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# Analysis of Medicosocial Determinant Factors in Mothers with Stunted Children

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## ABSTRACT

**Introduction:** Stunting is a linear growth disorder caused by malnutrition in chronic nutrient intake and chronic recurrent infectious diseases as indicated by height z-score according to age. Infancy is a period that is very sensitive to the environment so more attention is needed especially the adequacy of nutrition. Obstetric complications are very influential on several determinant factors, one of these factor is a medical society or social risk. Family socioeconomic status such as family income, parental education, mother's knowledge about nutrition, and the number of family members can indirectly relate to stunting.

**Methods:** A cross-sectional analytic with a retrospective approach. Processing data using regression tests.

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**Result:** The results of this Stunting study were obtained from nutritional status data on children under five in the province of West Sulawesi in January-June 2020 by taking samples using simple random sampling. The total number of samples in this study were 88 people taken from mothers who have Stunting children aged 2-5 years. Social risk is the condition of the mother during pregnancy including age, level of education, ethnicity, occupation, income, referral decision, cost considerations, distance traveled, referral mobilization, consideration of health insurance that is expected to be related to stunting.

**Conclusion:** In this study, it was found that the most influential medicosocial determinants were referral mobilization and employment.

**Key words**: Stunting; medicosocial; pregnancy

## Introduction

Stunting is a linear growth disorder caused by malnutrition in chronic nutrient intake and / or chronic and recurrent infectious diseases as indicated by the z-score of height for age (TB / U) less than –2 standard deviation (SD) based on World Health Organization standards. (WHO). (1–3)

According to the findings of the 2010 Basic Health Research (Riskesdas 2010), the prevalence of short children under the age of five has decreased by just 1.2 percent, from 36.8% in 2007 to 35.6 percent in 2010, while the RPJMN's goal for the prevalence of short children under the age of five must be reduced to 32% in 2014.(4,5)

Globally, one out of every four children under the age of five is stunted (UNICEF, 2013). According to the findings of basic health research (Riskesdas) in Indonesia, 37.2 percent of children under the age of five were stunted in 2013. It is known that 19.2 percent of children are short, and 18.0 percent are really short, based on this figure. In comparison to the 2010 Riskesdas, where 35.6 percent of children were stunted, the incidence of stunting has risen. (4,5)

The high prevalence of stunting among children aged 0 to 23 months in Indonesia today threatens the country's human resources (HR). Indonesian people are of poorer quality than those in neighboring Malaysia, Thailand, and the Philippines. In 2011, Indonesia was ranked 124th out of 187 countries on the Human Development Index (HDI), with Malaysia 61st, Thailand 103rd, and the Philippines 112nd.. (2)

West Sulawesi, with a stunting rate of 39.7%, is the province with the most stunted infants in Central Indonesia. Quite small toddlers account for 14.7 percent of the total and 25 percent of the total. Meanwhile, Bali had the fewest stunted babies, with just 19.7%, including 5.2 percent really short babies and 14.5 percent short babies.

Indirectly, family socioeconomic status, such as family income, parental education, mothers' dietary skills, and the number of family members, may be linked to the incidence of stunting. The findings of Riskesdas (2013) indicate that low parental income and education have a significant impact on the incidence of under-five stunting. (4,6)

Obstetric complications greatly influence several determinants, one of which is social medicine. This factor is a complex problem because it is related to many things such as health status including reproductive health status and maternal nutritional status before and during pregnancy. The incidence of obstetric complications is present in about 20% of all pregnant women, but cases of obstetric complications that are set for early 2012 to the end of 2016 are at least 12% of all pregnant women or 60% of cases of obstetric complications. The increase in cases of complications mentioned above is caused by social and medico obstetric determinants. Where are the social determinants, such as age, income, motivation, education, work and belief. (3)

The authors are interested in conducting research on social medical determinants of pregnant women

on the incidence of stunting babies in Mamuju Regency, West Sulawesi, because of the high incidence of stunting in Central Indonesia, specifically West Sulawesi Province, particularly in Mamuju Regency. Stunting is common in West Sulawesi, especially in the Mamuju District. With the goal of determining the social medico-determinant factors that have the greatest impact on pregnant women with stunted babies in Mamuju Regency, West Sulawesi.

## Methods

This type of research is an analytical survey. The research design used was a cross sectional approach (cross sectional) with a retrospective approach in which the cause and effect variables (related and independent variables) were measured at the same time and moment (point time approach).

The research was conducted in West Sulawesi Province's Mamuju Regency. The research was conducted from June to August 2019 in accordance with LP2S UMI's schedule. The subjects were stunted children in Mamuju Regency, West Sulawesi Province, in June - August 2019. people meeting the inclusion criteria. Stunting babies aged 2 to 5 years old, as well as their mothers, were willing participants in this study. Questionnaires, observation sheets, and checklists were used to collect data in this study. The regression test was used in this data analysis.

The operational definition of stunting variable is children aged 2-5 years with nutritional status based on Body Length (BL) / Age(A) or Body Height (BH) / Age (A) z-score <-2SD to -3SD for short status and <-3SD for very short status. In addition, the occupational variables are civil servants and non-civil servants. Maternal age at pregnancy is said to be at risk if it is less than 25 years and more than 35 years, while not at risk at the age of 25-35 years. Income is income per month which is divided into> 2.5 million and <2.5 million according to local UMR standards. And referral mobilization is a means of transportation used to mobilize patients to referral points. Mileage is the distance between the reference place and the reference location, which is divided into> 15 km and <15 km. The referral decision is the family / relative who gives written consent for the patient's referral.

## Result

The results of this stunting study were derived from simple random sampling of data on the nutritional status of children under the age of five in West Sulawesi province from January to June 2020. In this study, a total of 88 people were sampled, all of whom were mothers with stunted children aged 2 to 5. Because the effect of malnutrition on height would appear over a long period of time, the age range was chosen.

The following preliminary data on the nutritional status of children in West Sulawesi Province were obtained for this study:

**Table 1. Initial nutritional status data for children in West Sulawesi based on their height and age.**

| Regency/City | Very Short | | | | Short | | | | Normal | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0-2 Years | | 2-5 Years | | 0-2 Years | | 2-5 Years | | 0-2 Years | | 2-5 Years | |
| | L | P | L | P | L | P | L | P | L | P | L | P |
| Majene | 335 | 221 | 797 | 622 | 396 | 314 | 967 | 916 | 1354 | 1302 | 1687 | 1646 |
| Polewali Mandar | 467 | 285 | 1341 | 980 | 998 | 673 | 2447 | 2037 | 4315 | 4109 | 6419 | 5892 |
| Mamasa | 219 | 113 | 460 | 289 | 308 | 222 | 799 | 615 | 1234 | 1089 | 2646 | 2419 |
| Mamuju | 470 | 393 | 869 | 740 | 347 | 264 | 640 | 580 | 2766 | 2467 | 3861 | 3366 |
| Mamuju Utara | 195 | 85 | 456 | 339 | 273 | 186 | 921 | 752 | 1720 | 1690 | 2981 | 2854 |
| Mamuju | 33 | 19 | 116 | 72 | 81 | 37 | 198 | 152 | 541 | 465 | 1080 | 841 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tengah | | | | | | | | | | | | |
| Total | 1719 | 1116 | 4039 | 2420 | 2403 | 1696 | 5972 | 5052 | 11930 | 11122 | 18674 | 17018 |

Source: Primary Data

Stunting assessment uses the BL/A criteria, so in table 3, the number of cases of stunting based on Body Height (BH / Age (AM) in Mamuju District, West Sulawesi at 2-5 years old is 869 men and 740 women with a total of 1609 people child.

**Table 2 Analysis of the medicosocial determinants of the incidence of stunting**

| **Variable** | **Stunting Status** | | | | | | ***r*** |
|---|---|---|---|---|---|---|---|
| | **Short** | | **Very Short** | | **Total** | | |
| | **n** | **%** | **n** | **%** | **n** | **%** | |
| **Mother's Age** | | | | | | | |
| At Risk | 22 | 25 | 33 | 37,5 | 55 | 62,5 | **0,024** |
| No Risk | 14 | 15,9 | 19 | 21,6 | 33 | 37,5 | |
| **Tribe** | | | | | | | |
| Mandar | 25 | 28,4 | 35 | 40 | 60 | 68,4 | **0,031** |
| Bougenese | 6 | 6,8 | 8 | 9 | 14 | 15,8 | |
| Makassar | 3 | 3,4 | 5 | 5,6 | 8 | 9 | |
| Java | 2 | 2,3 | 4 | 4,5 | 6 | 6,8 | |
| **Profession** | | | | | | | |
| Civil Servant | 8 | 9,1 | 20 | 22,7 | 28 | 31,8 | **0,171** |
| Non Civil Servant | 28 | 31,8 | 32 | 36,4 | 60 | 68,2 | |
| **Income** | | | | | | | |
| <2,5Million | 14 | 15,9 | 17 | 19,3 | 31 | 35,2 | **0,064** |
| >2,5 Million | 22 | 25 | 35 | 39,8 | 57 | 64,8 | |
| **Referral Decision** | | | | | | | |
| Husband | 20 | 22,7 | 33 | 37,5 | 53 | 60,2 | **0,092** |
| Family | 9 | 10,2 | 13 | 14,8 | 22 | 25 | |
| Self | 5 | 5,7 | 3 | 3,4 | 8 | 9,1 | |
| Parents | 2 | 2,3 | 3 | 3,4 | 5 | 5,7 | |
| **Cost Considerations** | | | | | | | |
| Yes | 3 | 3,4 | 3 | 3,4 | 6 | 6,8 | **0,05** |
| No | 33 | 37,5 | 49 | 55,7 | 82 | 93,2 | |
| **Mileage** | | | | | | | |
| < 15 Kms | 34 | 38,6 | 50 | 56,8 | 84 | 95,4 | **0,04** |
| > 15 Kms | 2 | 2,3 | 2 | 2,3 | 4 | 4,6 | |
| **Referral Mobilization** | | | | | | | |
| Ambulance | 28 | 31,8 | 34 | 38,6 | 62 | 70,4 | **0,129** |
| Self-Help Car | 4 | 4,5 | 10 | 11,4 | 14 | 16 | |
| Motorcycle/Motorized Pedicab | 4 | 4,5 | 7 | 7,9 | 11 | 12,5 | |
| Private Car | 0 | 0 | 1 | 1,1 | 1 | 1,1 | |

Source: Primary Data

Based on the data above, it appears that there is a very weak relationship between the mother's age factor and the incidence of stunting with r 0.024, where the age at risk is more dominant in causing stunting (62.5%) with detailed data, namely the very short stunting status, which is 37.5 percent, and the short stunting is 25%. Also, based on this data, it appears that there is a very weak relationship between ethnic groups and the incidence of stunting (r 0.031), with the incidence of stunting being more prevalent in the Mandar tribe in this table. With a r of 0.171, it appears that there is a very weak relationship between work and the incidence of stunting, with non-civil servant jobs being more dominant in causing stunting (68.2%), with data showing that stunting status is very short, namely 36.4 percent and short stunting status is 31.8 percent. With a r of 0.064, there is a very weak relationship between income and the incidence of stunting, with income > 2.5 million being more dominant in causing stunting (64.8 percent) and data showing that stunting status is very short, namely 39.8 percent and short stunting status is 25 percent.

