Original Article

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One Year of Real-Life Practice in Treatment Strategies and Future Exacerbation among Asthma Patients with Exacerbation Required Emergency Department Visits

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Abstract:

Objective: To investigate the treatment patterns and clinical outcomes regarding future exacerbation in patients with a history of emergency department (ED) visited exacerbation.

Material and Methods: We analyzed the treatment patterns and moderate/severe asthma exacerbation rates over a year. The Kaplan-Meier method was used to determine the probability of an asthma exacerbation, and the time to the first exacerbation was compared.

Results: Of the 155 patients, 59 (38.1%) had naïve treatment, 53 (34.2%) and 43 (27.7%) received GINA-classified steps 1-2 and 3-5 treatments, respectively. Approximately 50% of those with naïve treatment lost adherence after a year of follow-up. However, the annual moderate/severe exacerbation rate was reported as the lowest and increased from 0.34 to 0.49 (p-value=0.236) compared to those with steps 1-2 and 3-5 treatments, from 0.66 to 0.47 (p-value=0.085) and 3.00 to 1.19 (p-value=0.006), respectively. Patients with GINA-classified steps 3-5 treatment were prescribed controllers 10.9 more than the 7.8 canisters prescribed to those with naïve treatment (p-value<0.001). In contrast, there were no differences in total reliever prescriptions between the groups (p-value=0.274). Finally, there was no significant difference in the likelihood of having future exacerbations (p-value=0.107). The estimated time of exacerbation in naïve treatment, GINA-classified steps 1-2, and 3-5 treatment were 42.2, 36.6, and 34.2 weeks, respectively.

Conclusion: This study confirms that the frequency of future exacerbations following an ED-visited exacerbation increases as the stepwise treatment increases. This finding may help clinicians understand the natural history of treatment patterns and exacerbation outcomes. Patients with naïve treatment may have a unique history of significantly less exacerbation despite discontinuing controllers.

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Introduction

Asthma is a significant public health non-communicable disease that affects an estimated 300 million people globally and tends to increase[1]. According to the Global Initiative for Asthma (GINA) guidelines, minimizing the future risk of asthma exacerbations is the ultimate goal in asthma management[2]. Unfortunately, several studies suggest asthma control remains poor, mainly due to the undertreatment of the disease, leading to the development of exacerbation[3-5]. Although asthma exacerbations requiring a visit to the emergency department (ED) are preventable events, approximately 60% of patients had not taken inhaled corticosteroids (ICS) as long-term control medication[6]. Compared to exacerbation required hospital admission, 40% of patients received an asthma diagnosis in the ED, and long-term treatment was found to be suboptimal based on the guidelines[7,8].

Regarding ED-visited exacerbation, only 65% were prescribed asthma medications after discharge from an ED[9]. The follow-up rate with primary care providers is often low despite patients with acute asthma being suggested for follow-up visits with the primary care providers for ongoing preventive care[10]. Although patients with more severe asthma, treated with more intense medications, were associated with poorer asthma-related outcomes[11,12], a significantly higher number of asthma patients who discontinued asthma treatment maintained symptom improvement compared to those who continued asthma medication[13]. Asthma can be managed but not cured, and exacerbation is the outcome, representing poor control of asthma. Although treatment options are related to those outcomes, a long-term follow-up for asthma patients after ED-visited exacerbation across the treatment baseline remains unknown. Therefore, an in-depth analysis may help clinicians understand the natural history of treatment patterns and asthma outcomes. This study compared treatment patterns and exacerbation outcomes between asthma patients with naïve treatment and previous, ongoing treatment following ED-visited exacerbation.

Material and Methods

Study design and population

This retrospective longitudinal observational study was conducted at Hatyai Hospital in Thailand. Based on the local epidemiological data, asthma exacerbation is widespread at the ED in our center, and deep analysis may help us to handle this problem. Therefore, we studied asthmatic patients who visited the asthma attack clinic with a history of visiting the ED with exacerbation within 2 weeks between July 9, 2020, and March 19, 2021. The first event was incorporated into the analysis for patients with multiple visits for exacerbation beyond the index event. They were older than 18 years and diagnosed with asthma by audit with a pulmonologist based on clinical presentation with or without a history of spirometry, according to the standard of the GINA guidelines 2. Patients diagnosed with chronic airway inflammation other than asthma, i.e., chronic obstructive pulmonary disease, chronic bronchitis, lung cancer, lung fibrosis, or tuberculosis history, were excluded. The study sample included 155 patients; each was followed up for 12 months in an asthma clinic after their first visit to an asthma-attack clinic. The Human Research Ethics Committee at Hatyai Hospital approved this study, and the approval number is HYH EC 069-65-01. The requirement for informed consent was waived due to no direct contact with patients.

