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Impact of Blood Infections on Inflammatory Markers and Liver Function in Neonates with Pathological Jaundice in Erbil City: A Comprehensive Study

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Abstract: Neonatal pathological jaundice is a significant health concern, often complicated by blood infections which can alter physiological responses and exacerbate conditions. Understanding the impact of such infections on blood parameters and liver enzymes in newborns can aid in better diagnosis and management strategies. This study included 125 newborns treated at the Department of Obstetrics and Gynecology - Neonatal Intensive Care Unit at Erbil Hospital from January 2022 to June 2023. Participants were divided into two groups: 75 neonates with jaundice and confirmed bacterial blood inflammation and 50 neonates with jaundice but no bacterial infection. A control group of healthy infants was also included. Blood markers such as WBC, hs-CRP, PCT, and TRF, along with liver enzymes AST, GGT, and ALP, were measured using standardized laboratory procedures. Significant differences in blood markers were observed between the groups. Infants with jaundice and blood inflammation displayed elevated levels of WBC, hs-CRP, and PCT, indicating a strong inflammatory response ($P < 0.05$). TRF levels were notably lower in neonates with bacterial infections compared to those without, suggesting alterations in iron metabolism due to inflammation ($P < 0.01$). Liver enzyme analysis revealed higher AST, ALP, and GGT levels in jaundiced infants, which were more pronounced in those with concurrent blood infections, pointing towards potential liver involvement.

The study highlights the clear impact of blood infection on both inflammatory markers and liver function in neonates with pathological jaundice. These findings suggest that close monitoring is critical for effective management of infants with jaundice. Future research should continue to explore the mechanisms driving these changes to enhance treatment protocols and outcomes in this vulnerable population.

Keywords: Neonatal jaundice, blood infection, liver enzymes, inflammatory markers, neonatal care.

Introduction

Physiological jaundice is a common condition, typically appearing on the second or third day of life in most newborns. It is the most common cause of clinical jaundice after the first day of life[1], characterized by yellowing of the skin and the whites of the eyes, representing about 50% of cases. However, only about 10% of newborns require phototherapy to treat jaundice. If the jaundice is pathological, it may appear on the first day of life, with total serum bilirubin (TSB) levels exceeding

age-specific bilirubin charts or with a rapid increase in bilirubin levels. In some cases, jaundice may persist for more than three weeks, especially in breastfed infants[2,3].

The underlying causes of jaundice in infants may be indicative of a problem with the child's nutrition, hydration level, or red blood cell lifespan, among other rare causes such as biliary atresia[4]. Imaging studies are crucial for distinguishing between different disorders of the extrahepatic bile ducts, including biliary atresia. In summary, the review provides valuable insights into the differential diseases of cholestasis in children and emphasizes the importance of diagnostic imaging techniques in differentiating between various disorders[5]. Mild jaundice is relatively common and usually harmless in newborns, but severe or prolonged jaundice, often referred to as congenital jaundice, can indicate underlying pathological conditions and may lead to serious complications. One potential cause of such complications is the relationship between congenital jaundice and systemic inflammation within the body[6]. The interaction between congenital jaundice and blood inflammation is a complex process that can lead to increased bilirubin levels, which may contribute to the development of jaundice. Furthermore, it has been observed that the inflammatory response in the body affects many important factors in the blood and alters the function of liver enzymes, which play a crucial role in the metabolism of bilirubin[7]. Interestingly, changes in certain blood parameters and liver enzymes have been associated with various pathological conditions, including liver diseases, hemolytic anaemia, and certain types of infections, all of which can present with jaundice as a symptom[8,9]. These observations suggest a complex interaction between congenital jaundice, blood inflammation, and changes in blood parameters and liver enzymes. However, many of the mechanisms and consequences of this interaction remain unclear[10]. In some countries, particularly in South Asia, jaundice complicates 3-5% of pregnancies and is considered a significant cause of morbidity and mortality among mothers and newborns worldwide. During gestation, physiological and hormonal alterations are prevalent[11,12]. Concurrently, jaundice can occur alongside blood infections, potentially leading to conditions like acute fatty liver of pregnancy. Additionally, it may be linked with various disorders including viral hepatitis, preeclampsia, HELLP syndrome, intrahepatic cholestasis of pregnancy, hyperemesis gravidarum, and liver cirrhosis accompanied by portal hypertension. Moreover, the use of certain medications during pregnancy can also induce jaundice[13]. Neonatal hepatitis, caused by various viruses such as cytomegalovirus, rubella, and hepatitis A, B, and C, can lead to hepatitis in infants. In some cases, the specific virus remains unidentified. Galactosemia, a rare disorder, occurs when an infant cannot metabolize galactose, a milk sugar. This can cause liver damage, inflammation, and jaundice[14]. Biliary atresia, characterized by the obstruction or underdevelopment of bile ducts, leads to the accumulation of bilirubin in the liver and causes jaundice. A key sign is the presence of very pale stools in the infant[15].

