INTRODUCTION

-Neonatal sepsis (NS) is a potentially life-threatening clinical condition. A population level estimate for neonatal sepsis of 2,202 per 100,000 live births was reported, with mortality between 11 and 19% (Fleischmann-Struzek C,et al., 2018)

-The nonspecific nature of symptoms and rapid progression of this disease emphasize the importance of early recognition. Various biomarkers have been associated with NS, including C-reactive protein (CRP), procalcitonin, and interleukin-6 **(**Gkentzi D,et al., 2017)

-However, these markers differ when they rise and when they return to normal during sepsis. Therefore, it is essential to identify new biomarkers that can detect onset of sepsis as early as possible for timely antibiotic therapy.

-Calcium is associated with bone formation and metabolism, and it participates in a range of physiological processes, including cell signaling, neurotransmission, and muscle contraction. It also acts as a cofactor of enzymatic reactions in the coagulation cascade [Aberegg SK..2016].

-Ionized calcium (iCa) is a biologically active form of calcium responsible for these physiological functions. Hypocalcemia can be characterized by serum iCa

concentrations < 4 mg/dL (1 mmol/L) [Thomas TC,et al., 2012]

-Hypocalcemia is often observed in neonates with sepsis and

has been attributed to an increase in procalcitonin secretion,

which is converted to calcitonin and in turn regulates

calcium metabolism [Kutílek Š,et al.,2019].

-Sepsis related death was defined as death within 14 days after developing sepsis [Sano H,et al.,2017].

-Neonatal sepsis was defined as the growth of potentially pathogenic organisms (bacteria or fungi) in the blood or cerebrospinal fluid of patients whose clinicopathologic characteristics were consistent with infection [Subspecialty Group of Neonatology Pediatric Society Chinese Medical Association, 2003].

AIM OF THE STUDY

The purpose of this study is to evaluate the prognostic value of hypocalcaemia in neonatal sepsis patients and to identify risk factors associated with sepsis related mortality.

Chapter (1): Neonatal sepsis

Neonatal sepsis is a clinical syndrome that includes systemic infection, circulatory shock, and multisystem organ failure in infants under 28 days old. Neonatal sepsis is either early-onset (EONS) or late-onset (LONS). EONS is infection and sepsis in the first 24–7 days of life. LONS is after 24 hours or after the first week of life, up to 28 days or 1 month. Most literature defines EONS as within 72 hours of birth and LONS as after 72 hours up to 28 days.**(Klingenberg et al., 2018)**

Etiology& Risk Factors

Pathogens from the female genitourinary system to the infant or foetus cause early-onset sepsis. These bacteria can invade the vagina, cervix, uterus, and amniotic fluid. Infection can occur during birth or in utero. Group B streptococci(GBS) , Escherichia coli, coagulase-negative Staphylococcus,

Haemophilus influenza, and Listeria monocytogenes are the most early onset sepsis (EOS) pathogens.**(Simonsen et al., 2014)**

After birth, infections from healthcare professionals or carers can cause late-onset sepsis (LOS). Late vertically transmitted infection may cause a percentage of LOS. Intravascular catheter insertion or other invasive procedures that damage the mucosa put infants at risk for late onset sepsis (LOS). **(Singh et al., 2021)**

Preterm neonates are at higher risk for sepsis/infection than term neonates. The increased susceptibility for infections seen in preterm neonates is mainly due to:

- Deficient immune system, mainly due to decreased IgG antibodies and incompetent opsonization and complement activation
- Comprised innate immune system, caused primarily by the immature epithelial barrier
- The increased need for invasive devices (vascular access, endotracheal tube, feeding tubes and uriarny tract catheters) due to associated severe illnesses

Coagulase-negative staphylococcal species, especially Staphylococcus epidermis, is the leading cause, responsible for greater than 50% of LOS cases in industrialized countries. However, many other bacterial and viral pathogens can be associated with LOS. **(Simonsen et al., 2014)**

In EONS, which is typically associated with vertical transmission of pathogens from mother to child, the most common pathogens are GBS, *Escherichia coli*, CONS, *Haemophilus influenzae*, and *Listeria monocytogenes*.**(Ershad et al., 2019)** In LONS, which is most commonly associated with iatrogenic or nosocomial infections, the most common pathogens

are CONS, followed by *Staphylococcus aureus* and *Escherichia coli*. **(Shah & Padbury, 2014)**

Invasive medical devices like central venous catheters and prolonged hospitalisation are risk factors. Preterm rupture of membranes, amnionitis, meconium aspiration, LBW, VLBW, ELBW, preterm birth, more than three vaginal examinations during labour, fever, or various infections in the mother during labour are further risk factors. **(Cortese et al., 2016)**

In full-term infants, males have a greater incidence of sepsis compared to female infants, an association not found in preterm infants. A study performed in the US found significant disparity and increased incidence of mortality secondary to neonatal sepsis among children from low household income backgrounds versus those from affluent household.**(Ocviyanti & Wahono, 2018)**

Epidemiology& Microbiology of Neonatal Sepsis.

Neonatal sepsis epidemiology is changing. Since the 1990s, universal GBS screening and intrapartum antibiotic prophylaxis have reduced EOS rates. LOS rates remain stable. Escherichia coli causes more EOS instances**(Procianoy & Silveira, 2020)**

EOS with positive blood cultures occurs 0.77–1 per 1,000 live babies in the US. If risk factors are present and/or clinically indicated, many asymptomatic neonates undergo a sepsis workup due to the nonspecific neonatal presentation and high mortality and morbidity without treatment. 7%–13% of neonates are tested for sepsis, but only 3%–8% have positive cultures.**(Stoll et al., 2015)**

Poor blood culture positivity may be due to maternal antibiotic use and low blood volume. Premature and very low birth weight (<1000 grammes) newborns

have a greater sepsis rate. Due to greater GBS carrier rates in African American females, African American infants are at higher risk of GBS and LOS. Sepsis and meningitis are more common in men, especially with gram-negative enteric bacilli.**(Simonsen et al., 2014).**