In the data above, it appears that the referral decision has a very weak relationship with the incidence of stunting and r 0.092. When it comes to referral decisions, the husband has a greater influence than the others. With r 0.050, we discovered a very weak relationship between cost considerations and the incidence of stunting. Without the influence of cost considerations, the incidence of stunting is higher in families.

With r 0.040, a very weak relationship was found between the distance traveled and the incidence of stunting, with the incidence of stunting being higher at distances of 15 km, 95.4 percent. According to this data, there appears to be a very weak relationship between referral mobilization and the incidence of stunting and r 0.129, with referral mobilization using ambulance dominating at 70.4 percent.

## Discussion

Because toddlers do not appear to be sick, the problem of malnutrition or stunting is not easily recognized by the government, society, or even families. Malnutrition, such as malnutrition in adults, is not always preceded by a lack of food and hunger. This means that even when food is plentiful, malnutrition in children under the age of five may occur. Age, education level, ethnicity, occupation, income, referral decision, cost considerations, mileage, referral mobilization, and health insurance considerations are among the risk factors examined in this study to determine the possible causes of stunting. (7,8)

The sample in this study were mothers who had stunted children aged 2-5 years. The age ive range was chosen because the effect of malnutrition on height would appear in a relatively long period of time. This is because the group of toddlers aged 2 years and over is more at risk of suffering from stunting compared to children under 1 year of age. Toddlers aged 0-23 months have a low risk of stunting because of the protection they get from breast milk.(9)

The largest ethnic group in this study is the Mandar tribe, this could be because the indigenous tribe in

Mamuju is the Mandar tribe, while several other tribes, namely Bougenese, Makassar and Javanese in the research subject are residents who have lived and worked in Mamuju for a long time.

The age factor on the incidence of stunting was found to have a very weak relationship with r 0.024, where the age at risk was more dominant to cause stunting (62.5 percent) with data that the stunting status was very short, namely 37.5 percent and the short stunting status was 25 percent. Early marriage may put mothers at risk at a young age. According to the World Health Organization, early marriage is defined as marriage before the age of 18 years, and the causes of early marriage include a variety of factors, one of which is societal cultural and social norms. Having a mother marry at a young age results in a lack of psychological readiness for the mother as well as a lack of knowledge about nutrition and parenting for the children, which can result in stunting. Ingka et al found that was correlation between early marriage and teen pregnancy and toddler stunting. The study found that toddlers with parents who married young were more susceptible to growth and development disorders. (10–13)

Based on maternal income, it appears that there is a very weak relationship between income and the incidence of stunting with r 0.064, where income> 2.5 million is more dominant in causing stunting (64.8%) with data that stunting status is very short, namely 39.8% and short stunting status is 25%. This is different from the research of Aridiyah et al (2015) where the results of the study of mothers who had more stunted children at low economic status in North Maluku. In this study, even having a high level of maternal income was found to be a risk factor for stunting. This could be due to mothers' lack of knowledge about proper child nutrition. The mother's understanding of nutrition will influence her behavior when it comes to feeding her child. Mothers who are well-versed in nutrition can provide the appropriate type and quantity of food to support their children's growth and development.(14,15)

The relationship between the incidence of stunting in children and work has a very weak relationship with *r* 0.171 where, non-civil servant jobs are more dominant in causing stunting (68.2%) with data that the stunting status is very short, namely 36.4% and short stunting status is 31.8. %. This means that it is in line with what has been researched by Farah et al. That work does not have a strong relationship to the incidence of stunting. However, it is different from the research conducted in the city of Semarang, that work has a significant effect. It was found that mothers who have jobs tend to be short. This can happen because working mothers do not have much time to accompany their children, especially in providing good nutrition. Non-civil servant jobs such as self-employed people have less time with their children than civil servants who already have predetermined working hours.(2,11)

The relationship between the decision to referral was obtained by a very weak regression test between the referral decision on the incidence of stunting with a r 0.092. In the referral decision, the husband is more dominant in making decisions than the others. This could be because the husband is the head of the household so that more decisions are made by the husband.(16)

The distance obtained in the study is dominant at <15 km, namely 95.4% with an r value of 0.040, which is a very weak relationship between the incidence of stunting and the distance traveled. Children to the referral hospital for examination of nutritional status.

In this study also found a very weak relationship between mobilization of referrals to the incidence of stunting with a reference of 0.129, where mobilization of referrals using ambulance was more dominant, namely 70.4%. In this case, it can be seen that the participation of regional health facilities towards facilitating stunting children to be taken to a referral hospital in order to receive more specific monitoring by pediatricians and nutrition specialists in their growth and development.

Based on the results of the bivariate analysis, there is a very weak relationship between income with stunting status, ethnicity with stunting status, work with stunting status, income with stunting status, decision on referral with stunting status, consideration of costs with stunting status, distance traveled with stunting status and referral mobilization. with a stunting status. In addition to medicosocial factors, there are several other factors that can influence such as the mother's knowledge of good parenting and the nutrition the child needs for growth and development, medicoobstetry and maternal nutrition during pregnancy can be a factor in child stunting as well.

**Conclusion**

Based on the results of the research we conducted regarding the analysis of medicosocial determinant factors in mothers with stunted children in Mamuju district, West Sulawesi based on age, ethnicity, occupation, income, referral decisions, consideration of costs, distance traveled and referral mobilization, it can be concluded that the most influential determinants are employment and referral mobilization.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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# Risk Factors of Death among Children with Dengue Hemorrhagic Fever

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## ABSTRACT

**Introduction:** Dengue hemorrhagic fever (DHF) is still periodically around developing countries including Indonesia. Early diagnosis and adequate management may decrease either morbidity or mortality of patients with DHF.

**Methods**: We conducted a retrospective study by reviewing the medical records of children less than 18 years old hospitalized with DHF from January 2016 to December 2018. The diagnosis was based on WHO criteria and serologically positive anti-dengue Ig M or positive anti-dengue IgM and Ig G.

**Results:** During the study period, 70 patients aged 1-17 years with the complete medical records enrolled in this study. The DHF severity consisted of 37 cases (52.9%) with shock (DSS) and 33 cases (41. 7%) without shock and most of them were admitted to the hospital on >3 days of fever (63 cases /90.,0%). Boys were predominantly (39/55.,7%) found than girls (31/44.,3%) and the majority of cases above 5 years (50/71,4%) with well-nourished patients in 46 cases (65.,7%). The hematocrit level of≥ 40 mg/dl, platelets ≤ 40.000/mm$^3$, and leukocyte ≤ 4000 mm$^3$/l were observed in 41 cases (5.,6%), 36 cases (51.,4%), and 48 cases (68.,6%); respectively. Death was observed in four girls (5.7%) (p=0,034/OR 1,148/ 95% CI 1,003 - 1,315) with DSS because of severe conditions on admission.

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**Conclusion:** Our study found that death was mostly found in girls admitted to the hospital with late condition of dengue shock syndrome. Therefore, it is recommended for patients to early visit the primary healthcare facilities and be referred to the hospital for close monitoring and better management before the patients develop shock to decrease the mortality rate of patients with DHF

**Keywords**: Risk factor; death; dengue hemorrhagic fever; children

## Introduction

Dengue and DHF are still endemic in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. An estimated 50 million dengue infections occur worldwide annually and approximately 500,000 hospitalized cases with DHF, particularly in children. [1]

Children with severe DHF maybe falling into DSS event death if inadequately managed.[2,3]An approximately 90% of them are children aged less than five years and about 2.5% of the affected children die.[4]

Despite, prevention and control programs of DHF performed on a national scale by the Ministry of Health of Indonesia since 1968, there was an increase in the annual incidence rate of DHF in Indonesia, from 0.05 cases per 100,000 person-years in 1968 to 77.96 cases per 100,000 person-years in 2016 and in 2017, there were 59,047 and 444 of DHF cases and DHF-associated deaths; respectively, with case fatality rate of 0,75%. [5]

Therefore, we aimed to retrospectively review the death of DHF patients aged ≤ 18 years old hospitalized in Wahidin Sudirohusodo Hospital Makassar.

## Methods

We conducted a retrospective study by reviewing the medical records of children less than 18 years old hospitalized with DHF from January 2016 to December 2018. This study was approved by the Institutional Review Board of the Wahidin Sudirohusodo Hospital Makassar.

Patients with complete medical records during the study period were collected and reviewed. DHF was diagnosed based on WHO criteria guidelines and serologically positive anti-dengue Ig M or positive anti-dengue IgM and Ig G by ELISA technique were included in the present study. [6,7,8,9] The patients with comorbidities and incomplete medical records were excluded from the study.

Diagnosis of DHF was clinically based on 1) fever 2-7 days, 2) bleeding manifestations such as positive tourniquet test, petechiae, ecchymoses, bleeding from the mucosa, gastrointestinal tract, or other locations, 3) thrombocytopenia (platelet count < 100,000 /mm$^3$), 4)evidence of plasma leakage manifested as elevated hematocrit level > 20% from baseline or > 40%. Severity of DHF was adedas 1) Grade-I, if DHF with positive tourniquet test, 2) Grade-II, if spontaneous bleeding exists in addition to the manifestations of grade-I, 3) Grade-III, if evidence of circulatory failure manifested by a rapid, weak pulse and pulse pressure < 20 mmHg or hypotension for age with the presence of cold, clammy skin and restlessness, and 4) Grade-IV: Profound shock with undetectable blood pressure or pulse. Leukopenia was defined as leukocyte count <4000 mm$^3$/l); hemoconcentration was confirmed by elevated hematocrit level > 20% from baseline or > 40% or progressive increased periodically, and thrombocytopenia was established if the platelets count <100,000 mm$^3$/l (6,7,8) The laboratory investigations on admission were all performed at Wahidin Sudirohusodo Hospital laboratory including anti-dengue Ig M and Ig G, hematocrit level, platelets count, and leukocyte count.

Nutritional status was based on WHO (body weight/body height SD) criteria, categorized as well-nourished { (>90 / (+2 SD) – (- 2 SD)}, poorly-nourished { (< 70 / (- 3 SD), and overweight ({ (>100 / (>+ 3 SD) – ( + 3 SD)}.(10)Data of patients collected from the medical records including age, sex, nutritional status, duration of fever, grading of DHF, hematocrit level, platelets count, white blood cells, and outcome of patients.Data of the enrolled patients was collected and analysed with SPSS 21. A chi-square, Fisher's exact test, crude odds ratio (OR), and 95% confidence interval (95%CI) was used to determine the risk factors of death. A p-value < 0.05 was considered statistically significant.