Data collection

Demographic and clinical data were extracted from the electronic medical record. The extracted data included demographic characteristics including age, gender, BMI, comorbidities, smoking status, asthma duration, treatment steps stratified by GINA guidelines stepwise management, and the number of moderate/severe exacerbations in the previous 12 months. The clinical parameters collected during the 12-month follow-up periods were the number of controllers and relievers prescribed (only short-acting Beta-2 agonist (SABA) with or without short-acting anti-muscarinic receptor antagonist), GINA-classified treatment steps, annual moderate/severe exacerbations rate, and the estimated time of exacerbation. The definition of asthma exacerbation is referenced elsewhere[14]. Severe asthma exacerbation includes at least one of the following: (a) use of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days, (b) a hospitalization or ED visit because of asthma requiring systemic corticosteroids. The definition of a moderate asthma exacerbation should include one or more of the following: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last 2 days or more but not be severe enough to warrant systemic corticosteroid use and/or hospitalization.

Statistical analysis

The statistical analyses were performed using Statistical Package for the Social Sciences version 23 for Windows. Continuous and ordinal variables are presented as means and standard deviations (S.D.) and were analyzed using unpaired t-tests. Categorical variables are reported as numbers and percentages and were analyzed using the Chi-square test. The Paired-Samples T-test was used to compare the means of 2 variables for a single group. The time to the first exacerbation after the study visit was compared using the log-rank test. A probability curve for a future asthma exacerbation across treatment baselines was constructed using the Kaplan-Meier method under a non-adjusted covariation factor. A p-value less than 0.05 was considered statistically significant for all the statistical tests analyzed.

Results

Demographic characteristics

One hundred eighty-nine asthma patients with unscheduled emergency visits with exacerbation were followed up at the asthma-attack clinic from July 9, 2020, to March 19, 2021. However, only 155 met the criterion and were included in the study for analysis. These patients were stratified by stepwise management, based on the GINA guidelines, into 3 groups, consisting of 59 patients (38.1%) with naïve treatment, 53 (34.2%) with GINA-classified step 1-2 treatment, and 43 (27.7%) with GINA-classified step 3-5 treatment. The demographic characteristics of the study population are summarized in Table 1. The mean age was 46.4±16.3 years. Older age was significantly associated with higher step treatment (p-value<0.001); the mean age of those receiving treatment with GINA classified step 3-5 was 55±13.2 years and 41.2±17.1 years in those with naïve treatment. Approximately 50% of patients with naïve treatment were 18 to 40, while 62.8% of those receiving treatment with GINA classified steps 3-5 were 41 to 60 (p-value<0.001). Most patients were female (61.9%), and the mean BMI was 25.6 kg/m^2. Patients in the treatment groups of GINA classified steps 1-2 and 3-5 had a higher percentage of comorbidities; 66% and 62.8% had 1-2 comorbidities, respectively, compared with 49.2% of patients with naïve treatment. Seventy patients (45.2%) were noted with allergic rhinitis, 45 (29%) with hypertension, and 30 (19.3%) with diabetes. Only 2 subjects reported having nasal polyps. Most patients (67.7%) were non-smokers.

Asthma characteristics

The asthma characteristics of the study population are summarized in Table 2. The mean asthma duration in study members was 14.2±12.9 years. Patients with naïve treatment had significantly less duration of asthma (10.8±9.9 years) than those with GINA-classified steps 1-2 treatment (15.6±13.9 years) and those with GINA-classified steps 3-5 treatment (16.9±14.3 years) (p-value=0.036). Before the study visit, the mean annual moderate/severe asthma exacerbation rate was 1.12±2.6. Patients with GINA classified steps 3-5 treatment experienced a significantly higher exacerbation rate of 3.0±4.07, while those with naïve treatment were 0.34±0.99 (p-value<0.001). Notably, those with naïve treatment had no history of severe exacerbation in the past year. Of 155 patients, 29 (18.7%) experienced 2 or more severe asthma exacerbations, 19 were treated with GINA-classified steps 3-5, 8 with GINA-classified steps 3-5, and only 2 with naïve treatment (p-value<0.001).

