the doctors. As such, we had to wait for the computer to be available during the busy hours of the weekdays. In the end, the data collection was foreshortened and only data from 49 patients were retrieved, not even reaching close to our sample size of 422.

Other than that, this study had information bias. Considering this study was done in a retrospective manner, missing data was also apparent due to poor documentation or due to variables that were not considered to be documented in advance. As such, some of the data provided by the nurses did not tally with the information stated in the system. The data retrieval process also was stagnant at a time as the patients' details were only extracted and organized by the nurses for the year 2020, not for the previous years. This was the reason as to why the data was only collected from June 2018 instead of January 2018, as we had to retrieve the data backwards from December 2020 towards June 2018. The data available in the PCICU was also limited, which means that the sample size of 422 would not have been reached anyway. This could have also been due to missing data from the year 2018 as there was no data available after August 2018 for that year. As for the data retrieval system, the only concern would be that there was a possibility that we missed out some valuable information as the majority of the medical records used medical abbreviations that we, preclinical students have not come across yet.

Another concern was the decrease in human resources for the second phase of this research. A research member dropped out, resulting in further limitation in the data collection time period as well as reduced input in completing this study.

6.3 RECOMMENDATIONS

Based on the study, the prevalence of *Klebsiella pneumoniae* nosocomial infection in PCICU Hospital Serdang was 5.43%. In general, nosocomial infections have significant morbidity and mortality for patients. Although the mortality rate was noted to be 13.3%, none of the patients developed neurological sequelae. This information is valuable for clinicians, especially in counselling the general outcome of patients with *K. pneumoniae* infections. The sample size in our study was small and our research only covers a small time frame from June 2018 to December 2020, hence further studies are required to validate our findings. This study will also improve on the nosocomial infection registry as it is important to get good reliable data for future research.

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APPENDICES

Proforma Sheet

DATA COLLECTION FORM OF PEDIATRIC CARDIAC INTENSIVE CARE UNIT PATIENT (PCICU)

1 Demographic

I Registration/SD No. : ______________

II I/C Number : ______________

III Date of Birth : ______________

IV Gender : ☐ Male ☐ Female

V Ethnicity : ☐ Malay ☐ Chinese ☐ Indians ☐ Others : ______________

VI Date of admission : ______________

VII Date of surgery : ______________

VIII Date of discharge : ______________

2 Diagnosis :

I Cardiac :

a. Acquired : ☐ Rheumatic Heart Disease ☐ Kawasaki Disease ☐ Others : ______________

b. Congenital : ☐ Cyanotic :

- a. Pulmonary Atresia ☐
- b. Tricuspid valve abnormalities ☐
- c. Transposition of the great vessel ☐
- d. Total anomalous pulmonary venous return ☐
- e. Truncus arteriosus ☐
- f. Tetralogy of Fallot ☐
- g. Others : ______________

☐ Acyanotic :

- a. Ventricular Septal Defect (VSD) ☐
- b. Atrial Septal Defect (ASD) ☐
- c. Atrioventricular Septal Defect ☐
- d. Patent Ductus Arteriosus (PDA) ☐
- e. Pulmonary Valve Stenosis ☐
- f. Aortic Valve Stenosis ☐
- g. Coarctation of Aorta ☐

II Non-Cardiac : ☐ Yes ☐ No

If Yes, underlying issues : ______________

3 Date of Diagnosis : ______________

4 Risk Factors :

I Type of Surgical Procedures :

- a. Complete AVSD repair ☐
- b. VSD closure ☐
- c. ASD closure ☐
- d. PDA ligation ☐
- e. Valve replacement / repair ☐
- f. Others : ______________

II Invasive Procedure : ☐ Yes ☐ No

If Yes: ☐ Mechanical Ventilator ☐ Chest Drain ☐ Urinary Catheter ☐ CVC ☐ Blood Transfusion

If Mechanical Ventilator :

- a. Before surgery ☐
- b. After surgery ☐
- c. Date of started : ______________
- d. Date of ended : ______________
- e. Type of ventilation : ______________

