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RESEARCH ARTICLE

Association between postnatal maternal serology and congenital cytomegalovirus infection in neonates with jaundice

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Abstract

Congenital cytomegalovirus (CMV) infection is one of the most prevalent infections at birth and can lead to severe health complications in neonates. Timely detection is crucial. However, polymerase chain reaction (PCR) testing is often unavailable in numerous healthcare settings. In such cases, maternal CMV antibody testing may assist in identifying at-risk infants. In the development of diagnostic methods to date, there is no single method for detecting CMV infection in pregnant women at all stages of pregnancy. This study examined the relationship between maternal CMV serology after delivery and congenital CMV infection in newborns presenting with symptoms including jaundice, prematurity, or low birth weight. Urine samples from neonates within the first 21 days of life were analyzed for CMV DNA via PCR, while maternal IgG and IgM antibodies were assessed within three weeks after delivery. A total of 87 neonates were examined, with 28 (32.2%) testing positive for CMV DNA. Neonatal jaundice was significantly associated with CMV infection, whereas prematurity and low birth weight were not. Maternal CMV IgM positivity was significantly correlated with neonatal CMV PCR positivity, while maternal IgG did not exhibit a significant relationship. In conclusion, maternal CMV IgM positivity post-delivery may assist in identifying newborns requiring confirmatory PCR testing, particularly in healthcare environments with constrained diagnostic resources.

1. INTRODUCTION

Cytomegalovirus (CMV) is a prevalent virus responsible for congenital viral infections globally. It is estimated that 0.5% to 2% of all live births are impacted by congenital CMV infections, with higher rates observed in populations exhibiting elevated maternal CMV seroprevalence. CMV can be transmitted from mother to child through the placenta during

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pregnancy, especially during initial infection or viral reactivation. Congenital CMV infection can cause a wide range of symptoms, such as sensorineural hearing loss, neurodevelopmental delay, visual impairment, microcephaly, jaundice, low birth weight, and prematurity. Some affected infants show symptoms at birth, but many do not (1). In Indonesia, the reported prevalence of congenital CMV ranges from 0.2% to 2.5%. However, systematic screening remains limited because awareness of the disease is still low and access to diagnostic facilities is not yet widely available (2).

Interpreting CMV serology during the perinatal period continues to be difficult. Maternal CMV-specific antibodies may provide indirect information regarding the risk of vertical transmission, but neonatal serological testing is less reliable because maternally derived IgG antibodies can cross the placenta. In addition, maternal CMV IgM positivity may indicate recent infection, but it can also occur during viral reactivation or persist for several months after primary infection, reducing its diagnostic specificity. Meanwhile, maternal IgG seropositivity mainly reflects prior exposure and cannot distinguish recent infection from past infection (3–5). These limitations emphasize the need to better understand whether postpartum maternal serological status has clinical value in predicting congenital CMV infection.

Neonatal jaundice is one of the most common clinical conditions seen in infants and often leads to further tests. Congenital infections, including CMV, are believed to account for approximately 5–20% of neonatal jaundice cases (6,7). Consequently, evaluating neonates with jaundice may serve as an effective and clinically significant method for detecting congenital CMV infection, particularly in resource-limited settings.

Many healthcare facilities still do not offer routine neonatal PCR screening, even though polymerase chain reaction (PCR) testing for CMV DNA is widely regarded as the most reliable method for diagnosing congenital CMV infection due to its high sensitivity and specificity (8). Consequently, identifying maternal serological markers associated with neonatal CMV infection may assist clinicians in determining which infants require targeted confirmatory testing. This study sought to examine the relationship between postpartum maternal CMV IgG and IgM serostatus and PCR-confirmed congenital CMV infection in neonates exhibiting jaundice. It specifically assessed whether maternal postpartum CMV IgM seropositivity could act as a predictor of congenital CMV infection identified via neonatal PCR testing.

2. MATERIALS AND METHODS

2.1. Study Population and Sampling

This analytical observational study with a cross-sectional design was conducted to assess the correlation between clinical risk indicators and congenital cytomegalovirus (CMV) infection in neonates. The study was conducted from September to December 2023 at the Clinical Pathology Laboratory of Dr. Soetomo General Academic Hospital is in Surabaya, Indonesia.

