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Risk factors for mortality in children with cyanotic congenital heart disease associated with brain abscess

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***Abstract*---**Brain abscess is a local infection within the brain parenchyma. Predisposing factors include cyanotic congenital heart disease (CHD). Identification of risk factors for mortality is important to determine the prognosis. A case-control study of children with cyanotic CHD associated with brain abscess was conducted in the pediatric ward of a hospital from January 2016 to December 2020. Data were collected from medical records with the case to controls ratio of 1:3.07. A total of 61 children were evaluated, 46 children survived and 15 children non-survived. From 11 risk factors evaluated, 6 risk factors had a significant different of mortality risk included the level of hemoglobin (p=0.07), leukocyte (p=0.063), Neutrophil-to-lymphocyte ratio (NLR) (p<0.001), peripheral oxygen saturation (SpO_2) (p=0.00), multiple abscesses (p=0.008), brain abscess diameter (p<0.001). Multivariate logistic regression analyses revealed significant risk factors for mortality in cyanotic CHD children

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with brain abscesses were NLR (OR 13.62, 95%CI 2.123-87.319, p=0.006); SpO_2 (OR 1.5, 95% CI 1.25-2, p=0.04); brain abscess diameter (OR 7.61, 95%CI 1.064-54.434, p=0.043). NLR, brain abscess diameter, and SpO_2 were the risk factors in increasing mortality in cyanotic CHD children with brain abscess. The prevention of abscess cerebral development and cyanotic CHD management are needed to reduce the mortality.

***Keywords*---**brain abscess, children, cyanotic congenital heart disease, mortality, risk factors.

Introduction

A total of 50,000 infants are born with cyanotic congenital heart disease (CHD) each year in Indonesia. Most of them are rarely received corrective cardiac surgery, thus increasing the risk of brain abscess (Firdausy et al., 2018). Approximately 33% of abscess cases are developed in cyanotic CHD children, 25-46% of brain abscess cases are caused by uncorrected cyanotic CHD, with manifestations occurring between 2 and 12 years old (Hegde et al., 1986; Ozsürekci et al., 2012). The mortality from brain abscesses due to uncorrected cyanotic CHD in children is 27.5%–71% (Lakhani et al., 2020). Tetralogy of Fallot (ToF) is the largest cyanotic CHD in 10% of brain abscess cases. It is well-known that brain abscess is a fatal complication in patients with uncorrected cyanotic CHD, especially in the 4-7 year age group. Approximately 5%-18.7% of patients with cyanotic CHD develop a brain abscess later in life. Cyanotic CHD accompanied by a right-to-left shunt is one of the most common predisposing factors found in cases of brain abscess in children aged around 5%-18% who then develop brain abscess complications (Atiq et al., 2006).

Cyanotic congenital heart disease and arteriovenous malformation are frequently reported in association with brain abscesses. The incidence of brain abscessed in cyanotic CHD children decreased between 1981-2000 compared to 1945-1980, with prompt diagnosis and immediate decisive action. The decline was recorded at 50%-25% (Kudo-Kubo et al., 2020). Knowing the risk factors for cyanotic CHD mortality in children with a brain abscess can support early detection and prevention of brain abscess, lowering morbidity and mortality. The risk factors of mortality in cyanotic CHD children with brain abscess are rarely studied, thus we aims to investigate the risk factors for mortality in cyanotic CHD children with brain abscess.

Method

A case-control study of cyanotic CHD pediatric patients with brain abscesses was conducted in Pediatric Outpatient Ward at Dr. Soetomo General Hospital, Surabaya from January 2016 to December 2020, with ages ranging from 0 to 18 years. The inclusion criteria in this study were cyanotic CHD children who were diagnosed with brain abscesses and had complete medical records data related to risk factors. We divided the children between survived and non-survived groups. Exclusion criteria in this study were 1) incomplete medical record data; 2)

