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Original Article

The impact of budesonide inhalation suspension for asthma hospitalization: In terms of length of stay, recovery time from symptoms, and hospitalization costs

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ABx antibiotics
BIS budesonide inhalation suspension
DPC/DPS the diagnosis procedure combination/per diem payment system
GINA the Global Initiative for Asthma
ICSs inhaled corticosteroids

ABSTRACT

Background: Hospitalization is a major cause of medical expenditure for asthma. Budesonide inhalation suspension (BIS) may assist in reducing asthma-related symptoms in severe asthma exacerbation. However, its effectiveness for hospitalized patients remains poorly known. The objective of this study is to determine associations of BIS with asthma hospitalization.

Methods: We retrospectively analyzed 98 patients who were admitted to our hospital due to severe asthma exacerbation (24 treated with BIS in combination with procaterol) from April 2014 to January 2019. Length of stay, recovery time from symptoms (wheezes), and hospitalization costs were compared between the 2 groups according to clinical factors including the use of BIS and signs of respiratory infections (i.e. C-reactive protein, the presence of phlegm, and the use of antibiotics). Multivariate logistic regression analysis was performed to determine factors contributing to hospitalization outcomes.

Results: The use of BIS was associated with shorter length of stay, faster recovery time from symptoms, and more reduced hospitalization costs (6.0 vs 8.5 days, 2.5 vs 5.0 days, and 258,260 vs 343,350 JPY). Signs of respiratory infection were also associated with hospitalization outcomes. On a multivariate regression analysis, the use of BIS was a determinant of shortened length of stay and reduced symptoms and medical costs for asthma hospitalization along with signs of respiratory infection.

Conclusions: BIS may contribute to shorten length of hospital stay and to reduce symptoms and medical expenditure irrespective of the presence or absence of respiratory infection.

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Introduction

The prevalence of asthma has been increasing worldwide.¹ Medical costs for asthma in Japan amounted to ¥ 333.7 billion according to the national medical expense in 2017 published by Japanese Ministry of Health, Labour and Welfare, 85% of which were occupied by biologics for outpatients (<https://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/17/dl/toukei.pdf>). On the other hand,

a systematic review has demonstrated that hospitalization is the most important direct medical costs for asthma and contributes to the impaired socio-economic activities for a few decades.^{2–5} In an epidemiological survey regarding asthma hospitalization conducted in the United States, hospitalization costs and length of stay in 2010 were higher than those in 2001.⁶ Therefore, reduced expenditure and shortened length of stay for asthma hospitalization remain important problems.

Inhaled corticosteroids (ICSs) has a crucial role in the treatment of asthma in clinical practice. Budesonide, one of ICSs, reduces the risk of asthma exacerbation and improves asthma control and lung function in mild adult asthmatics^{7,8} even if patients have been

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smoking.⁹ Several delivery devices are available for the inhalation of budesonide; dry powder and metered dose inhalers, and a nebulizer.^{10,11} Budesonide inhalation suspension (BIS) using a nebulizer showed a comparable tolerability and efficiency to other ICSs adopting dry powder and metered dose inhalers in patients with moderate to severe asthma, as a controller medication.¹² For asthma exacerbations, BIS may assist in alleviating wheezes after its commencement in both childhood and adult asthma.^{13–15} Also, the use of BIS in emergency room could prevent asthma hospitalization in pediatric asthma.^{16,17} Thus, additional BIS in combination with short-acting β_2 agonists and systemic corticosteroids may be useful for hospitalization due to severe asthma exacerbation not only in children but also in adults. However, there is no report regarding whether additional BIS could contribute to reduce expenditure and shorten length of stay for asthma hospitalization in adult asthma. Also, it remains poorly known which clinical factors are associated with hospitalization length and costs for asthma.