The study population comprised neonates aged 21 days or younger and their biological mothers. Participants were consecutively recruited from both inpatient and outpatient services at Dr. Soetomo General Academic Hospital. The study specifically included neonates with clinical conditions considered possible risk indicators for congenital CMV infection, namely neonatal jaundice, low birth weight (LBW), or prematurity.

Neonates were eligible for inclusion if they were 21 days old or younger at the time of sample collection and had at least one of the following conditions: neonatal jaundice (defined as total serum bilirubin above the 95th percentile for hour-of-life according to AAP and IDAI guidelines or requiring phototherapy), low birth weight (<2500 g), or prematurity (<37 weeks of gestation). Because participants were selected based on these predefined risk factors, the study population represented neonates at higher clinical risk rather than the general neonatal population.

During the study, 92 samples of urine from newborns were taken. After the eligibility criteria were applied, 87 neonates (35 females and 52 males) were included in the final analysis. Five samples were excluded because the neonates were older than 21 days at the time of sampling (n = 3), urine volume was insufficient for PCR testing (n = 1), or laboratory results were invalid (n = 1). Biological mothers of eligible neonates were enrolled after providing written informed consent.

As data regarding congenital CMV prevalence among jaundiced neonates in this setting were limited, no formal sample size calculation was performed. The study was conducted as an exploratory hospital-based investigation using consecutive sampling throughout the study period.

2.2. Sample Collection and Handling

Neonatal urine specimens were obtained using sterile clean-catch urine collection bags applied to the perineum after cleansing with sterile water to reduce contamination. All urine samples for CMV PCR testing were collected within the first 21 days of life, which is consistent with the recommended diagnostic window for distinguishing congenital CMV infection from postnatal acquisition. Whenever possible, urine sampling was performed early after admission and before prolonged breastfeeding exposure in order to reduce the possibility of detecting postnatally acquired CMV. Samples were inspected within 2 hours of collection, and if the volume was insufficient, the procedure was repeated until adequate material was obtained.

Maternal venous blood samples (5 mL) were collected within the three weeks postpartum using serum separator tubes. Samples were then centrifuged at 3000 rpm for 10 minutes at room temperature. The serum was separated and

stored at –80 °C until analysis. Maternal serological testing the early postpartum period served as an indirect indicator of maternal immune status during late pregnancy. However, postpartum serology does not provide definitive evidence of infection timing in pregnancy Interpret these results cautiously.

2.3. Laboratory Methods

Maternal CMV-specific IgG and IgM antibodies were measured using a fully automated chemiluminescence immunoassay (CLIA) platform (MAGLUMI 2000 Plus Analyzer, Shenzhen New Industries Biomedical Engineering Co., Ltd., Shenzhen, China). The reagent kits used were MAGLUMI CMV IgM (catalog no. 130212006M) and MAGLUMI CMV IgG (catalog no. 130212005M). Testing procedures were performed according to the manufacturer's instructions. Results <2.0 AU/mL were considered non-reactive, whereas results ≥2.0 AU/mL were considered reactive. Quality control procedures were performed daily using manufacturer-supplied control materials. Samples yielding reactive or borderline serological results were re-evaluated in accordance with laboratory standard operating procedures to ensure analytical reliability. It should be noted that IgG avidity testing was not performed in this study. Therefore, differentiation between primary CMV infection, viral reactivation, or past infection could not be determined solely on the basis of serological results (9,10).

2.4. PCR Protocols

CMV DNA was detected in neonatal urine using qualitative conventional polymerase chain reaction (PCR). Viral DNA was extracted with the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany; Cat. No. 51304) and eluted in 50 µL per manufacturer's instructions Neonatal urine specimens were analyzed for CMV DNA using qualitative conventional polymerase chain reaction (PCR). Viral DNA was isolated with the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany; Cat. No. 51304) and eluted in a final volume of 50 µL according to the manufacturer's instructions. The PCR assay focused on the glycoprotein B gene (gB; UL55) of human cytomegalovirus, a conserved region commonly employed for viral detection and molecular characterization. Previously documented primers were utilized to produce an amplicon of approximately 580 base pairs: forward primer (gB-F) 5′-GAGGACAACGAAATCCTGTT-3′ and reverse primer (gB-R) 5′-GTCGACGGTGGAGATACTGA-3′ (11,12). Each PCR reaction was performed in a total volume of 25 µL containing 12.5 µL of 2× PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), 0.5 µM of each primer, 2.5 µL of extracted DNA template, and nuclease-free water. Thermal cycling was performed using a PCR thermal cycler (Applied Biosystems, Foster City, CA, USA) under the following conditions: an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute, with a final extension step at 72°C for 10 minutes.