cyanotic CHD children with brain abscess accompanied by congenital neurological disorders, such as cerebral palsy, congenital hydrocephalus, spina bifida, epilepsy; 3) cyanotic CHD children with brain abscess accompanied by a history of previous brain infections that are not due to cardiogenic brain abscesses, such as meningitis, meningoencephalitis, encephalitis; 4) cyanotic CHD children with brain abscess with hydrocephalus history, whether or not had a surgery history; cyanotic CHD children with brain abscess with a previous head surgery; 5) cyanotic CHD children with brain abscess accompanied by chromosomal disorders or other congenital diseases, such as Down syndrome, congenital hypothyroidism. We used the T-test, and Mann-Whitney U test to determine the differences between variables. The bivariate and multivariate logistic regression analyses were performed to explore the odds ratio (OR) and 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. This research was approved by the Clinical Research Unit, the Ethical Committee of Dr. Soetomo General Hospital Surabaya number 1909/KEPK/III/2020.

Results

Seventy-two medical records of cyanotic CHD children with brain abscesses were collected from January 2016-December 2020. A total of 11 medical records were excluded due to incomplete data. Three children suffered from central hypothyroidism, 1 (one) with epilepsy, 2 (two) children with Down syndrome, 1 with hydrocephalus and meningitis, and 4 children have incomplete medical records. This study involved a total of 61 eligible participants with cyanotic CHD children with brain abscesses consisting of 15 children who were being non-survived, and 46 children having survived outcomes. Table 1 reports the baseline characteristic of cyanotic CHD children with brain abscesses. The independent variables used to determine the effect and risk factors for increased mortality in cyanotic CHD children with brain abscess consisted of 11 parameters, namely: Hb, leukocytes, platelets, CRP, NLR, peripheral SpO_2, the diameter of brain abscess, number of brain abscesses (single or multiple), acid-base status, type of cyanotic CHD, and nutritional status (Table 2 & 3). Table 4 presents the multivariate analysis of the eligible risk factors included. From these results, we found that NLR, SpO_2, and brain abscess diameter affect the mortality of brain abscess diameter with a p-value of 0.006, 0.04, and 0.043 respectively.

Discussions

Baseline characteristics of research participants

Sixty-one cyanotic CHD children with brain abscesses. The comparison between the non-survived and the survived group was 15:46 or 1: 3.06. A total of 61 study participants consisted of 26 females and 35 males, and the ratio of cases between women: men was 1: 1.35. Brain abscesses were more common in boys than girls (Moorthy & Rajshekhar, 2008). A research conducted by Erdoğan et al (Erdoğan & Cansever, 2008). in 2008 stated that the proportion of brain abscesses occurred more in boys than girls, with a ratio of 3.1:1 (Erdoğan & Cansever, 2008).

There are 24 participants under the age of 5, and 37 participants between the ages of 5 and 18. For children, cyanotic CHD with brain abscess is more common in children over the age of 5, with a proportion of 1: 1.47 compared to children under the age of 5. The average age of cyanotic CHD cases with brain abscesses was 6.214.054 years, with 1 case reported at the earliest age of 10 months and the oldest reported age of 16 years and 3 months. Approximately 15-30% of children under the age of 15 are affected (Erdoğan & Cansever, 2008). According to European research, brain abscesses were most common in children aged 4 to 10. According to the findings in Ireland, the incidence of brain abscesses was 1.2% in children under the age of seven. Reports from the United Kingdom, the prevalence of brain abscesses among children aged 0 to 19 years is as high as 32% (Mameli et al., 2019).

Table 1
Baseline characteristics of the participants

Variable	Survived (n=46)	Non-survived (n=15)	p-value
Gender			0.770
Male	27	8	
Female	19	7	
Age of early diagnosis (year)			0.767
< 5	22	6	
≥ 5	24	9	
LOS (days)			0.000*
≥ 4 weeks	42	1	
< 4 weeks	4	14	
Pneumonia	20	4	0.394
UTI	7	1	0.660
Acute otitis media (AOM)	0	3	0.013*
Infective endocarditis	1	1	0.434
Caries	15	7	0.372
Surgical action	7	0	0.178
CSF fluid analysis	12	2	0.350
Echocardiography ToF	15	10	0.043*
DORV	5	3	0.393
Eisenmenger's syndrome	23	1	1
TGA	3	1	0.89
Residence			0.344
Surabaya	17	3	
Outside Surabaya	29	12	
Breastfeeding history	38	13	0.770
Immunization history	24	10	0.382

There were 41 children with comorbid infections and 20 children without comorbid infections. Pneumonia comorbid infections were observed in 24 out of 61 children, urinary tract infection (UTI) comorbid infection in 8 out of 61 children, chronic suppurative otitis media (CSOM) in 3 out of 61 children, frontal sinusitis found in one child, and infective endocarditis in two children with a p-

value of 0.37, there was no significant difference between the two groups. A total of 15 of 45 participants in the surviving group had dental caries, whereas 46% of children in the non-survived group did not.