**Result**

During the study period, 70 patients aged 1-17 years with the mean age of 8,17 years (SD4,47) were enrolled in this study. The DHF severity consisted of dengue shock syndrome in 37 cases (52,9%) and another 33 cases (41,7%) of DHF without shock. Boys were predominantly (39/55,7%) encountered than girls (31/44,3%) with mostly of the cases was observed in patients>5 years (50/71,4%) and 0 – 5 years in 20 cases (28,6%). Nutritional status of the patients in this study was mostly in well-nourished (46 cases/65,7%), followed by poorly-nourished 13/18,6% and overweight 9/12,9%. Most of the patients entered the hospital with fever >3 days (63 cases/90,0%) and ≤ 3 days in 7 cases (10,0%). Laboratory features of the patients were elevated hematocrit level of ≥ 40 mg/dl in 41 cases (58,6%) ranged from 38.20 to 49.00 % with the mean of 42.07% (SD 2.91) and the median of 41.00%, platelets count ≤ 40.000/mm$^3$in 36 cases (51.4%) ranged from 6000 to 98000 cells/mm$^3$ with the mean of 40.500, cells/mm$^3$ (SD 24757.81) and the median 35500.00 cells/mm3., and leukocyte count≤4000 mm$^3$/l in 48 cases (68,6%)ranged from 1600 to 5890 cells/mm3 with the mean of 3727,85 cells/mm3 (SD 890.378) and the median of 3700,00 cells/mm3.We observed 66 cases

(94,3%) were alive and 4 cases (5,7%) passed away all of them being girls with dengue shock syndrome baseline data of the patients shown in Table 1.

According to the statistical analysis, death was observed significantly in 4 girls (5,7%) with dengue shock syndrome (p0,034//OR 1,148/ 95% CI 1,003 - 1,315). We suspect that death in those patients were admission to hospital accompanied with severe condition. The outcome of children with DHF were shown in table 2.

**Discussion**

Seventy (70) patients with DHF hospitalized from2016 to 2018were enrolled in this study. Our observation revealed that boys predominantly (39/55,7%) suffered from DHF than girls (31/44.3%) with the most cases being in children > 5 years (50/71,4%). Faridi MA et al. also showed 76 % of all their patients aged ≥ 6 years old (11) and nearly similar to others observing DHF in patients aged 5 to 10 year old.(9,12) Sahana KS et al. documented that boys was slightly more affected than girls (12)as well as a study by Athira PP et el.34 cases(59,0%)on boys.(13)The average age of our patients was 8.17 ± 4.47 and almost similar to a study by Athira PP et al.(7.6 years ± 4.8).(13)

In the present study, the elevated hematocrit level > 40 mg/dl were found in 41 cases (58.6%), the platelets count<40000/$mm^3$ in 22 cases (31.4%), 40000- 98.000/$mm^3$in 48 cases (68.6%), and leukocyte count≤ 4000 $mm^3$/l in 48 cases (68,6%); respectively. The above three laboratory features may be considered as important clues to support the diagnosis of DHF. Faridi MA et al.[(11)]and Aggarwal A et al.[(14)] also reported the similar findings. Mittal H et al. documented that a positive tourniquet test and leukopenia are helpful in making early diagnosis of dengue infection with a positive predictive value of 70%–80%.(15)In our study, the anti-dengue Ig G and/or Ig M were positive in all patients for detection of dengue infection, which was almost similar to some previous studies.(16,17)

Although most of patients were alive, unfortunately4 girls (5.7%) died due to admitting to the hospital with the late phase of Dengue shock syndrome. Dhooria GS et al. noted that all of death in DHF patients belonged to DSS.(18)Our figure of death was relatively higher than Ahmed et al.(19)and Faridi MA et al.(11)observing death of 3% and 3.7%cases ; respectively and less than 6% cases of death studied by Agrawal A et al.(14)All of the death among DHF patients may be due to delayed diagnosis of subsequently management of patients with DHF.

**Limitation**

A major limitation of our study is that it is a retrospective study with secondary data collected from the medical records. This may draw the possibility of record bias and the data obtained were only from a single hospital. However, this study can be an important issue for the next multicentre hospital studies.

**Conclusion**

Our study found that death was mostly found in girls admitted to the hospital with late condition of dengue shock syndrome. Therefore, it is recommended for patients to early visit the primary healthcare facilities and be referred to the hospital for close monitoring and better management before the patients develop shock to decrease the mortality rate of patients with DHF. Further prospective study design in multicentre hospitals and a larger number of subjects are needed.

**Table 1. Baseline Data among Patients with DHF**

| Variables | Patients | |
|---|---|---|
| | Total | % |
| Age (years) | | |
| Range 1-17 | | |
| Mean 8,17 (SD 4,47) | | |
| Median 8,5 | | |
| 0-5 | 20 | 28,6 |
| > 5 | 50 | 71,4% |
| Sex | | |
| Boys | 39 | 55,7% |
| Girls | 31 | 44,3% |
| Nutritional status | | |
| Well-nourished | 46 | 65,7% |
| Poorly-nourished | 13 | 18,6% |
| Overweight | 9 | 12,9% |
| Duration of fever (days) | | |
| ≤ 3 | 7 | 10,0% |
| >3 | 63 | 90,0% |
| Leukocyte counts(cells/mm3) | | |
| Range 1600 - 5890 | | |
| Mean 3727,85( SD 890.378) | | |
| Median 3700,00 | | |
| ≤ 4000 | 48 | 68,6% |
| > 4000 | 22 | 31,4% |
| Platelets counts (cells/mm3) | | |
| Range 6000 - 98000 | | |
| Mean 40500 (SD 24757.81) | | |
| Median 35500.00 | | |
| ≤ 40.000 | 22 | 31,4% |
| > 40.000 | 48 | 68,6% |
| Hematocrit level (%) | | |
| Range 38.20-49.00 | | |
| Mean 42.07 (SD 2.91) | | |
| Median 41.00 | | |
| > 40 | 41 | 58,6% |
| ≤ 40 | 29 | 41,4% |
| DHF severity | | |
| Shock | 37 | 52,9% |
| No shock | 33 | 47,1% |

| | | |
|---|---|---|
| Death | | |
| Yes | 4 | 5,7% |
| No | 66 | 94,3% |
| Total | 70 | 100,0% |

**Table 2. Risk factors of death among patients with DHF**

| Variables | Death | | Total (n/%) | P value | OR | 95% CI |
|---|---|---|---|---|---|---|
| | Yes (n/%) | No (n/%) | | | | |
| Age<br>• 0-5 years<br>• > 5 years | 1/25,0<br>3/75,0 | 19/28,8<br>47/71,2 | 20/28,6<br>50/71,4% | 1,000 | ,825 | ,081 - 8,433 |
| Sex<br>• Boys<br>• Girls | 0/0.0<br>4/100,0 | 39/59.1<br>27/40,9% | 39/55,7<br>31/44,3 | 0,034* | 1,148 | 1,003 - 1,315 |
| Nutritional status<br>• Good<br>• Malnutrition<br>• Overnutrition | 2/50,0<br>0/0.0<br>2/50,0 | 46/69,7<br>13/19,7<br>7/ 10,6 | 48/68,6<br>13/18,6<br>9/12,9 | ,062 | NC** | NC** |
| Duration of fever<br>• ≤ 3 days<br>• >3 days | 0/0.0<br>4/100.0 | 7/10,6<br>59/89,4 | 7/10,0<br>63/90.0 | 1,000 | 1,068 | 1,001 - 1,139 |
| Leukocyte counts<br>• ≤ 4000<br>• > 4000 | 1/25,0<br>3/75.0 | 42/63,6<br>24/36,4 | 43/61,4<br>27/38,6 | ,291 | ,190 | ,019 - 1,934 |
| Platelets counts<br>• ≤ 40.000<br>• > 40.000 | 4/100.0<br>0/0.0 | 44/66,7<br>22/33,3 | 48/68,6<br>22/31,4 | ,301 | ,917 | ,842 - ,998 |
| Haematocrit level<br>• > 40<br>• ≤ 40 | 1/25,0<br>3/75.0 | 40/60,6<br>26/39,4 | 41/58,6<br>29/41,4 | ,300 | ,217 | ,021- 2,197 |
| DHF severity<br>• Shock<br>• No shock | 4/100.0<br>0/0.0 | 33/50.0<br>33/50.0 | 37/52,9<br>33/47,1 | ,117 | ,892 | ,797 - ,998 |
| Total | 4/5.7 | 66/94.3 | 70/100.0 | | | |

*Significant p-value. ** NC = not calculated


### Conflict of interest

None

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**ORIGINAL ARTICLE** **Open Access**

# Soil-Transmitted Helminthiasis, Nutritional Status, and Hemoglobin Levels of School-Age Children in Makassar

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## ABSTRACT

**Introduction:** Soil-transmitted helminthiasis (STH) is common in areas with poor sanitation. In Indonesia, the prevalence of the disease is still high ranging from 16–72%, despite the elimination efforts that have been done. This study aimed to determine the prevalence of STH, nutritional status, and hemoglobin levels of elementary school-age children in of slum area in Makassar.

**Methods:** This was an observational study with a cross-sectional approach. Subjects were 33 elementary school-age children in one of the slum areas in Makassar, South Sulawesi, Indonesia. Stool samples were collected and examined using the Kato-Katz method. Hemoglobin levels were examined with the Azidemet hemoglobin method using capillary blood samples. Assessment of nutritional status was carried out anthropometrically using weight for height, height for age, and body mass index (BMI) for age as indicators.

**Results:** The prevalence of STH in this study was 27%, all of them had low nutritional status. As many as 15% and 45% of subjects were severely wasted and wasted, respectively, based on the weight for height indication, 61% were wasted based on the BMI for age indicator, and 12% were stunted based on the height for age indicator. Ten percent of the subjects had low hemoglobin levels, none of them had STH.

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**Conclusion:** The STH prevalence of school-age children in one of the slum areas in Makassar is still high. Subjects with STH also experienced low nutritional status.

**Keywords**: STH; nutritional status; hemoglobin level, school-age children; Makassar

## Introduction

Neglected tropical diseases (NTDs) are a disease that affects more than 1 billion people and occur mostly in tropical and subtropical regions. The diseases are called neglected because it does not get attention like other diseases. Twenty diseases include in the NTDs group, one of them is Soil-Transmitted Helminthiasis (STH) (1).

There are more than 1.5 billion people who suffer from STH worldwide. The disease is common in the tropics and subtropics, especially in sub-Saharan Africa, China, and East Asia (2). In Indonesia, complete data on the prevalence of STH is challenging to find. However, there are data on the prevalence of STH from several cities in Indonesia which ranging from 16% to 72% (3)(4)(5)(6)(7).

STH is transmitted through worm eggs in human feces which will contaminate soil in poorly sanitized environments. The most common types of worms found in STH are roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and hookworms (*Necator americanus* and *Ancylostoma duodenale*) (2).