Table 1 Demographics and baseline clinical characteristics stratified by stepwise management based-on GINA guidelines

Characteristic	All (n=155)	Naive treatment (n=59)	GINA-classified step 1-2 (n=53)	GINA-classified step 3-5 (n=43)	p-value
Age (years)					
Mean (S.D.)	46.4 (16.3)	41.2 (17.1)	45.1 (14.2)	55.0 (13.2)	<0.001
Age groups (years), n (%)					
18-40	55 (35.5)	29 (49.2)	22 (41.5)	4 (9.3)	
≥41-60	68 (43.9)	19 (32.2)	22 (41.5)	27 (62.8)	<0.001
≥61	32 (20.6)	11 (18.6)	9 (17.0)	12 (27.9)	
Sex, n (%)					
Female	96 (61.9)	35 (59.3)	31 (58.5)	30 (69.8)	0.459
BMI (kg/m^2)					
Mean (S.D.)	25.6 (5.9)	25.8 (6.5)	25.1 (5.8)	25.8 (5.3)	0.777
BMI groups (kg/m^2)[b], n (%)					
<18.5	16 (10.3)	6 (10.2)	7 (13.2)	3 (7.0)	
≥18.5-24.9	65 (41.9)	29 (49.2)	20 (37.7)	16 (37.2)	0.265
≥25-29.9	44 (28.4)	10 (16.9)	18 (34.0)	16 (37.2)	
≥30	30 (19.4)	14 (23.7)	8 (15.1)	8 (18.6)	
Allergic rhinitis, n (%)					
Yes	70 (45.2)	28 (47.5)	27 (50.9)	15 (34.9)	0.262
Number of comorbidities, n (%)					
None	48 (31.0)	23 (39.0)	16 (30.2)	9 (20.9)	
1-2	91 (58.7)	29 (49.2)	35 (66.0)	27 (62.8)	0.093
≥3	16 (10.3)	7 (11.9)	2 (3.8)	7 (16.3)	
Smoking status/history, n (%)					
Smoker	50 (32.3)	20 (33.9)	18 (34.0)	12 (27.9)	0.773
Non-smoker	105 (67.7)	39 (66.1)	35 (66.0)	31 (72.1)	

S.D.=standard deviation, n=number, BMI=body mass index

Table 2 Asthma characteristics stratified by stepwise management based-on GINA guidelines

Characteristic	All (n=155)	Naïve treatment (n=59)	GINA-classified step 1-2 (n=53)	GINA-classified step 3-5 (n=43)	p-value
Asthma duration (years)					
Mean (S.D.)	14.2 (12.9)	10.8 (9.9)	15.6 (13.9)	16.9 (14.3)	0.036
Median (min, max)	10 (1, 60)	8 (1, 45)	10 (1, 60)	12 (1, 55)	0.089
Asthma duration by group (years), n (%)					
1-5	51 (32.9)	22 (37.3)	17 (32.1)	12 (27.9)	0.372
6-10	38 (24.5)	18 (30.5)	12 (22.6)	8 (18.6)	
11-20	27 (17.4)	10 (16.9)	8 (15.1)	9 (20.9)	
≥5	39 (25.2)	9 (15.3)	16 (30.2)	14 (32.6)	
Asthma exacerbation rate, 12 months before the study visit, mean (S.D.)					
Moderate/severe	1.12 (2.60)	0.34 (0.99)	0.66 (1.33)	3.0 (4.07)	<0.001
Moderate	1.08 (2.37)	0.34 (0.99)	0.60 (1.21)	2.63 (3.74)	<0.001
Severe	0.12 (0.58)	0	0.06 (0.23)	0.37 (1.05)	0.003
Number of moderate/severe asthma exacerbations 12 months before the study visit, n (%)					
0	94 (60.6)	46 (78.0)	36 (67.9)	12 (27.9)	<0.001
1	32 (20.6)	11 (18.6)	9 (17.0)	12 (27.9)	
≥2	29 (18.7)	2 (3.4)	8 (15.1)	19 (44.2)	

