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RESEARCH ARTICLE

A Descriptive Study of Asthma Control in A Historical Cohort of Step 3 And 4 Asthma Patients in the Indonesian National Health Insurance Setting

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ABSTRACT

Asthma is a significant global health issue. Data on asthma control, particularly for moderate to moderately severe cases, is limited in Indonesia. The study aimed to assess the proportion of GINA step 3 and 4 asthmatic patients with controlled asthma (ACT score > 20) 6 to 12 months after starting ICS/LABA therapy in Indonesian National Health Insurance (JKN) hospitals. Secondary objectives included assessing patient demographics, comorbidities, clinical characteristics, exacerbation frequency, and treatment duration. A retrospective, non-interventional study was conducted using medical records from JKN hospitals (January 2014 to February 2020). The cohort was predominantly female (79.0%), with a mean age of 48.1 ± 12.97 years. At index, nearly 46% had comorbidities, including GERD (35.7%), hypertension (30.4%) and allergic rhinitis (20.9%). Approximately 67% had controlled asthma after 6 to 12 months, and the mean change in ACT score was 4.3 points (from 15.8 ± 4.35 to 19.7 ± 4.45), which is above MCID (≥3).[35] Specifically, 10.7% were categorized as having total control (ACT score = 25), 56.3% were well-controlled (ACT score 20-24), and 32.9% remained uncontrolled. The average treatment duration including prescription gaps was 321.8 ± 53.48 days. The findings suggest that maintenance ICS/LABA therapy is effective in managing patients with moderate to moderately severe asthma, with the majority of patients reporting control after 6 to 12 months. Nevertheless, the persistence of uncontrolled asthma in a notable subset of patients underscores the need for further research into factors affecting asthma control in this population.

INTRODUCTION

Asthma is a common lung condition that causes inflammation and affects people worldwide. It can be triggered by viruses and allergens, and each case may have different underlying causes (WHO, 2024). Asthma can develop suddenly and worsen over time, leading to changes in the airways and respiratory system (Aalbers et al., 2016; Amelink et al., 2013; Custovic, 2015; Porsbjerg et al., 2015).

The Global Initiative for Asthma (GINA) classifies asthma by severity and control. For patients not managed by low to moderate doses of inhaled corticosteroids (ICS) alone, GINA recommends combining ICS with long-acting beta-agonists (LABA) for moderate to moderately severe asthma

(step 3 and 4). If symptoms persist, adding a long-acting muscarinic antagonist (LAMA) can also be beneficial (Aalbers et al., 2016). This dual therapy has shown promising results in treating moderate to moderately severe asthma and is recommended by GINA as a standard treatment approach for this patient population (Papi et al., 2013). Inhaled medications are typically taken as needed or twice daily. Recent studies indicate that a combination of ICS and LABA - whether as controller, reliever, or in a fixed-dose combination - is effective in preventing moderate to moderately severe asthma exacerbations (Aalbers et al., 2016; de Groot et al., 2015; Global Intitiative for Asthma, 2022; Lipworth, 2014; Loymans et al., 2014; WHO, 2024). The goal of asthma management is to control symptoms and reduce the risk of severe exacerbation. The Asthma Control Test (ACT) is a globally recognized self-administered tool used to help identify individuals with poorly controlled asthma. It evaluates the frequency of shortness of breath and general asthma symptoms, the use of rescue medications, the impact of asthma on daily functioning, and overall self-assessment of asthma control, with a score range from 5 to 25. However, while the ACT provides valuable insights into asthma control, it is important to still consider other factors such as medication adherence, recent illnesses, and comorbidities, as these can also significantly influence asthma management and control (Aalbers et al., 2016; Loymans et al., 2014; Stanford et al., 2010). In Indonesia, ICS/LABA treatment has been available since 2002 and has been part of the national healthcare system since 2014. Despite this, there is limited data on asthma control, especially among patients classified as GINA step 3 and 4 patients in Indonesian National Healthcare (Jaminan Kesehatan Nasional (JKN)) facilities.

