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Original Article

Care of children with congenital rubella syndrome (CRS) in Indonesia

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Abstract

Introduction: Congenital rubella syndrome (CRS) is associated with severe birth defects, that lead to disability in later life. Hence, early detection and intervention are needed to prevent permanent disability and mortality in children with CRS. We evaluated the time to diagnosis or correction intervention related to survival rate using survival analysis.

Methodology: A retrospective cohort study was conducted to evaluate the follow-up of CRS-confirmed cases from 2011–2018 at a national referral hospital in Jakarta, Indonesia. Parents of eligible children who registered in the national CRS registry as laboratory-confirmed CRS cases were contacted through phone calls or home visits and interviewed about the current situation of their child's health. We also obtained clinical data from the medical records.

Results: Fifty children, age 4 to 14 years, identified with laboratory-confirmed CRS were included in this study. Half (54%) of these children were female. All were born from mothers with no previous rubella vaccination history. Ophthalmic abnormalities such as congenital cataracts (88%) were the most common birth defect. Multiple congenital abnormalities including congenital heart disease, ocular abnormalities, and auditory defects were identified in 52% of the children. Based on Kaplan-Meier analysis, 50% of children were diagnosed at four months. Ophthalmic corrections such as cataract surgery were performed earlier than heart or auditory correction, with 50% of children undergoing eye correction one month after the diagnosis.

Conclusions: There is a vital need to implement CRS surveillance in Indonesia to know the burden of CRS and reinforce the preventive actions, including vaccination against rubella.

Key words: Congenital; rubella; vaccine.

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Introduction

Congenital rubella syndrome (CRS) is associated with severe birth defects, which can lead to disability in later life. This multi-organ syndrome results from the teratogenic effects of rubella virus infection during pregnancy, most frequently in the first trimester [1,2]. Unlike congenital rubella infection, CRS refers to various birth defects, such as hearing impairment, congenital heart defects, cataracts, and pigmentary retinopathy, which can have long-term effects on the growth and development of the child.

CRS is rare in developed countries with established rubella immunization programs and typically occurs in nations without nationwide immunization programs, affecting approximately 110,000 infants annually. The estimated incidence of CRS is approximately 0.05 per 1000 live births in Yogyakarta, Indonesia [3]. Rubella vaccination programs were introduced in 2016 in many countries in Asia, such as Bangladesh, Bhutan, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste. Indonesia introduced the National Rubella Immunization Program in 2017, where rubella vaccine is given in combination with measles vaccine. The measles-rubella (MR) program in Indonesia is targeted to all children from 9 months to < 15 years of age, regardless of vaccination status or previous history of measles and rubella infection, with a national coverage rate of 87.33% [4].

Maternal to fetal transmission of the rubella virus is hematogenous and occurs during maternal viremia. After infecting the placenta, the virus spreads through the vascular system of the developing fetus, resulting in

birth defects caused by cytopathic damage to the blood vessels that leads to ischemia in the affected organs. Clinical manifestations vary depending on the time of maternal infection, with the highest risk to the fetus observed when infection occurs in the first 10 weeks of gestation. Structural cardiac and eye defects typically result from maternal infections that occur before the 8th gestational week, whereas hearing loss may be observed when maternal infections occur up to the 18th gestational week. If infection occurs after 18–20 weeks of gestation, birth defects are unlikely [5]. Early intervention is needed to prevent permanent disabilities in children with CRS. However, these children are often presented to the hospital at older ages, and thus, birth defects are typically detected and corrected too late. In this study, we evaluated the clinical characteristics, time to diagnosis, and interventions for confirmed CRS cases.

Methodology

Study design and population

A retrospective cohort study was conducted to evaluate the follow-up of CRS-confirmed cases in Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. The data were taken from medical records and confirmed by calling the parents. This study included children aged 0–18 years registered in the CRS national surveillance registry from 2011–2018 as laboratory-confirmed CRS cases. These cases are defined by the National Health Ministry as (1) infants (< 6 months old) with clinically confirmed CRS with a positive blood test for rubella-specific immunoglobulin M (IgM) or (2) children (aged 6 months to 1 year) with positive blood tests for (i) both IgM and IgG or (ii) IgG at two consecutive examinations 1 month apart. A clinically confirmed case is defined as an infant in whom a qualified physician detected at least two complications, which are divided into the following two categories: (a) cataracts, congenital glaucoma, congenital heart disease, hearing loss, or pigmentary retinopathy and (b) purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, or jaundice within 24 hours after birth. The two complications could both be from category (a) or (b), or one complication could be in category (a) and the other in category (b) [6]. Children were excluded from the study if they had any other syndrome, such as Down syndrome; confirmed congenital Cytomegalovirus (CMV) infection; or congenital toxoplasmosis; or if they had an incomplete medical record.

