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Research Article

Early Detection of Communicable Viral Causes of Neonatal Jaundice: A Hospital-Based Study From Kyrgyzstan

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I N F O

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A B S T R A C T

Introduction: Neonatal jaundice affects more than half of all term newborns, yet pathological hyperbilirubinaemia continues to contribute to preventable morbidity in resource-limited settings. While metabolic and haematologic causes are well recognised, congenital and perinatally acquired viral infections such as cytomegalovirus (CMV) and herpes simplex virus (HSV) remain underdiagnosed contributors.

Materials and Methods: A prospective observational study was conducted from January to December 2024 across two major neonatal referral centres in Bishkek, Kyrgyzstan. Full-term infants with pathological hyperbilirubinaemia were evaluated through clinical examination, transcutaneous and serum bilirubin measurements, and graded using the Kramer scale. Phototherapy was administered according to standardised protocols. Infants with persistent jaundice or inadequate phototherapy response underwent CMV and HSV Polymerase Chain Reaction (PCR) testing.

Results: Among 150 enrolled infants, the mean age at presentation was 23.4 ± 13.2 days, with 78% presenting after 15 days of life. Moderate or severe jaundice was observed in 95% of infants. Continuous Intensive Care Unit (ICU)-based phototherapy achieved greater bilirubin reduction (31% at 24 hours; 66% at 120 hours) compared with outpatient therapy.

Conclusion: HSV infection accounted for a notable proportion of persistent neonatal jaundice cases. Incorporating viral PCR testing into jaundice evaluation protocols may enhance early detection of communicable causes in resource-limited settings.

Keywords: Neonatal Jaundice, Hyperbilirubinaemia, Herpes Simplex Virus, Cytomegalovirus, Congenital Infections, Viral Hepatitis in Neonates

Introduction

Neonatal jaundice is one of the most common conditions encountered during the early postnatal period, affecting more than half of all term newborns worldwide. While most cases are physiological and self-limited, a subset progresses to pathological hyperbilirubinaemia, which poses a substantial risk of bilirubin encephalopathy, kernicterus, long-term neurodevelopmental impairment, and mortality. In low- and middle-income countries, delays in recognition and treatment remain a major contributor to poor outcomes, largely due to early postnatal discharge, inadequate follow-up, and limited access to diagnostic resources.[1]

Although metabolic and haematologic causes are well-recognised, communicable infections constitute an underdiagnosed but critical contributor to pathological neonatal jaundice.[2] Congenital and perinatally acquired viral infections—particularly herpes simplex virus (HSV) and cytomegalovirus (CMV)—can lead to hepatocellular injury, cholestasis, and haemolysis, resulting in persistent or severe jaundice.[3] These infections carry high morbidity and mortality when unrecognised, yet their clinical presentation may initially be subtle, with jaundice often preceding systemic manifestations. Early detection is therefore essential to initiate timely antiviral therapy and prevent progression to severe disease.

Globally, congenital CMV infection is one of the leading infectious causes of neonatal liver dysfunction, whereas neonatal HSV infection may present with jaundice before evolving into disseminated or central nervous system disease.[4] Despite their public health importance, routine screening for these viral pathogens is seldom incorporated into neonatal jaundice evaluation protocols in many resource-limited settings, including Kyrgyzstan.[5] As a result, infants with persistent jaundice may undergo repeated phototherapy or prolonged hospitalisation without identification of the underlying infectious aetiology.[6]

Kyrgyzstan faces unique challenges in neonatal care, including limited availability of laboratory diagnostics, delayed presentation of newborns after discharge, and varying clinical practices across health facilities. These gaps underscore the need for integrated screening strategies that combine non-invasive bilirubin assessment with targeted testing for communicable viral infections in infants with atypical or persistent jaundice. This hospital-based study was undertaken to address these gaps by evaluating the role of HSV and CMV polymerase chain reaction (PCR) testing in newborns presenting with pathological hyperbilirubinaemia. By identifying the proportion of viral infections among infants with persistent jaundice and analysing their clinical profiles and treatment outcomes, this study aims to provide evidence for strengthening neonatal infection surveillance systems and incorporating infectious disease diagnostics into jaundice management protocols in Kyrgyzstan and similar resource-limited settings.