This study aims to provide real-world data on asthma management and control for patients with moderate to moderately severe asthma (GINA steps 3 and 4) in Indonesia. It assesses asthma control using the ACT, and examines demographics, comorbidities, clinical characteristics, exacerbation frequency, treatment duration and treatment adherence among patients covered by Indonesia's JKN program. By examining these factors in detail, this study seeks contribute to the overall asthma management approach for patients treated with ICS/LABA in Indonesia's JKN facilities.

Material and Methods

This multicentre, real-world evidence (RWE), retrospective, observational study gathered data from patients' medical records at four JKN hospitals in Indonesia: Persahabatan Hospital in Jakarta, dr. Saiful Anwar Hospital in Malang, Prof. dr. Chairuddin P. Lubis Hospital in Medan, and Madina Hospital in Bukittinggi. Given the retrospective and non-interventional nature of the study and the fact that anonymized data from medical records were collected, the Ethics Committee waived the requirement to obtain Informed Consent from the subjects. The study adhered to all relevant laws concerning participant privacy, ensuring that no direct subject contact or primary collection of individual human subject data took place. Prior to the initiation of the study, ethics committee/IRB approval was obtained from each hospital, and submission to the Regulatory Agency (BPOM) was completed as a notification only.

The study included adult patients with moderate to moderately severe asthma who were newly initiated on ICS/LABA treatment between January 2014 and September 2019. Relevant study data were collected from patient medical records starting from the ICS/LABA initiation date (defined as the index date) up to 12 months' post-initiation, and entered into a standardized electronic case report form (eCRF) tudy Flow

Eligible patients met the GINA guidelines for step 3 or 4 asthma, were at least 18 years old at index, had a documented asthma diagnosis, and had at least one ACT score/outcome recorded 6-12 months post-Index date. Exclusion criteria included participation in a clinical/ interventional study at any point during index or post-Index date and reporting one or more occurrences of the following diagnoses recorded at Index date: chronic obstructive pulmonary disease (COPD), asthma-COPD overlap syndrome (ACOS), an interstitial lung disease, cystic fibrosis, lung cancer, eosinophilic granulomatosis with polyangiitis (EGPA), allergic bronchopulmonary aspergillosis (ABPA), or active tuberculosis. Lastly, they could not have concurrent use of phenotypic therapies (biologics, aspirin desensitization, immunotherapy) and biologics for severe asthma at index date.

Moderate to severe exacerbations were defined as those requiring systemic corticosteroids, emergency department visits, or hospital admissions (Cohen et al., 2009). Patients at JKN hospitals were expected to consult a physician monthly for prescriptions; thus, prescription gaps were

identified as periods exceeding 30 days without documentation of a prescription in the medical record.

Data were analyzed using R version 4.2.0. Descriptive statistics were employed for both the primary and secondary objectives. For continuous variables, the number of observations (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum are presented where appropriate. The number of observations and percentages of subjects are presented for categorical variables.

RESULTS

A total of 252 eligible patients were included in the study. Demographic and clinical characteristics are presented in Table 1. The average age of the study participants was 48.1 ± 12.97 years, and 199 (79.0%) were females. The Body Mass Index (BMI) distribution showed that 123 patients (48.8%) were categorized as normal, 58 (23.0%) as obese, and 47 (18.7%) as pre-obese. Around 53% (n=134) of participants had smoking history recorded in their medical records; 106 (42.1%) participants had never smoked, while 13 (5.2%) were current smokers and 15 (6.0%) were former smokers. Similarly, only 150 (59.5%) of patients had comorbid conditions data available in the medical record; 115 (45.6%) patients reported having at least one comorbidity, some of which reported multiple conditions.