This research aims to delve deeper into seeking to uncover the effects of congenital jaundice and blood inflammation on blood markers and liver enzymes. We hope that a better understanding of these processes will not only provide valuable insights into the pathophysiology of congenital jaundice and related conditions but also contribute to improved diagnostic and therapeutic strategies

Materials and Methods

A total of 125 newborns diagnosed with neonatal pathological jaundice were enrolled in a study conducted at the Department of Obstetrics and Gynecology - Neonatal Intensive Care Unit at Erbil Hospital from January 2022 to June 2023. The patients were categorized into two groups: 75 cases with jaundice and confirmed bacterial blood inflammation through hospital laboratory reports, and 50 cases with jaundice but without bacterial infection. Additionally, a control group consisted of healthy infants. The study received approval from the hospital’s ethics committee, and consent forms were signed by the families of the patients, indicating their voluntary participation.

Fasting venous blood samples were obtained from each infant patient in the early morning after admission. The collected blood was placed in K2-EDTA anticoagulant tubes for routine blood analysis. Serum samples were acquired by centrifuging self-coagulated venous blood at 3000 revolutions per minute[16], and were utilized for assays such as high-sensitivity C-reactive protein

(hs-CRP), procalcitonin (PCT), White Blood cells (WBC) and transferrin (TRF), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (GGT), and Alkaline phosphatase (ALP). Routine blood testing was conducted using a fully automated hematology analyzer, the SYSMEX XS-1000i. PCT and TRF tests were performed on a fully automated The Roche E601 analyzer, which employs the electrochemiluminescence immunoassay method, was utilized. Tests for hs-CRP, TRF, Liver enzyme tests for ALT, AST, GGT, and ALP were conducted using a fully automated biochemistry analyzer (Siemens ADVIA 2400). Original reagents provided with the instruments were utilized, and operational protocols were strictly adhered to. Quality control measures met all specified requirements. The reference ranges for the tested markers were as follows: WBC, (15.00 to 20.00) x10^9; hs-CRP, (0.00 to 5.00) mg/L; PCT, (0.00 to 0.25) ng/mL; TRF, (28.60 to 51.90) micrometer; AST, (0.00 to 50.00) U/L; GGT, (0.00 to 50.00) U/L; ALP, (36.00 to 150.00) U/L[17,18].

Statistical Method

Data processing and analysis were performed using SPSS 22.0 (Chicago, IL, USA). The t-test and $\chi 2$ test were employed for statistical analysis. Measurement data were presented as mean ± standard deviation (mean±s). An independent sample t-test was utilized to compare means between groups, while the $\chi 2$ test was used to compare proportions in count data. Pearson correlation analysis was conducted to assess relationships between variables. Statistical significance was established at a p-value of less than 0.05.