Clinical manifestations of STH are generally mild and non-specific and some are asymptomatic. Lack of appetite, abdominal pain or discomfort, diarrhea, and weight loss are some of the common clinical manifestations in STH. Anemia in STH may occur and is caused by intestinal mucosal bleeding or generalized inflammation (8).

Anthropometry is a measurement of nutritional status by comparing body size (weight, height, body mass index, head circumference, etc) with predetermined standards. (9). Several anthropometric indicators can be used to determine adults' nutritional status, such as weight, height, and body mass index (BMI). In children, weight, height, and BMI indicators are adjusted according to age (9). This study aimed to determine the prevalence of STH, nutritional status, and hemoglobin levels of elementary school-age children in a slum area in Makassar.

## Methods

This study was an observational study with a cross-sectional approach. The study was conducted in March–April 2020 in an elementary school in one of the slum areas in Makassar, South Sulawesi, Indonesia.

The sample collecting method was total sampling. The research subjects were all elementary school students present during the study and expressed their willingness (or represented by their parents) to participate by signing the informed consent form. The exclusion criteria in this study were students experiencing diarrhea during data/sample collection.

Before data collection, students and their parents received an explanation about the research procedure. After the explanation, the student's weight and height were measured and their blood was taken to check hemoglobin levels. Then, capillary blood collection and hemoglobin level examination were carried out by trained laboratory workers using the Azidemet hemoglobin method (10). The results of hemoglobin levels are compared with normal hemoglobin values for children by age (11).

All anthropometric measurements were carried out by trained enumerators using calibrated instruments. Each measurement was carried out twice and the average value was calculated. If there was a difference greater than 0.2 kg or 0.2 cm in two measurements, the same enumerator made a third measurement. BMI was calculated by dividing the child's weight in kilograms by the square of height in meters. The measurement results are plotted into Z score tables.

Before going home, each student received equipment for stool collection, i.e. stool pots, stool scoops, and gloves. Students and parents are asked to fill the bench pot with a student stool which is approximately the size of a teaspoon. The pot filled with feces, was immediately given to the laboratory assistant to be examined in the laboratory on the same day using the Kato-Katz method. The results of the stool examination were qualitative.

The data obtained from the research subjects were processed using the Statistical Package for Social Sciences (SPSS) 20 program.

This research has received approval from the Health Research Ethics Commission of the Universitas Muslim Indonesia and the Ibnu Sina Hospital of the UMI Waqf Foundation with the registration number UMI012002047.

## Result

A total of 33 boys and girls aged 7-13 years were included in this study. The data on the characteristics of the subjects are presented in the following table.

**Table 1. Characteristics of the Subjects (N = 33)**

| Characteristics | n | % |
|---|---|---|
| Sex | | |
| Girl | 20 | 61% |

| | | |
|---|---|---|
| Boy | 13 | 39% |
| STH | | |
| Positive | 9 | 27% |
| Negative | 24 | 73% |
| Nutritional status (Weight for height) | | |
| Obese | 0 | 0% |
| Normal | 13 | 39% |
| Wasted | 15 | 45% |
| Severe wasted | 5 | 15% |
| Nutritional status (Body mass index for age) | | |
| Obese | 0 | 0% |
| Normal | 13 | 39% |
| Wasted | 20 | 61% |
| Severe wasted | 0 | 0% |
| Nutritional status (Height for age) | | |
| Tall | 0 | 0% |
| Normal | 29 | 88% |
| Stunted | 4 | 12% |
| Severe stunted | 0 | 0% |
| Hemoglobin levels | | |
| Normal | 30 | 90% |
| Low | 3 | 10% |

A total of 27% of the subjects were identified as having STH, and 67% of them (having STH) were wasted (BMI for age), 22% were stunted (height for age), 33% were wasted (weight for height), and 33% were severely wasted (weight for height). None of the subjects with STH had low hemoglobin levels.

**Table 2. Nutritional status of STH identified subjects (N = 9)**

| Characteristics | n | % |
|---|---|---|
| Nutritional status (Weight for height) | | |
| Obese | 0 | 0% |
| Normal | 3 | 33% |
| Wasted | 3 | 33% |
| Severe wasted | 3 | 33% |
| Nutritional status (BMI for age) | | |
| Obese | 0 | 0% |
| Normal | 3 | 33% |
| Wasted | 6 | 67% |
| Severe wasted | 0 | 0% |
| Nutritional status (Height for age) | | |
| Tall | 0 | 0% |
| Normal | 7 | 78% |
| Stunted | 2 | 22% |

| Severe stunted | 0 | 0% |
|---|---|---|

**Discussion**

*Ascaris lumbricoides* is spread almost all over the world, especially in areas with poor sanitation (12). Ascaris worms live in the human intestine. Ascaris worm eggs come out with feces from a person with Ascariasis (8). Therefore, soil contamination by Ascaris eggs occur if the patient defecates on the soil. The entry of Ascaris mature eggs in the human body can occur in several ways, namely (2): 1) A person consumes vegetables or fruit contaminated with Ascaris mature eggs (vegetables or fruit is not washed and appropriately cooked), 2) A person consumes water that has been contaminated with Ascaris eggs, and 3) Children play on soil contaminated with Ascaris mature eggs and then eat or touching their mouth without washing their hands first.

STH affects the digestion of food. Cumulatively, STH (*A. lumbricoides*) can cause a loss of nutritional needs due to a lack of calories and protein as well as the occurrence of blood loss due to damage to the intestinal mucosa by hookworms (*Necator americanus* and *Ancylostoma duodenale).* Besides inhibiting physical development, intelligence, and work productivity, STH can also reduce the body's immunity so that the body is susceptible to other diseases (2).

Patients with STH are generally asymptomatic or only show mild symptoms such as abdominal discomfort or abdominal pain. In severe conditions, many adult worms in the intestine will cause intestinal obstruction which will inhibit the absorption of food. This condition causes nutritional disorders in people with worms (13). In this study, it was found that all subjects who experienced STH had low nutritional status.

This study also found that 67% of subjects who did not experience STH also had low nutritional status. This may be due to the inadequacy of the subject's nutritional intake. STH, which occurs in patients who have previously experienced malnutrition, will further aggravate the condition of malnutrition.

The majority of subjects had normal hemoglobin levels and only 3 (10%) subjects had low hemoglobin levels. Two of the three subjects who had low hemoglobin levels also had low nutritional status (BMI for

age) while one other subject had low BMI for age and height for age. None of the three subjects were infected with STH. It was indicated that this low hemoglobin might be due to malnutrition rather than STH.

**Conclusion**

The high prevalence of STH among elementary school-aged children in one of the slum areas in Makassar city indicates that there are still many STH cases in Makassar. Apart from medical treatment, preventive efforts such as education on clean and healthy living behavior must continue to be encouraged to reduce the prevalence of STH to a minimum.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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# Maternal Age Distribution of Down-Syndrome at Pediatric Growth and Development Clinic, 2015-2019

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## ABSTRAT

**Introduction:** Down Syndrome is a common chromosome abnormality among infants. This condition is Present in 1 over 800 deliveries. Advanced maternal age is a risk factor for Down syndrome. Other miscellaneous factors are radiation, infection, autoimmune and paternal age. The Aim is to determine maternal age distribution of Down syndrome at pediatric growth and development polyclinic, Wahidin Sudirohusodo hospital.

**Methods:** A Descriptive study. Study population was all outpatients at Pediatric Growth and Development polyclinic, Wahidin Sudirohusodo hospital in Makassar 2015-2019. Samples in this study were collected from total sampling of population data that met the criteria of new Down syndrome patients with complete medical records

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**Results:** This study found 237 new pediatric down syndrome patients admitted to growth and development polyclinic from January 2015 – December 2019, 95 complete medical records from 237. 52% (49) boys, 48 % (46) girls from 95 children. No gender difference was found in the presentation. Parental age of Down syndrome patients, the most advanced maternal age was >35, found 46 (48,42%), the most advanced paternal age was >35, found 63 (66,32%). Parity < 3rd, the most maternal age between 25-35 (23,16%), parity ≥ 3rd, the most maternal age was >34, found 30 (31,57%).

**Conclusion.** Advance maternal and/ or paternal age is a risk factor of Down Syndrome.

**Keywords:** Maternal age; Down Syndrome; Child growth and development

**Introduction**

Down Syndrome is a common chromosome abnormality among infants. This condition presents in 1 over 800 deliveries. Most of the cases (92.5%) due to nondisjunction; as a result of nondisjunction, fertilized ovum comprised from three duplication of chromosome 21 (trisomy 21); using standard cytogenetic nomenclature, trisomy 21 set as 47, XXX, +21 or 47, XY, +21. [1]

In 1866, John Langdon Haydon Down initially described clinical features and health problems corresponding with Down Syndrome. Lejune and Jacobs, in 1959, first time found this abnormality due to Trisomy 21. This trisomy consists of 3 types. First, nondisjunction or failure of separation during meiotic phase of the oocyte. This is the most common type (94%) in Down Syndrome. Second, a translocation type which consists of some or entire extra chromosome 21 joining with other chromosomes (chromosome 14, or 15, or 21, or 22), this type covers 3.5% of the cases. Third, a mosaic type. A mixture between normal diploid and cell that develops trisomy 21, nondisjunction occurs in mitosis during early embryogenesis; covers 2,5% of the cases.

First type related to the increasing maternal age during conception. On the second type, no age related found, around 75% translocation occurs de novo, and around 25% occurs genetically. The third type, mosaic, usually owns phenotype features slightly better than trisomy 21 or translocation of chromosome 21.[2]

Light/moderate cognitive disturbance is a characteristic of Down-Syndrome, such as hypotonic. This newborn could develop long-term physiology icterus, polycythemia and temporary leukemoid reactions. Eating disorders may develop during the infant period. Around one- third to half of Down syndrome child, frequently develop endocardial or other septal disorders. [3]

Advanced maternal age is a risk factor of down syndrome, but recent studies showed that young maternal age are vulnerable. [4] Many cases of child with down syndrome from young mothers were related with alcohol, cigars, poison and drugs that may cause nondisjunction. [5] Other miscellaneous factors are radiation, infection, autoimmune and paternal age. [2]

*World Health Organization* (WHO) 2018 estimates there are 8 million with syndromes disability in the

world. Specifically, there are 3,000-5,000 children born with chromosomal abnormalities per year. Riset Kesehatan Dasar (Riskesdas) 2018, Health ministry has announced, in Indonesia, there were 0.12% people with Down syndrome in 2010. This figure increased to 0.13% in 2013 and in 2018 increased to 0.21%. The number of new cases of Down syndrome outpatients in Indonesia hospital based from SIRS Online report 2015 data found 768 men, 889 women, in 2016 2,238 men, 2,011 women, and 2017 2,006 men, 2,124 women. [6,7,8]

This study aims to determine maternal age distribution of Down syndrome at Pediatric Growth and Development Polyclinic, Dr. Wahidin Sudirohusodo hospital in Makassar for the period of 2015-2019.