Table 1. Demographic and Clinical Characteristics at Index

Characteristic	**N = 252**
Gender, n (%)	
Female	199 (79.0)
Male	53 (21.0)
Age (years), mean ± SD	48.1 ± 12.97
Body mass index (kg/m^2), mean ± SD	24.02 ± 4.40
Body mass index categories[a] (kg/m^2), n (%)	
Underweight (<18.5)	24 (9.5)
Normal (18.5-25.0)	123 (48.8)
Pre-obesity (25.1-27.0)	47 (18.7)
Obesity (>27.0)	58 (23.0)
Smoking status, n (%)	
Never smoked	106 (42.1)
Current smoked	13 (5.2)
Former smoker	15 (6.0)
Unknown	118 (46.8)
Educational level, n (%)	
Not Finishing Formal Education	29 (11.5)
Senior high school	114 (45.2)
Bachelor	55 (21.8)
Postgraduate	2 (0.8)
Unknown	52 (20.6)
Employment status, n (%)	
Employed	26 (10.3)
Self-employed	6 (2.4)
Student	63 (25.0)
Unemployed	129 (51.2)

Unknown	28 (11.1)
Years since asthma diagnosis, n (%)	
Known[b]	30 (11.9)
0-4	14 (46.7)
5-9	3 (10.0)
10-14	4 (13.3)
15-19	3 (10.0)
≥20	6 (20.0)
Not recorded	222 (88.1)
FEV_1 (ml) (n=93), mean ± SD	1501.2 ± 651.34
FVC (ml) (n=93), mean ± SD	2052.9 ± 790.42
FEV_1 (%) (n=144), mean ± SD	57.6 ± 17.66
FVC (%) (n=143), mean ± SD	64.3 ± 18.42
FEV_1/FVC (%) (n=145), mean ± SD	74.4 ± 13.20
Number of patients with medical history available, n (%)	
Yes	150 (59.5)
No	102 (40.5)
Number of patients with at least 1 comorbidity[c], n (%)	
Any of the below[d]	115 (45.6)
Gastroesophageal Reflux Disease (GERD)	41 (35.7)
Hypertension	35 (30.4)
Allergic Rhinitis	24 (20.9)
Diabetes	16 (13.9)
Congestive Heart Failure (CHF)	13 (11.3)
Obesity	13 (11.3)
Stroke	5 (4.3)
Arthritis	2 (1.7)
Cataracts	2 (1.7)
Atherosclerosis	1 (0.9)
Cancer	1 (0.9)
Other lung Disease	1 (0.9)

FEV, Forced Expiratory Volume. FVC, Forced vital Capacity

[a] BMI categories according to the Ministry of Health of the Republic of Indonesia (Kemenkes RI), 2018.

[b] The denominator for the individual time periods is the count of patients with “Known” years since asthma diagnosis.

[c] The denominator for the "Any of the below" percentages is the count of patients with comorbidities recorded in their medical records. The denominator for individual comorbid conditions is the count of patients within the "Any of the below" category. Therefore, the percentages may exceed 100%, as one patient can have multiple conditions.

[d] Denominator for “Any of the below” percentage equals patient count whose medical history was available.

Table 2 presents the ACT data at Index and 6-12 months post-Index. At Index, most patients (72.5%) had uncontrolled asthma. Of the 221 participants with a numeric ACT score at both Index and 6-12

months post-Index, the mean ± SD change in ACT score was 4.3 ± 4.76 points. A difference of 3 or more points for the ACT is considered the minimal clinically important difference (MCID) (Liza et al., 2021).