S.D.=standard deviation, n=number

Study outcomes

Treatment patterns

All subjects were treated following option 2 of the GINA guidelines[2] during a year follow-up period. The study result showed a significant difference in the number of controllers prescribed among the 3 groups (p-value<0.001). Across a year, patients receiving GINA-classified steps 3-5 treatment were prescribed controllers 10.9 canisters (95% confidence interval [CI], 10.1 to 11.7), which was significantly higher than the 7.8 canisters (95% CI, 6.5 to 8.9) prescribed to those with naïve treatment and the 9.6 canisters (95% CI, 8.4 to 10.7) prescribed to those with GINA-classified steps 1-2 treatment. In contrast, there was no significant difference in the number of reliever prescriptions among the 3 groups (p-value=0.274), with rates of 1.21 canisters/year (95% CI, 0.63 to 1.79), 0.85 canisters/year (95% CI, 0.60 to 1.09), and 1.14 canisters/year (95% CI, 0.98 to 1.29), respectively (Figure 1).

The treatment ratio is shown in Figure 2. In the first month, 22% of patients with naïve medication were prescribed GINA-classified step 2 treatment, 44.1% with step 3, and 33.9% with step 4. However, the proportion of patients without treatment increased from the third month. It continued to rise throughout the study period, with approximately 50% of patients with naïve medication returning to no treatment because they were lost to follow-up. Patients initially receiving GINA-classified steps 1-2 treatment were stepped up to steps 3 and 4 at 47.2% and 47.2%, respectively. Similarly, the proportion of patients without treatment increased after the second month, and

one-third were lost to follow-up after 12 months. In the GINA-classified steps 3-5 treatment group, most patients received step 3 treatment (27.9%), followed by step 4 (53.5%) and step 5 (18.6%). Only 14% of patients in this group were not receiving treatment at the end of the 12-month follow-up period. Moreover, 25.6% of them were stepped up to step 5 therapy during the study.

Exacerbation

The annual moderate/severe exacerbation rates before and after the study visit: the rates decreased in the treatment groups of GINA-classified steps 1-2 and 3-5 (from 0.66 to 0.47 (p-value=0.085) and 3.00 to 1.19 (p-value=0.006), respectively). In comparison, an increase from 0.34 to 0.49 (p-value=0.236) was observed in those with naïve treatment; however, it was lower than in those with GINA-classified steps 3-5 treatment despite there being more patients with no treatment at the end of the study period (Figure 3). Furthermore, the likelihood of having future exacerbation in patients with naïve treatment was lower than in patients in the treatment groups of GINA-classified steps 1-2 and 3-5 (Figure 4); however, no significant difference was found (p-value=0.107). The estimated time of exacerbation in naïve treatment, GINA-classified steps 1-2 and 3-5 treatment were 42.2, 36.6, and 34.2 weeks, accordingly.

