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Effectiveness of vitamin d3 supplements in Javanese ethnic with stable asthma in Indonesia: Improving asthma symptoms by identifying vdr gene polymorphism

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ABSTRACT

Background: Monitoring asthma control is crucial as it directly impacts the patient's quality of life. The asthma control test (ACT) questionnaire is used to assess clinical symptoms for asthma control. Vitamin D deficiency can influence asthma symptoms. A study was conducted to evaluate how vitamin D affects symptoms in asthma patients through the identification of VDR gene polymorphism.

Method: This research was an experimental study with a pre-post test design method. Sampling with purposive sampling and snowball sampling techniques. To see an increase in clinical symptoms of asthma using a one-way ANOVA test and a descriptive technique for the VDR gene polymorphism test.

Result: The study sample was about 26 people aged ≥18 years with a minimum education level of SMA. Vitamin D was given at a dose of 400 IU for 8 weeks. ACT increased significantly in treatment frequency (p = 0.011), asthma control (p = 0.03, p = 0.02), and total ACT (p = 0.014, p = 0.023). There was a change in the increase in ACT scores at week 0 and week 8 after giving intervention in the form of vitamin D3. Improvements occurred in asthma control rates and total ACT scores. In this study, the distribution of the Taq1 polymorphism was the same between the control and test groups, namely the homozygous wild type.

Conclusion: Vitamin D supplementation has been shown to be effective in improving symptom control in asthma patients with wild-type homozygotes.

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Introduction

Respiratory diseases affect every country and all socioeconomic groups. The cost of lung disease reaches billions of dollars every year due to lost productivity and medical expenses [1,2]. In Indonesia alone, in 2013 there were 18 provinces that had an asthma prevalence that exceeded the national figure which reached 4.5%. Based on data from the Ministry of Health for 2020, Asthma is one of the most common types of disease suffered by Indonesian people. By the end of 2020, the number of asthma sufferers in Indonesia was 4.5% of the total population of Indonesia, or more than 12 million [3]. Therefore, asthma is a health problem that needs serious attention because it can interfere with one's activities.

Asthma treatment is an important key in controlling asthma symptoms. But asthma is also heavily influenced by the patient's lifestyle which is not good and can then trigger asthma symptoms. There have been many studies addressing the effects of nutrition on asthma [1,4]. One of the nutrients currently being studied is the use of vitamin D which shows a role in improving asthma symptoms as done by Salmanpour et al. [4], Lorensia et al. [5], Ogeyingbo et al. [6], and Alvi et al. [7]. In theory, vitamin D intake contributes to improving respiratory tract function to reduce asthma symptoms.

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Vitamin D levels are significantly related to asthma control levels, because the lower the vitamin D levels, the less controlled asthma is [6,8]. Vitamin D and asthma are a relationship between vitamin D intake and the inflammatory reaction that occurs in asthma, and low levels of vitamin D in asthmatic patients are at risk of increasing the severity of asthma [6,9,10]. Asthma therapy can be considered effective through monitoring during therapy. Monitoring the effectiveness of asthma treatment is a decrease in asthma symptoms. The instrument used to measure the increase in asthma symptoms is the Asthma Control Test (ACT), which is a simple, self-administered questionnaire and an easy-to-calculate assessment tool [11,12]. The ACT is a simple alternative instrument that can be used to assess asthma severity without the use of special tools [11,12].

Despite increasing public awareness about the various health benefits of vitamin D, epidemiological studies have revealed a very high prevalence of vitamin D deficiency worldwide, especially in Asian countries [13–15]. Indonesia, which is a tropical country and there is a lot of exposure to sunlight and sun, is not spared from the problem of deficiency of vitamin D intake [16,17]. This was proven by Poh et al. [18], through a cross-sectional study involving 16,744 participants in Southeast Asia including Indonesia.

The effect of a treatment can differ from one person to another and is closely related to a person's genetics because genetic factors contribute to a range of 20%–95% for different drugs [19]. Vitamin D is known to regulate receptors involved in processes of inflammation, immunity, and cell proliferation. The target for vitamin D activity is the vitamin D receptor (Vitamin D Receptor/VDR). Upon entering the cell, vitamin D binds to the VDR, and forms an active complex that translocates to the nucleus to bind to the vitamin D response element (Vitamin D Receptor Element/VDRE) in the genome [20,21]. VDR becomes active at the cellular level in lung tissue. The VDR gene itself is located on chromosome 12, which also binds to genes that determine the diagnosis of asthma and the severity of asthma [20]. Through a series of complex mechanisms, it is hoped that vitamin D intake can improve asthma control associated with genetic polymorphisms. The association of the VDR gene polymorphism with asthma is supported by a systematic review, meta analysis conducted by Tizaoui et al. [21], in eight case-control studies which showed that there was a relationship between the Taq1, Bsm1, and Fok1 polymorphisms in VDR with the susceptibility of developing asthma, especially Taq1. Now genetic information is needed to achieve optimal treatment. In Indonesia, no research has been conducted on the relationship between vitamin D and asthma, which is associated with the VDR gene polymorphism.

This study aimed to determine the effectiveness of vitamin D in asthma symptoms in adult asthma participants (≥18 years) who have at least high school or equivalent education. The educational level can affect asthma control [22]. The purpose of this study was to analyze the increase in clinical symptoms by administering vitamin D to outpatient asthma as measured by the ACT questionnaire by identifying VDR gene polymorphism.

Method

Research design

The research design used in this study was a one-group pre-post test design, to determine the effectiveness before and after administration of vitamin D supplementation on improving asthma symptoms. This research will be conducted for 8 weeks according to the results of research from Menon et al. [23]. Vitamin D products that use vitamin D3 at a dose of 400 IU comply with BPOM regulations which say that the maximum dose of vitamin D is 400 IU per day orally [24]. The study was conducted from May to September 2023. The ethical test score was 127/KE/V/2023 from the University of Surabaya.

Asthma symptoms were measured using the ACT questionnaire. ACT was a specific instrument for assessing asthma control in chronic asthma patients who describe the participant's current asthma condition. It consists of five questions covering restricted activity, duration of congestion, nocturnal asthma symptoms, frequency of use of reliever medication, and asthma control calculated over 4 weeks. Each question was given a 5-Likert scale answer choice. Patients will complete the ACT at study entry (week 0), fourth week, and eighth week after being given the intervention [25]. The range of values for this questionnaire was 5–25. A score of 20–25 was defined as well-controlled asthma, 16–20 was defined as uncontrolled asthma, and 5–15 is considered very poorly controlled asthma. The contents of this questionnaire consist of 4 questions related to symptoms plus the patient's opinion regarding asthma control [11,12].

The genetic factor studied is the vitamin D receptor (VDR). The interaction of VDR with

1,25-dihydroxyvitamin D3 affects various biological activities, such as regulation of helper T cell activation and cytokine secretion. VDR has 4 common SNPs (Single-Nucleotide Polymorphism), namely TaqI, FokI, ApaI, and BsmI. In this study, one of the SNPs considered to have the most influence was examined, namely TaqI [21]. In this study, sampling was carried out using the buccal swab method because the method was easier and considered convenient for the participants.