Table 2. ACT Score at Index and Post-Index

Variable	**N = 252**
ACT Outcome at Index [a], n (%)	
Controlled (score 20-25)	69 (27.5)
Uncontrolled (score ≤19)	182 (72.5)
ACT Outcome 6-12 months post-index, n (%)	
Controlled (score 20-25)	169 (67.1)
Uncontrolled (score ≤19)	83 (32.9)
Change in ACT Outcome [a], n (%)	
Improved	112 (44.6)
Worsened	13 (5.2)
No change[b]	126 (50.2)
Uncontrolled at Index and remained	70 (55.6)
Controlled at Index and remained	56 (44.4)
ACT numerical score, mean ± SD	
ACT numerical score at index (n=224)	15.8 ± 4.35
ACT numerical score 6 to 12 months post-index (n=248)	19.7 ± 4.45
Changes in ACT score from index to 6 to 12 months post-index (n=221)	4.3 ± 4.76

[a] One patient did not have an ACT outcome recorded at Index.

[b] The denominator for the individual categories under "No change" is the "No change" patient count.

As shown in Table 2 and Figure 2, nearly 45% of subjects demonstrated an improvement in ACT outcome. After 6 to 12 months of ICS/LABA use, 10.7% of participants reported total control, 56.3% reported well-controlled, and 32.9% reported uncontrolled asthma (Figure 1).

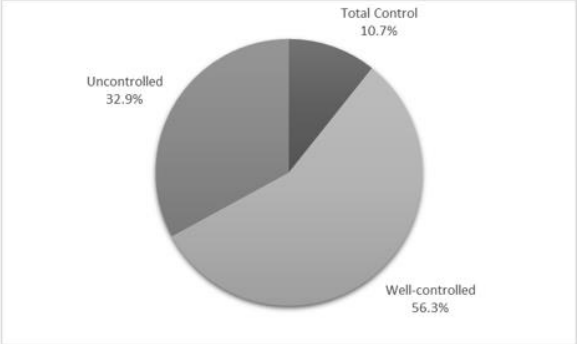

Figure 1. Proportion of Asthma Control Post Index

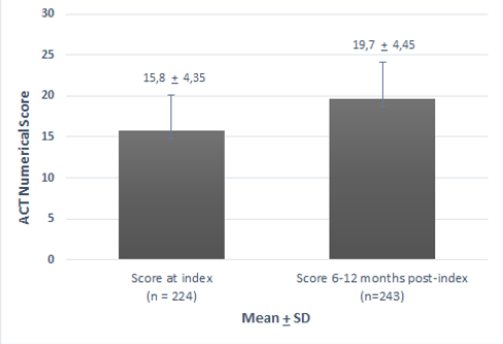

Figure 2. ACT Score Improvement

Only 23 (9.6%) participants during the study data review period had record of at least one exacerbation of any kind, as shown in Table 3. Of these patients, the mean ± SD number of exacerbations per year was 1.7 ± 1.02; 20 (87.0%) participants required an emergency room (ER)

visit, 5 (21.7%) were hospitalized and 3 (13.0%) required an outpatient visit and steroids. Overall, 12 (52.2%) of these patients required steroid treatment for their exacerbation.

Table 3. Exacerbation Status Post-Index

Variable	**N = 252**
Exacerbations per year, of patients who had at least 1 exacerbation, mean ± SD	1.7 ± 1.02
Number of patients who had an asthma exacerbation (of any kind) based on the frequency per year [a,b], n (%)	
At least 1 exacerbation	23 (9.1)
1 exacerbation	14 (60.9)
2 exacerbations	4 (17.4)
3 exacerbations	5 (21.7)
Number of patients requiring steroid treatment for their asthma exacerbation [a,c], n (%)	12 (52.2)
Number of patients with an asthma exacerbation event requiring healthcare resource use [c,d], n (%)	
Physician visit	3 (13.0)
Emergency room visit	20 (87.0)
Hospitalization	5 (21.7)

[a] Includes exacerbations requiring physician visit, steroid use and/or ER or hospitalization.

[b] Denominator for "at least 1 exacerbation" percentage equals total patient count; denominator for 1, 2, and ≥3 equals patient count within "at least 1 exacerbation".

[c] Denominator equals patient count within "at least 1 exacerbation"

[d] The total count of patients who experienced exacerbations and visited a healthcare facility, whether or not they used steroids, may exceed the overall count of patients with asthma exacerbations. This is because a single patient can have multiple exacerbations, with or without steroid use.