Table 1. Sociodemographic characteristics of infants and their mothers.

Parameters	CRS-positive (n = 50)
Infant	
Gender (n, %)	
Male	23 (46)
Female	27 (54)
Age median (range) in months	**37 (4–169)**
Birth weight (g)	2280 (1300–3200)
Birth length (cm)	45.7 (32–54)
Mode of delivery	
Vaginal	25 (50)
Caesarean	14 (28)
Unknown	11 (22)
Gestational age at birth in weeks	
Normal (36 – 42 weeks)	20 (40)
Premature (< 36 weeks)	11 (22)
Unknown	19 (38)
Maternal (n, %)	
Rubella vaccination history	0 (0)
Diagnosed with rubella infection during pregnancy	4 (8)

Ethical statement

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia — Cipto Mangunkusumo Hospital on 8 October 2018 (approval number: 1060/UN2.F1/ETIK/2018). Informed consent was taken from parents of eligible children that were included in this study via phone call.

Data collection

Parents of eligible children who registered in the CRS national surveillance registry as laboratory-confirmed cases were contacted via phone call or home visit (if permitted) and interviewed about the current situation of their child's health, including mortality, comorbidities, and history of procedures or target organ corrections. Clinical data was also obtained from the medical records, including gender, age, clinical characteristics, time to diagnosis of CRS, correction status, and time to target organ correction.

Statistical analysis

Statistical analysis was performed using SPSS v25. [7]. In addition to the descriptive results from the baseline table, this study also used a survival analysis tool from Kaplan–Meier [8]. Survival graphics were made using Kaplan–Meier survival analysis. The results from this Kaplan–Meier graph were analyzed to assess the survival rate and median survival using each patient's time.

Results

Infant and maternal characteristics of CRS

A total of 50 children were identified from 2011 to 2018 based on laboratory-confirmed CRS with the CRS

surveillance at Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. Half of these 50 children were female (54%) (Table 1). The median age was 37 months (range: 4–169 months), and the average birth weight and length were 2,280 grams and 45.7 cm, respectively. Eleven children (22%) were born premature (< 36 weeks). During pregnancy, 4 out of 50 mothers were diagnosed with rubella infection. Moreover, none of the mothers had previously received a rubella vaccination.

Clinical characteristics of congenital rubella syndrome (CRS)

Among the confirmed CRS cases, ophthalmic abnormalities were the most common clinical characteristics. Of the 50 CRS cases, 44 (88%) presented with ophthalmic abnormalities, of which congenital cataracts were the most common ocular finding, whereas none presented with congenital glaucoma. Furthermore, 38 children (76%) had auditory defects, such as sensorineural hearing loss (SNHL), and 37 children (74%) had congenital heart disease. Patent ductus arteriosus was the most frequent congenital cardiovascular abnormality (n = 18, 49%), followed by pulmonary arterial stenosis (30%), and atrial septal defects (2.7%). Apart from these three major abnormalities found in children with CRS, 29 children (58%) presented with developmental delays, and 27 children (54%) had microcephaly. Among the children with clinical characteristics, 52% had multiple congenital abnormalities, including congenital heart disease and ophthalmic and auditory defects. Infants with compatible CRS clinical categories were confirmed with laboratory examinations using a rubella-specific IgM and IgG test (Table 2).

Table 2. Clinical features of congenital rubella syndrome (CRS).