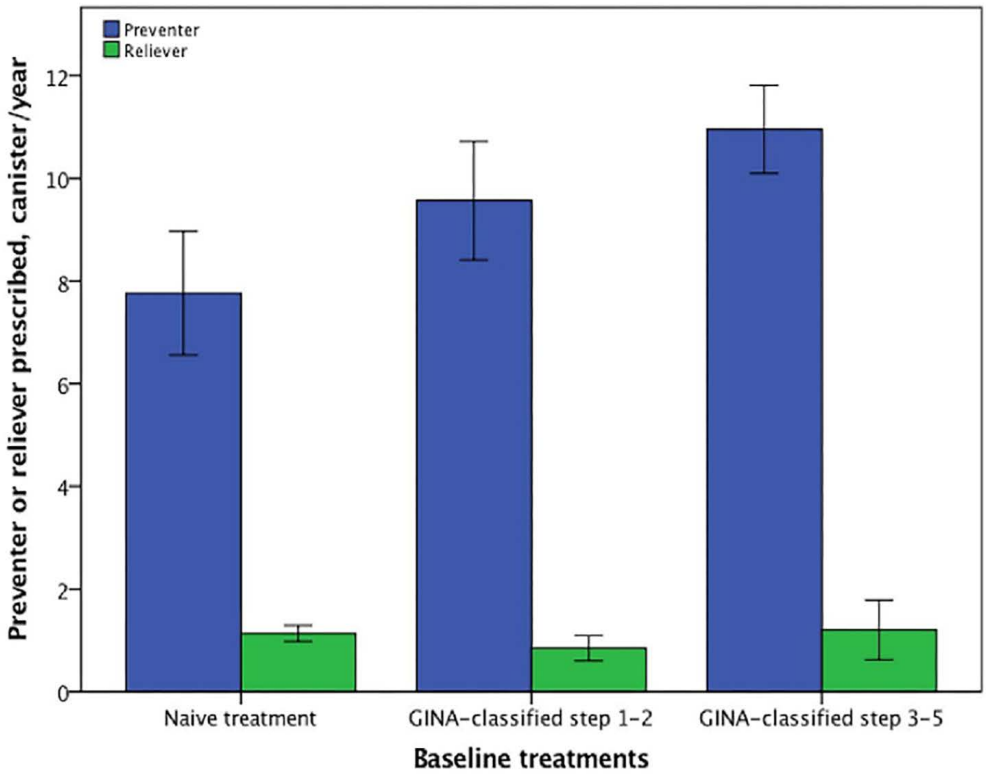

Figure 1 The number of controllers and relievers across the baseline treatments

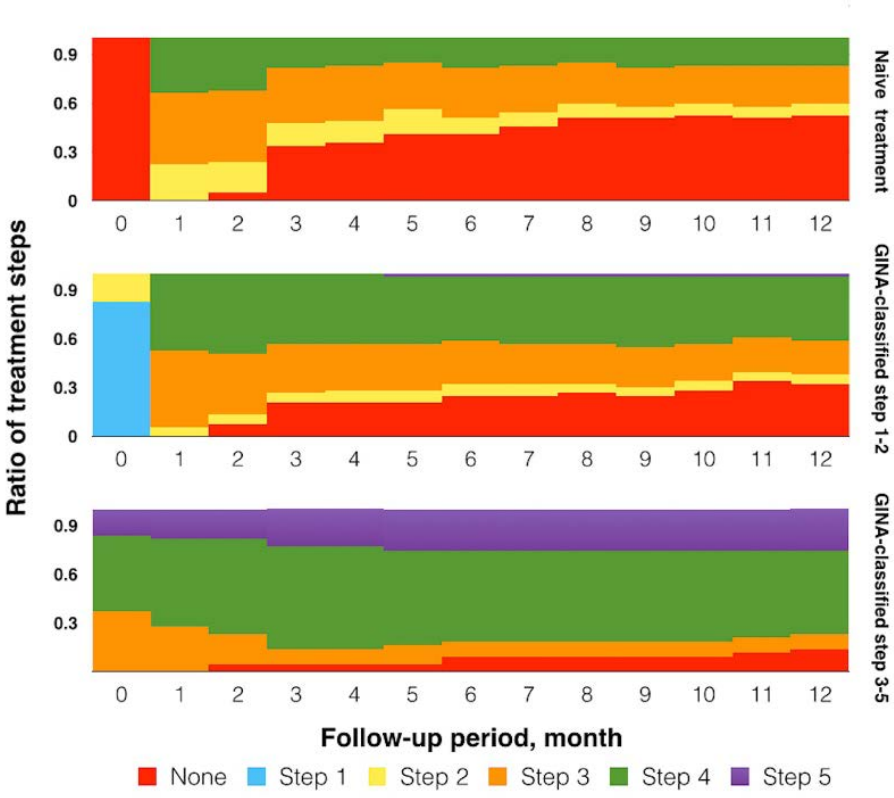

Figure 2 The proportion of GINA-classified step treatment received over a year

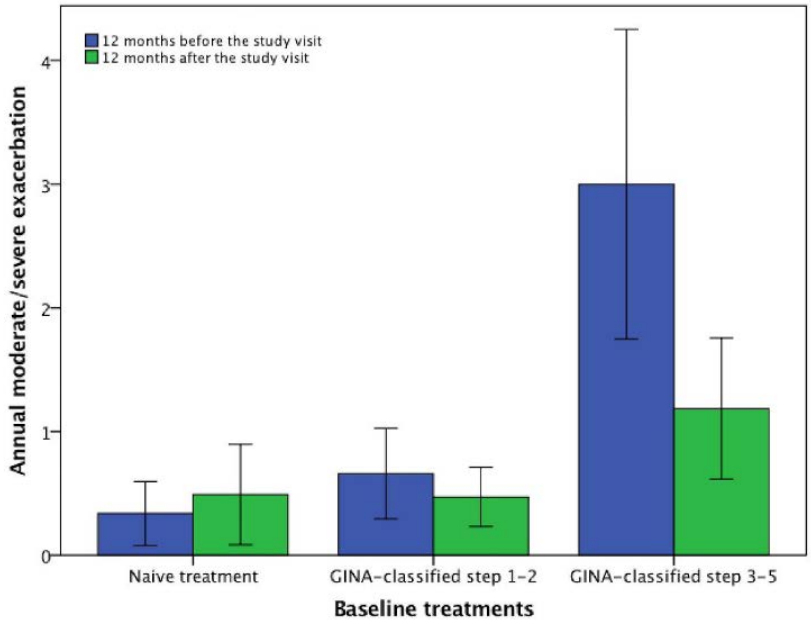

Figure 3 The annual moderate/severe exacerbation before and after the study across the baseline treatments

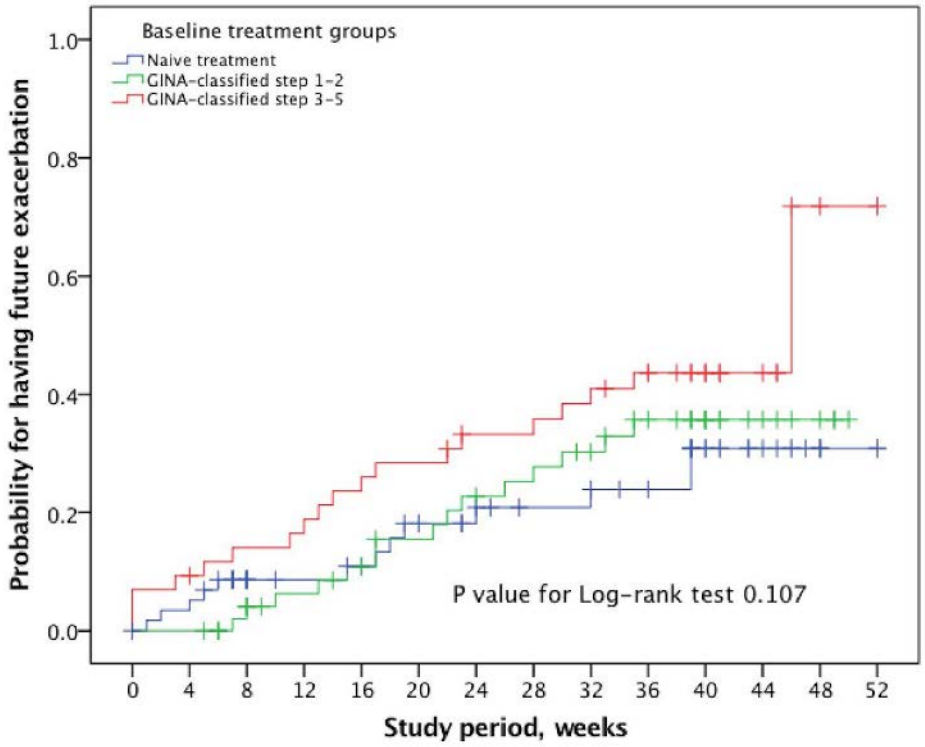

Figure 4 Kaplan-Meier curves indicate the probability of having future exacerbations following ED-visited exacerbation classified by baseline treatments

Discussion

The study found that maintenance medications were modulated into higher treatment steps after ED-visited exacerbation across all baseline treatment groups. However, as the stepwise asthma treatment increased, the future exacerbation rate also increased. Patients treated with GINA-classified steps 3-5 as baseline reported the highest annual moderate/severe exacerbation rate after stepping up therapy, and there was a trend of a greater probability of developing those events in shorter time intervals compared to those with GINA-classified steps 1-2 and naïve treatment. This data could provide insight into the relationship between the severity of asthma and asthma exacerbations. Notably, the annual future moderate/severe exacerbation rate did not show a significant change, only slightly increasing from 0.34 to 0.49 (p-value=0.236), despite approximately 50% of the naïve treatment group being lost to follow-up with a diagnosis of asthma for at least ten years and receiving only 7.8 canisters of controllers yearly. Among younger patients: fewer comorbidities and no previous exacerbations in the past year were significant asthma characteristics. Overall, this study provides robust data that could guide the appropriate strategies for managing asthma in patients with poor adherence and sporadic asthma exacerbation patterns.