## Methods

This study is a retrospective method with data collection of Down syndrome outpatient medical records at Pediatric Growth and Development, Wahidin Sudirohusodo hospital for the period of 2015-2019.

The study population was medical record data of outpatients at Pediatric Growth and Development, Wahidin Sudirohusodo from January 2015 to December 2019. Samples in this study were collected from total sampling of population data that met the criteria of new Down syndrome patients with complete medical records.

## Result

In this study, 237 children admitted to Growth and Development clinics as new Down syndrome patients from January 2015 to December 2019, 95 were obtained from 237 complete medical record data. Table 1 shows the characteristics of Down syndrome patients, male 49 (51.57%) and female 46 (48.43%). Observed from the age of visitation at Growth and Development clinic, Wahidin Hospital, the most cases are between 1 month - 2 years of age, counted as 74 children (77.89). The order of delivery in most Down syndrome patients found the third parity 30 (31.57%) and the first parity 28 (29.47%). Planned pregnancies were 65 (68.42%) and the unplanned were 30 (31.52%).

**Table 1. Characteristics of Down Syndrome Patients**

| Characteristics | n | % |
|---|---|---|
| Gender | | |
| Male | 49 | 51,57 |
| Female | 46 | 48,43 |
| Age of visitation | | |
| 1 month - 2 years | 74 | 77,89 |
| 3 years- 4 years | 10 | 10,61 |
| 5 years-6 years | 5 | 5,2 |
| 7 years-8 years | 1 | 1,05 |
| 9 years-10 years | 2 | 2,1 |
| 11 years-12 years | 2 | 2,1 |
| 13 years-14 years | 1 | 1,05 |

| | | |
|---|---|---|
| Parity | | |
| 1st | 28 | 29,47 |
| 2nd | 17 | 17,89 |
| 3rd | 30 | 31,57 |
| 4th | 13 | 13,71 |
| 5th | 3 | 3,16 |
| 6th | 2 | 2,1 |
| 7th | 2 | 2,1 |
| Planned/ Unplanned pregnancies | | |
| Planned | 65 | 68,42 |
| Unplanned | 30 | 31,52 |

Table 2 shows maternal age from children with Down syndrome, 46 (48.42%) >35 years old (48.42%), age between 35-35 years old 43(45.26%). Most paternal age > 35 years old were 63 (66.32%), age between 25-35 years were 29 (30.53%).

**Table 2. Maternal and Paternal Age**

| Age (years) | Maternal | | Paternal | |
|---|---|---|---|---|
| | n | % | n | % |
| <25 | 6 | 6,32 | 3 | 3,16 |
| 25-35 | 43 | 45,26 | 39 | 30,53 |
| >35 | 46 | 48,42 | 63 | 66,32 |

Table 3 parity and maternal age, parity < 3rd the most maternal age between 25-35 years old were 22 (23,16%), parity ≥ 3rd the most maternal age >35 years old were 30.

**Table 3. Parity and Maternal Age**

| Parity and Maternal age | n | % |
|---|---|---|
| < 3rd | | |
| < 25 years | 6 | 6,32 |
| 25 - 35 years | 22 | 23,16 |
| > 35 years | 16 | 16,84 |
| ≥ 3rd | | |
| < 25 years | 0 | 0 |
| 25 - 35 years | 21 | 22,11 |
| > 35 years | 30 | 31,57 |

Table 4 shows the hemoglobin levels of patients with Down syndrome when they first admitted at Pediatric Growth and Development Clinic, Wahidin hospital. The table shows the list of hemoglobin levels by age. At <6 months, 3 had hemoglobin levels below normal <9 g / dl. For ages between 6 months-6 years, 11 had hemoglobin levels below normal <11 g / dl. Between 6 years and 12 years of age, there are no hemoglobin levels below normal. The ferritin level of Down syndrome patients when first admitted at Pediatric Growth and Development Clinic, Wahidin hospital. The highest ferritin levels between 30-100, 28

(48.28%), the ferritin levels <30 were 22 (37.93%).

**Table 4. Hemoglobin and ferritin level of patients with Down syndrome**

| Level | n | % |
|---|---|---|
| Hb | | |
| < 6 month | | |
| <9 gr/dl | 3 | 9,09 |
| >9 gr/dl | 30 | 90,91 |
| 6 month – 6years | | |
| <11 gr/dl | 11 | 22,44 |
| >11 gr/dl | 38 | 77,56 |
| >6 years | | |
| <12 gr/dl | 0 | 0 |
| >12 gr/dl | 7 | 100 |
| Ferritin | | |
| <30 | 22 | 37,93 |
| 30-100 | 28 | 48,28 |
| >100 | 8 | 13,79 |

Table 5 shows the examination of FT4 and TSHS levels in Down syndrome patients when first admitted at Pediatric Growth and Development Clinic, Wahidin hospital. 81 showed normal FT4 levels and only 1 had low Ft4 levels. Normal children's TSHS level was 38, and those who experienced an increase of TSHS were 50.

**Table 5. FT4 and TSHS level of patients with Down syndrome**

| | FT4 | | | TSHS | | |
|---|---|---|---|---|---|---|
| | <0,3 | 0,3-1,71 | 1,71 | <0,27 | 0,27-4,2 | >4,2 |
| Total | 1 | 81 | 6 | 0 | 38 | 50 |

**Discussion**

In this study, 237 children with Down syndrome enrolled at Pediatric Growth and Development Clinic from January 2015-December 2019, from 237 complete medical record data were obtained, namely 95 children. 95 male 49 (51.57%) and 46 female (48.43%) the prevalence of Down syndrome based on gender was not significant difference, this is in line with the results of new Down syndrome outpatients in Indonesia hospital based from SIRS Online report 2017 data for male 2,006, female 2,124.[6]

Down syndrome is categorized into three types based on its pathogenesis, failure to separate (nondisjunction), translocation, and mosaic. The category of nondisjunction Down syndrome related to maternal age. The age of the pregnant mother is related to the length of meiosis. The length of time allows the destruction of proteins that have a role in the process of separating chromosomes 7, in this study maternal age > 35 years was 48.42%. In line with previous studies, Down syndrome increases in maternal age over 30 years to 45 years. On the other hand, the age of the paternal has a minor role in the occurrence of Down syndrome. A recent systematic review study concluded that paternal age is associated with a slight increase in the

incidence of trisomy 21. Paternal age over 49 years showed an increased incidence of Down syndrome .[10] Age-related epigenetic changes in sperm. In men, age has an impact on mitosis rather than meiosis. Although mitotic errors are thought to be more relevant in older age, paternal meiotic errors are reported to account for about 10% of Down's syndrome cases.[11]

In this study, the percentage of young mothers with Down syndrome children was quite high. Research in Bosnia and Herzegovina shows the prevalence of young mothers with Down syndrome children were due to only advance maternal age were able to undergo amniocentesis and those who have large percentage of pregnancies with Down syndrome end in abortion. It is likely that young mothers lack sleep, an unbalanced diet, a lot of burden that leads to an unhealthy pregnancy. Habitual risk factors for young mothers and often associated with unwanted pregnancy.[5]

There have also been reports of a positive association between parity and Down syndrome in women who are younger (less than 35 years) and older (over 35 years). Women with parity> 3 should have prenatal screening for Down's syndrome. In this study, the frequency of Down's syndrome delivery is higher in the third child onwards, which is in line with previous studies. Therefore higher parity is a contributing factor in bearing a child with Down syndrome. [12]

The age of the mother and / or father is a risk factor for Down's syndrome, this study shows that young mothers are also vulnerable. A study in India found that 80.7% of trisomy 21 children were born to mothers aged 30 years, even though the mean age, 23 was low, 17 years was the first child.[13]

Hb levels that were below normal were only found in some patients, but ferritin levels were between 30-100, around 48.28 %%. This study shows that most children still experience iron depletion. The incidence of iron deficiency anemia in children with Down syndrome is increasing. Recommendations for anemia screening are based on the fact that irreversible cognitive impairment is associated with iron deficiency anemia and as children with Down syndrome are at higher risk for neurocognitive deficits. Previous research has shown lower iron intake among 10 children with Down syndrome. This is due to eating disorders in children with Down syndrome.[14]

Down syndrome is associated with an increased risk of endocrine disorders, especially thyroid disorders. The prevalence of congenital hypothyroidism in Down syndrome is estimated to be 28-35 times higher than the prevalence in the general population. Most of the reported cases of congenital hypothyroidism are due to thyroid hypoplasia. Normal FT4 levels were 81 children, but there were many increases in TSHS levels, namely 50 children. The presence of congenital hypothyroidism which is a differential diagnosis of Down syndrome. One of the other types of disorders is subclinical hypothyroidism, increased TSHS and normal thyroid hormone. In this study most likely were subclinical hypothyroidism. [15]

## Conclusion

The advanced age of the mother is a risk factor for Down syndrome. Our results also show a high incidence of Down's syndrome in the maternal age group <35 years, and a reason for a multidisciplinary approach to identify triggers for trisomy.

## Suggestion

Further study to assess risk factors and conditions during pregnancy can help us to develop strategies that minimize the incidence of Down syndrome.

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ORIGINAL ARTICLE Open Access

# Study of Differences in Children Nutrition Status Aged 6-24 Months with Exclusive and Non-Exclusive Breastfeeding in Mattampa Bulu Village

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## ABSTRACT

**Background: :** Breast milk is the most ideal biological and physiological first food during the growth and development process due to the presence of protective and nutritional factors and also the needs of children according to their age and phase of growth and development.

**Methods:** This study aims to determine differences in nutritional status based on BB/U and PB/U for children aged 6-24 months in Mattampa Bulu Village. This study used 47 samples which were measured for body weight and length then the mother filled out a questionnaire.

**Result**: The results of the study using the Chi Square test showed that there was a significant difference between nutritional status based on body weight in children with exclusive and non-exclusive breastfeeding history with $p < 0.05$ (p = 0.011), but there was no difference in nutritional status based on PB/ U with $p > 0.05$ (p=0.913).