Population and Sample

The study population was asthma patients in the city of Surabaya, East Java, Indonesia. Subjects in this study were asthmatic patients who had met the inclusion and exclusion criteria and had filled out an informed consent form with criteria including: age ≥18 years, minimum high school education, having respiratory/kidney/heart problems, non-smokers, and not using asthma medications continuously (according to GINA Guideline [26], in step 1). The sampling technique used was purposive sampling to select the research sample. The sample calculation method uses the equation of the Lameshow formula (n = Z2.P.Q/d^2), with Z = 1.96; p = 0.017; Q = 1-0.017 = 0.983; and d = 0.05. Thus, the minimum sample size (n) was 25.67∼26 people. Participants in this study were obtained by purposive sampling and snowball sampling methods. This sampling was carried out by searching for stable asthma patients who live in the Rungkut sub-district, and then the search for potential research subjects was developed by asking other research subjects.

Methods of data collection and data analysis

Asthma symptoms were measured using the ACT questionnaire which was carried out before being given treatment, week 4, and week 8 after being treated. The VDR gene polymorphism will be tested at the Purification and Molecular Biology Laboratory, Faculty of Biotechnology, University of Surabaya. Genomic DNA was extracted from SK-2 buccal swabs using the QIAmp DNA Mini kit (Qiagen) protocol. The genomic DNA of each participant was used as a template for the PCR reaction [27]. PCR reactions were carried out in GoTaq Green 2x Master mix PCR reaction mixture (Promega). There are several types of PCR techniques depending on the purpose. In this study, the technique used was PCR-ARMS (Amplification Refractory Mutation System) to identify genomic DNA polymorphisms. The primers used in this analysis were Taq1 primers with sequences Taq1/TT (wild) CAGGACGCCGGCGCTGATT, Taq1/tt (mutant) CAGGACGCCGCGCTGATC.

Asthma symptom analysis was tested for normality of data distribution using the Shapiro-Wilk test. If the p value > 0.05, then the data were normally normally distributed [28]. Then different tests were performed with one-way ANOVA.

Result and Discussion

The study was filling out questionnaires to participants and providing interventions in the form of capsules containing Vitamin D3 400IU. Participants in this study were stratified by sex, age, and medical history (Table 1). The number of research samples based on the characteristics of the participants including age and gender. The largest age category was late adolescent patients (17–25 years) which was 92.60% and the highest number were women, namely 84.6%.

This study used vitamin D3 at a dose of 400 IU which was taken once a day. The use of vitamin D in Indonesia is limited by BPOM with a daily dose of only 400 IU. However, in the RDA table

Table 1. Distribution of research subject frequency characteristics.

Characteristics		Frequency (n: 26)	Percentage (%)
Gender	Male	4	15.40
	Female	22	84.60
Age (years)	Late adolescence (17–25)	25	96.15
	Early adulthood (26–35)	1	3.85
Treatment history	Oral short-acting beta-2 agonists (if needed)	5	19.23
	Inhaled short-acting beta-2 agonist (if needed)	9	34.62
	Not currently using any medication	11	3.85
	Oral corticosteroids (only used if symptoms worsen)	1	42.31

Table 2. Frequency distribution of control asthma symptom values.

ACT Questions	Category	ACT Assessment					
		T0		T4		T8	
		Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Asthma control based on activity limitation (over the past 4 weeks)	Always	0	0	0	0	0	0
	Often	0	0	1	3.85	0	0
	Sometimes	0	0	1	3.85	3	11.54
	Seldom	24	92.31	20	76.92	16	61.54
	Never	2	7.69	4	15.38	5	19.23
	Total	26	100	26	100	26	100
Asthma control based on the frequency of shortness of breath (during the last 4 weeks)	Always	0	0	1	3.85	0	0
	Often	0	0	1	3.85	0	0
	Sometimes	1	3.85	1	3.85	1	3.85
	Seldom	17	65.38	14	53.85	15	57.69
	Never	8	30.77	9	34.61	10	38.46
	Total	26	100	26	100	26	100
Asthma control Based on Asthma symptoms that cause night awakenings (in the past 4 weeks)	≥ 4 times a week	0	0	2	7.69	0	0
	2–3 times a week	2	7.69	1	3.85	3	11.54
	Once a week	3	11.54	3	11.54	1	3.85
	1–2 times a month	10	38.46	5	19.23	9	34.61
	Never	11	42.31	15	57.69	13	50.00
	Total	26	100	26	100	26	100
Asthma control based on frequency of use of asthma reliever medications (during the last 4 weeks)	≥ 3 times a day	1	3.85	0	0	0	0
	1–2 times a day	1	3.85	2	7.69	0	0
	2–3 times a week	2	7.69	2	7.69	1	3.85
	≤ 1 time a week	10	38.46	7	26.92	8	30.77
	Never	12	46.15	15	57.69	17	65.38
	Total	26	100	26	100	26	100
Asthma control based on level of asthma control (over the past 4 weeks)	Not controlled at all	0	0	0	0	0	0
	Less controlled	6	23.08	2	7.69	1	3.85
	Pretty controlled	6	23.08	4	15.38	4	15.38
	Well controlled	11	42.31	12	46.15	14	53.85
	Completely controlled	3	11.54	6	23.08	7	26.92
	Total	26	100	26	100	26	100
Total ACT Score	Not controlled (≤ 19)	0	0	2	7.69	0	0
	Partially controlled (20-24)	14	53.85	5	19.23	9	34.62
	Fully controlled (25)	12	46.15	19	73.08	17	65.38
	Total	26	100	26	100	26	100

T0 = Observations at week 0
T4 = Observations in the 4th week
T8 = Observations in the 8th week

from PERMENKES No. 75 of 2013 regarding the amount of nutritional adequacy recommended for Indonesians, it is stated that the need for Vitamin D per day for adults is 15 mcg or 600 IU [29]. Vitamin D has the ability to help absorb calcium. If the consumption of vitamin D is excessive, it will increase the absorption of calcium and cause high levels of calcium in the blood (hypercalcemia). Symptoms of

Table 3. Changes in asthma symptom control values with vitamin D therapy.

ACT Questions	ACT Assessment	Changes in ACT scores (*n*: 26)		
		increase	Fixed	Decrease
Asthma control based on activity limitation (over the past 4 weeks)	T0 & T4	3	20	3
	T0 & T8	6	16	4
Asthma control based on the frequency of shortness of breath (during the last 4 weeks)	T0 & T4	6	16	4
	T0 & T8	6	15	5
Asthma control based on asthma symptoms that cause night awakenings (in the past 4 weeks)	T0 & T4	9	12	5
	T0 & T8	8	14	4
Asthma control based on frequency of use of asthma reliever medications (during the last 4 weeks)	T0 & T4	9	13	4
	T0 & T8	9	16	1
Asthma control based on level of asthma control (over the past 4 weeks)	T0 & T4	14	10	2
	T0 & T8	17	6	3
Total ACT Score	T0 & T4	18	2	6
	T0 & T8	19	3	4

T0 = Observations at week 0
T4 = Observations in the 4th week
T8 = Observations in the 8th week

hypercalcemia are nausea, vomiting, fatigue, confusion, and frequent urination [30,31].

The highest number of each ACT question did not change between weeks 0, 4, and 8 (Table 2). Based on the normality test of the *p* values of the five ACT questions and the total ACT scores indicate scores, both at T0, T1, and T2 show *p* values < 0.05, meaning that the data distribution is not normal.

Table 3 shows that most of the participants experienced improved asthma control. And when viewed from the total ACT score, the majority of participants experienced an increase.