Our study found that 38.1% of patients did not use medication despite having a previous asthma diagnosis for at least 10 years. Previous research has found that

approximately 40% of those admitted to ED for asthma attacks were not previously known to have asthma[7]. Only 35–80% of asthma patients take ICS as a long-term control medication[6,15]. This finding suggests that this patient group needs medication compliance and adherence. Compared to a previous study on hospitalized patients, only 14% did not use medication[16]. This variation reflects the natural course difference between these 2 settings of asthma exacerbation. It raises awareness and more attention to managing the patients experiencing ED-visited exacerbation without admission due to the limited time for a written asthma action plan in the ED.

In addition, our study observed that patients with more treatment steps were significantly older and had higher comorbidities. These findings are consistent with earlier studies, suggesting that older age and comorbidities are characteristics that lead to poor adherence to treatment and poor asthma outcomes[5,17]. Differences in patients' characteristics should be considered when assessing disease severity and the impact on asthma control. While the ultimate goal of asthma management is to minimize future exacerbations, taking ICS as a long-term control medication is critical to achieving the desired outcomes. Our study found that the more treatment steps, the higher the future exacerbation rates. These data might represent utilizing a medication regimen below their disease severity level. However, all our subjects received more asthma therapy across groups and were associated with lower exacerbation events in later years. Improved adherence and increasing treatment steps contributed to this favorable outcome.

Regarding treatment strategies, stepping up therapy and prescribing adequate preventers and relievers can decrease the exacerbation rate[5,16,18]. In addition, stepping-up therapy usually occurs after exacerbations, which can increase adherence to medication[19]. However, the inhalation technique and avoidance of possible triggers should be assessed at each scheduled visit before increasing the treatment level. These interventions may also be a primary key to improving future asthma outcomes.

A surprising result of our study was that approximately 50% of naïve treatment patients returned to no treatment due to being lost to follow-up. Although good adherence is associated with a lower risk of severe asthma exacerbations[20,21], there was no significant change in the exacerbation rate among those with naïve treatment despite poor adherence to long-term asthma controllers. Authors suggest that patients with ED-visited exacerbation in the naïve treatment and GINA-classified steps 1-2 treatment groups may have a similar natural history of mild asthma because of a low rate of future moderate/severe exacerbation and tend to be lost to follow-up. The mildest form of asthma has minimal impact on daily life; several studies indicate that patients with mild asthma take less than 50% of the recommended doses of maintenance treatment, and 10–15% of patients refill prescriptions for maintenance inhaled treatments, over a 1-year timeframe[22-24]. Particularly in patients with naïve treatment, improving patient education, adherence, access, and treatment optimization should play a significant role in their asthma management, which may affect future asthma exacerbation. Treatment with as-needed low-dose ICS-formoterol, as in the GINA track 1 strategy, may be appropriate for these patients because it reduces the risk of asthma exacerbation and overusing SABA-only treatment in patients with infrequent or mild symptoms[2].

Our study has some imitations. Due to the retrospective study, its findings may not have external validity. Our database did not include data on asthma assessment tools for asthma control, which is another outcome of asthma management. Moreover, the study covered only one year and had a relatively small number of

patients, who may have needed a more extended follow-up period. Based on the statistical analysis, we suggest using the Kaplan-Meier method under adjusted covariation factor in future studies; it may affect the risk of exacerbations.

Conclusion

In summary, this retrospective analysis confirms that future exacerbations following ED-visited exacerbations increase in frequency as the stepwise treatment increases, and patients with naïve treatment have unique disease characteristics. They had significantly fewer exacerbations despite a significant loss of long-term asthma control.

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Conflict of interest

There are no potential conflicts of interest to declare.

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