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**Results:** Based on the research, it may be concluded that children with exclusive breastfeeding have good nutritional status based on the indicators of BB/U and there is no difference in the incidence of stunting in children with a history of exclusive and non-exclusive breastfeeding

**Keywords**: Exclusive Breastfeeding; Non-Exclusive Breastfeeding; Nutritional Status

**Introduction**

Breast milk is the most ideal biological and physiological first food during the growth and development process due to the presence of protective and nutritional factors and according to the needs of infants in the first 6 months of life where the highest metabolic rate and growth occur at this time.[1,2] This is according to the United Nations Children Fund (UNICEF, 2016) which were later adopted by the Government of Indonesia through PP No.33 of 2012 Article 2 by setting a target of achieving 80% exclusive breastfeeding for 6 months, which previously was only 4 months. It aims to achieve the SDGs in 2030 which contains 17 goals with 169 targets, on point “Ending Hunger” which targets nutrition improvement and “Good Health and Prosperity”.[3]

Epidemiological data shows that the National Exclusive Breastfeeding graph from year to year has fluctuated until in 2018 it was at 65.16%. As for regionally in South Sulawesi, it was 73.56%. Even though the above percentage is from the national figure, exclusive breastfeeding in South Sulawesi Province is still considered lacking because it has not reached the national target. In Bone district itself, the coverage of exclusive breastfeeding has not yet reached the target, according to the Health Office of South Sulawesi which reached the target only East Luwu Regency (87.1%), North Luwu Regency (84.8%), Sinjai Regency (83.8%). , and Soppeng Regency (81.2%). As for nutrition problems, Bone Regency is included in the 5 districts with the highest cases of malnutrition (BB/PB), namely 8.9% and malnutrition (BB/U) 36.08%, and stunting (TB/U) 34.3%. Lamuru Health Center is one of the health service units in Lamuru District that covers 12 villages/ward with 28 integrated healthcare centers. Among the 12 villages/ward, according to the monthly report for the November 2019 period, there are villages with the highest number of BRL (Below the Red Line) nutritional status cases, namely Mattampa Bulu village with 3 cases of 100% exclusive breastfeeding coverage.[4] Children with a history of not getting exclusive breastfeeding are known to be 10% sick and continue to die at the age of less than 5 years. This can reduce the quality of Human Resources (HR) related to intelligence, productivity, and individual creativity with poor nutritional status which has an impact on achievement and low performance that will affect life, family, and the next generation, as in Islam on how to prepare and make their descendants to become a quality generation, can be realized by giving the best

nutrition which is breast milk that explained in QS Al-Baqarah/2: 233. The sentence explained that Al-Qur'an has outlined that breast milk, both by biological mother or not, is the best nourishment for infants up to 2 years old as an order not an obligation. However, it was a suggestion that was strongly emphasized, as if it was an obligatory command.[5]

Based on the information above, the authors are interested in examining differences in nutritional status based on BB/U and PB/U in children aged 6-24 months with exclusive and non-exclusive breastfeeding history in Mattampa Bulu Village.

**Methods**

This research was conducted in Mattampa Bulu Village, Lamuru District, Bone Regency for 1 month. This research is a descriptive survey research using a cross sectional study approach. The population in this study were all children aged 6-24 months who live in Mattampa Bulu Village, Lamuru District, Bone Regency. The sample used was determined using a simple random sampling technique with inclusion criteria, namely willing to be a respondent, children aged 6-24 months, born full month by weight ≥ 2500 grams without complications and exclusion criteria. Not willing to be a respondent, date, month, and the year of birth of the baby is unknown, the respondent's mother suffers from a mental disorder, or is unable to communicate, and the child has a congenital disease or other chronic disease that can interfere with growth and development. The number of samples used in this study was determined using the Slovin formula with the results of 47 children.

The sample was then measured its weight using *baby scale* and body length using a length board which is then converted into a Z-score and interpreted based on the WHO-NCHS growth chart, where BB/U is categorized as over nutrition (>+2 SD), good nutrition (-2SD to +2SD) and poor nutrition (-3SD to <-2SD) and PB/U are categorized into stunting (<-2 SD) and not stunting (≥-2 SD) -. Then to find out the breastfeeding history, the mother was given a questionnaire containing questions about the identity of the mother, father, and child as well as the breastfeeding history which was validated through an interview.

The data obtained were then processed using Statistical Package Social Science (SPSS) for windows with un-variety analysis to determine the frequency distribution of respondents' characteristics and using the Chi Square test to determine the significant relationship between variables with a significance value of $p < 0.05$.

**Result**

**Table 1. Frequency Distribution of Respondent Characteristics based on Children's Age, Childrend's Gender and Exclusive Breastfeeding History in Mattampa Bulu Village 2020**

| Characteristic | | Frequency | Percentage |
|---|---|---|---|
| **Children's Age** | 6-11 | 13 | 27.6 |

| | | | |
|---|---|---|---|
| | 12-17 | 20 | 42.6 |
| | 18-24 | 14 | 29.8 |
| **Children's Gender** | Male | 25 | 53.2 |
| | Female | 22 | 46.8 |
| **Exclusive Breastfeeding History** | Yes | 28 | 59.6 |
| | No | 19 | 40.4 |

The results of the un-variety analysis obtained the frequency distribution of the respondent's characteristics which can be seen in table 1. Based on Table 1 shows that the age group of respondents at most is 12-17 months with a total of 20 respondents (42.6%) and the least is 6-11 months with a total of 13 respondents (27.6%). The frequency distribution of respondents based on gender in Table shows that it was dominated by boys with a total of 25 children (53.2%) and girls as many as 22 children (46.8%). The frequency of distribution of respondents based on breastfeeding history shows that children with exclusive breastfeeding are 28 children (59.6%) and non-exclusive breastfeeding are 19 children (40.4%).

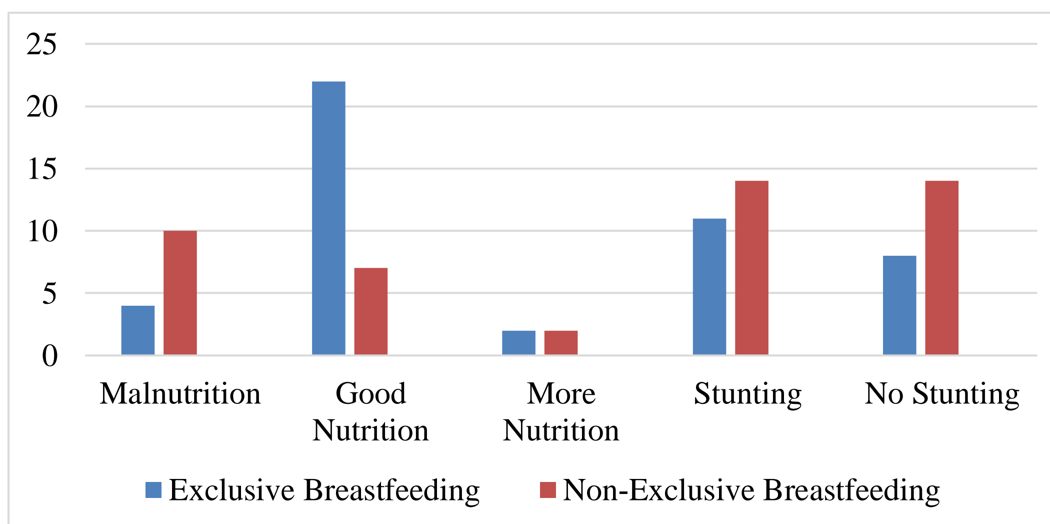
**Table 2. Relationship between Exclusive and Non-Exclusive Breastfeeding with Nutritional Status**

| Nutritional status | Exclusive Breastfeeding (n) | | *p-value* |
|---|---|---|---|
| | Yes | Not | |
| **BB/U** | | | |
| **Malnutrition** | 4 | 10 | 0.011 |
| **Good Nutrition** | 22 | 7 | |
| **More Nutrition** | 2 | 2 | |
| **PB/U** | | | |
| **Stunting** | 11 | 14 | 0.91 |
| **No Stunting** | 8 | 14 | |

Table 2 shows the results of bivariate analysis with $p < 0.05$ ($p = 0.011$), which means that there is a significant relationship between nutritional status based on body weight in children aged 6-24 months with exclusive and non-exclusive breastfeeding history in Mattampa Bulu Village.

Table 2 shows the results of bivariate analysis with $p < 0.05$ ($p = 0.913$), which means that there is no significant relationship between nutritional status based on PB/U in children ages 6-24 months with exclusive and non-exclusive breastfeeding history in Mattampa Bulu Village.

**Graph 1. Frequency Distribution of Nutritional Status of Children Aged 6-24 Months with a History of Exclusive and Non-exclusive Breastfeeding in Mattampa Bulu Village 2020**




From Graph 1, the difference in the frequency distribution of nutritional status can be seen based on BB/U and PB/U in children with exclusive and non-exclusive breastfeeding history. Nutritional status based on body weight is dominated by good nutrition with exclusive breastfeeding history and more or less nutrition is experienced by children with non-exclusive breastfeeding history. As for the nutritional status based on PB/U, the number of stunted and non-stunted children is the same in children with exclusive breastfeeding history and for children with a history of non-exclusive breastfeeding more stunting.

## Discussion

### a. Relationship between Nutritional Status (BB/U) with Exclusive and Non-Exclusive Breastfeeding History

From the results of the study, children with good nutrition who have exclusive breastfeeding history are 22 children, but there are still 7 children who have non-exclusive breastfeeding history, this was cause by their mothers who work so the high mobility and activities outside the house make the baby suction stimulation on the nipple is reduced which can physiologically affect milk production. Lack of maternal knowledge, makes them choose not to give breast milk or try to stimulate milk production through baby sucking and replace it with formula milk or giving MP-ASI before the age of 6 months, which can change children's food habits so that in the end they no longer want to consume breast milk or in some cases the baby has nipple confusion, based on some mothers' statements from interviews. Besides that, work can also increase maternal stress. Stress can trigger the secretion of adrenaline which can cause vasoconstriction of blood vessels in the alveoli, resulting an impaired let-down reflex so that milk does

not flow.[5,6]

According to Molgaard (2011), there is a correlation between a child's weight and exclusive breastfeeding because the whey protein content of 60% in breast milk is known to increase muscle mass. Whey protein contains amino acids that are very similar to muscle protein and has many branched chains of amino acids that can increase protein synthesis in muscle. The high content of lysine and arginine can stimulate anabolic hormones, namely growth hormones which play a dominant role in the growth phase of children. Oligosaccharides are also known to have an effect on growth.[7]

Whey protein: casein is also found in formula but in smaller amounts, namely 20%: 80%. While in breast milk 60%: 40%. It is said that the composition of nutrients in breast milk is more optimal for infant growth. Some literature also says that formula-fed children have a bigger risk of developing obesity in later life.[8] This is based on the casein protein content in formula milk which can stimulate insulin growth factor 1 (IGF-1) which synergizes with anabolic hormones and has a proteolysis inhibitory effect. Although the protein is present in formula milk, the ratio of whey protein: casein in breast milk is far more optimal and easily absorbed by the baby's digestion.[1]

Another factor that also plays a role in exclusive breastfeeding is motivation. Even if the mother works or has less milk production, with high motivation, she will always try to breastfeed her baby under any circumstances. Because children are a gift as well as a great responsibility from Allah swt to parents (mother and father). Because the meaning of a child is so great, his presence is highly anticipated. In historical flashes, many prophets and apostles prayed to Allah swt so that they would be blessed with a child, who not only asked for the gift of mere offspring, but also descendants who had pious qualities, thayyiban, qurrata a'ayun and imam al-muttaqin. Among the efforts to get a child who is thayyibah since the beginning of his birth is by giving exclusive breastfeeding.[5]

The high urgency of the parental responsibility in this case for mothers to give exclusive breastfeeding which in QS Al-Baqarah/2: 233 has been explained and as the hadith of the Prophet Muhammad, namely:

*"A husband is the leader of his family members and will be asked about the family he leads. A wife is the head of her household and children and will be asked about her responsibilities.* " HR. Bukhari: 2278

**b. Relationship between Nutritional Status (PB/U) and Exclusive and Non-Exclusive Breastfeeding History**

The results of the statistical test in table 4.26 show that there is no significant relationship (p-value: 0.913) between the exclusive and non-exclusive breastfeeding history on the child's PB/U. This is in accordance with the research of Azevedo, et al (2019) which said that there was no significant

relationship between body length (PB/U) of toddlers (6-59 months) to the history of exclusive and non-exclusive breastfeeding with p value = 1.00.