Amplified products were separated by electrophoresis on a 2% agarose gel using a horizontal electrophoresis system (Bio-Rad Laboratories, Hercules, CA, USA). The gels were stained with ethidium bromide and visualized under ultraviolet illumination using a gel documentation system. PCR detection of CMV DNA in urine samples collected within the first 21 days of life was considered laboratory evidence compatible with congenital CMV infection. Real-time quantitative PCR, which is generally considered more sensitive than conventional PCR, was not available at the study laboratory; therefore, conventional PCR was used for viral detection.

Each PCR run included both positive and negative controls. Laboratory procedures were conducted using a unidirectional workflow in physically separated areas for reagent preparation, DNA extraction, and amplification to minimize contamination. PCR-positive samples were confirmed through repeat amplification in a separate run. Any faint non-specific bands occasionally observed in the negative control were interpreted as non-specific amplification or primer–dimer artifacts, as no band corresponding to the expected amplicon size (~580 bp) was detected.

2.5. Statistical Analysis

Statistical analysis was performed utilizing IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized the principal characteristics of the study population. Associations between maternal CMV serological markers and neonatal CMV PCR findings were analyzed using the Chi-square test or Fisher's exact test, as suitable. The strength of these associations was measured using the phi (φ) coefficient. Maternal age and parity were also documented. Multivariable analysis to adjust for potential confounding factors was not performed because of the limited sample size; therefore, the findings should be considered exploratory. All statistical tests were two-tailed, and a p-value of less than 0.05 was deemed statistically significant.

3. RESULTS AND DISCUSSION

3.1. Patient Characteristics

A total of 92 neonates suspected of congenital CMV infection were initially enrolled. Five were excluded during eligibility screening: Five were excluded during eligibility screening: one for an invalid PCR result, one for insufficient urine

volume, and three for age over 21 days at the time of sampling. Consequently, 87 neonates (52 males, 35 females) were included in the final analysis. The mean neonatal age at sampling was 8.9 ± 6.3 days, with a male predominance (59.8%). All samples were collected during the postnatal period, considered appropriate for PCR-based diagnosis of congenital CMV infection. The mean maternal age was 33.1 ± 4.4 years. The recruitment and selection process are illustrated in Figure 1.

Table 1 provides an overview of the initial demographic and clinical attributes of the mothers and neonates participating in the study. Jaundice was noted in 15 neonates (17.2%), while low birth weight and prematurity were each identified in 28 cases (32.2%). The average maternal age was 33.1 ± 4.4 years. Maternal CMV IgG seropositivity was identified in 75 mothers (86.2%), whereas CMV IgM positivity was detected in 12 mothers (13.8%).