If Chest Drain : ☐ Unilateral ☐ Bilateral

Date of Insertion : ____________

If CVC :

a. Type of CVC : ____________

b. Site of Insertion : ____________

c. Date of Insertion : ____________

If Blood Transfusion : ☐ Central-line ☐ Peripheral-line

Date of Transfusion : ____________

III Complete parenteral nutrition : ☐ Yes ☐ No

IV Broad spectrum antibiotics : ☐ Yes ☐ No

If Yes : ☐ Sulphonamide ☐ Chloramphenicol ☐ Tetracycline ☐ Trimethoprim ☐ Others : ____________

Date of Initiation : ____________

5 **Signs of Infections :**

I Full Blood Count (FBC) :

a. Total WBC : ____________ c. Platelet : ____________

b. Absolute Neutrophil Count : ____________ d. Haemoglobin : ____________

II C-reactive protein (CRP) : ____________

III Liver Function Test (LFT) :

a. ALP : ____________ c. ALT : ____________

b. AST : ____________ d. Total Bilirubin : ____________

IV Renal Profile :

a. Creatinine : ____________ c. Potassium : ____________ e. Chloride : ____________

b. Urea : ____________ d. Sodium : ____________

5 **Klebsiella pneumoniae nosocomial infection :** ☐ Yes ☐ No

If Yes : I Date of Isolation : ____________

II Site of Infection :

a. Respiratory Tract ☐ c. Blood ☐ e. Others : ____________

b. Urinary Tract ☐ d. Surgical Site ☐

III Site of Isolation :

a. Sputum / Tracheal aspirate ☐ e. Blood ☐

b. Bronchoalveolar Lavage ☐ f. Urine ☐

c. Catheter ☐ g. Others : ____________

d. Wound ☐

IV Resistant *K. pneumoniae* : ☐ Yes ☐ No

If Yes : ☐ ESBL ☐ CRKP

V Treatment after isolation of *K. pneumoniae* :

a. Aminoglycoside ☐

b. Penicillin ☐

c. Carbapenem ☐

d. Polymyxin ☐

e. Cephalosporin ☐

f. Other : ____________

6 **Outcome :**

I Respiratory Sequelae : ☐ Yes ☐ No

If Yes : a. ☐ Pneumonia c. ☐ Lung Abscess

b. ☐ Empyema d. ☐ Others : ______________

II Neurological Sequelae : ☐ Yes ☐ No

If Yes : a. ☐ Brain Abscess b. ☐ Meningitis c. ☐ Others : ______________

III Sepsis / Infection : ☐ Yes ☐ No

If Yes : a. ☐ BSI c. ☐ SSI e. ☐ Others : ______________

b. ☐ VAP d. ☐ Catheter Related Infection

IV Post Operative complications : ______________

7 **Analysing Data :**

I Age : ______________

II Measures of morbidity :

a. Duration of PCICU stay : ______________

b. Mortality : ☐ Yes ☐ No

If Yes, Cause of Death : ______________

III Duration of ventilator : ______________

NMRR Ethics Approval

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ref : KKM/NIHSEC/ P21-266 (4)
Date: **01-Mar-2021**

Dr Sithra A/P Rengasamy @Ragasamy
UNIVERSITY PUTRA MALAYSIA (UPM)

Dear Sir / Mdm,

ETHICS INITIAL APPROVAL: NMRR-21-111-58247 (IIR)
Prevalence, profile of Nosocomial Infections of Klebsiella pneumoniae and resistance patterns in a Pediatric Cardiac Intensive Care Unit Hospital Serdang

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations, including the Access to Biological and Benefit Sharing Act 2017.