Table 2
Bivariate analysis of independent variables with numerical data scale

Risk factors	Non-survived	Survived	p-value
Hb	20.0333±3.76253	15.2978±4.3013	0.049*
Leukocytes	11351.33±4016.964	14027.39±13204.980	0.000*
Thrombocytes	58213.3333±32181	301978.2609±140084.6	0.000*
CRP	7.0200±6.01880	3.9704±8.37479	0.000*
NLR	8.31338±5.81857	2.8584±3.24110	0.000*
SpO_2	74.60±4.050	85.30±6.095	0.01*
Brain abscesses diameter	2.9000±.82980	1.7420±0,642	0.026*

*p<0.05: significant

Risk factors for brain abscess can be acute conditions or chronic conditions. Acute conditions such as direct trauma to the head area, sinusitis, infections of the teeth/caries, and otogenic source (Gunawan & Romdhoni, 2021). Chronic conditions that cause brain abscess are cardiogenic, namely the emergence of circulatory shunts in conditions of infective endocarditis, osteomyelitis, pneumonia, and infections of the skin that allow bacteria to spread hematogenously to brain areas without passing through the phagocyte function of the pulmonary circulation (Mameli et al., 2019, Prismadani & Agus, 2020). Infection of the teeth is the source of infection of brain abscess with hematogenous spread (Boother et al., 2017; Mylonas et al., 2007). Cardiogenic brain abscess was reported as a more common occurrence in areas with poor hygiene. Based on several case reports, it is stated that the incidence of cardiogenic brain abscess in children occurs in many developing countries, such as India and Pakistan (Lakhani et al., 2020).

Table 3
Bivariate analysis of independent variables with numerical data scale

Variables	OR	95 %CI	p-value
Hb	18.2	2.205-150.245	0.07
Leukocytes	0.219	0.044-1.083	0.063
Thrombocytes	-	-	0.997
NLR	19.0	4.338-83.226	<0.001*
CRP	1.8	0.487-6.413	0.386
SpO_2	1.5	1.25-2	0.00*
CHD Type	-	-	0.13
Metabolic acidosis	1.36	0.423-4.337	0.606
Total of brain abscesses (single/ multiple)	5.4	1.550-18.813	0.008*
Abscess diameter	15.75	3.674-67.524	<0.001*
Nutrition status	-	-	0.999

p<0.25: will be included in multivariate analysis; *p<0.05: significant

A total of 10 participants in the survived group experienced seizures, and one from 15 participants in the non-survived group experienced seizures with a p-value = 0.265, there was no significant difference between the two groups. Decreased consciousness occurred in 29 participants from 46 participants in the survived group and all participants in the non-survived group experienced seizures, with a p-value = 0.00, there was a significant difference in the two groups. A large number of 41 from 46 participants in the survived group had a fever, and all data in the non-survived group had a fever, with a p-value = 0.321 with no significant difference in the two groups. A total of 40 participants from 46 participants in the survived group complaints of headaches, while all participants in the non-survived group experienced headaches, with a p-value of 0.321, there was no significant difference between the two groups. Approximately 41.3% of the surviving group experienced vomiting, and 73.3% of the non-survived group also experienced vomiting, with a p-value = 0.04, there was a significant difference between the two groups. The non-survived group had more frequent vomiting symptoms than the survived group. There was no significant difference between limb weakness in the two groups with a p-value of 0.0554.