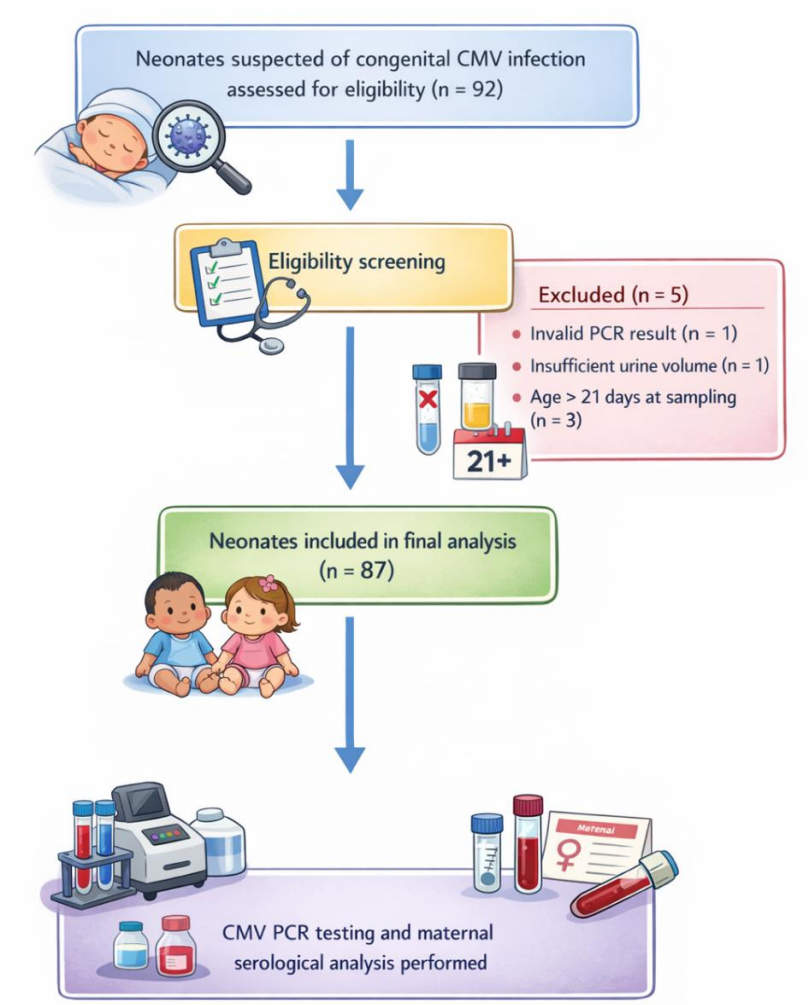

Figure 1. Shows the process of participant recruitment and eligibility screening. A total of 92 neonates with clinical features suspicious for congenital cytomegalovirus (CMV) infection were initially evaluated for inclusion. Five neonates were excluded due to an invalid PCR result (n = 1), insufficient urine volume for analysis (n = 1), or age above 21 days at the time of sample collection (n = 3). In the end, 87 neonates were included in the final analysis, and all underwent PCR testing for CMV DNA.

Table 1. Neonatal and maternal characteristics

Variable	Mean ± SD	n (%)
Neonatal Age (days)	8.90 ± 6.29	
Sex		
Male		52 (59.8)
Female		35 (40.2)
Jaundice		15 (17.2)
Low birth weight		28 (32.2)
Prematurity		28 (32.2)
Maternal Age (years)	33.11 ± 4.39	
Maternal CMV IgG Positive		75 (86.2)
Maternal CMV IgM Positive		12 (13.8)

3.2. Association Between Neonatal Clinical Signs and PCR Results

CMV PCR amplification products were examined using agarose gel electrophoresis, as presented in Figure 2. Table 2 summarizes the relationship between neonatal clinical characteristics and CMV DNA detection by PCR. Because some neonates had more than one clinical condition, the total number across categories may be higher than the total number of PCR-positive cases. Among neonates with low birth weight (LBW), 25 (33.8%) were PCR-positive and 49 (66.2%) were PCR-negative. No significant association was found between LBW and CMV PCR positivity ($p = 0.446$; $\varphi = 0.082$). Among neonates with jaundice, 9 (60.0%) were PCR-positive and 6 (40.0%) were PCR-negative. Neonatal jaundice showed a statistically significant association with CMV positivity ($p = 0.004$; $\varphi = 0.308$). Among premature neonates, 18 (36.0%) were PCR-positive and 32 (64.0%) were PCR-negative. Prematurity was not significantly associated with CMV detection ($p = 0.228$; $\varphi = 0.129$).