Table 4 presents data on the ICS/LABA prescribed during the study period. The mean ± SD duration of ICS/LABA treatment was 214.3 ± 90.85 days, excluding prescription-free periods; 99 (39.3%) of patients had ICS/LABA prescriptions recorded for less than 180 days, 78 (31.0%) had prescriptions for 180–270 days, while 75 (29.8%) had prescriptions for more than 270 days. The minimum number of days on treatment according to medical record data was 44, while the maximum was 365.

The mean ± SD duration of treatment, including prescription gaps was 321.8 ± 53.48 days. The majority (70.2%) of patients were treated with ICS/LABA for 10-12 months, despite not having continuous prescription data available in the medical records. At therapy start (index), 38.9% (n = 98) of participants had a low daily ICS/LABA dose, 54.4% (n=137) had a medium dose, and 6.7% (n=17) had a high dose. After 6-12 months, this daily dose distribution persisted. During the study period, most participants (73.8%, n=186) did not have their daily ICS/LABA dose modified, while 9.9% (n=25) of patients had a dose increase, 8.3% (n=21) had a dose decrease, and 7.9% (n=20) had multiple dose adjustments.

Table 4. Maintenance ICS/LABA use

Variables	**N=252**
Average ICS/LABA treatment duration including prescription gaps (days), mean ± SD	321.8 ± 53.48
Average ICS/LABA treatment duration excluding prescription gaps (days), mean ± SD	214.3 ± 90.85
ICS/LABA treatment duration excluding prescription gaps, n (%)	
<180 days	99 (39.3)
180 – 270 days	78 (31.0)
>270 days	75 (29.8)
ICS/LABA daily dose[a], n (%)	
Index	
Low	98 (38.9)

Medium	137 (54.4)
High	17 (6.7)
Post-index	
Low	94 (37.3)
Medium	141 (56.0)
High	17 (6.7)
Number of patients with ICS/LABA dose changes, n (%)	
No changes	186 (73.8)
Increased dosage	25 (9.9)
Decreased dosage	21 (8.3)
Experienced multiple dosage changes	20 (7.9)

[a] The data range for low, medium, and high dose levels is defined according to the ICS dose levels based on the Global Initiative for Asthma Guidelines (GINA Global Strategy for Asthma Management and Prevention, 2023). For ICS/LABA doses of 160/4.5 or 80/4.5, the categories are as follows: low: 200-400 mcg, medium: >400-800 mcg, and high: >800 mcg. For other ICS/LABA doses, the categories are: low: 100-250 mcg, medium: >250-500 mcg, and high: >500 mcg.

DISCUSSION

The results of this study provide valuable insights into asthma control among patients classified as GINA steps 3 and 4 and treated with ICS/LABA within Indonesia's National Health Insurance (JKN) system. Of the 252 participants, roughly 67% reported controlled asthma after 6 to 12 months of therapy, while 33% remained uncontrolled, highlighting that there are ongoing challenges in asthma management in this population. These findings align with previous studies, which have also identified barriers to effective control (Bateman et al., 2007; Bousquet et al., 2017; Maneechotesuwan et al., 2022; Price et al., 2015).

Several factors can contribute to uncontrolled asthma, including improper inhaled corticosteroid use, reduced lung function, tobacco exposure, and comorbidities like gastroesophageal reflux disease (GERD) and obesity.(Boulet & Boulay, 2011) In this study, only 60% of participants had medical record data that included comorbidities; of those patients 77% (which is 46% of the entire population) reported having at least one comorbidity. Previous research has shown that comorbidities are associated with poorer asthma control, with patients having more than three comorbidities experiencing worse outcomes compared to those with fewer.[31] Additionally, only 53% of patients had data recorded on smoking history, which showed roughly 5% of patients were current smokers and 6% were former smokers. Understanding smoking status is imperative to treatment, as current smokers with asthma show worse clinical and respiratory outcomes compared to non-smokers and former smokers (Tiotiu et al., 2021). This underscores the importance of addressing modifiable risk factors, such as smoking, and assessing comorbidities before initiating treatment, as recommended by GINA guidelines.[7,33] However, in this study, nearly half of the participants had missing documentation regarding their smoking history or comorbidities, revealing a gap in medical record-keeping that could hinder effective asthma management.