There are no pathognomonic signs of brain abscess occurrence, clinical symptoms of brain abscess arise from the location of the abscess and the magnitude of the mass pressure effect on the head. Symptoms of a brain abscess can include fever, headache, nausea, vomiting, impaired consciousness, convulsions, and weakness of the limbs are the most common symptoms. Based on research reports, it is stated that only 30-55% of patients with brain abscesses have a fever between 38.5-40°C (Erdoğan & Cansever, 2008). Other studies declare if the fever that occurs in brain abscess is a fever that is not high (Moorthy & Rajshekhar, 2008). Seizures are found in about 16–50% of patients with brain abscesses. According to the location of the lesion on the skull, 40-60% of patients have limb paralysis. The classic triad of brain abscess consists of fever, headache, and limb weakness in 15–30% of patients (Erdoğan & Cansever, 2008). Frontal region brain abscess will show symptoms if the diameter of the abscess is large (Mameli et al., 2019).

Table 4
Multivariate analysis of risk factors for mortality in cyanotic CHD children with brain abscesses

Variables	OR	95 % CI	p-value
Hb	7.167	0.634-81.024	0.111
Leukocyte	0.18	0.022-1.496	0.112
NLR	13.62	2.123-87.319	0.006*
SpO_2	1.5	1.25-2	0.04*
Abscess diameter	7.61	1.064-54.434	0.043*

*p<0.05: statistically significant.

Seven children in the survived group underwent surgical treatment, and no children in the non-survived group underwent surgery, with a p-value = 0.178. There was no significant difference between the two groups. Several types of surgery are performed on brain abscess conditions. Antibiotics remain used in conjunction with surgical treatment (Erdoğan & Cansever, 2008).

About 82.6% of the survived group has a breastfeeding history, as does 86% of the non-survived group. There were no significant differences between the two groups. Fifty-two percent of the survived group have immunization history according to age and 66.7% of the non-survived group have incomplete immunization history, with a p-value = 0.382, there was no significant difference between the two groups. The distribution and frequency of cases of cyanotic CHD in children with brain abscesses came from various regions in East Java. The research participants were dominated by the Surabaya, followed by other areas from East Java, such as Sidoarjo, Gresik, Pasuruan, Bangkalan, Probolinggo, Banyuwangi, Lamongan, Sampang, Pamekasan, as well as from Purworejo, Central Java. Brain abscesses were reported as the incidence of infection, which was more common in areas with poor hygiene.

Based on several case reports, cardiogenic brain abscess incidence in children occurs in several developing countries, such as India and Pakistan (Lakhani et al., 2020). The prevalence of cardiogenic brain abscesses have been reported frequently in children living in out-of-town areas with relatively difficult access to health facilities (Kanneganti et al., 2021). In the survived group, the age of children with cyanotic CHD with brain abscess was 6.5±4.314 years, while for the non-survived group, children with cyanotic CHD with brain abscess had an average age of 5.33±3.0866 years. The non-survived group had a lower mean age than the survived group. The length of treatment in the survived group was 48.8 ± 10.4 days, while the length of treatment in the non-survived group was 17.6 ± 13.75 days, with a p-value = 0.000, there were significant differences between the two groups. When compared with the survived group, the treatment days for the non-survived group were shorter.

In the non-survived group, it was reported that only three participants had Cerebrospinal fluid (CSF) analysis data, where two participants showed CSF analysis results of bacterial infection, while the CSF analysis results of one participant were normal. Twelve participants in the surviving group have CSF analysis, which showed 11 participants with bacterial infection results, while one participant has CSF analysis that showed normal results, with a p-value = 0.35 there was no significant difference between the groups. Lumbar puncture examination in patients with brain abscesses can be performed but it is necessary to consider the risks that can occur, carried out under ideal conditions there are no signs of increased intracranial pressure, and there is a suspicion of meningitis and ventriculitis infection. From several studies, it is stated that the examination of CSF culture in cases of brain abscess is only about 10-30% which shows positive results (Erdoğan & Cansever, 2008; Moorthy & Rajshekhar, 2008).