The results showed that changes in ACT values increased from 14 participants (53.85%) who were not controlled for conditions before therapy and then became well controlled in 17 participants (65.38%) at the end of therapy. Although participants experienced improvement in ACT scores, there are several factors that can influence ACT scores, including:

a. Gender and age [32,33]. At the time before puberty, male asthma patients are more than female. However, when entering adulthood what happens is the opposite, namely the prevalence of female asthma patients is greater than that of men.
b. Genetic factors contribute to the severity of asthma and the effects of asthma medications [34,35].
c. Exposure triggers or triggers for asthma flare-ups due to factors such as contact with triggers, food, excessive physical activity, and so on. May affect the control of asthma symptoms [33,36,37].

Table 4 showed that there was a significant improvement in asthma control rates and total ACT values from both 4 weeks of Vitamin D administration and up to 8 weeks of Vitamin D administration.

Genetic test results on 26 patients, it was found that 1 sample could not be identified, so only 25 genetic samples were obtained. Figure 1 shows an example of the electrophoretic results of the VDR polymorphism using the Taq1 SNP. Figures showing the presence of a single band in the T region only as seen in T7 indicates the presence of a wild-type homozygote allele. The images showing the presence of double bands on T and t as in T8-t8 indicate the presence of heterozygote alleles. Each reaction contains an Internal Control to ensure the success of the amplification process.

Polymorphism testing in this study used the Amplification Refractory Mutation System method which had previously been used by Lombard et al. [38] in detecting VDR gene polymorphisms. Participants were divided into control and test groups as shown in Table 5. The SNP used is Taq1 because it refers to research from Tizaoui et al. [21] and Papadopoulou et al. [39], which showed that the polymorphism of Taq1 in VDR had an effect on asthmatic conditions. There are also studies saying that Taq1 has an important role in the balance of TH1 and TH2 in the immune system [40].

Table 4. Tests of different values for controlling asthma symptoms with vitamin D therapy.

ACT Questions	Average ACT Score			*p* value		Test used
	T0	T4	T8	T0 & T4	T0 & T8	
Asthma control based on activity limitation (over the past 4 weeks)	4.08	4.04	4.15	1.000	0.527	Friedman Test
Asthma control based on the frequency of shortness of breath (during the last 4 weeks)	4.27	4.12	4.35	1.000	0.527	Friedman Test
Asthma control based on asthma symptoms that cause night awakenings (in the past 4 weeks)	4.15	4.15	4.23	0.405	0.248	Friedman Test
Asthma control based on frequency of use of asthma reliever medications (during the last 4 weeks)	4.19	4.35	4.62	0.166	0.011*	Friedman Test
Asthma control based on level of asthma control (over the past 4 weeks)	3.42	3.92	4.04	0.03*	0.002*	Friedman Test
Total ACT Score	19.65	20.58	21.27	0.014*	0.023*	Friedman Test

* = there is a significant difference ($p < 0.05$, Ho is rejected, meaning there is a significant difference).
T0 = Observations at week 0
T4 = Observations in the 4th week
T8 = Observations in the 8th week

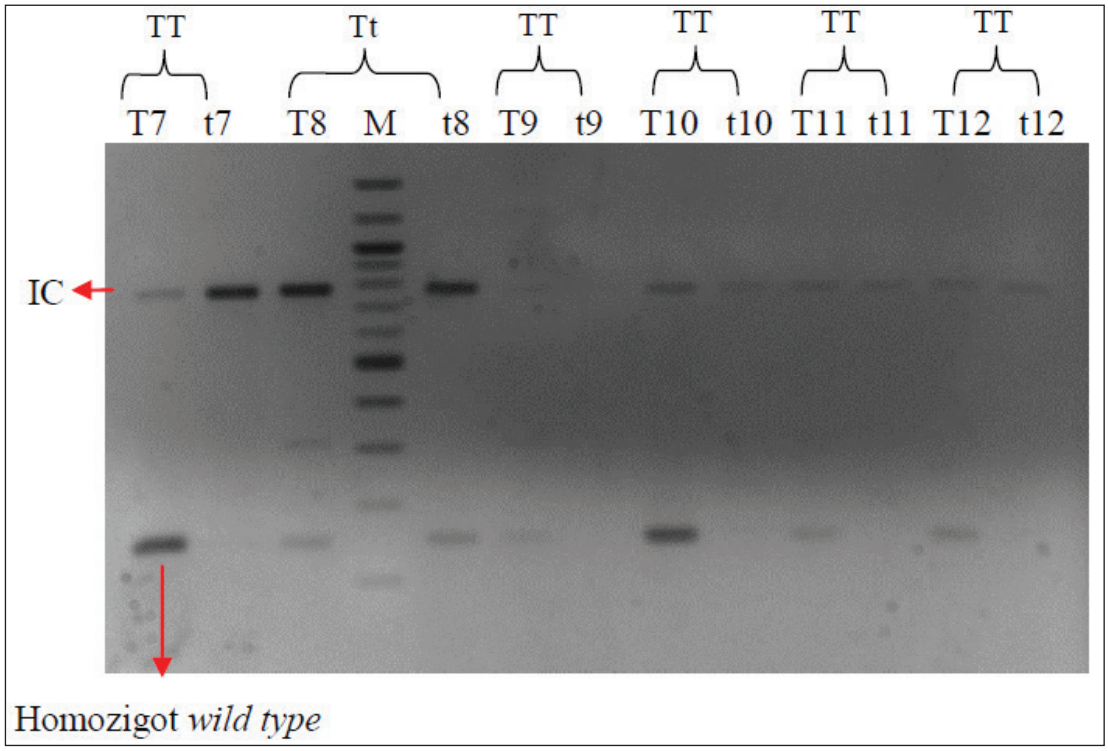

Figure 1. Snippet of observation results of genetic polymorphism.

Information :
TT = wild type homozygous allele
Tt = heterozygous allele
IC = Internal Control
M = Markers

In this study, most of the participants in the control and test groups were detected to have homozygous wild type (TT) polymorphisms, namely in the control group there were 8 people, in the test group there were 22 people. There were 2 participants who were heterozygous in the control group

Table 5. Frequency distribution of the effect of VDR gene polymorphism on changes in ACT values.

Genotype type	Test group (*n* = 25)				Control group
	Changes in ACT scores				
	Increase	Fixed	Decrease	Total	
Homozygote wild type (TT)	14	4	4	22	8
Homozygote mutant type (tt)	0	0	0	0	0
Heterozygote type (Tt)	1	0	0	1	2

and only 1 person in the test group. Participants did not find any homozygous mutant genotype (tt). The highest number was found in the wild homozygous polymorphism with ACT measurement results of 14 people experiencing improvement, 4 people experiencing no improvement, and 4 people experiencing decreased asthma control. In the heterozygous group, only 1 person who experienced improved asthma control was measured using ACT.

The results obtained by Papadopoulou et al. [39], who tested the VDR polymorphism in adolescent asthmatic patients in the Republic of Cyprus showed that there were significant differences in the distribution of the Taq1 polymorphism (TT, tt, Tt) in the control group and the asthmatic group. In a different experiment, when the vitamin D levels were normal in both the test and control groups, the homozygous mutant polymorphism (tt) was more prevalent in asthmatic patients. However, in this study, there was no treatment involving the administration of vitamin D. In this study, all participants showed most of the participants experienced an increase in ACT scores. Most of the participants had wild-type homozygous polymorphism (TT). When observed individually, both participants with the homozygous wild type (TT) or heterozygous (Tt) genotypes showed a response to vitamin D administration in the form of increased ACT values.