The PB/U indicator is used to interpret the linear growth of children who are further categorized as stunting or not. Stunting occurs in children with chronic malnutrition, certain nutritional deficiencies, and chronic infectious diseases.

However, according to Yablonski (2015) malnutrition or deficiency of certain nutrients is related to children's linear growth problems or called stunting. The linear growth of the appendicular skeleton is the result of a cascade formed in the cartilaginous growth center of long bones, called the epiphyseal growth plate (EGP) which is controlled by complex interactions between growth hormone and extracellular matrix components. Good nutrition will ensure the availability of "building blocks" for the growth process including proteins, lipids, and carbohydrates. Thus, malnutrition can impair the longitudinal growth rate of bone and reduce the length of the EGP. Animal studies have demonstrated a link between the effects of protein malnutrition on linear growth, but in humans it is still difficult to determine specifically the role of nutritional, environmental, and hormonal factors such as IGF-1, thyroid hormone, leptin, and sex hormones that can stimulate fibroblast growth factor 21 and vitamin D which can also be caused by nutritional and environmental factors. Moreover, it is known that growth hormone (GH) plays a dominant role in the growth phase of children.[9,10]

The results of the study found that from 47 children there were 25 children (53.2%) who were stunted. According to the researchers' observations, one of the factors that may play a role is the culture of the local community. In the research process, the researchers found a quite interesting culture from the research location area, namely "Mabakkang". In this Mabakkang tradition, people who are in the territory of the customary holders, which are included in the research location, are required not to consume any type of meat within 40 days at any given time. Limitation consumption of meat, which is a source of animal protein and iron, forming new tissue during growth, in a long time can cause protein deficiency which will inhibit its growth. This is in accordance to Nuryanto's research (2016) which states that there is a significant relationship between protein intake and Z-score TB/U in toddlers. Where Indonesia is also known to be a country with a higher protein energy deficiency (PEM) rate than other ASEAN countries and South Sulawesi is included in an area with low protein consumption per capita.[11]

In addition, for mothers who carry out this tradition, breastfeeding mothers need more protein intake which has been regulated in the lactation RDA of +20 grams/day. Protein production in milk for 6 months total exclusive breastfeeding is about 1,500 g (1.5 kg). For a 60 kg woman with 25% body fat, lean body mass is 45 kg, or about 11 kg protein. Assuming that the efficiency of conversion from body protein to milk protein is approximately the same as the conversion of dietary protein to milk protein (70%), a woman consuming only the RDA for protein for non-pregnant and non-lactating women needs

to mobilize about 19% of tissue body to support milk production for 6 months. That is, if the intake of protein from the mother's diet is less, then the production of protein in milk will also be reduced, which is needed for infants 0-6 months at least 9 grams/day (National Academy Press, 2001). In addition, it is known that mothers who are malnourished or who experience CED during pregnancy can cause intrauterine growth restriction (IUGR) which contributes to the incidence of stunting in children.[12]

The theory states that the prevalence of stunting and linear growth of the body is absolutely influenced by intake, with intake that meets the NAN (Nutrition Adequacy Number) then toddlers will grow optimally, intake that meets the NAN must meet 13 general guidelines for balanced nutrition, which includes carbohydrates, proteins, vitamins, minerals, and water (Latif, 2017). Thus, children who do not receive exclusive breastfeeding but receive nutritional supplementation from other sources such as complementary feeding in terms of quantity and quality can also have normal linear growth (body length) and age-appropriate growth. According to the results of the Agricultural Census (BPS, 2013), the main commodities in Mattampa Bulu Village are cocoa (466 households), lowland rice (390 households), beef cattle (335 households), and corn (171 households). Where cocoa contains 20/100 grams of protein, corn 3.27/100 grams of protein and beef 26/100 grams of protein and rice which contains 28/100 grams of carbohydrates. With nutritional intake from these food sources, it can replace nutritional intake that is not obtained from exclusive breast milk which contains 7 g/100 ml of carbohydrates and 0.9 g/100 ml of protein.[13,16]

This is in line with research by Molgaard (2011) which explains that there is a significant the relationship between giving formula cow's milk to children's linear growth through the mechanism of stimulation of IGF-1 synthesis and insulin secretion. However, it has not been able to explain the mechanism specifically.[14]

## Conclusion

Nutritional status based on BB/U in children aged 6-24 months with exclusive and non-exclusive breastfeeding history had significant differences. As for the nutritional status based on PB/U, no significant relationship was found, this may be influenced by other factors that are more dominant and were not investigated in this study, so it is recommended for further research to examine more specifically and more broadly the factors that may be involved in determining the nutritional status of children.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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**ORIGINAL ARTICLE** **Open Access**

# Antifibrotics and Antioxidants of Chlorogenic Acid Inhibits Toll-Like Receptors-4 as Liver Fibrotic Marker

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## ABSTRACT

**Introduction:** Chlorogenic Acid (CGA) is an antifibrotic and antioxidant for fibrotic tissues. These double roles be able to inhibit or fibrotic tissues chains because of internal and external issues. For example, virus, bacteria or other pathogens and also by drugs, alcohol, cigarettes, etc. as external factor that affect quality of body tissues. Toll-Like Receptor-4 (TLR-4) as a marker fibrotic tissues. It is a key for researcher could be find out by expression performance. The aim of this study is to reveal the CGA as a candidate of antifibrotic & antioxidant in liver fibrosis that induced by $CCL_4$.

**Methods:** This is a pure experimental research with a simple experimental design or post-test only control group design. The total 29 mices of 2.5-month-old male Swiss mices with weigh 35-40 gram divided into 6 group: 3 groups of controls (injected by natrium chloride, CGA, and $CCL_4$) and 3 groups of treated (injected by CGA doses 42 mg/kg, 63 mg/kg or 84 mg/kg). Liver organ was used to examine the expression of TLR-4 by rt-PCR. This research revealed that expression of TLR-4 lower than the $CCL_4$ control group (respectively, p=0.042; p=0.005; p=0.006; and p=0.001). Higher dose of CGA showed greater ability as anti-fibrotic through inhibit the expression of TLR-4. Some research found the expression of TLR-4 has been decreased by treatment of Clorogenic Acid (CGA).

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**Conclusion:** To sum up, CGA has double roles to repair liver fibrotic tissues. The greater doses of CGA, the stronger inhibition of TLR-4 expression.

**Keywords**: $CCL_4$ antifibrotic; antioxidant; TLR-4; Liver; CGA

## Introduction

Liver disease is one of five big killer diseases to human in the world that Liver chirrhosis, age-standardized death rates (15+), per 100,000 population [1]. Liver problem should be treated early to achieve Sustainable Development Goals (SDGs)[2]. Liver is a one of accessories organ in the human body. It does digestion process when food and water available [3]. Damaging of Liver tissue will be decreasing quality and functional of liver tissue. Liver tissue problem would be found out by roles of Toll-Like Receptors as a marker of inflammatory cytokine [4]. TLR-4 is transmembrane receptor that play roles for natural and adaptive immunity. Roles of TLR-4 could be found by Pathogen-associated molecular patterns (PAMPs) recognition. They will associate or works together to send signals and activate natural and adaptive immunity responds. TLR-4 also has play roles in liver tissue injury and as one of PAMPs family member.It would be activated by some signals from ligan of cellular compartment. The increasing of TLR-4 expression could be seen by tissue damage and matrix degradation. Then, it would be the formed damage-associated molecular patterns (DAMPs) [5].

Liver disease is one of five big killer diseases to human in the world that Liver chirrhosis, age-standardized death rates (15+), per 100,000 population [1]. Liver problem should be treated early to achieve Sustainable Development Goals (SDGs)[2]. Liver is a one of accessories organ in the human body. It does digestion process when food and water available [3]. Damaging of Liver tissue will decreasing quality and functional of liver tissue. Liver tissue problem would be found out by roles of Toll-Like Receptors as a marker of inflammatory cytokine [4]. TLR-4 is transmembrane receptor that play roles for natural and adaptive immunity. Roles of TLR-4 could be found by Pathogen-associated molecular patterns (PAMPs) recognition. They will associate or works together to send signals and activate natural and adaptive immunity responds. TLR-4 also has play roles in liver tissue injury and as one of PAMPs family member.It would be activated by some signals from ligan of cellular compartment. The increasing of TLR-4 expression could be seen by tissue damage and matrix degradation. Then, it would be the formed damage-associated molecular patterns (DAMPs) [5].

## Methods

Type of this research was *post-test only control group design*. The samples were used Swiss male mice, which is 2,5 months old, ± 35-40 gram, and 29 in number. Every mice are healthy, active and categorized in 6 groups by Federer technique design [34]. Each group contains of 4-5 mice. Group I (S0=NaCl), II (S1=CGA), III (S2=$CCL_4$), IV (S3=$CCL_4$ 0.5 mL/kg BW + CGA 42 mg/kg BW), V (S4=$CCL_4$ 0.5 mL/kg BW + CGA 63 mg/kg BW), dan VI (S5=$CCL_4$ 0.5 mL/kg BW + CGA 84 mg/kg BW). The mice are fed 1 gr/mouse/day dry feed in pellet form and provided with clean water that replaced every 3 days in order to protect from bacteria or any other danger that may disturb the absorption process on CGA and CCL $_4$ [32]. The main substance in this research is $CCl_4$ (250 mL) (Merck) which is dissolved in olive oil (1:0,5), CGA (1000 mg) (Sigma-Aldrich) in a dosage of 42 mg/kg, 63 mg/kg and 84 mg/kg [32] based on human doses consumes [31] and NaCl (250 mL) [33]. The mice are measured once in a week to determine the dosage since thetreatment is based on body weight and are inducted by NaCl, $CCL_4$, CGA, and $CCL_4$+CGA for 4 week. NaCl and CGA treatments are done once in 24 hours through intragastric while $CCL_4$ treatment is done twice in a week through intraperitoneal.[12] This research procedure hasbeen approved by preclinical research ethic committee of LPPT-UGM Yogyakarta (No.Ref. 00002/04/LPPT/II/2017). After the treatment, next step was examined the blood serum and the liver was taken out from Linea Mediana part for RNA extraction to saw the expressions of TLR-4. The data of TLR-4 was analyzed by One Way ANOVA with significance grade $p<0,05$.