Examination of CSF analysis showed varying results in cases of brain abscess. Most of the results showed a decrease in glucose levels, an increase in leukocyte levels, and protein increasing levels. Examination of CSF fluid analysis showed normal results in 30% in a study conducted by Shachor-Meyouhas et al., (Shachor-Meyouhas et al., 2010) and 16% in a systematic review study conducted (Brouwer & Van De Beek, 2017; Mameli et al., 2019). In the non-survived group, brain abscesses were reported predominantly in the frontal, temporal and parietal lobes in both hemispheres of the brain, and cerebellar abscesses were reported. In the survived group, more abscesses were found in the form of single abscesses,

both in the frontal, temporal, and parietal regions. According to previous studies, brain abscesses commonly form in the frontal and parietal lobe areas, which are asymptomatic at first and only become symptomatic after the mass pressure effect starts (Udayakumaran et al., 2017).

The antibiotic ceftriaxone was reported to be used in 13 participants out of 15 participants in the non-survived group and 31 participants out of 46 participants in the survived group. In the non-survived group, 93% of metronidazole antibiotics were used, compared to 59% in the survived group. In addition to ceftriaxone and metronidazole antibiotics, 13% of the non-survived group and 13% of the survived group received ampicillin combination antibiotics, and 13% of the non-survived group and 13% of the survived group received antibiotics. In the surviving group, 6% of the people used the antibiotic cefazolin. The use of amikacin antibiotics in 6% of the survived group. The use of antibiotic meropenem was reported to be used in 6% of the surviving group. Giving antibiotics ceftriaxone and metronidazole is part of the management of brain abscesses.

Penicillin and chloramphenicol are the antibiotics of choice in cases of brain abscesses because they have a high ability to penetrate the blood-brain barrier. Third-generation cephalosporins such as cefotaxime and ceftriaxone are the treatment of choice for brain abscesses because of their good ability to penetrate the blood-brain barrier. The use of metronidazole was chosen to eradicate anaerobic bacterial infections, such as *Bacteroides fragilis*. So choice of a combination of class 3 cephalosporin antibiotics or penicillin and metronidazole is the treatment of choice for brain abscesses (Udayakumaran et al., 2017). Staphylococcus spp. dominated 9 of the 15 blood culture participants in the non-survived group, according to the results of blood culture and CSF fluid culture. Pseudomonas spp infection was found in one out of 15 participants in the non-survived group. Acinetobacter spp. infection was found in two participants out of fifteen in the non-survived group. In the surviving group, *Staphylococcus spp.*, *Pseudomonas spp.*, *Acinetobacter spp.* infection and sterile culture results were found in 12, 8, 7, and 19 out of the survived group, respectively.

A meta-analysis involving 6663 adult patients and 1023 pediatric patients stated that the most common cause of brain abscess was *Streptococcus spp*, followed by *Staphylococcus spp* infection by 18%. The most common gram-negative bacteria were *Proteus spp.*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacteriae*, accounting for 16% of brain abscess cases. Examination of blood culture and CSF culture showed positive results in about 22.7% in the study conducted by Raffaldi et al., (Raffaldi et al., 2017) while the study conducted by Lee et al. (Lee et al., 2010) stated a positive value in 28.6% of cases of brain abscess. Research conducted by Canpolat et al. (Canpolat et al., 2015) reported that 100% of the blood culture results of brain abscess patients showed sterile results, according to a research report conducted by Auvichayapat et al., (Auvichayapat et al., 2007) which stated that 2.8% of participants with positive blood culture resulted in infection. Some studies say that less than 50% of abscess cultures show growth (Mameli et al., 2019).

Risk factors for mortality in cyanotic CHD children with brain abscess

Hemoglobin

Hemoglobin in the non-survived group showed Hb levels with a mean of 20.03±3.76 g/dL, while in the survived group with an average of 15.29±4.3 g/dL Hb levels in the non-survived group were relatively higher than the survived group. with a value of p=0.049 (p<0.05). This shows that relatively higher Hb levels have a relationship with the risk of mortality in cyanotic CHD children with brain abscesses. The results of the bivariate analysis showed that between the group of cyanotic CHD children with brain abscesses, the risk of mortality was 18.2 times if there was an increase in Hb levels above 16 g/dL.