Conclusion

There was a change in the increase in ACT scores at week 0 and week 8 after giving intervention in the form of vitamin D3. Improvements occurred in asthma control rates and total ACT scores. In this study, the distribution of the Taq1 polymorphism was the same between the control and test groups, namely the homozygous wild type. Further research needs to focus on developing factors that can affect vitamin D levels, such as age, asthma severity, sun exposure, physical activity, and intake of foods containing vitamin D. In addition, the role of gene polymorphisms other than VDRs can also be developed.

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EFFECTIVENESS OF VITAMIN D3 SUPPLEMENTS IN JAVANESE ETHNIC WITH STABLE ASTHMA IN INDONESIA: IMPROVING ASTHMA SYMPTOMS BY IDENTIFYING VDR GENE POLYMORPHISM

Amelia Lorensia.

ABSTRACT

Abstract

BACKGROUND: Monitoring asthma control is crucial as it directly impacts the patient's quality of life. The Asthma Control Test (ACT) questionnaire is used to assess clinical symptoms for asthma control. Vitamin D deficiency can influence asthma symptoms. A study was conducted to evaluate how vitamin D affects symptoms in asthma patients through the identification of VDR gene polymorphism.

METHOD: This research was an experimental study with a pre-post test design method. Sampling with purposive sampling and snowball sampling techniques. To see an increase in clinical symptoms of asthma using a one-way ANOVA test and a descriptive technique for the VDR gene polymorphism test.

RESULT: The study sample was about 26 people aged ≥18 years with a minimum education level of SMA. Vitamin D was given at a dose of 400 IU for 8 weeks. *ACT increased significantly in treatment frequency (P=0.011), asthma control* (P=0.03, P=0.02), and total ACT (P=0.014, P=0.023). There was a change in the increase in ACT scores at week 0 and week 8 after giving intervention in the form of vitamin D3. Improvements occurred in asthma control rates and total ACT scores. In this study, the distribution of the Taq1 polymorphism was the same between the control and test groups, namely the homozygous wild type.

CONCLUSION: Vitamin D supplementation had been shown to be effective in improving symptom control in asthma patients with wild-type homozygotes.

Key words: asthma symptoms, vitamin D, VDR

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by Amelia Lorensia

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Difference in Rill Costs With INA-CBGs Rates and Treatment Rationality of Inpatient Asthma Children

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Abstract

Asthma in children may affect children's efficiency at school because frequent attacks occur which disrupt children's activities, so that asthma in children is a serious problem that requires appropriate treatment. The aim was to know the difference in real costs and INA-CBGs rates and to analyze Drug-Related Problems (DRP) based on the severity of asthma and the real costs for childhood asthma at Anwar Medika Sidoarjo Hospital. The design of this study was retrospective using patient medical record data collection, for January 2020-December 2022. Data collection containing real cost data and BPJS claim cost data. Analysis of DRP based on PCNE (Pharmaceutical Care Network Europe) includes problems and causes. There were 77 subjects. the real costs for the severity of mild asthma class I, class III, and moderate asthma class II were high when compared with the INA-CBGS rates, while the severity level of severe asthma class III it was found that the real costs were lower than the INA-CBGS rates. There is no difference between total real costs and INA-CBGS rates for asthma cases in BPJS participating children. The average real cost is Rp. 2,557,453 and the average INA-CBGs tariff is Rp. 2,792,873. There was no significant difference between real costs and INA-CBGS rates (P=0.162). All respondents experienced DRP (100%) and the highest incidence of DRP was M3.1 and P1.2 in 44 people (57.14%) with 180 cases (60.82%). In 77 patients with a total number of cases of 296, the real costs were mostly incurred in class III mild asthma patients (58 people), namely DRP type M3.1 with P1.2 with an average cost of Rp. 2,640,221.

Keywords: Asthma, real costs, INA-CBGs, drug-related problems

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1 Introduction

Asthma according to the Global Initiative for Asthma is a heterogeneous disease, characterized by chronic inflammation of the airways, with respiratory symptoms such as wheezing, shortness of breath, chest tightness, and characterized by a cough that varies from time to time [1]. Asthma is a chronic inflammatory disorder associated with airway hyperresponsiveness which causes repeated episodes (wheezing) [2]. Although asthma cannot be cured most of the time, asthma symptoms can be controlled by avoiding or reducing exposure to asthma triggers (allergies and irritants) and by following recommendations for asthma education and appropriate medical care [3]. The global prevalence of asthma in children has increased significantly over the last 40 years and childhood asthma has a high prevalence rate compared to adults [4,5]. Currently globally there are around 300 million people suffering from asthma throughout the world, and it is likely that there will be an increase of 100 million cases by 2025 [4]. In 2018, Indonesia had a national figure for asthma cases of 2.4% [6]. In the 2007-2018 period, the prevalence of asthma according to provinces in Indonesia shows that the province of East Java has experienced an increase from previously being below the national figure to now being above the national figure for asthma sufferers [7]. As prevalence increases, Indonesia needs more effective treatment and therapy to prevent asthma, especially asthma exacerbations [8]. Asthma exacerbations can also be called attacks. Asthma exacerbations are a major cause of disease morbidity, increases in health care costs, and, in some patients, a greater progressive loss of lung function. Patients with asthma exacerbations have significantly higher total health care costs. In patients who frequently experience asthma exacerbations and whose asthma is not controlled, this can lead to reduced productivity, low quality of life, and can increase health costs for asthma sufferers [9,10].

Asthma is a world health problem which is a factor causing medical costs to increase so that it becomes an economic burden for patients and society [11]. Asthma, especially in patients experiencing asthma exacerbations, affects half of all children in the United States under the age of 18 years, and is a major driver of the economic burden of health care costs [12]. In relation to the economic burden of the United States, childhood asthma costs 50 million dollars each year and is the main cause of inpatient hospital visits [13].

Asthma in children may affect children's efficiency at school because frequent attacks occur which disrupt children's activities, so that asthma in children is a serious problem that requires appropriate treatment [14]. Asthma attack patients need fast care and treatment, therefore health insurance coverage is very beneficial for patients regarding access to appropriate care and treatment facilities when experiencing an asthma attack. For asthma sufferers in Indonesia who are health insurance participants (JKN/ *Jaminan Kesehatan Nasional*), participants receive cost insurance from the JKN organizer, namely the Social Security Administration (BPJS/ *Badan*

Penyelenggaraan Jaminan Sosial). BPJS provides coverage for medical costs for chronic diseases, one of which is asthma [15]. JKN is a guarantee in the form of health protection so that participants obtain health care benefits and protection in meeting basic health needs provided to everyone who has paid contributions or whose contributions are paid by the government [16].

The JKN payment method organized by BPJS in health services is to use a prospective method, namely tariffs (INA-CBG's Indonesian Case Based Groups) [17]. INA-CBG's tariff is the amount of payment that BPJS claims to hospitals as an advanced reference for service packages based on the grouping of diagnosed diseases and the treatment given to patients [18]. However, in hospitals very often there are inequalities or differences between the amount of fees paid in the INA-CBG system and the hospital's real costs [19]. The cause of the difference in real costs and INA-CBGs rates usually lies in the patient's length of stay. If the patient is hospitalized for a long time then the care and treatment provided is also high so that the costs incurred by the hospital increase, whereas the INA-CBGS rates do not assess whether it is long or not. inpatients because they only see the patient's initial diagnosis [20]. Inappropriate or irrational use of medications can also have a negative impact on costs [15]. The latest data was recorded in 2017, the highest number of hospitalized asthma cases in Indonesia was recorded in East Java with 7,942 cases [7].