Clinical characteristics	Total (n, %)
Ophthalmic abnormalities	44 (88)
Congenital cataract	44 (88)
Congenital glaucoma	0
Auditory defects	
Sensory-Neural Hearing Loss	38 (76)
Congenital heart disease (CHD)	37 (74)
Patent ductus arteriosus	18 (49)
Pulmonary arterial stenosis	11 (30)
Atrial septal defects	1 (2.7)
Minor abnormalities	
Purpura	0
Microcephaly	27 (54)
Meningoencephalitis	1 (2)
Icteric 24-hours post-partum	0
Splenomegaly	0
Developmental delay	29 (58)
Radiolucent bone disease	0
Combination of abnormalities	
CHD* and ophthalmic abnormalities	6 (12)
CHD* and auditory defects	3 (6)
Ophthalmic and auditory defects	7 (14)
CHD, ophthalmic and auditory defects	26 (52)
Correction Status	
Ophthalmic	39/44 (88.6)
Auditory	11/38 (28.9)
Cardiovascular	8/37 (21.6)
Time to achieve diagnosis median (range) in months	4 (0 – 31)
Time to achieve ophthalmic correction median (range) in months	3 (0 – 97)
Time to achieve auditory correction median (range) in months	5 (1 – 58)
Time to achieve heart correction median (range) in months	1 (0 – 96)

The average time needed to achieve a working diagnosis in this study was 4 months (range: 0–31 months), and 50% of the cases were diagnosed at 4 months. The median times after diagnosis needed to achieve auditory, ophthalmic, and heart correction were 5 months (range: 1–58 months), 3 months (range: 0–97 months), and 1 month (range: 0–96 months), respectively (Table 2).

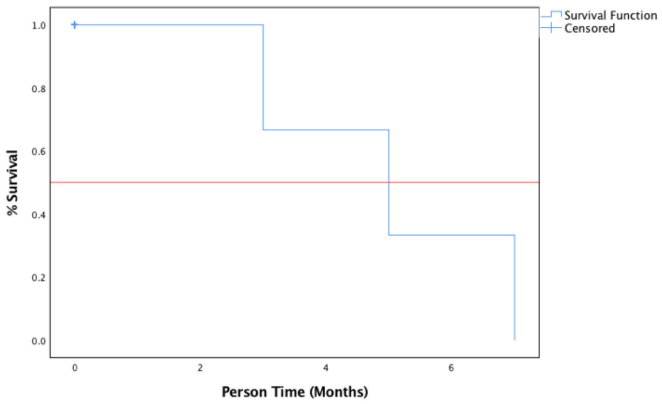
Survival analysis of CRS

Three children died during follow-up. Based on Kaplan–Meier survival analysis, the overall median survival time of CRS children was 5 months (Figure 1). The median time to diagnosis was 4 months. Half of the patients had defect corrections, and the median time to achieve ophthalmic, auditory, and heart correction was 1, 5, and 9 months after diagnosis, respectively (Figure 2).

Discussion

CRS is a critical public health problem because of its potential to lead to overwhelming abnormalities and its ability to cause significant long-term disability. Hence, early detection is needed for infants born with any malformation suggesting CRS, and early intervention, such as abnormality corrections, is required to reduce the morbidity and mortality of CRS.

Figure 1. Survival of children with congenital rubella syndrome (CRS).



The purpose of this study was to examine all the parameters using descriptive analyses and identify the outcomes of infants with laboratory-confirmed CRS within less or more than 1 year using a survival analysis tool from Kaplan–Meier. The Kaplan–Meier method used the time to diagnose and correct each abnormality by parameterizing and incorporating the event as it was diagnosed and corrected.

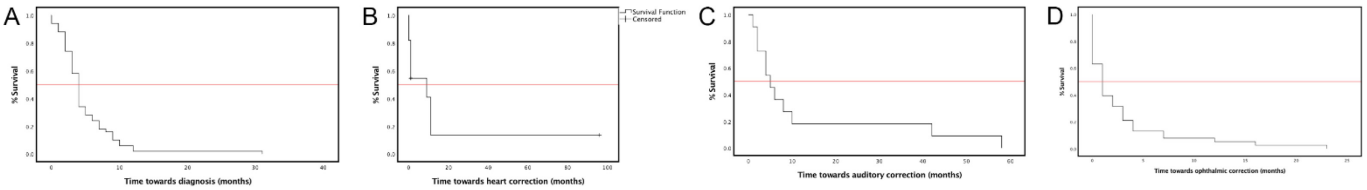
In the present study, the average time needed to achieve a working diagnosis was 5 months. However, according to the Kaplan–Meier survival analysis, 50% of children were diagnosed earlier, at 4 months, and the median survival for children with CRS was 5 months. It is crucial to be aware of the signs suggestive of CRS in newborns to allow earlier interventions for birth defects. Surveillance protocols should be maintained to identify rubella in pregnant mothers and the signs of CRS in newborns to mitigate the morbidity and mortality of CRS [9]. The Morbidity and Mortality Weekly Report (MMWR) in Maryland, Alabama, and Illinois reported three CRS cases that were confirmed at a hospital laboratory by a positive test for IgM specific to rubella, followed by an examination of rubella-specific IgM in a public health laboratory and the Centers of Disease Control and Prevention (CDC), which were completed at birth or until 1 month after birth [10].