Results and Discussion

The results presented in Table 1 compare the levels of inflammation markers (WBC, TRF, hs-CRP, and PCT) in the Peripheral blood samples were compared among three groups: patients with neonatal pathological jaundice associated with bacterial pathogenic infection, patients with jaundice without blood inflammation, and healthy infants. The data reveal that infants with jaundice accompanied by blood inflammation exhibited significantly higher levels of these markers compared to both the jaundice-only group and the healthy infants, with the observed differences being statistically significant ($P < 0.05$). Additionally, the TRF (Transferrin) levels in the group with bacterial infections were significantly lower than those in the non-infected jaundiced group ($P < 0.01$). This study underscores the influence of blood inflammation on specific blood parameters in infants suffering from neonatal jaundice. The elevated levels of hs-CRP, WBC, and PCT in the group with jaundice and blood inflammation suggest an ongoing inflammatory response, potentially exacerbating the jaundice. Conversely, the decreased TRF levels in the bacterial infection group might reflect disturbances in iron metabolism commonly observed in inflammatory conditions. These findings highlight the critical role of monitoring inflammatory markers in infants with neonatal jaundice to evaluate the risk of complications and tailor appropriate treatment strategies.

Table 1: The impact of neonatal jaundice and blood inflammation on certain blood parameters

Group	Transferrin TRF (μM)	White Blood cells WBC ($x10^9$/L)	high-sensitivity C-reactive protein hs-CRP (mg/L)	procalcitonin PCT (ng/mL)
Jaundice and blood infection	11.73±1.03[a]	26.03±3.01[a]	18.43±1.32[a]	5.39±2.54[a]
Jaundice without blood infection	40.56±3.65[b]	12.11±2.71[b]	4.86±0.55[bc]	0.42±0.54[b]
Control	4.76±3.76[c]	4.042[c]	4.64[c]	5.08[ca]
P	0.004	0.014	0.001	0.004

[a,b,c]$P<0.05$, compared with control group

The data in Table 1 reveal statistically significant differences in various blood parameters among three groups: cases of jaundice with blood infection, jaundice without blood infection, and a control group without any infection, with significance levels at $P < 0.05$. These parameters include white blood cell count (WBC) in $x10^9$/L, high-sensitivity C-reactive protein (hs-CRP) in mg/L,

procalcitonin (PCT) in ng/mL, and total bilirubin (TRF) in μM. Notably, the WBC count is significantly higher in the group with jaundice and blood infection compared to the jaundice-only and control groups, suggesting a link between elevated WBC counts and the presence of jaundice coupled with blood infections. Furthermore, hs-CRP levels are markedly elevated in the jaundice and blood infection group, indicating a robust inflammatory response associated with jaundice when concurrent blood infection is present. Similarly, PCT levels are significantly higher in this group, typically indicative of bacterial infections. Conversely, TRF levels are highest in the non-infected jaundice group, consistent with jaundice being characterized by elevated bilirubin levels due to impaired liver function. The presented P values (0.014, 0.001, 0.004, 0.004) underscore the statistical significance of the differences in WBC, hs-CRP, PCT, and TRF levels among the groups. These low P values suggest that the observed differences are highly unlikely to be due to chance, illustrating distinct patterns in blood parameters between the groups, which emphasize the impact of blood infection on inflammatory markers and the effect of jaundice on bilirubin levels.

The effect of jaundice and blood inflammation on liver enzymes

The results depicted in Figure 1 demonstrate the effect of neonatal jaundice, either concurrent with blood inflammation or without, in comparison to healthy infants, on the liver enzyme aspartate aminotransferase (AST).