Previous research regarding the difference between real hospital costs and INA-CBG's rates for asthma patients hospitalized in a hospital in 2019 obtained data results that showed the total difference in class 3 mild asthma patients with a total of 5 patients amounting to Rp. 55,505,650 from the calculation of the difference in total hospital real costs which is less compared to the larger total INA-CBG rates [21]. The difference in costs that occurs between real costs and INA-CBGS rates, and children's asthma, including the economic burden, will have an impact on operations in the future, affecting the hospital's financial management as well as the quality of its services [20]. Therefore, research was conducted at the Anwar Medika Sidoarjo General Hospital to find out whether there was a difference in costs between the real hospital costs and the INA-CBG's rates for childhood asthma.

Efficient treatment is also related to the rationality of treatment for optimal treatment and preventing unnecessary costs [9,22]. Drug-Related Problems (DRPs) are undesirable conditions that befall patients caused by errors in drug therapy related to the patient's recovery. DRPs include, among other things, therapy without indications, under-over dosage, administration of drugs without indications, inappropriate drug selection, drug side effects, and patient failure to receive the drug [23].

Previous research related to DRP in asthma treatment used the PCNE classification, as carried out by Lorensia and Fatmala [24], to analyze DRP in outpatient asthma treatment in outpatient asthma patients in Surabaya. The results showed that of the 40 respondents the DRP was 34 respondents (85.00%). The domain related to the effectiveness is that the drug effect is not optimal (88.24%) and other drugs are not needed (11.76%) and the cause of drug selection is the improper combination of drugs (2.87%). Another study by Lorensia and Wijaya [25], with the number of patients analyzed was 60 inpatient asthma patients at a hospital in Surabaya. The results of the study showed that there was a correlation between the number of drugs and the type of DRPs that were less appropriate, so that the more types of drugs used by patients with asthma, the greater the risk of the patient getting inappropriate drugs. The aim of the research was to find out whether there was a difference in real costs and INA-CBGs rates and to analyze Drug-Related Problems (DRP) based on the severity of asthma and the real costs for childhood asthma at Anwar Medika Sidoarjo Hospital.

2 Methods

2.1 Research design

The design of this study was retrospective using patient medical record data collection. This study compares two medical costs, namely real costs with INA CBG's rates for asthma in children at Anwar Medika Sidoarjo Hospital, and uses medical record data for January 2020 - December 2022.

2.2 Research variable

Pediatric asthma patients are patients with asthma exacerbations and diagnosed with asthma based on standard diagnostic criteria at RSU Anwar Medika Sidoarjo. Real costs are direct medical costs, namely room costs, doctor's services, pharmacy costs, laboratory costs, medical equipment rental costs, radiology costs and medical equipment costs. INA-CBGs costs are costs for patients registered as BPJS patients at Anwar Medika Sidoarjo General Hospital class C private hospitals and are grouped based on class I, class II and class III BPJS patients (Table 1).

Table 1. INA-CBGs Rates in 2016 Regional 1 Private Hospital Class C Government Inpatient [26]

Code INA- CBGS	Description code INA CBG's	Rates class 1 (Rp.)	Rates class 2 (Rp.)	Rates class 3 (Rp.)
J-4-18-I	Asthma and bronchiolitis (mild)	3,263,900	2,797,600	2,331,300
J-4-18-II	Asthma and bronchiolitis (moderate)	4,489,200	3,847,900	3,206,600
J-4-18-III	Asthma and bronchiolitis (severe)	4,725,400	4,050,400	3,375,300

2.3 Population and Sample.

The population in this study were all pediatric patients who experienced asthma exacerbations who were hospitalized with INA-CBGS codes J-4-18-I, J-4-18-II, J-14-18-III [26], at Anwar Medika Hospital Sidoarjo for 2020-2022. The sample in this study was BPJS participating patients at Anwar Medika Sidoarjo Hospital who had to meet the inclusion criteria: aged <18 years and have complete data (patient identity and cost data during treatment). This research uses a purposive sampling technique. The sample size in this research is determined using the Slovin formula (Equation 1).

$$n = \frac{N}{1 + N(d)^2} \quad \text{(Equation 1)}$$

Note:
n= Estimated sample size;
N= Estimated population size;
D= Error rate used (d=0.05).
The minimum sample in this study was 64 samples.

2.4 Data Collection and Analysis.

Data collection containing real cost data and BPJS claim cost data. Real costs are classified into room costs, doctor services, nurse services, laboratory costs, pharmacy costs, equipment rental costs, and other health services according to the patient's medical needs.

In the research used in this analysis are real costs and costs that have been determined by BPJS, namely the INA-CBS tariff, with a ratio scale. After collecting data from medical records and patient cost data, the data is then analyzed using a normality test. In this study, the number of samples obtained was 77 patients, so a normality test was carried out using Kolmogorov-Smirnov because the number of samples was >50. If the significance value (sig.) was >0.05 then the research data is normally distributed and continued with parametric statistical analysis using the independent t-test to determine the significant difference between real hospital costs and INA CBG inpatient rates based on each class and room. If the significance value (sig.) was <0.05 then the research data is not normally distributed and continues with non-parametric statistical analysis using Mann-Whitney, followed by the Kruskal Wallis test to determine the difference in real costs and INA-CBGS for pediatric asthma patients based on class level. I, II, III, and overall mild, moderate, and severe severity levels.

Analysis of drug-related problems (DRP) based on DRP in this study includes problems and causes. Based on the guidelines on the PCNE [23], a classification scheme was used for drug-related problems and causes of DRP occurrence (Table 2).

Table 2. Scope of DRP based on PCNE Covering Problems and Causes

MTO based on:	Code	Main domain	Problem	Information
Problem	M1.1	Therapeutic effectiveness	There is no effect from drug therapy even if the drug is used correctly	Analyze the effectiveness of asthma therapy and other treatments received by patients
	M1.2		The drug effect is not optimal	Analyze the effects of drugs that are not optimal in asthma patients
	M1.3		There are indications or symptoms that are not treated	Analyze the presence of indications or symptoms that are not treated in patients with asthma attacks
	M2.1	Therapy safety	There has been (or may occur) an undesired drug reaction or drug-related adverse event	Analyzing the incidence of ADRs in the treatment of asthma patients, including (data in medical records). - Cardiovascular disorders = blood pressure, pulse rate, respiratory rate - Indigestion = diarrhea, nausea, vomiting, constipation - Nervous Disorders = dizziness
	M3.1	Etc	Unnecessary medication	Analyze the presence of unnecessary medications in asthma patients
Reason	P1.1	Drug Selection	Selection of drugs not in accordance with guidelines (therapy guidelines) or formulary (including contraindications)	Analyze whether patients receive medications that are not in accordance with therapy guidelines for asthma patients
	P1.2		There is no indication for the choice of this drug	Analyze the presence of drug indications in asthma patients
	P1.3		Inappropriate combinations (drug-drug, drug-herb, or drug-supplement combinations)	Analyzing drug interactions in asthma patients
	P1.4		Inappropriate duplication of therapeutic classes (drug classes) or active drug ingredients	Analyzing inappropriate drug duplication in asthma patients
	P1.5		There are indications, but the medication is not prescribed or the medication selected/prescribed is incomplete	Analyzing any indications in patients who received medication but did not comply with what was prescribed
	P1.6		Too many different drugs or active ingredients are prescribed for the same indication	Analyzing too many different drugs but the same indication
	P2.1	Selection of dosage form	Inappropriate/unsuitable dosage form/drug formulation (for that patient)	Analyzing drug dosage forms that are not suitable for treatment in asthma patients
	P3.1	Dosage selection	The drug dose is too low	Analyzing low drug doses in asthma patients
	P3.2		The drug dose is too high	Analyzing high drug doses in asthma patients
	P3.3		Dosage adjustments are less frequent	Analyzing underdosing in asthma patients
	P3.4		Dosage adjustments too frequently	Analyzing too frequent dosing in asthma patients
	P3.5		Instructions for how to use/time to administer the drug are wrong, unclear, or non-existent	Analyze the timing rules for administering medication to asthma patients
	P4.1	Determining the length of treatment	Length/duration of treatment is too short	Analyzing the effects of treatment that is too short in asthma patients
	P4.2		Length/duration of treatment is too long	Analyzing the effects of too long treatment in asthma patients