## Result

1. TLR-4 Expressions in Liver Fibrotic Tissues

TLR-4 is one of transmembrane receptors that have important role in liver fibrosis. The statistical analysis shows that more significant differences between groups of treatment S1 (1.85±0.43), S2 (1.72±0.76), and S3 (1.54±0.61) than the group of control K3 (3.34±1.29). Based on what the graph shows (Illustration A) regarding the role of CGA on the expression of TLR4, group S1(CGA 42 mg/kg BW), S2(CGA 63 mg/kg BW) and S3(CGA 84 mg/kg BW) could inhibit $CCL_4$ (0.5 mL/kg BW) became fibrosis. Whereas, one-way ANOVA test showed some significant differences on TLR-4 between groups (p=0.005). rt-PCR showed on illustration B. Based on that finding, CGA can lower the expression of TLR-4 on liver tissues which experience fibrosis. [12] The induction of $CCL_4$ can strengthen the expression of

TLR-4. This research uses fibrosis model because it is inducted by $CCL_4$. The results showed the expression of TLR-4 which wassignificant on group S1(1.85±0.43), S2(1.72±0.76), and S3(1.54±0.61) compared to the groupof control K3(3.42±1.22). rt-PCR shows there is damaging on the liver tissue.[12]

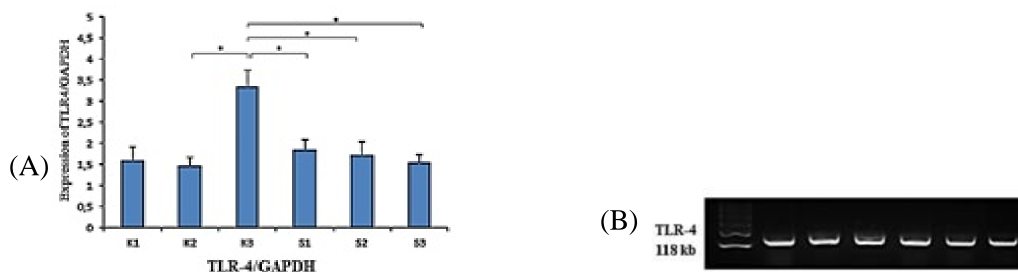


Illustration: [A] Expression of TLR-4/GAPDH; [B] Expression of TLR-4 by RT-PCR and densitometry analyzes using Image J software; Notes: K1(NaCl 0.5 mL/kgBW), K2(CGA 63 mL/kgBW), K3($CCL_4$ 0.5 mL/kgBW), S1($CCL_4$ 0.5 mL/kgBW+CGA 42 mg/kgBW), S2($CCL_4$ 0.5 mL/kgBW+CGA 63 mg/kgBW), and S3($CCL_4$ 0.5 mL/kgBW+CGA 84 mg/kgBW). (*) TLR-4($p=0.005$)[12]

**Discussion**

**1. TLR-4 Expressions in Liver Fibrotic Tissues**

Increasing expression of TLR-4 happens because TLR-4 is capable to identify pathogenic activity through understanding on pathogenic ligands from damaging of molecular pattern which is like matrix and cellular damage, thus the signals of TLR-4, MyD88, and NF-$\kappa$B are activated. [8-9] Then, some cytokine and chemokine proinflammatory are activated which is make free radicals turn into trichloromethyl peroxidase radical ($CCL3O^-$) then enter to cellular apoptotic pathways. Through mediator of IGF-1, PDGF, TGF-β, ET-1, ROS, then liver stellate cells are activated and then changed into myofibroblast. Next, myofibroblast contractility triggers increasing of matrix deposition and extracellular matrix which finally result in fibrotic. [15,19]

Inflammation is a normal process in which to maintain homeostatic of the body. But if the inflammation going to level of fibrotic and it will change functionality and quality of the tissue. also due to effect of the external and internal environment. For example, liver fibrotictissue. Liver inflammation tissue that progresses to liver fibrosis due to exposure of toxins, autoimmunity, ROS, and oxidative stress to B cells, NK cells, extracellular matrix, dendritic cells. These cells release pro-inflammatory cytokines to activate hepatic stellate cell (HSC) and stimulates bone marrow-derived cells, fibroblast and epithelial to-mesenchymal transition (EMT). Subsequently, myofibroblasts are activated by proliferation and migration to apoptosis. So, there is an imbalance between synthesis and degradation of collagen which causes liver tissue failure or damage [14-15]

Liver fibrotic in this research that has been done by using Carbon Tetrachloride ($CCL_4$). $CCL_4$ was used due to its toxic property to the liver. Liver damage caused depends on the large dose was given. The

main principle action that takes place in mechanism of $CCL_4$ in liver fibrotic cells by the presence of free radicals, lipid peroxidase and decreased activity of enzymes antioxidants. Histological appearance could be observed by fat infiltration, necrosis centrolobular then eventually to be cirrhosis. [28-29]

As mention before, damaging of liver tissue will decrease the quality and functional of itself. Liver tissue problem would be find out by the expression of Toll-Like Receptors (TLR-4) as the marker of inflammatory cytokine. TLR-4 is transmembrane receptor that play roles for naturaland adaptive immunity. Roles of TLR-4 could be found by Pathogen-associated molecular patterns (PAMPs) recognition. They will associate or works together to send signals and activate natural and adaptive immunity responds. TLR-4 also has play roles in liver tissue injury and as one of PAMPs family member. It would be activated by some signals from ligan of cellular compartment. The increasing of TLR-4 expression could be seen by tissue damage and matrix degradation. Then, its formed damage-associated molecular patterns (DAMPs) [4-5].

**2. Expressions of TRL-4 after CGA treatment**

However, the induction of CGA causes the expression of TLR-4 significantly decrease ($p=0.005$). The results showed the expression of TLR-4 was lowers significantly on the groups of S1($1.85\pm0.43$), S2($1.72\pm0.76$), and S3($1.54\pm0.61$) compared to the group of control K3($3.34\pm1.29$). Also, group of treatment S1($1.85\pm0.43$), S2($1.72\pm0.76$), and S3($1.54\pm0.61$) are compared to group of control K2 ($1.47\pm0.44$), group of treatments are lower. The results showed that the expression of TLR4 fell significantly. CGA treatment be able to decrease expression of PDGF, ROS production, free radical, phosphorylation of ERK1/2, proliferation of HSC,expression of collagen I/III and TIMP, which means that fibrogenesis pathways was inhibited [5,18].

During exposure to viral hepatitis, alcohol, autoimmune diseases, and toxins on parenchymal cells (hepatocytes) and non-parenchyma (Kuffer cells, endothelial cells, and fat stores) immediately activate the TLR4 signaling pathway.[[5] After binding TLR-4 with its ligand thenthe signal goes to MyD88 via modulation TIRAP and TRAM proteins which then mediate the TIR adapter protein with MyD88. Furthermore, the TRAM adapter protein connects the TIR and TRIF regions between the cell. Then the MyD88 pathway will attract IRAK and TRAF6 proteins. Protein TRAF6 activates TAK1. TAK1 activates the later IKK complex enter the NF-kB activation pathway. TAK1 also activates the MAPK pathway as well as causes the release of proinflammatory cytokines such as IL-1/10/4/6, CD40L, and radicals free . In addition, other pathways besides MyD88 are TRIF pathways. The TRIF pathway interacts with RIP1 and TRAF6. Activation of RIP1 and TRAF6 proteins further activates NF kB and MAPK. The TRIF protein also interacts with TRAF3 which also activates TBK1/IKKi and both activate other proteins, namely IRF3 and IRF7 which then triggers the release of pro-inflammatory cytokines such as INF- type 1. After that, the tissue inflammatory conditions would be appeared. Inflammatory tissue conditions also because of the

synthesis and degradation of the extracellular matrix was not balanced. [5,17-21]

### 3. CGA has ability (Antifibrotics and Antioxidant) to repair liver fibrotic

The results of the study clearly reveal the expression of TLR-4 was decreased by treatment of CGA. The greater doses of CGA, the stronger inhibition of TLR-4 expression. CGA was reduced the amount of PDGF, ROS production, free radicals, ERK1/2 phosphorylation, HSC proliferation, collagen I/III . expression and TIMP resulting in inhibition of fibrosis. [22-25] In addition to the large dose of CGA, need to be considered, as well as the influence of the food and drink consumed for the process repair network. Also role of nutrition is very helpful in recovery process of liver tissue injury. The double role of CGA able to inhibit formation and reaction of free radical chains with oxygen. These two molecules are dangerous to damage membranes and plasma membranes. [27,28] So, also CGA as antioxidant due to it have 3-caffeoylquinic acid (3-CQA), 4-caffeoylquinic acid (4-CQA),5-caffeoylquinic acid (5-CQA), 3,4-dicaffeoylquinic acid (3,4-diCQA), 3,5-dicaffeoylquinic acid (3,5-diCQA), and 4,5-dicaffeoylquinic acid (4,5-diCQA).

Additional, minor CGAs including 3-feruloylquinic acid (3-FQA), 4-feruloylquinic acid (4-FQA), 5-feruloylquinic acid(5-FQA), 3-p-coumaroylquinic acid (3-p-CoQA), 4-p-coumaroylquinic acid (4-p-CoQA), and5-p-coumaroylquinic acid (5-p-CoQA) are also present in traceable amounts in coffee beverages. These electrochemical chains as power to inhibits fibrogenesis pathways. [30] A review study reported that content of CGA e.g. 5-CQA has antioxidants activity and be able to inhibits various of disease models. The ability of 5-CQA indicate to down regulate pro-inflammatory cytokine, through modulation of key transcription factors but if high doses of 5-CQA given to rat by intravenous, it would appear inflammatory reaction. So, researcher should be more carefully to use CGA as an antioxidant. [29] Otherwise, for this research was different methods and sample for CGA treatment. It might be the reason for CGA roles as antifibrotic and antioxidants inhibit fibrogenesis pathways in liver fibrotic tissue model. By this research reveal, Phenolic compounds of CGA very important for repairing is liver fibrotic tissue. Liver tissue recovery depends on doses of CGA. The greater of doses the better recovery of the tissue. Not only to concern on doses but also adequacy for nutritional, water, and external environment exposure e.g. temperature would be helpful to maintain the good quality of the liver tissues.

## Conclusion

CGA is a phenolic compound with nine (9) electrochemical powers. These powers have the ability to inhibits fibrogenesis pathway especially TLR-4. The expression of TLR-4 depends on level of liver fibrotic tissue. Also, recovery of the fibrotic tissue depends on the amount of Phenolic (CGA). The greater doses of CGA, the stronger inhibition of TLR-4 expression. Not only to concern on dosses but also adequacy of nutrition and water would be helpful for maintain the good quality of the liver tissues.

**Recommendation**

This research was focused on TLR-4 but it might be more helpful also for next study to see the other marker like Myd88 expression, it is also as a root of liver fibrogenesis pathways.

**Conflicts of Interest**

None

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