Cyanotic CHD includes cyanogenic cardiopathy which makes it easier for bacteria to enter the cerebral circulation, and polycythemia due to tissue hypoxia and ischemia, thereby increasing blood viscosity, as one of the supporting factors for the development of bacteria (Basantwani et al., 2015). Patients with cyanotic CHD will experience a secondary erythrocytosis process which is a response to tissue hypoxia. Secondary erythrocytosis is divided into 2, namely: (1) compensated stable erythrocytosis with adequate iron supply and no/slight hyperviscosity symptoms and (2) decompensated erythrocytosis group with iron deficiency and microcytic erythrocyte forms. Microcytic erythrocytes are erythrocytes that are rigid and resistant to high shear stress in microcirculation. Dehydration and iron deficiency can trigger symptoms of hyperviscosity (Rose et al., 2007). The incidence of polycythemia in cyanotic CHD will induce the occurrence of small infarcts in blood vessels which causes bacteria or microorganisms to easily penetrate the blood-brain barrier (Parra et al., 2018; Sabah et al., 2016; Takeshita et al., 1992).

Leukocytes

Leukocytes in the non-survived group were 11351.33±4016.96, while in the survived group were 14027.39±13204.98, with a p-value of 0.000 (p<0.01). The value represents the difference in leukocytes between the case and survived groups. Examination of leukocytes, CRP, leukocytes, and erythrocyte sedimentation rate (ESR) is a laboratory examination that can be done quickly as a means of support to look for possible infectious or inflammatory processes as a diagnosis of brain abscess (Mameli et al., 2019). Research conducted by Udayakumaran et al. (Udayakumaran et al., 2017) said that only 20% of cases of cardiogenic brain abscess showed abnormal CRP, leukocyte, and ESR results. Examination with normal leukocyte results was also reported in 25% of cases in the study conducted by Atiq et al., (Atiq et al., 2006) nearly 67% of the study participants conducted by Shachor-Meyouhas et al., (Shachor-Meyouhas et al., 2010) stated that the results of the examination were within normal limits. Leukocytosis was reported to be more common than leukopenia (Mameli et al., 2019).

Platelet

The number of platelets in the non-survived group was 242036±161746/µL, while the survived group was 301978±140084.65/µL, with a value of p=0.00 (p<0.05). This value shows a significant difference in platelet levels in the non-survived group with platelet levels in the survived group. Platelet levels in the non-survived group were relatively lower than those in the survived group. Decreased platelet levels were not a risk factor for cyanotic CHD mortality in children with brain abscesses. The occurrence of thrombocytopenia in patients with cyanotic CHD is caused by 1) decreased platelet production, 2) decreased megakaryocyte production, 3) increased platelet breakdown, and 4) increased platelet activation (Chamanian et al., 2015). Thrombocytopenia and suppression of platelet aggregation have been identified as underlying factors for bleeding in patients with cyanotic CHD and Eisenmenger syndrome. The number of platelets is inversely proportional to the hematocrit value (Ht). Research Horigome et al., (Horigome et al., 2002) stated a significant relationship between the number of platelets microparticles (PM) and the value of Ht. PM production increases sharply at Ht levels above 60-65%. Increased PM production is associated with platelet activation stimulated by high shear stress on blood hyperviscosity, which is demonstrated in studies of adult patients with coronary heart disease, where vascular stenosis will create turbulent flow and high shear stress on the platelet surface causing excessive PM production (Matter et al., 2018; Puspitasari & Harimurti, 2010).

Neutrophil Lymphocyte Ratio (NLR)

The NLR value in the non-survived group was 8.31±5.8, while in the survived group it was 4.199±4.624, with a p-value = 0.000 (p<0.005). The result shows that there is a relationship between NLR values and the risk of cyanotic CHD mortality in children with brain abscesses. The results of data processing in bivariate analysis between 2 groups showed an OR value of 19 (95% CI 4.338-83.226) p<0.001. Children with cyanotic CHD with brain abscesses will have a 19-fold risk of mortality with increased NLR. Multivariate analysis showed a 13-fold risk of mortality in cyanotic CHD children with brain abscess if accompanied by an increase in the diameter of the abscess, and a decrease in SpO_2. Research conducted by Kanneganti et al. (Kanneganti et al., 2021) stated that there was an increase in NLR in the incidence of cardiogenic brain abscesses. The neutrophil to lymphocyte ratio reflects the balance between innate and adaptive immune functions where the NLR value will increase in cases of inflammatory conditions (Kanneganti et al., 2021). Research related to NLR, a novel marker of infection, inflammation, malignancy, and cardiovascular cases has begun to be carried out because NLR examination is considered easy. NLR examination is used to assess the prognosis and positive correlation to the incidence of infection, inflammation, and cardiovascular disorders (Meshaal et al., 2019). There haven't been many studies that have used these NLR parameters to assess risk factors for mortality in cyanotic CHD children with brain abscesses.