Materials and Methods

This hospital-based prospective observational study was conducted from January to December 2024 at the City Children's Clinical Emergency Hospital and the Balazhan Outpatient Diagnostic Clinic in Bishkek, Kyrgyzstan. These facilities serve as major referral centres for neonatal care and provide access to both outpatient and inpatient populations with suspected pathological jaundice. The institutional bioethics committee of I.K. Akhunbaev Kyrgyz State Medical Academy approved this study (Protocol No. 5, dated February 11, 2025). All participants provided written informed consent for inclusion and for the use of anonymized data in the study.

Study Population

The study included 150 full-term newborns presenting with pathological hyperbilirubinaemia. Infants were eligible if they met one or more of the following criteria:

- Transcutaneous or serum bilirubin levels exceeding normal physiological ranges for age and gestational maturity
- Jaundice persisting beyond 14 days of life
- Bilirubin levels continuing to rise despite phototherapy
- Presence of systemic or neurological symptoms suggestive of severe hyperbilirubinaemia or underlying infectious aetiology

Infants were excluded if they were born before 35 weeks of gestation, had physiological jaundice that resolved without treatment, or had jaundice attributable to congenital metabolic disorders unrelated to bilirubin metabolism.

Screening and Clinical Assessment

Transcutaneous bilirubin (TcB) measurements were performed using a certified bilirubinometer (AGFn-04 BILITEST 2000, Russia). Measurements were obtained from the forehead or sternum under standardised conditions. Serum bilirubin levels were ascertained when TcB values exceeded institutional thresholds or when infants required inpatient or intensive care.

Clinical assessments included evaluation of:

- Neurological status (irritability, lethargy, and abnormal posturing)
- Feeding behaviour and weight progression
- Stool and urine colour
- Signs of systemic illness or sepsis

Jaundice severity was graded using the Kramer scale. Decisions regarding management were guided by TcB levels as follows:

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- **< 20 units:** Outpatient monitoring with reassessment in 24–48 hours
- **30–40 units:** Repeat evaluations on days 3, 5, and 7; phototherapy considered if persistent
- **40–50 units:** Hospital admission for intensive phototherapy
- **> 50 units or urgent neurological symptoms:** Immediate transfer to the neonatal intensive care unit (NICU)

Phototherapy Protocol

Phototherapy was administered using LED-based devices emitting light in the 430–530 nm spectrum (OFN-02, JSC PO UOMZ, Russia).

- Outpatient phototherapy was delivered for 10–20 hours per day under family doctor supervision.
- Inpatient phototherapy was delivered intermittently with daily bilirubin monitoring.
- Intensive Care Unit (ICU) phototherapy consisted of continuous exposure, with bilirubin levels measured every 1–2 hours.

Phototherapy continued until bilirubin levels fell below 10 units and clinical improvement was documented.

Infectious Disease Testing

Infants with persistent jaundice, poor response to phototherapy, or clinical suspicion of viral infection underwent molecular testing. Whole blood samples were collected for the detection of CMV and HSV types 1 and 2 (HSV-1/2) using PCR assays. Positive cases received targeted antiviral therapy and extended monitoring as clinically indicated.

Data Collection and Statistical Analysis

Data were recorded in a standardised database and included demographic details, clinical features, bilirubin levels, treatment modality, and PCR results. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean ± standard deviation, median, and range, while categorical variables were presented as frequencies and percentages. Normality was assessed using the Shapiro–Wilk test. Comparisons between the outpatient and ICU groups were performed using:

- Student's t-test or Mann–Whitney U test for continuous variables
- Chi-square test or Fisher's exact test for categorical variables

Changes in bilirubin levels over time were examined using repeated-measures ANOVA. Statistical significance was defined as $p < 0.05$.

Results

A total of 150 full-term infants with pathological hyperbilirubinaemia were included in this study. The mean age at first clinical evaluation was 23.4 ± 13.2 days (range: 3–67 days). Only 7 infants (4.7%) presented within the first week of life, while 26 infants (17.3%) presented between 8 and 14 days. The majority, 117 infants (78.0%), were evaluated after 15 days of life, indicating delayed recognition of jaundice in the community (Table 1).