Alongside comorbidities and smoking history, BMI and gender are also key factors influencing asthma control. In this study, approximately 10% of participants were classified as underweight, while 19% and 23% were classified as pre-obese and obese, respectively. Previous studies have shown that both underweight and obese individuals are more likely to experience more severe asthma, highlighting the role of BMI in asthma severity.(Liu et al., 2015; Sun et al., 2024; Yang et al., n.d.) Additionally, nearly 80% of participants were female in this study, aligning with previous literature findings that asthma is more common and severe in women, possibly due to hormonal influences (Pignataro et al., 2017; Tidemandsen et al., 2021). Women with asthma tend to report more symptoms, use more rescue medications, and are more likely to experience severe cases (Tidemandsen et al., 2021). This gender-specific burden is influenced by both anatomical factors and the effects of sex hormones. However, current asthma management guidelines often overlook these differences, revealing a critical gap in personalized care (Chichi et al., 2024). Lastly, socioeconomic factors, such as education, may also impact asthma control, although the relationship between this factors and asthma outcomes varies in different studies (Ilmarinen et al., 2022).

Patients with ongoing uncontrolled asthma risk airway remodeling, which refers to structural changes in the bronchial wall, including subepithelial fibrosis, increased smooth muscle mass, gland enlargement, neovascularization, and epithelial alterations. These structural alterations are often associated with a specific asthma phenotype that can lead to poor clinical outcomes, impaired lung function, and reduced treatment response (Tiotiu et al., 2021). This study incorporated spirometry data from 93 patients who had data on FEV1 and FVC in milliliters and 144 patients with percent-predicted values, which indicated reduced lung function and therefore may indicate asthma remodeling in this population. However, the missing data and lack of post-bronchodilator measurements make it difficult to draw any meaningful conclusions. Nevertheless, the importance of ensuring patients achieve asthma control goes beyond improving quality of life and reducing healthcare resource use, as airway remodeling is irreversible.

Poorly controlled asthma is also a risk factor for COPD. Given the average age of the study population (48.1 ± 12.97 years), further diagnostic testing should be considered to evaluate the presence of COPD in these patients, especially since the prevalence of COPD rises after the age of forty (Liu et al., 2015). The reduced lung function shown in this study indicates airway obstruction. However, post-index spirometry data were only available for an even smaller subset of patients, and thus were excluded as no meaningful interpretation could be deduced. Nevertheless, spirometry remains a crucial tool for diagnosing and monitoring conditions such as pre-COPD, which is defined as having risk factors or symptoms of COPD without meeting full diagnostic criteria, and COPD; highlighting the importance of early detection to prevent disease progression. In sum, although the limited spirometry findings point to reduced lung function, the substantial amount of missing data from the medical records, especially post-index, and not having any post-bronchodilator data, is a considerable information gap.