3 Results and Discussion

This research was conducted retrospectively by looking at medical record data of pediatric asthma patients to determine the difference in real costs and INA-CBGS. This research was conducted at Anwar Medika Sidoarjo Hospital from May to June 2023 in the medical records and finance department. There were 77 subjects who were registered as asthma patients and who met the inclusion criteria, consisting of patients with class I, class II and class III asthma attacks.

3.1 Research Sample Characteristics Data.

Patients are 100% BPJS patients and it is known that the gender characteristics of 49 patients (63.64%) are more male than female, 28 patients (36.36%). The highest number of children with asthma was in the 7-17 year age range, as many as 68 people (88.31%). The longest inpatient treatment was 2 days in 23 people (Table 3). This is in accordance with data from Aulia's research which shows that the prevalence of asthma is higher in boys [4]. However, at children aged <14 years, asthma in male children is higher than in female children because the diameter of the respiratory tract in

male children is narrower than in female children [1].

3.2 Total Real Cost Profile of Asthma by Classroom and Severity Level.

The real rate is calculated based on the rate for health services at the hospital including components of facility services, services, medical needs and service according to each service, and inpatient rates. Meanwhile, the INA-CBGS tariff calculation is based on diagnosis codes whose tariff standards have been set by the government. The health service rates include components of procedure costs, medical personnel costs, drug costs, supporting facilities costs and others. The INA-CBGS tariff calculation is calculated based on a combination of diagnosis codes and action procedures whose standard tariffs have been set by the government. The real cost components based on class and severity level can be seen in Table 4. It is known that the real costs for the severity of mild asthma class I, class III, and moderate asthma class II are high when compared with the INA-CBGS rates, while the severity level of severe asthma class III it was found that real costs were lower than the INA-CBGs rates (Table 5).

Table 3. Patient Characteristics Based on Asthma Severity Level

Characteristics		Asthma Severity Level							
		Mild (n=59)		Moderate (n=4)		Severe (n=14)		Total (n=77)	
		Freq.	(%)	Freq.	(%)	Freq.	(%)	Freq.	(%)
Gender	Male	35	45.45	3	3.90	11	14.29	49	63.64
	Female	24	31.17	1	1.30	3	3.90	28	36.36
Age (Year) [27]	5-6	4	5.19	0	0.00	5	6.49	9	11.69
	7-17	55	71.43	4	5.19	9	11.69	68	88.31
Length of Treatment	1	14	18.18	1	1.30	0	0.00	15	19.48
	2	20	25.97	2	2.60	1	1.30	23	29.87
	3	17	22.08	1	1.30	4	5.19	22	28.57
	4	7	9.09	0	0.00	6	7.79	13	16.88
	5	0	0.00	0	0.00	2	2.60	2	2.60
	6	1	1.30	0	0.00	1	1.30	2	2.60
Room class	Class I	1	1.30	0	0.00	0	0.00	1	1.30
	Class II	0	0.00	4	5.19	0	0.00	4	5.19
	Class III	58	75.32	0	0.00	14	18.18	72	93.51

Table 4. Real Cost Components Based on Classroom and Severity Level

Total and Average Costs							
		Classroom			Severity Level		
Direct Medical Cost Categories	Category	Class I (n=1)	Class II (n=4)	Class III (n=72)	Mild (n=59)	Moderate (n=4)	Severe (n=14)
		Average (Rp.)	Average (Rp.)	Average (Rp.)	Average (Rp.)	Average (Rp.)	Average (Rp.)
Action Medical personnel	Cost of non-surgical procedures	634,000	417,500	246,000	240.203	417,500	298.143
	Consultation fees	420,000	307,500	250,417	228,051	307,500	356,786
	Expert costs	30,000	30,000	30,000	30,000	30,000	30,000
	Nursing costs	342,000	259,500	206,417	195,085	259,500	263,857
Supporting facilities	Supporting costs	102,000	102,000	102,000	102,000	102,000	102,000
	Radiology Fees	115,000	115,000	107917	110,678	115,000	96,786
	Laboratory Fees	936,000	699,000	455,694	455.203	699,000	492,071
	Room Fees	1,200,000	900,000	625,000	586,441	900,000	828,571
Medicine and others	Drug costs	377,000	303,303	258,669	238,078	303,303	353,913
	Cost of medical equipment	613,832	484,565	260,500	249,365	484,565	322,664
	BMHP costs	587,400	310,950	126,157	144,393	310,950	82,250
	Equipment rental costs	17,000	89,000	20,167	20,864	89,000	17,000

Table 5. Differences in Total Costs for Asthma Severity Levels and Classrooms Based on Real Costs Compared with INA-CBGS Rates

Room class	Mild (n=9)			Moderate (n=4)			Severe (n=14)		
	Freq.	Real Cost (Rp.)	Rates INA-CBGS (Rp.)	Freq.	Real Cost (Rp.)	Rates INA-CBGS (Rp.)	Freq.	Real Cost (Rp.)	Rates INA-CBGS (Rp.)
Class I	1	5,374,455	3,263,900	-	-	-	-	-	-
Class II	-	-	-	4	16,073,272	11,190,400	-	-	-
Class III	58	148,046,907	135,215,400	-	-	-	14	45,556,580	47,254,200

Direct medical costs in this study include components of action costs, medical personnel costs (consultation from doctors, experts and nurses), drug and other costs (drugs, medical equipment and consumable medical materials) and supporting facilities (equipment rental, rooms, support , radiology and laboratory). The cost analysis used in this research uses direct medical costs [28].

In this study, the average cost for patients with mild asthma attacks in class I was higher than the cost for INA-CBGs, where the real cost was Rp. 5,374,455 and the INA CBGS tariff is IDR. 3,263,900. The average real cost for patients with moderate asthma attacks in class II is also higher than the INA CBGs rate, where the real cost is Rp. 4,018,318/patient and INA CBGs of Rp. 2,797,600/patient, with a negative difference indicating that INA-CBG's claim rate is smaller than the real costs incurred. The results of this study are different from previous research [21], which provided a positive difference, where the total real costs were lower than INA-CBG's rates. However, in class III heavy attacks, the real costs are lower compared to the INA-CBGS tariff, namely IDR. 3,254,041/patient and Rp. 3,375,300/patient for the INA-CBGS rate, with a positive difference indicating that the INA-CBG rate claim is greater than the real costs incurred. A positive difference means that the direct medical costs incurred by the hospital in treating pediatric asthma patients do not exceed the rates set by the government, so it does not cause potential losses for the hospital. The results of this study are in accordance with other studies [21], which provide a positive difference, where the total real costs are lower than the INA-CBG's rates, which means the hospital's success in carrying out treatment efficiently and effectively.