3.3. Association Between Maternal Serology and Neonatal PCR Results

This study evaluated neonates with suspected congenital CMV infection. Maternal CMV IgM seropositivity during the early postpartum period was significantly correlated with neonatal CMV infection confirmed by PCR, whereas maternal IgG serostatus did not demonstrate a significant association. Utilizing neonatal CMV PCR as the reference standard, maternal IgM seropositivity exhibited a sensitivity of 35.7%, specificity of 96.6%, positive predictive value (PPV) of 83.3%, and negative predictive value (NPV) of 76.0%. Due to its high specificity and PPV, maternal IgM positivity may serve as an effective initial screening marker to identify newborns most likely to benefit from confirmatory CMV PCR testing, thereby enhancing diagnostic efficiency and optimizing resource utilization

Table 3 shows the link between maternal CMV serology and neonatal PCR. Maternal CMV IgG was present in 25 PCR-positive and 50 PCR-negative neonates. IgG negativity appeared in 3 PCR-positive and 9 PCR-negative neonates. There was no significant association between maternal CMV IgG serostatus and neonatal CMV PCR positivity ($p = 0.566$; $\varphi = 0.062$). Maternal CMV IgM seropositivity was significantly linked to neonatal CMV PCR positivity. Of IgM-positive mothers, 10 neonates were PCR-positive, and 2 were PCR-negative. Of IgM-negative mothers, 18 neonates were PCR-positive, and 57 were PCR-negative. This association was statistically significant ($p < 0.001$; $\varphi = 0.438$).

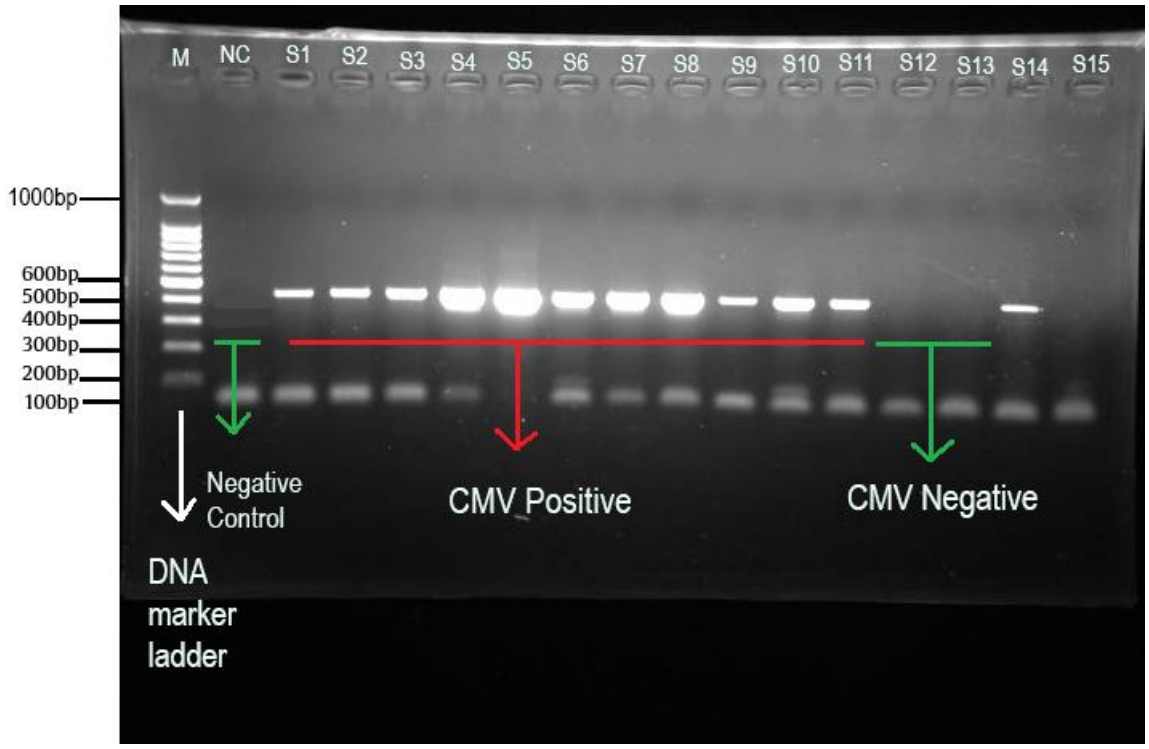

Figure 2. Representative agarose gel electrophoresis of conventional PCR products targeting the cytomegalovirus glycoprotein B gene (gB, UL55) from neonatal urine samples. Lane M: 100 bp DNA ladder; Lane NC: no-template negative control. Lanes S1–S11 and S14 show CMV-positive samples with the expected amplicon at approximately 580 bp, while lanes S12, S13, and S15 show CMV-negative samples with no detectable bands. Any faint bands occasionally seen in the negative control did not match the expected amplicon size and were therefore interpreted as non-specific amplification or primer–dimer artifacts.