Lastly, according to the GINA guidelines, patient treatment—both pharmacological and non-pharmacological—should be adjusted based on patient's response to therapy. For those with uncontrolled asthma, it is essential to first evaluate adherence, inhaler technique, risk factors, and comorbidities before considering a change in medication or increasing treatment dosage. In this study, nearly 74% of patients had no change in their ICS/LABA dosage over the course of one year, with most remaining on a medium dose, despite 33% still classified as uncontrolled. The GINA guidelines recommend stepping up to a high dose of ICS/LABA or adding LAMA or LTRA for step 4 uncontrolled patients. The lack of dosage adjustment observed in this study could be due to physician's reluctance to step up the treatment or to the limited availability of high dose ICS/LABA and other asthma medications in some health care facilities. Not to be overlooked though is educating patients, as this is crucial for improving treatment adherence by helping them understand their condition and the importance of regular medication intake. The observed average treatment duration of 214 days (excluding gaps in prescriptions) in this study suggests patients could have been without medication for certain periods of time, which can have affected asthma control. However, these gaps in prescriptions might also reflect missing data from medical records, as the data did not come from pharmacy records. Nevertheless, these considerations highlight the importance of not only considering treatment adjustments based on patient response, but also ensuring consistent medication adherence, to achieve asthma control.

There are limitations to this study. First, it focused solely on patients from four JKN hospitals, which may not fully represent the broader asthma population in Indonesia. The use of the ACT as an inclusion criterion could have introduced selection bias, as it is unclear whether patients without ACT data differ significantly from those included. The retrospective design, relying on medical chart data, may have led to information bias, especially since patients' baseline characteristics could have varied depending on the timing of their index date. While it was assumed that patients would be uncontrolled at the index date, some patients were reportedly controlled (possibly due to ICS/LABA mono-therapy shortages), which may have overestimated the proportion of patients with controlled asthma post-index. Furthermore, the absence of pharmacy records might have led to under reporting of the duration and continuity of ICS/LABA therapy. Despite these limitations, this study provides valuable real-world insights into asthma control among JKN patients newly initiated on ICS/LABA therapy between 2014 and 2020.

CONCLUSION

The results of this real-world study found that the majority of the study population reported controlled asthma 6 to 12 months after ICS/LABA initiation. However, despite this positive outcome, a meaningful proportion of patients continued to experience uncontrolled asthma, highlighting a critical unmet need within the study population. Thus, while the efficacy of maintenance ICS/LABA therapy in asthma management is well-documented, our findings underscore that there may be specific challenges faced by patients within Indonesia's JKN system. Further research into the determinants of uncontrolled asthma for Indonesian patients is warranted.

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Conflicts of interest

Wiyono WH received sponsorship to attend international meetings, honoraria for lecturing, and fees for attending advisory boards from various pharmaceutical companies, including GSK, AstraZeneca, Boehringer Ingelheim, Chiesi, and Novartis, grant/research report from GSK and declared no specific conflict of interest related to this paper.

Damayanti T received sponsorship to attend international meeting, honoraria for lecturing or attending advisory boards from various pharmaceutical companies including GSK, Astra Zeneca, ZP Therapeutics, Zambon, Novartis, grant/research report from GSK and declared no specific conflict of interest to report regarding this paper.

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Tarigan AP received sponsorship to attend international meetings, honoraria for lecturing, and fees for attending advisory boards from various pharmaceutical companies, including GSK, AstraZeneca, Boehringer Ingelheim, and Novartis, grant/research report from GSK and declared no specific conflict of interest related to this paper.

Herman D received sponsorship to attend international meetings from Novartis and fees for attending advisory boards from various pharmaceutical companies, including GSK, AstraZeneca, and Boehringer Ingelheim, grant/research report from GSK and declared no other specific conflicts of interest related to this paper.

Teichman L, Supriya K, Patricia C, Phansalkar A, Fikri F and Hamouda M are employees of GSK.

Phansalkar A and Hamouda M hold stock and shares in GSK.

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Author contribution

The authors contributed to the study in various capacities: Wiyono WH, Teichman L, Patricia C, Phansalkar A, and Fikri F were responsible for the study concept and design, while data acquisition was carried out by Wiyono WH, Djajalaksana S, Damayanti T, Herman D, and Tarigan A. Data analysis was performed by Supriya K, and data interpretation involved Wiyono WH, Djajalaksana S, Damayanti T, Herman D, Tarigan A, Teichman L, Patricia C, Phansalkar A, Hamouda M, and Fikri F. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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