Clinical Presentation

All infants (100.0%) demonstrated visible skin jaundice, and 95.3% exhibited scleral icterus. Irritability was reported in 129 infants (86.0%), constipation in 38 infants (25.3%), lethargy in 21 infants (14.0%), and refusal to breastfeed in 20 infants (13.3%). Regurgitation was uncommon, occurring in only 3 infants (2.0%) (Table 2a). These findings reflected a high burden of moderate-to-severe clinical symptoms at the time of presentation.

Severity of Jaundice

Based on the Kramer scale, 123 infants (82.0%) were classified as having moderate jaundice (zones 3–4), while 20 infants (13.3%) exhibited severe jaundice (zone 5). Only 7 infants (4.7%) had mild jaundice (zones 1–2) (Table 2b). Infants with severe jaundice more frequently demonstrated systemic or neurological warning signs and were prioritised for ICU admission.

Phototherapy Outcomes

Phototherapy was provided either as continuous ICU-based treatment or outpatient therapy. In the ICU group (n = 20), continuous phototherapy resulted in a 31% reduction in bilirubin levels within the first 24 hours, and a 66% reduction by 120 hours (Table 3).

In contrast, the outpatient group (n = 130) demonstrated a 23% reduction at 24 hours and 55% reduction by 120 hours. Serum bilirubin in ICU-treated infants decreased from 333 ± 52 µmol/L at admission to 118 ± 39 µmol/L after five days of therapy. These reductions corresponded closely with transcutaneous bilirubinometry trends, confirming phototherapy effectiveness.

Viral Screening and Infectious Aetiology

PCR testing for congenital viral infections was performed in 20 infants who exhibited persistent jaundice or inadequate response to phototherapy.

- HSV-1/2 DNA was detected in 2 infants (10%).
- CMV DNA was not detected in any infant.

Infants with HSV-positive results required prolonged ICU care and received antiviral therapy. Although bilirubin decline was slower in these infants, both recovered

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without neurological complications. All infants in the study demonstrated a reduction in bilirubin levels following treatment, and no fatalities occurred during the study period. Infants admitted to the ICU required longer hospitalisation but showed more rapid bilirubin clearance. Outpatient infants generally had moderate jaundice and did not require intensive care.

Table 1.Age at First Presentation for Medical Care

(N = 150)

Age Group (Days)	Number of Infants (n)	Percentage (%)
1–7	7	4.7
8–14	26	17.3
≥ 15	117	78.0
Mean ± SD	23.4 ± 13.2	—
Range	3–67	—

Table 2.Clinical Features and Severity of Jaundice

a.Clinical Presentation

(N = 150)

Clinical Feature	Number (n)	Percentage (%)
Skin jaundice	150	100.0
Scleral icterus	143	95.3
Irritability	129	86.0
Constipation	38	25.3
Lethargy	21	14.0
Refusal to breastfeed	20	13.3
Regurgitation	3	2.0

b.Severity (Kramer Scale)

Severity Category	Number (n)	Percentage (%)
Mild (zones 1–2)	7	4.7
Moderate (zones 3–4)	123	82.0
Severe (zone 5)	20	13.3

Table 3.Response to Phototherapy

Group	n	Bilirubin Reduction at 24 h (%)	Reduction at 120 h (%)	Serum Bilirubin At Admission (µmol/L)	Serum Bilirubin After 5 Days (µmol/L)
ICU continuous therapy	20	31 ± 6	66 ± 8	333 ± 52	118 ± 39
Outpatient phototherapy	130	23 ± 5	55 ± 7	—	—

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Discussion

In this hospital-based study from Kyrgyzstan, we found that among 150 term infants with pathological neonatal hyperbilirubinaemia, a subset (20 infants) with persistent jaundice underwent PCR screening for viral pathogens; 2 (10%) tested positive for HSV-1/2, while no cases of CMV were detected. Continuous phototherapy, especially in the ICU setting, was effective in reducing bilirubin levels, but the identification of HSV in a fraction of non-resolving jaundice cases underscores the potential role of neonatal viral infections as aetiological agents in otherwise unexplained hyperbilirubinaemia.