Table 2. Relationship between clinical signs and PCR

Clinical Feature	PCR Positive n (%)	PCR Negative n (%)	p
LBW	25 (33.8)	49 (66.2)	0.446
Jaundice	9 (60.0)	6 (40.0)	0.004
Premature	18 (36.0)	32 (64.0)	0.228

Table 3. Association between maternal CMV serology and neonatal PCR results

Variable	PCR Positive n (%)	PCR Negative n(%)	p-value	Phi coefficient
CMV IgG				
Positive	25 (33.3)	50 (66.7)	0.566	0.062
Negative	3 (25.0)	9 (75.0)		
CMV IgM				
Positive	10 (83.3)	2 (16.7)	<0.001	0.438
Negative	18 (24.0)	57 (76.0)		

Statistical analysis revealed distinct roles for maternal CMV IgG and IgM antibodies. Maternal IgG seropositivity reflects prior CMV exposure and was not significantly associated with neonatal CMV PCR positivity ($p = 0.566$, $\varphi = 0.062$). These findings suggest that maternal CMV IgM seropositivity may indicate high specificity and positive predictive value for identifying neonates who warrant confirmatory CMV PCR testing.

In contrast, maternal CMV IgM seropositivity detected within the first three weeks after delivery was significantly associated with congenital CMV infection. In this cohort, 83.3% of neonates born to IgM-positive mothers were PCR positive, whereas only 24.0% of neonates born to IgM-negative mothers exhibited positive PCR results. This disparity was statistically significant ($p < 0.001$) with a moderate effect size ($\varphi = 0.438$), indicating a significant association between maternal IgM positivity and congenital CMV infection. However, maternal serology in this study was evaluated during the postpartum period. The presence of CMV IgM post-delivery does not inherently indicate primary infection during pregnancy, as IgM antibodies may persist for several months following initial infection and can also appear during viral reactivation or reinfection. Therefore, maternal IgM positivity in this context should be interpreted as a sign of recent or ongoing maternal immune activity rather than definitive proof of primary infection during pregnancy. This constraint must be acknowledged when interpreting the observed correlation (13,14).

Notwithstanding this limitation, the robust association identified in this study implies that maternal IgM positivity may signify infection during late pregnancy or at the time of delivery, potentially enhancing the risk of transplacental viral transmission. These results align with prior research that acknowledged the limitations of postnatal serology while also affirming its potential utility in detecting recent maternal infection linked to congenital CMV transmission (15). By comparison, maternal CMV IgG seropositivity was not associated with congenital CMV infection in this study. Previous studies have shown that vertical transmission can still occur in women who are already seropositive, meaning IgG alone is not a reliable predictor of transmission risk (16). This highlights the different clinical significance of maternal antibody profiles. Markers of recent or active infection appear to be more informative for transmission risk than markers of past exposure. Although maternal CMV IgM positivity was significantly associated with neonatal CMV PCR positivity, it should not be considered diagnostic of congenital infection. Maternal IgM may act as a risk-stratification marker to prioritize neonates for confirmatory molecular testing, especially in situations where universal CMV PCR screening is unfeasible (17). The inclusion of IgG avidity testing may improve diagnostic accuracy beyond IgG serostatus alone (18).

Biologically, maternal IgM positivity may indicate recent immune activation against CMV, correlating with an increased risk of transplacental transmission. Active or recent infection, particularly alongside low-avidity IgG antibodies, may elevate the risk of fetal infection. CMV can infect placental trophoblasts and endothelial cells, undermine placental integrity, and facilitate the virus's entry into fetal circulation. Once transmitted, the virus may spread to fetal tissues, resulting in the multisystem manifestations typical of congenital CMV infection (19). In contrast, maternal IgG antibodies may provide partial passive protection to the fetus, potentially explaining the lack of association observed in this study.