In the technical instructions for the 2023 Indonesian Minister of Health Regulation, it is explained that the INA-CBG tariff components include service administration components, accommodation, doctor's services, hospitalization, examination, treatment, basic medical consultation in the emergency unit, medical equipment, ambulances and health services. others according to the patient's medical needs [29].

3.3 Real Cost Differences Compared to INA-CBGs Rates

On the difference between real costs and INA-CBG's rates at the Anwar Medika Sidoarjo General Hospital, the real rates are calculated in detail on the types of services including components of care services, experts, non-surgical procedures, radiology, laboratories, rooms, medicines, medical devices and medical materials. disposable. Meanwhile, the calculation of INA-CBG's rates is calculated based on the accumulation or combination of diagnosis codes and procedure/action codes into an INA-CBG's code whose standard rates have been determined by the government. The average real cost is Rp. 2,557,453 and the average INA-CBGs ratesf is Rp. 2,792,873. The results of the normality test using Kolmogorov Smirnoff with a value of P=0.000 (P<0.05), which means it is not normally distributed. Then proceed with the Mann-Whitney test. The test results are different between the two with a value of P=0.162, meaning there is no significant difference between real costs and INA-CBGS rates.

3.4 Analysis of Drug-Related Problems (DRP).

All respondents experienced DRP (100%), both in the emergency room and in the inpatient room. The highest incidence of DRP was M3.1 and P1.2 in 44 people (57.14%) with 180 cases (60.82%). The results of the percentage of occurrences of drug-related problems experienced by the sample while in the ER and overall hospitalization can be seen in Table 6. The use of DRP-related drugs based on problems and causes can be seen in Table 7.

Table 6. Frequency of Number of Drug-Related Problems Based on Problem

Treatment in	MTO type		Based on Number of Samples		Based on Number of Cases	
	based on Problem	based on Cause	Frequency (n=77)	Percentage of Total Sample (%)	Number of Cases (n=296)	Percentage of Total Cases (%)
IGD	M1.2	P3.1	**8**	10.39	**8**	2.70
	M3.1	P1.1	**50**	64.94	**50**	16.89
	M3.1	P1.2	**44**	57.14	**90**	30.41
Inpatient	M1.2	P3.1	**8**	10.39	**8**	2.70
	M3.1	P1.1	**49**	63.64	**50**	16.89
	M3.1	P1.2	**44**	57.14	**90**	30.41

M1.2 = Drug effect is not optimal
M3.1 = Medication not needed
P1.1 = Drug selection does not comply with *guidelines* (therapy guidelines) or formulary (including contraindications)
P1.2 = There is no indication for selecting this drug

Table 7. Use of MTO-Related Medications Based on Problems and Causes

Treatment in	MTO related drugs		MTO type		Based on Number of Samples		Based on Number of Cases	
	Drug Class	Medicine name	based on Problem	based on Cause	Frequency (n=77)	Percentage of Total Samples (%)	Number of Cases (n=296)	Percentage of Total Number of Cases (%)
IGD	Oxygen	Oxygen	M3.1	P1.2	5	6.49	5	1.69
	ICS	Budesonide	M3.1	P1.2	6	7.79	6	2.03
	Penicillin	Ampicillin Na and Sulbactam	M3.1	P1.2	6	7.79	6	2.03
	SABA	Salbutamol	M3.1	P1.1	50	64.94	50	16.89
	NSAIDs	metamizole	M3.1	P1.2	5	6.49	5	1.69
		Ibuprofen	M3.1	P1.2	14	18.18	14	4.73
	Cephalosporins	Ceftriaxon	M3.1	P1.2	16	20.79	16	5.41
	H2 receptor antagonist	Ranitidine	M3.1	P1.2	23	29.87	23	7.77
	Serotonin receptor antagonist	Ondansetron	M3.1	P1.2	13	18.88	13	4.39
	Acetaminophen	Paracetamol	M3.1	P1.2	1	1.30	1	0.34
	PPI	Omeprazole	M3.1	P1.2	1	1.30	1	0.34
	Systemic corticosteroids	Methylprednisolone	M1.2	P3.1	8	10.39	8	2.70
Inpatient	Oxygen	Oxygen	M3.1	P1.2	5	6.49	5	1.69
	ICS	Budesonide	M3.1	P1.2	6	7.79	6	2.03
	Penicillin	Ampicillin Na and Sulbactam	M3.1	P1.2	6	7.79	6	2.03
	SABA	Salbutamol	M3.1	P1.1	49	63.63	50	16.89
	NSAIDs	metamizole	M3.1	P1.2	5	6.49	5	1.69
		Ibuprofen	M3.1	P1.2	14	18.18	14	4.73
	Cephalosporins	Ceftriaxon	M3.1	P1.2	16	20.79	16	5.41
	H2 receptor antagonist	Ranitidine	M3.1	P1.2	23	29.87	23	7.77
	Serotonin receptor antagonist	Ondansetron	M3.1	P1.2	13	18.88	13	4.39
	Acetaminophen	Paracetamol	M3.1	P1.2	1	1.30	1	0.34
	PPI	Omeprazole	M3.1	P1.2	1	1.30	1	0.34
	Systemic corticosteroids	Methylprednisolone	M1.2	P3.1	8	10.39	8	2.70

NSAID : *Non Streoidal Anti Inflammatory Drugs*
ICS : *Inhaled CorticoSteroid*
PPI : *Proton Pump Inhibitor*
SABA : *Short-Acting Beta Agonis*

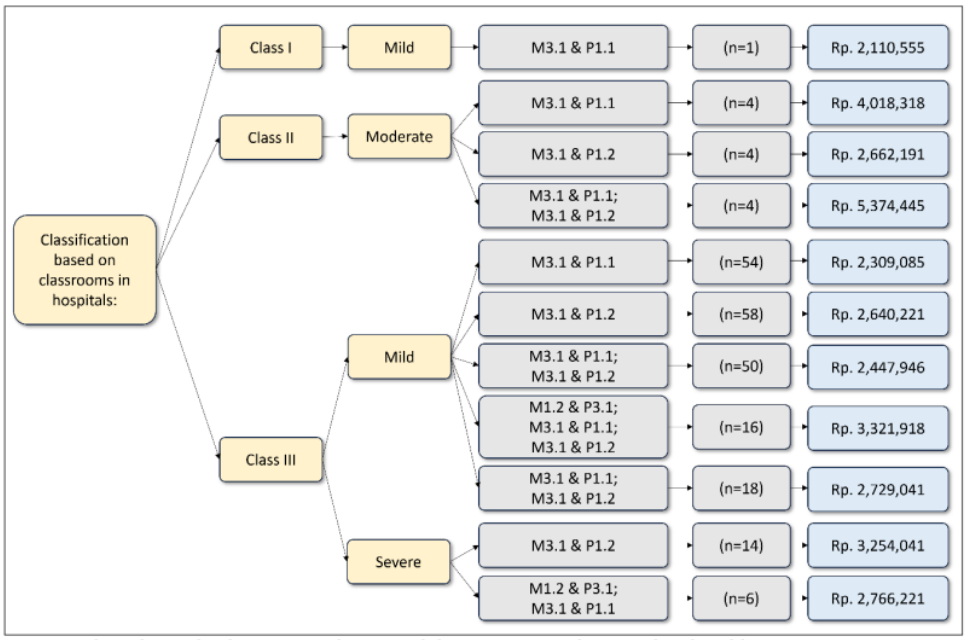

Figure 1. The Relationship between Real Costs and the Occurrence of Drug-Related Problems