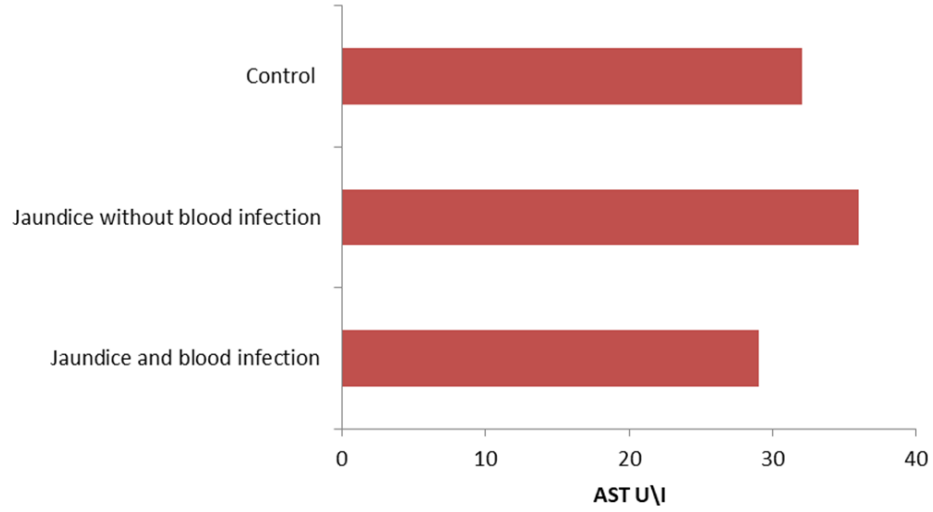

Figure 1: The effect of congenital jaundice and blood inflammation on the enzyme Aspartate aminotransferase (AST),LSD 5%=1.204.

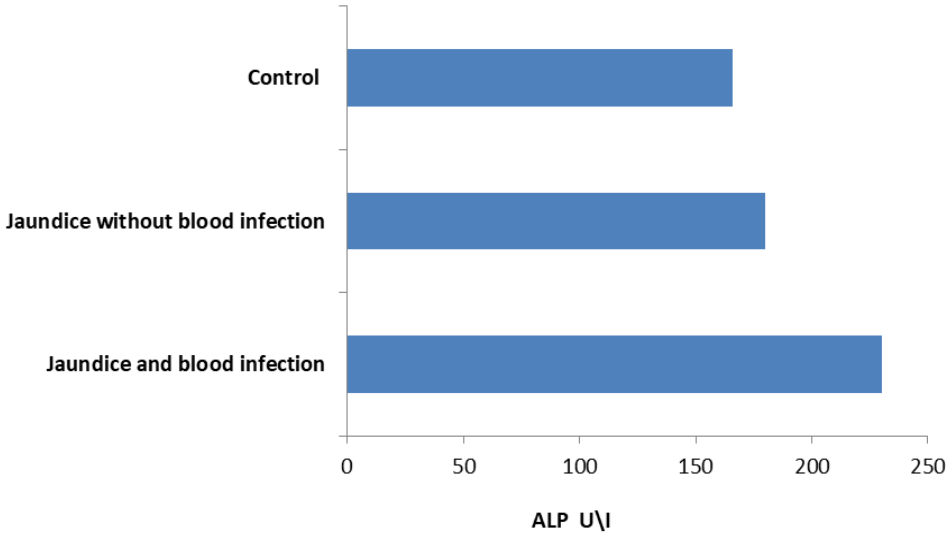

Figure 2: The effect of jaundice and blood inflammation on the enzyme Alkaline phosphatase(ALP),LSD 5%=2.650.

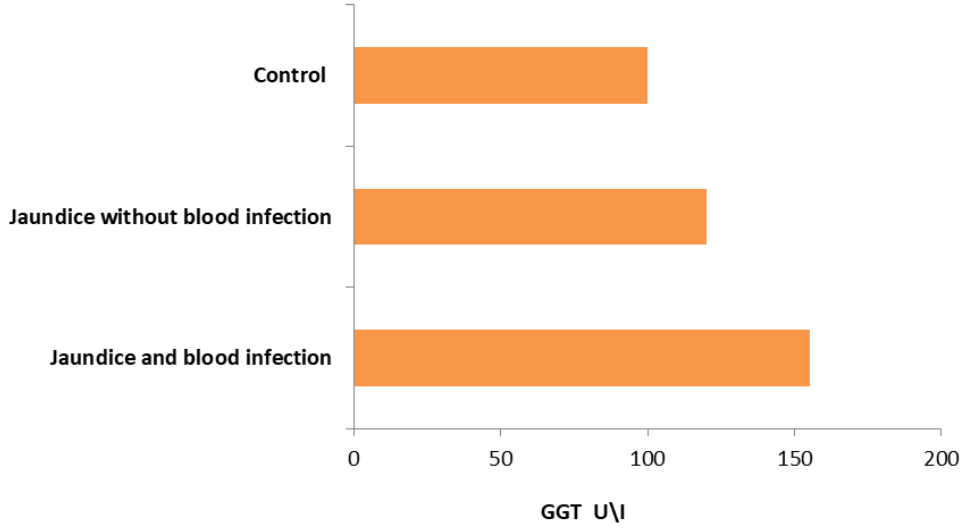

Figure 3: The effect of jaundice and blood inflammation on the levels of the glucuronosyl transferase enzyme (GUTI),LSD 5%=2,976.