The sociodemographic characteristics of the infants revealed that the majority were female. Considering that the results were not well-known and the number of positive CRS cases was limited, we cannot conclude that CRS is more common in females than in males. Furthermore, our results were slightly different from those of research in Surabaya, Indonesia, which found that the ratio of males to females was 1.06:1 [11]. The patients identified in this study ranged in age from 4 months to 14 years, and the median age was 3 years, whereas most of the studies conducted in Indonesia focused on infants less than 6 months old [11].

The clinical characteristics of CRS include congenital heart disease, congenital cataracts, congenital glaucoma, pigmentary retinopathy, hearing impairments, and other abnormalities, such as developmental delay, microcephaly, meningoencephalitis, purpura, icteric, splenomegaly, and radiolucent bone disease [12]. The most common clinical characteristics observed in this study were ophthalmic abnormalities, and congenital cataracts. This result is supported by a study by Ashlesha *et al.,* which reported that CRS accounted for 10–15% of all pediatric cataract cases, and 10–50% of all children with congenital anomalies had laboratory evidence of CRS [13]. A systematic review from the Philippines demonstrated that CRS was the most common cause of secondary congenital cataracts among all patients with congenital cataracts and the most frequent cause of secondary congenital sensorineural hearing loss [14].

Our findings revealed that ophthalmic abnormalities manifesting as congenital cataract were the most common abnormality found and which were then immediately treated whenever possible. Cataract surgery followed by visual rehabilitation of the existing amblyopia was the standard procedure to achieve the best visual function. Compared to other clinical signs of CRS, cataracts are generally easy to identify without the need for special medical devices. In addition, several patients with other clinical characteristics were neither corrected nor followed up. According to the Kaplan–Meier survival analysis, ophthalmic corrections were performed earlier than heart or auditory corrections. The median survival of ophthalmic correction was 1 month. The rubella virus damages the eye by inhibiting and altering cell division and maturation and infecting every part of the developing fetal eye through capillary network association. Early diagnosis and prompt interventions for ocular and hearing impairments are needed to provide positive impacts on the development of visual acuity and language development, respectively [15]. A case report from the United States described a male infant born by an emergency cesarean section because of fetal cardiac decelerations. The infant's clinical features were left cataract without retinal involvement, congenital heart disease, sensorineural hearing loss, and a bone abnormality. The patient underwent cataract removal surgery by 6 weeks of age, and at the time of the report, he was developing well, even though his growth was borderline [16].

Figure 2. A: Median time to achieve diagnosis; **B:** ophthalmic; **C:** auditory and **D:** heart correction.



Congenital heart disease was found to be the least common abnormality in this study, yet cardiovascular malformation is a common finding in CRS. In previous research, congenital heart disease was detected in 38%–70% of patients with CRS. In a prospective review in Khanh Hoa, Vietnam that evaluated 36 children with CRS using echocardiography, 72% of the children had cardiovascular malformations, mostly patent ductus arteriosus followed by atrial septal defects [15]. In addition, researchers in Yogyakarta, Indonesia conducted a retrospective study and demonstrated that during observation over 5 years, congenital heart disease was the prevailing birth defect among CRS laboratory-confirmed cases [17]. Despite this, the present study found that 26 children (42.6%) had more than one abnormality, commonly a combination of congenital heart disease, ophthalmic, and auditory defects. Many birth defects have been found among CRS cases, but according to a cross-sectional study from Ethiopia, the most common birth defects in infants with laboratory-confirmed CRS were ophthalmic abnormalities, congenital heart disease, and hearing impairments [18].