CRP Value

The CRP value in the non-survived group was 7.02±6.01, while the CRP level in the survived group was 4.72±7.9 with p=0.19 (p<0.05). The results show a significant difference between the relatively lower CRP levels in the survived group compared to the non-survived group. The CRP value is not a risk factor for cyanotic CHD mortality in children with brain abscesses. Normal values of CRP were reported in 30% of cases of brain abscess and 17% normal values of CRP (Cole et al., 2012; Mameli et al., 2019; Raffaldi et al., 2017).

Peripheral Oxygen Saturation (SpO_2)

The results showed that there were differences in SpO_2 in the non-survived group, the average SpO_2 was 74.6±4.05%, while in the survived group the average SpO_2 was 85.3±6.09%, with p-value = 0.01 (p<0.05). This demonstrates that there is a significant difference in SpO_2 levels between the non-survived group and the survived group. The results of multivariate analysis showed that the percentage of peripheral SpO_2 levels had an OR value of 1.5, which means that the percentage of peripheral SpO_2 affected increasing the risk factors for cyanotic CHD mortality in children with brain abscesses by 1.5 times. Peripheral SpO_2 percentage below 84% is a risk factor for cyanotic CHD mortality in children with brain abscess by 1.5 times compared to cyanotic CHD children with brain abscess who have SpO_2 percentage above 84%.

Takeshita et al. (Takeshita et al., 1992) showed that the risk factors for brain abscess in patients with cyanotic CHD included oxygen saturation levels (SpO_2), oxygen partial pressure (PaO_2), O_2 content, and base excess compared to controls. The cardiovascular system's response to chronic hypoxemia is blood flow redistribution, increased blood flow to the heart and brain that is not followed by an increase in cardiac output, cerebral artery vasodilation, and the inability to reduce blood viscosity. Increased blood viscosity and decreased cerebral microcirculation blood flow lead to cerebral thrombosis (Lakhani et al., 2020; Takeshita et al., 1992; Theodore et al., 1985).

Types of Cyanotic CHD

The dominant types of cyanotic CHD causing brain abscess in children are ToF and double outlet right ventricle (DORV) based on medical record data from the echocardiographic examination. Tetralogy of Fallot involves interventricular communication with a ventricular septal defect, obstruction of the right ventricular outflow tract, overriding of the aortic root, and right ventricular hypertrophy (Juliana et al., 2021). In the non-survived group, 66.7% of them were dominated by ToF, while in the survived group 33% were dominated by ToF, with a p-value = 0.43. DORV was diagnosed in 20% of the non-survived group, and 10.09% in the survived group, with a p-value = 3.93. This shows that there is no correlation between the ToF and cyanotic CHD in children with brain abscesses.

Cyanotic CHD abnormalities that often cause brain abscess in children if not corrected immediately are ToF (61.2%), followed by Dextro-Transposition of the Great Arteries (d-TGA) (9.6%), DORV (3.2%). Patients with cyanotic CHD will have

peripheral circulation problems as a result of chronic hypoxia and metabolic acidosis, which leads to increased blood concentrations as a result of the secondary polycythemia process. Brain perforation disorders, as well as bacterial translocation from the blood, occur at the junction of white matter and gray matter. Shunts from right to left create a blood-filtering shortcut, resulting in impaired pulmonary filtration. Patients with cyanotic CHD have an average SpO_2 of 72-80% (Boother et al., 2017; Udayakumaran et al., 2017).