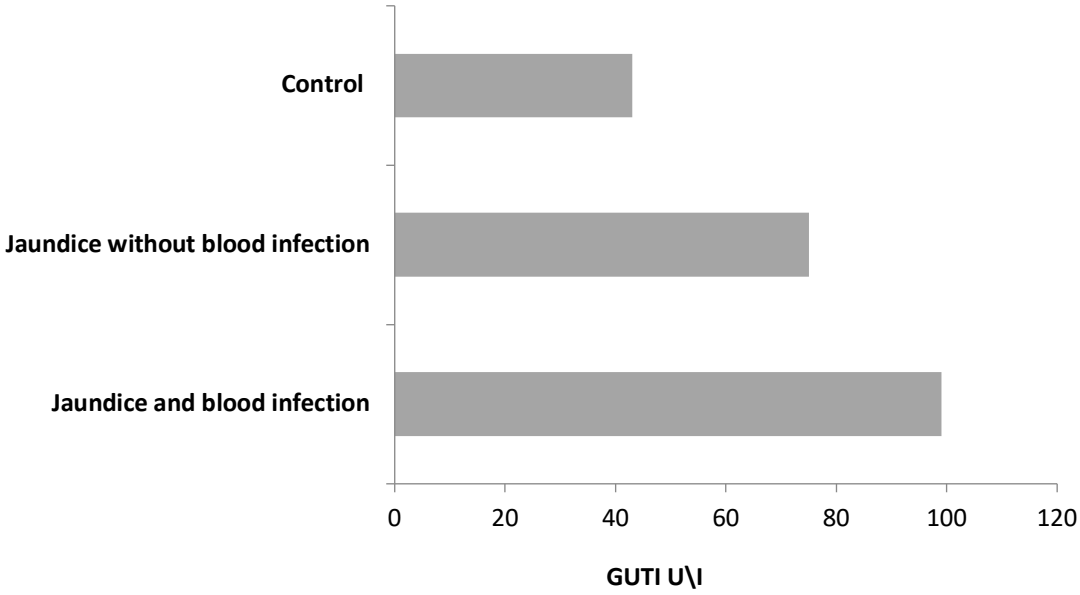

Figure 4: The effect of jaundice and blood inflammation on the levels of The enzyme Gamma-Glutamyl transferase peptidase (GGT),LSD5%=3.650.

The results are shown in Figures 1, 2, 3, and 4 present the liver enzyme levels (AST, ALP, GGT, and GUTI) for cases of jaundice with or without blood inflammation and the control group of healthy infants. The comparison aims to understand the relationship between liver enzymes and jaundice, with or without blood inflammation, compared to the control group. AST levels are relatively higher in both the jaundice with blood infection group and the jaundice without blood infection group compared to the control group. This suggests potential liver injury or stress in both conditions associated with jaundice, with the highest level being 36 units/L (jaundice without blood infection) and the lowest being 29 units/L (jaundice with blood infection). ALP levels are significantly elevated in both jaundice groups compared to the control group, with the highest level being 230 units/L in cases where jaundice coincides with inflammation and 180 units/L in cases without inflammation. Elevated ALP levels are often associated with liver and bile duct problems, indicating the potential involvement of the liver and biliary system in jaundice. GGT levels are higher in both jaundice-related groups compared to the control group, with levels being 155 units/L in cases of jaundice with inflammation and 120 units/L in cases of jaundice without inflammation. Elevated GGT levels are often associated with liver and bile duct diseases, also suggesting the potential

involvement of the liver and biliary system in jaundice. The results also showed Glucuronosyl transferase enzyme levels, which were highest at 99 units/L in cases of jaundice with inflammation, while they were 75 units/L in jaundice without blood inflammation. Elevated levels of AST, ALP, and GGT in both jaundice-related groups compared to the control group suggest the potential involvement of the liver and biliary system in jaundice. The presence of blood infection with jaundice may have contributed to an unhealthy increase in most enzymes compared to statistical values. These results are consistent with the known association between jaundice and liver function disorders, as well as the potential dysfunction of the biliary system.