The use of medication for pediatric asthma attack patients at Anwar Medika Sidoarjo Hospital found that oxygen was mostly used in patients with mild asthma with a total of 4 patients (57.14)%, salbutamol was used most often in patients with mild asthma, namely 47 patients (70.15%) , the corticosteroid group (dexamethasone) was the most common in mild asthma, 10 patients (52.63%), the corticosteroid group (methylprednisolone), which was the most common in mild asthma patients, namely 31 patients (86.11), and for the drug budesonide, the most common in mild asthma patients with a total of 5 patients (62.50%) (Table 7). Discussion of DRP experienced by respondents included:

a. The incidence of DRP in the sample was M1.2 (not optimal drug effect) with P3.1 (drug dose too low). The drug associated with DRP was methylprednisolone, the number of cases was 8 (5.41%), according to the GINA 2023 literature [1] , the recommended dose for children is 1-2mg/kg/day up to a maximum of 40mg/day, whereas in the sample it was less than that dose.
b. The incidence of DRP that occurred in the sample was M3.1 (drug not needed) with P1.1 (selection of drug not in accordance with guidelines (therapy guidelines) or formulary (including contraindications), namely salbutamol, the number of cases was 50 (33.78%), according to in the GINA 2023literature [1], for treatment of mild-moderate asthma exacerbations, it is sufficient to use Salbutamol MDI alone, but in the samples using Salbutamol Nebulizer. The inhaled short-acting β-2 agonist (SABA) is the first line of therapy for asthma exacerbations, and salbutamol is a SABA that is often used for asthma attacks. Selection of SABA as first line can cause bronchial smooth muscle to relax through increasing intracellular cyclic adenosine monophosphate (cAMP) [30,31].
c. DRP that occurred in M3.1 (the drug was not needed) with P1.2 there was no indication for the drug, namely Budesonide with the number of cases 6 (4.06%). According to GINA (2023), ICS corticosteroids are used if the patient does not receive systemic corticosteroids but in the sample

corticosteroid therapy has been given [1,32].

d. The DRP events that occurred in M3.1 (no medication needed) with P1.2 (no indication for medication) were the antibiotic drug Ceftriaxon with a number of cases 16 (10.82%), sultamicilin with a number of cases 6 (4.06%) [1,33]. The use of antibiotics is not necessary in the treatment of asthma because there is insufficient evidence to support the use of antibiotics unless there is strong evidence that the patient has a lung infection (such as fever, pneumonia) and in GINA 2023 [1], administration of antibiotics can be considered after administration of corticosteroids and it is best to Asthma exacerbations antibiotic therapy is not routinely prescribed. This research is also in line with previous research that antibiotics should not be given because there is a lack of strong evidence [1,34].
e. The DRP events that occurred in the sample were M3.1 the drug was not needed with P1.2 there was no indication for the drug, namely Oxygen, the number of cases was 5 (3.38%), according to GINA in 2023 [1], the value for oxygen saturation for asthma attack patients given If the oxygen saturation is <90% (target for children is 94-98%), and in the sample the oxygen saturation value is within the range so there is no need to give oxygen therapy. The aim of oxygen therapy in asthma patients is to correct the condition of low oxygen levels in the blood (hypoxemia), reduce respiratory workload, increase oxygen levels and increase the patient's sense of comfort [35,36].
f. The incidence of DRP that occurred for gastrointestinal drugs in the sample was M3.1 the drug was not needed with P1.2 there was no indication for the drug, namely the drug Omeprazole with the number of cases 1 (0.68%), Ranitidine with the number of cases 23 (15.54%), Ondansetron with a total of 13 cases (8.78%), is intended for nausea and vomiting, but if you look at the patient's medical record data, the sample has no complaints of nausea and vomiting so that there is not enough therapy for nausea and vomiting. precise because there is no indication as to the destination. Gastrointestinal disorders in cases of asthma exacerbations often appear together and in some cases they are also associated with nausea and vomiting which is the earliest common event [37]. Aminophylline used in asthma patients has side effects, namely nausea and vomiting. Aminophylline is a common asthma drug for asthma therapy in Indonesia and is a narrow therapeutic range drug that causes ADRs to occur. Inappropriate aminophylline therapy can cause many side effects which can result in a person experiencing medical problems caused by side effects that are more severe than the main medical problem [1,38].
There are several connections between nausea and vomiting in asthma patients. Nausea and vomiting in asthma patients can cause gastric disorders, namely stress ulcers. Stress ulcer is a syndrome characterized by acute bleeding or perforation of the upper gastrointestinal tract due to mucosal damage in patients suffering from critical illness or severe trauma. Asthmatic respiratory disorders can cause hypoventilation and circulatory hypoperfusion disorders which result in tissue hypoperfusion. As a result of hypoventilation and hypoperfusion, the oxygen and nutrients needed to maintain the integrity and regeneration of mucosal cells are not sufficient so that the integrity of the mucosa and the ability to regenerate the mucosa decreases to the point of cell death [39].
g. The incidence of DRP that occurred in samples, namely in the NSAID drug class, was M3.1 (drug not needed) with P1.2, there was no indication for the drug, namely metamizole with a sample size of 5 (3.38%), ibuprofen with a number of cases 14 (9 .46%). It is contraindicated for asthma sufferers to take NSAIDs because they can cause allergic reactions and asthma exacerbations which are characterized by bronchospasm [40], so medication is not needed.
h. The DRP incidence that occurred for analgesic antipyretic drugs in the sample was M3.1 the drug was not needed with P1.2 there was no indication for the drug, namely the drug Paracetamol with the number of cases 1 (0.68%). Paracetamol is an analgesic

and antipyretic drug, this drug is intended to reduce a child's temperature, fever reducing is indicated if the body temperature is >38 °C [41]. The results of this study are the same as previous studies, namely that the use of paracetamol is not necessary because there is no diagnosis of fever and there is no increase in temperature in the patient [42].

4 Conclusions

There is no difference between total real costs and INA-CBGS rates for asthma cases in BPJS participating children. The average real cost is Rp. 2,557,453 an the average INA-CBGs ratesf is Rp. 2,792,873. There was no significant difference between real costs and INA-CBGS rates (P=0.162). All respondents experienced DRP (100%) and the highest incidence of DRP was M3.1 and P1.2 in 44 people (57.14%) with 180 cases (60.82%). In 77 patients with a total number of cases of 296, the real costs were mostly incurred in class III mild asthma patients (58 people), namely DRP type M3.1 with P1.2 with an average cost of Rp. 2,640,221.

5 Declarations

5.1 Acknowledgements

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5.2 Author contributions

AL, developed the concept and designed the manuscript, director, supervisor and final coordinator of manuscript; AL and MMAJ provided key information and intellectual support. AFA and FSA provided conducting research, collecting data and compiling manuscripts.

5.3 Ethic

Ethical has been approved by the Commission on Health Research Ethics University of Surabaya No.163/KE/XI/2022.

5.4 Conflict of Interest

The authors declare no conflict of interest.

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