3. The investigators and study sites involved in this study are:

   HOSPITAL SERDANG
   Dharenrow A/L SV Ganthirao
   Dr Ani Suraya Bt Ghani
   Dr Sithra A/P Rengasamy @Ragasamy (Penyelidik Utama)
   Mohammad Nazrul bin Abdul Ghani
   NUR SYASYA ILYANA BT SHAHRUM
   Prof NORLIJAH OTHMAN

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Study Protocol_Version 1.2, dated 22-Feb-2021
2. Data Collection Form_Version 1.2, dated 22-Feb-2021
3. Investigator's documents : Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
   a) Dharenrow A/L SV Ganthirao
   b) Dr Ani Suraya Bt Ghani
   c) Dr Sithra A/P Rengasamy @Ragasamy (Penyelidik Utama)
   d) Mohammad Nazrul bin Abdul Ghani
   e) NUR SYASYA ILYANA BT SHAHRUM
   f) Prof NORLIJAH OTHMAN

5. Please note that ethical approval is valid until **28-Feb-2022**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the National Medical Research Register (NMRR) website.

Budget planning

ITEMS	PRICE
Photocopy	RM 20.00
Printing	RM 40.00
Hardcover and Binding	RM 100.00
Miscellaneous	RM 15.00
Total	RM175.00

Table 2: Budget Plan

Gantt Chart

Activity	Dec	Jan	Feb	March	Aprl	May	June	July
Proposal Preparation								
Proposal Submission								
Preparation of Proposal Presentation								
Proposal Presentation								
Preparation of Ethical Approval								
Ethical Approval								
Data Collection								

Data Analysis and Presentation Report Writing and Poster Preparation																																
Submission of Final Reports & Scientific Article																																
Preparation of Final Presentation																																
Final Report Presentation																																
Submission of Poster & Scientific Article																																
Poster competition																																
Correction of Final Report and Scientific Article																																

Submission of Log Book and Final Reports																																

Table 1: Gantt chart

Sample size

Variables	Prevalence	Sample size estimation	Reference
Prevalence of *Klebsiella pneumoniae* nosocomial infection	P = 0.153	N=199	(Radji et al., 2011)
Sociodemographic factors			
Age	P=0.57	N=377	(Hlophe & Mc-Kerrow, 2014)
Gender : Female Male	P=0.43 P=0.57	N=377 N=377	(Hlophe & Mc-Kerrow, 2014)
Malay	P=0.182	N=229	(Pillai et al., 2016)
Chinese	P=0.545	N=381	(Pillai et al., 2016)
Indian	P=0.273	N=305	(Pillai et al., 2016)
Patients factors			
- Site of isolation			
Blood	P=0.515	N=384	(Low et al., 2017)
Urine	P=0.58	N=374	(Low et al., 2017)
Wound	P=0.26	N=296	(Heloise et al., 2016)
Catheter	P=0.04	N=59	(Zarkotou et al., 2011)
Tracheal aspirate	P=0.353	N=351	(Low et al., 2017)
Sputum	P=0.143	N=188	(French et al.,1996)
Bronchoalveolar lavage	P=0.077	N=374	(Antoniadou et al., 2007)

- Site of infection			
Blood stream	P=0.58	N=374	(Wang et al., 2018)
Respiratory tract	P=0.163	N=210	(Wang et al., 2018)
Urinary tract	P=0.390	N=366	(Wang et al., 2018)
Surgical site	P=0.074	N=105	(Bissenova & Yergaliyeva, 2017)
Medical intervention factors			
Cardiac surgery	P=0.73	N=303	(Low et al., 2017)
Invasive procedure: Mechanical ventilation Urinary catheter Central venous catheter Blood transfusion	 P=0.453 P=0.43 P=0.244 P=0.534	 N=381 N=377 N=283 N=382	(Aktar et al., 2016)
Total parenteral nutrition	P=0.12	N=162	(Gracia et al., 2017)
Broad spectrum antibiotic	P=0.558	N=379	(Aktar et al., 2016)
Long term surveillance	P=0.523	N=383	(Aktar et al., 2016)
Antimicrobial resistance patterns			
Extended spectrum beta lactamase	P=0.001	N=2	(Cheikh et al., 2016)
Carbapenem resistance *Klebsiella pneumoniae*	P=0.09	N=126	(Daikos et al., 2016)