Congenital jaundice in newborns often results from elevated levels of bilirubin, a yellow pigment found in hemoglobin, which is responsible for carrying oxygen in red blood cells. As these cells degrade, the body generates new red blood cells to replace them. The liver processes the old cells, but if it cannot efficiently manage their breakdown, bilirubin builds up in the body, leading to the yellowing of the skin and whites of the eyes [19]. Jaundice may also indicate various conditions that cause blood inflammation or other abnormalities, resulting in excessive bilirubin production. This overproduction can surpass the liver's capacity to conjugate bilirubin with glucuronic acid, thus causing jaundice [20, 21]. Furthermore, the white blood cell count is a standard measure for detecting bacterial infections in routine blood tests. These cells play a crucial role in the body's defense mechanisms and are commonly used as a clinical marker for neonatal infections, aiding in the evaluation of infection severity and immune status assessment. C-reactive protein (CRP), synthesized by the liver during acute phases, serves as a vital indicator of inflammation. Typically low in healthy individuals, CRP levels are extensively monitored in clinical settings to track the progression of jaundice and bacterial infections, helping in the diagnosis of neonatal infections [22]. High-sensitivity C-reactive protein (hs-CRP) is an advanced method for the measurement of minimal CRP levels, effectively identifying low-grade infections[23]. Recognized as a sensitive acute-phase response protein, hs-CRP markedly rises during inflammation, often before other clinical symptoms such as fever become apparent[24]. Notably, elevated hs-CRP concentrations are observed in the serum of individuals with jaundice stemming from bacterial infections. This characteristic makes hs-CRP a valuable biomarker for detecting bacterial infections. Moreover, in the context of neonatology, hs-CRP testing serves as a critical diagnostic tool to differentiate bacterial from viral infections, thereby aiding in the accurate diagnosis of neonatal pathological jaundice associated with bacterial infections[25].

Liver enzymes play a crucial role in bilirubin metabolism. The enzyme uridine diphosphate glucuronosyltransferase (UGT) is needed for the conjugation of bilirubin. In newborns, the activity of this enzyme is much lower than in adults, which may contribute to the development of jaundice[26]. Any condition that affects the liver's ability to function properly, such as liver disease or damage, can affect liver enzyme levels and thus impact bilirubin processing, potentially leading to jaundice[27]. Jaundice in children with serious illnesses can be associated with blood infections, highlighting hyperbilirubinemia associated with sepsis as a critical consideration in patients with serious diseases who experience disproportionate increases in bilirubin[28]. In a related study, levels of White Blood Cells (WBC), high-sensitivity C-reactive Protein (hs-CRP), and Procalcitonin (PCT) were notably higher in the group with bacterial infections than in those without infections, whereas Transferrin (TRF) levels were decreased in the infected group [29]. No definitive diagnostic criteria exist for cholestasis induced by sepsis; diagnosis depends on historical, clinical, and laboratory findings. Patients with cholestasis resulting from sepsis often display jaundice and other clinical indicators of infection, although jaundice might occasionally present without additional symptoms [30]. It is relatively uncommon for these patients to experience pruritus and abdominal pain. Hepatomegaly can occur, and the levels of transaminases and Serum Alkaline Phosphatase (SAP) are generally moderately elevated, with conjugated bilirubin levels ranging between 2-10 mg/dl. An atypical feature in our case was the exclusive elevation of conjugated bilirubin without increases in transaminases, SAP, or Gamma-Glutamyl Transferase (GGT) [31]. Sepsis-related cholestasis is typically linked to intra-abdominal infections caused by Gram-negative bacteria, though cases associated with Staphylococcal sepsis and pneumonia have also been