Metabolic Acidosis

The results revealed that in the non-survived group, 53.3% of the participants had acid-base disorders, namely metabolic acidosis, while in the survived group 45.7% had metabolic acidosis, with a p-value of 0.826. The incidence of metabolic acidosis is not a risk factor for mortality in cyanotic CHD children with brain abscesses. The incidence of metabolic acidosis in cyanotic CHD with brain abscess occurs due to chronic hypoxaemic conditions. In patients with cyanotic CHD, there will be a right-to-left heart shunt that cuts off the pulmonary circulation. Patients with cyanotic CHD will experience chronic hypoxemia which triggers metabolic acidosis and an increase in blood viscosity due to a secondary polycythemia response (Moorthy & Rajshekhar, 2008; Theodore et al., 1985).

Number of Brain Abscess on a Head Computed Tomography (CT) Scan

The medical record data from the CT scan of the head showed that in the non-survived group there were multiple brain abscesses 60%, while in the survived group the results of the CT scan of the head with multiple brain abscesses were 21.7%. The survived group showed a single abscess of 78.3%, while the non-survived group showed a single abscess of 40%, with a p-value = 0.01 ($p < 0.05$). The results of the bivariate analysis revealed that multiple brain abscesses had an OR value of 5.4 (95% CI 1.550-18.813) p = 0.008, whereas the cyanotic CHD children with multiple brain abscesses had a mortality risk of 1.5 times compared to the cyanotic CHD children with a single brain abscess. Multiple brain abscesses have been reported to occur for 19-33% of the total brain abscesses, which is associated with hematogenous spread following the distribution of the middle cerebral artery (Mameli et al., 2019).

Brain Abscess Diameter

The diameter of the brain abscess was measured using secondary data from the CT scan of the head with contrast, where the diameter taken was the largest diameter on the CT scan of the head. Data on the diameter of the brain abscess, both single abscess, and multiple abscesses, were taken from the largest brain abscess diameter data. The survived group showed brain abscess diameter data of 1.74±0.64 cm, while the non-survived group showed brain abscess diameter data of 2.9±0.83 cm. The result shows that in the 2 groups there are differences in the diameter of the brain abscess with a p-value of 0.026 ($p < 0.05$). The diameter of a brain abscess has an OR value of 7.61, which means that a brain abscess diameter of more than 2.9 cm is a risk factor for mortality of cyanotic CHD in children with brain abscesses of 7.61 times compared to the cyanotic CHD group in children with brain abscesses of diameter abscess less than 2.9 cm. Medical

therapy in the form of antibiotics for a long time is the treatment of choice for brain abscess if the abscess diameter is 1.5 cm and does not show symptoms of increased intracranial pressure in two hemispheres of the brain, where single abscesses are more common in 64-76%, whereas multiple brain abscesses in 10-27% of cases (Erdoğan & Cansever, 2008; Ghafoor & Amin, 1985).

Nutrition Status

Based on the results of the study, it was shown that 93.3% of the non-survived group had poor nutritional status, while the surviving group was dominated by moderately malnourished (43.5%), with a p-value of 0.000 ($p < 0.05$). This shows that there is a relationship between anthropometric status and risk factors for mortality in cyanotic CHD children with brain abscesses. Saputri et.al (2020) showed that malnutrition is common cause of morbidity and mortality amongst children with TOF (Saputri et.al., 2020). The limitation of this study is the small number of study participants, which causes the analysis of certain risk factors for cyanotic CHD mortality in children with brain abscesses to be confined. Apart from this, genetic factors are not considered to influence the increased risk of cyanotic CHD mortality in children with brain abscesses. However, we believe that this study is relevant because the long sampling period is around 5 years, which is expected to provide sufficient numbers to contribute an overview of the condition in cyanotic CHD children with brain abscesses. This study collected a large amount of basic data from participants to observe the characteristics of the disease. Additionally, the data collection of risk factors assessed is substantial.

Conclusion

NLR, brain abscess diameter, and peripheral oxygen saturation were the risk factors that played a role in increasing mortality in cyanotic CHD children with brain abscess. The prevention of abscess cerebral development and cyanotic CHD management are needed to reduce the mortality rate.

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Conflict of Interest

The authors declare there is no conflict of interest in this study.

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