In addition to maternal serology, neonatal clinical findings yielded significant insights. Neonatal jaundice showed a strong link to congenital CMV infection ($p = 0.004$), but low birth weight and prematurity did not. This correlation is biologically plausible, as CMV can induce liver inflammation and cholestasis, resulting in prolonged neonatal jaundice (20,21). However, jaundice is not a specific sign and can be caused by hemolytic disease, infection, metabolic disorders, or factors related to breastfeeding. Therefore, it should be looked into further instead of being seen as proof of CMV infection alone (22). Previous studies have shown that jaundice is a common sign of congenital CMV infection, often linked to hepatosplenomegaly and hematologic problems (23). The clinical significance of these findings is further corroborated by the timing of neonatal testing, with a mean neonatal age at PCR examination of 8.9 days, aligning with the recommended

timeframe for diagnosing congenital CMV infection. Detection of CMV DNA within the first 21 days of life is an accepted diagnostic criterion because it helps distinguish congenital infection from postnatal acquisition (24,25). Although postnatal transmission can occur through perinatal exposure or breast milk, testing during this early period greatly reduces the likelihood that PCR positivity reflects postnatal infection (26).

The average age of mothers was 33.1 years, which shows that vertical CMV transmission can happen in mothers of all ages and with different numbers of children. In populations with high CMV seroprevalence, reinfection during pregnancy can happen, leading to congenital transmission (27). This aligns with findings from other Asian populations, where maternal seropositivity and congenital CMV rates remain significantly high due to extensive exposure to the virus (28). These results are especially important for public health in places like Indonesia, where money and infrastructure problems may make it hard to do universal neonatal CMV PCR screening (29). In this context, maternal CMV IgM serology may serve as an effective method to identify newborns at higher risk of congenital CMV infection. Infants born to IgM-positive mothers may subsequently be prioritized for confirmatory PCR testing. This targeted strategy may enhance the efficiency of limited healthcare resources. The integration of maternal serology with neonatal molecular testing may thus provide a more cost-effective method for early detection when universal screening is impractical (30).

A significant strength of this study is its pragmatic assessment of postpartum maternal CMV serology as a risk-stratification method for congenital CMV infection in a resource-limited environment. While many previous studies have focused on prenatal screening or universal newborn testing, this study demonstrates that maternal IgM positivity assessed post-delivery may still yield clinically pertinent information.

Combining maternal IgM serology with visible clinical signs in newborns, particularly jaundice, could yield a more thorough screening approach that merges laboratory tests with bedside evaluations. This combined approach could enhance the early detection of high-risk neonates in low- and middle-income countries with constrained resources (31).

This study has several limitations. Maternal serology was evaluated post-delivery, which may not accurately represent immune status during gestation. Additionally, the absence of IgG avidity testing impeded the distinction between primary and non-primary maternal infection and the assessment of the timing of infection during pregnancy. Future research should incorporate serial maternal serology throughout gestation, alongside supplementary tests such as avidity assays or quantitative PCR. These measures may enhance diagnostic accuracy and facilitate the development of more effective screening protocols in resource-constrained settings.

This study revealed a significant correlation between maternal CMV IgM seropositivity and neonatal CMV infection confirmed by PCR. When evaluated alongside clinical indicators such as neonatal jaundice, maternal serology may aid in identifying neonates necessitating confirmatory molecular testing, particularly in situations where universal CMV PCR screening is unfeasible. Further research utilizing longitudinal maternal sampling and improved diagnostic methodologies is imperative to refine screening strategies and more precisely identify high-risk neonates in resource-limited contexts.

4. CONCLUSIONS

Maternal CMV IgM seropositivity assessed in the early postpartum period correlated with neonatal CMV PCR positivity in this high-risk neonatal cohort, while maternal CMV IgG did not demonstrate a significant association. These results indicate that maternal IgM serology may offer supplementary insights when evaluating targeted molecular testing for CMV in neonates, especially in contexts where routine PCR screening is not easily accessible

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Ethics statement: This study was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (approval number 0694/KEPK/VI/2023). Written informed consent was obtained from the biological mothers of all participating neonates before enrollment.

Conflict of interest: The authors declare no conflicts of interest.

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