observed. Additional risk factors for cholestasis due to sepsis include prematurity, the severity and duration of sepsis, total parenteral nutrition, and coexisting liver diseases. If performed, liver biopsies usually show minimal or no inflammation, prominently featuring intrahepatic cholestasis, though such biopsies are seldom required for diagnosis [32, 33]. Currently, there are no specific pharmacological treatments to alter the course of the cholestatic process. Therefore, treatment primarily aims at eliminating the infection through robust antimicrobial therapy and, when needed, surgical drainage, along with supportive care measures. Certain medications are known to induce cholestasis or hepatocellular damage and should be avoided or used with caution. These include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), sodium valproate, and rifampicin. On the therapeutic front, there are several treatments with anecdotal evidence suggesting efficacy in managing such conditions. These include enteral nutrition, ursodeoxycholic acid, and glycine. Additionally, agents such as nitric oxide (NO) donors, for example, molsidomine, N-acetyl cysteine, corticosteroids, anti-TNF agents, and methods like extracorporeal liver support have also been cited for their potential benefits in treatment regimens[34].

Current research highlights that there is no universally accepted set of diagnostic criteria for cholestasis induced by sepsis; rather, the diagnosis typically relies on historical, clinical, and laboratory data. Patients suffering from this condition often exhibit jaundice and signs of infection, although in some cases, jaundice may be the sole symptom [35]. It is infrequent for these patients to experience itching or abdominal pain. Hepatomegaly might be observed, and levels of transaminases and serum alkaline phosphatase (SAP) tend to be moderately raised. A distinctive finding is conjugated bilirubin levels ranging from 2 to 10 mg/dL. Notably, an unusual feature in certain cases includes elevated conjugated bilirubin without a corresponding rise in transaminases, SAP, or gamma-glutamyl transferase (GGT) [36]. Most instances of sepsis-related cholestasis are linked to intra-abdominal infections caused by Gram-negative bacteria, though associations with Staphylococcal infections and pneumonia have also been documented. Additional risk factors for cholestasis due to sepsis encompass prematurity, the severity and duration of the infection, total parenteral nutrition, and coexisting liver diseases. Although liver biopsy might reveal mild to absent inflammation and pronounced intrahepatic cholestasis as key histological features, this procedure is seldom required for diagnosis [37]. Current management of cholestasis lacks specific pharmacological treatments and focuses primarily on infection control through robust antimicrobial therapy and, when necessary, surgical measures, complemented by supportive care. It is crucial to avoid or cautiously use drugs such as acetaminophen, NSAIDs, sodium valproate, and rifampicin, which may exacerbate cholestasis or liver damage. Anecdotal evidence supports several therapeutic approaches that may benefit liver function; these include enteral nutrition, ursodeoxycholic acid for improving bile flow, glycine for its hepatoprotective properties, nitric oxide donors like molsidomine for vascular modulation, N-acetyl cysteine for oxidative stress reduction, corticosteroids for inflammation control, anti-TNF agents for targeting inflammatory pathways, and extracorporeal liver support systems as a temporary support mechanism for liver function[38]. Newborns with severe jaundice caused by blood group incompatibility were studied. Childhood jaundice caused by neonatal hepatitis and biliary atresia was found to be exacerbated by bacterial infection if it lasted for more than a month [39]. Bacterial infections cause jaundice in a variety of ways, with some evidence suggesting increased hemolysis and liver necrosis in severe cases. Antibiotics have been effective in treating jaundice associated with bacterial infection, with jaundice usually resolving within 72 hours of starting treatment [40].

Conclusion

This research underscores the significant impact of blood infections on neonatal jaundice, revealing marked elevations in inflammatory markers (WBC, hs-CRP, PCT) and disruptions in iron metabolism (lower TRF levels) in infants with jaundice and concurrent bacterial infections. Elevated liver enzymes (AST, ALP, GGT) further suggest heightened liver involvement, indicative of the severe physiological strain imposed by the infection. These findings highlight the critical importance of vigilant monitoring and management of blood parameters and liver function in jaundiced neonates. By improving our understanding of the interactions between jaundice and blood

infections, the study supports more targeted diagnostic and therapeutic strategies, aiming to mitigate the risks and improve outcomes for affected infants.

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