Although the majority of neonates with congenital CMV infection are asymptomatic at birth, symptomatic disease may present with a variety of clinical features, including prolonged or cholestatic jaundice, hepatosplenomegaly, and abnormal liver function tests.[7,8] In particular, a significant review of congenital infections pointed out that while many cases remain subclinical, liver involvement — including jaundice — is among the recognised manifestations in symptomatic neonates.[9] In line with this, a 2020 case report described prolonged indirect hyperbilirubinaemia in an infant with postnatally acquired CMV infection.[10] Other recent reports and case series have documented neonatal CMV infection manifesting with jaundice, hepatosplenomegaly, and cholestasis, even when other systemic signs were mild or absent.[11] Thus, the absence of CMV-positive cases in our cohort (despite screening) diverges from these prior observations. This difference may arise from several factors, including the following:

- Low prevalence of congenital or perinatal CMV infection in our study population
- Timing of sample collection (after the immunologic "window period" where viral DNA might decline)
- The possibility that some cases were missed because we limited PCR testing to infants with persistent jaundice rather than to all enrolled infants

Other non-viral causes (e.g. metabolic, haematologic, or structural) accounted for most jaundice cases in our cohort

Discovery of HSV DNA in 10% of tested infants is notable. While data on HSV presenting primarily as neonatal jaundice is sparse, congenital or perinatal HSV infection is a well-known cause of neonatal morbidity and mortality.[12] In some newborns, hepatic involvement, including elevated bilirubin, may precede or accompany systemic disease.[12] Given that HSV can be transmitted perinatally (e.g. during passage through the birth canal) and may present initially with non-specific features such as jaundice, the identification of HSV in infants with persistent jaundice in our study supports the argument for including molecular viral diagnostics in neonatal jaundice protocols — especially in cases unresponsive to standard phototherapy.

Our findings suggest that in resource-limited settings such as Kyrgyzstan, neonatal jaundice — especially when persistent or unresponsive — should prompt consideration of viral aetiologies, not just the conventional causes (e.g. haemolytic disease, metabolic disorders, and physiological jaundice). This approach aligns with recommendations in the broader literature that call for expanded diagnostic evaluation in cholestatic or protracted neonatal jaundice, including infectious work-up.[13]

Moreover, early identification of HSV (or other viral agents) may enable timely antiviral therapy, possibly reducing the risk of systemic complications or long-term sequelae. Several reviews emphasise that even though many congenital CMV or HSV infections are asymptomatic initially, early detection and monitoring are critical given risks of neurologic impairment, hearing loss, or other late-onset complications.[14] Thus, our study supports the integration of viral PCR (or other molecular diagnostics) into neonatal jaundice management protocols, particularly for infants with persistent or atypical jaundice — a strategy that could improve diagnostic yield and guide more precise interventions.

Limitations

Several limitations must be acknowledged. First, only a subset (20 of 150) of infants underwent viral PCR testing, which may underestimate the true prevalence of viral aetiologies. Second, we did not perform liver biopsy, serology, or long-term follow-up to distinguish between congenital, perinatal or postnatal infection — limiting our ability to define timing and the full spectrum of disease. Third, given the limited sample size for PCR-tested infants, the 10% HSV-positivity should be interpreted cautiously; larger studies are needed to validate this rate. Finally, we did not assess other viral or non-viral infectious agents (e.g. TORCH panel beyond CMV/ HSV), which may also contribute to neonatal jaundice.

Conclusion

In conclusion, our study demonstrated that a non-negligible proportion of infants with persistent neonatal jaundice may harbour HSV infection, and that standard phototherapy alone may not address underlying viral aetiologies. Given the potential for long-term morbidity associated with congenital or perinatal viral infections, our findings emphasise the need for broadened diagnostic protocols — including molecular viral testing — in neonatal jaundice evaluation, particularly in resource-limited settings.

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Authors' Contribution

Conceptualisation: SB and FN; Methodology: SZ and GA; Data collection: IS; Writing—original draft preparation: ZA and TT; and review and editing: TT. All authors have read and agreed to the published version of the manuscript.

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