Half of the patients in the present study had a heart correction by the age of 9 months. A cross-sectional study from South Africa demonstrated that the most frequent anomaly of CRS between 2015 and 2017 was congenital heart disease (81%), which was usually observed soon after birth [18]. However, the study did not clarify the time between diagnosis and heart correction. The ability to diagnose congenital heart disease associated with CRS has dramatically improved because of the use of cardiac catheterization and echocardiography [15]. The National Heart, Lung, and Blood Institute of the United States stated that repairing congenital heart defects using a catheter is easier than surgical methods [19]. Mortality increases in CRS cases with congenital heart disease mainly because of respiratory distress due to cardiac failure and significant disparities in access to care and outcomes exist throughout the world. Therefore, timely intervention for cardiac defects can be lifesaving [20]. However, in rare cases, respiratory distress without congenital heart disease may occur because of interstitial pneumonia, a complication of CRS that can cause a higher mortality rate [21].

Auditory defects were the second most common clinical characteristic in this study. A different result was observed in a study in Surabaya, in which hearing impairment (most commonly bilateral) was the most frequent anomaly in CRS patients. The same result was found in an earlier study in the United States and Oman, in which 66–90% of children with CRS had hearing impairments. These impairments were primarily bilateral sensorineural hearing loss. Sensorineural hearing loss was associated with maternal infections that occurred up to the 18th to 20th gestational week; however, other abnormalities related to rubella infections, such as cataracts and heart defects, only appeared after infections during the 9th to 11th gestational weeks [15]. In newborns and infants with suspected rubella infections, the examinations for cardiac, auditory, ophthalmologic, and neurologic abnormalities must be correctly conducted with laboratory confirmation and continuous follow-up, especially during the first 6 months [11,15].

A study conducted by Toizumi *et al*. following 21 children diagnosed with CRS in Vietnam showed that 95% of children had an abnormal score in at least one Ages and Stages Questionnaire (ASQ) domain or a suspect score in at least one area of the Denver Developmental Screening Test II. The study concluded that the high incidence of hearing impairments and autism spectrum disorder (ASD) in children with CRS resulted in language and communication disorders [15]. Because of the long-term impact of CRS, the World Health Organization (WHO) recommends initiating rubella surveillance that focuses on identifying infants between 0 and 11 months old who present with features of CRS (possible or confirmed according to the WHO CRS case definitions) at health facilities [13]. In infants (1 year of age), diagnosis of CRS becomes challenging because a negative rubella laboratory test result does not exclude CRS [22]. Our findings suggest that in order to achieve a better outcome, in patients who meet the clinical criteria for surgery, surgical correction (followed by rehabilitation management) of the existing cardiac, ophthalmologic, and auditory defects should be performed immediately.

Many countries have reported a dramatic decrease in global rubella incidences annually after the implementation of rubella vaccination programs [4]. This also proves that maintaining an MR immunization program is the only way to promote herd immunity to protect against CRS, and also measles; especially in developing countries such as Indonesia where these diseases are still widely found [23]. The latest surveillance study in Indonesia after the first implementation of the MR nation vaccine program in 2017, also reported a similar finding, with a 60.95% decrease in CRS incidence in Yogyakarta, Indonesia. However, high-quality surveillance systems are needed to understand disease control and to prevent outbreaks [4,24].

This study has limitations in collecting the necessary retrospective data. Many patients' medical records could not be retrieved for various reasons. In addition, there was the challenge of contacting the patients again to follow their progress. However, the CRS capture in this surveillance may be the tip of the iceberg, therefore strengthening the CRS surveillance is crucial to obtain the true burden. The effort and financial cost for the corrections of the defect in CRS are very costly; and this highlights the need to reinforce the rubella vaccination program, along with measles vaccination.

Conclusions

Confirmation of CRS diagnosis was accomplished in 50% of patients 4 months after initial detection. The primary clinical characteristics found in this study were ophthalmic abnormalities, which were congenital cataracts, and many patients had a combination of congenital heart disease, ophthalmic, and auditory abnormalities. Ophthalmic corrections were typically initiated promptly, with 50% of children undergoing eye corrections 1 month after diagnosis. However, most patients were already at an older age at the time of diagnosis. Delay in diagnosis and treatment increases the risk of amblyopia, which eventually may affect the visual results following the surgery. Corrections of abnormalities such as cardiac, ophthalmologic, and auditory defects should be carried out as soon as the patient matches the clinical criteria for surgery while also taking into account the children's age to achieve a better outcome. Therefore, the CRS surveillance needs to be implemented to obtain the true burden of CRS in Indonesia, and the rubella vaccination program should be reinforced.

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