In this study, we aimed to clarify the efficacy of BIS in acute asthma patients who were admitted to hospital in terms of length of stay, recovery time from symptoms, and hospitalization costs. Associations of these indices with other factors such as sex, age, smoking habit, clinical signs of respiratory infection [i.e. fever, white blood cell count, C-reactive protein (CRP), the presences of phlegm] and the use of ICSs, oral corticosteroids/biologics, antibiotics (ABx)/anti-influenza viral agents, and oxygen requirements were also evaluated.

Methods

Patients recruitment, diagnosis of severe asthma exacerbation, and endpoints of this study

We retrospectively analyzed patients who were admitted to our hospital due to severe asthma exacerbation from April 2014 to January 2019. Patients were selected from database in our hospital using the International Statistical Classification of Diseases and Related Health Problems, 10th revision coding system¹⁸ at the time of admission as follows; (1) bronchial asthma, (2) bronchial asthma attack, (3) status asthmaticus, and (4) severe asthma. Patients were excluded if they required management of ventilation, did not receive systemic corticosteroids (SCSs) during hospitalization periods, or had obvious pneumonia on chest X-rays. Diagnosis of severe asthma exacerbation was made on the basis of exacerbated symptoms, such as dyspnea, wheezing, cough, and chest tightness, that required SCSs, short-acting β_2 agonists with or without oxygen at the emergency unit or outpatient clinic. The primary endpoint was set at length of stay, and the secondary endpoints at recovery time from symptoms and hospitalization costs. This study was approved by the Ethics Committee of Nagoya City University (Number 60-18-0204).

Criteria of admission to the hospital

Patients were considered to require hospitalization if symptoms had been still persisting or exacerbating despite the administration of SCSs in combination with short-acting β_2 agonists at the emergency unit or outpatient clinic, or they required oxygen because of hypoxemia.

Treatments against severe asthma exacerbation during hospitalization

Treatments against severe asthma exacerbation was conducted by asthma specialists (YKa, KF, and MT) with residents specialized in respirology (KI, YIn., HN, SY, and YKi) according to the Global

Initiative for Asthma (GINA) 2015 guideline.¹⁹ Briefly, they received SCSs such as 1–4 mg of betamethasone or 10–40 mg of prednisolone twice or three times daily intravenously and 0.3 mL of procaterol inhalation through nebulizers four times daily during hospitalization. Oral or intravenous ABx/anti-influenza viral drugs were also administrated if respiratory infection was suspected by asthma specialists. All controller drugs for asthma including ICSs were not withheld during hospitalization periods. All patients who had not received any anti-asthma controller treatments at clinics or hospitals received a combination of moderate doses of ICSs (fluticasone propionate equivalent 400 μ g daily) and long-acting β_2 agonists after being admitted to hospital. All patients underwent education programme at least twice from pharmacists for the purpose of improving inhalation technique and maintaining medication adherence after discharge.²⁰ From April 2018, BIS 0.25 mg four times daily (1 mg/day) was added to the nebulized regular procaterol for all patients. Outcomes of these patients (BIS+ group) were compared with those of patients enrolled before April 2018 (BIS– group) as a historical control.

Definition of recovery time from symptoms

Symptoms such as dyspnea, wheezing, cough and chest tightness were considered to be alleviated if they were no longer felt out by patients themselves. When wheezes were not audible on chest examination, it was noted in medical records. Length until resolution of wheezes was calculated from medical records and adopted as an objective index of recovery time from symptoms. When wheezes were relieved within 3 days after admission, patients were arbitrarily classified as well responders to treatments.

Criteria of discharge from the hospital

Patients were permitted discharge from the hospital if their symptoms improved and were able to do daily activities without oxygen. To avoid the recurrence of severe asthma exacerbation, all patients were examined for their conditions and were prescribed 3–5 days of oral corticosteroids (prednisolone equivalent 20–30 mg daily) at the discharge. Early dischargers were arbitrarily defined as patients who discharged from hospital within 6 days after admission.

Hospitalization costs

Hospitalization costs were calculated by Medical Professions Division of our hospital on the basis of the diagnosis procedure combination/per diem payment system (DPC/DPS).²¹ It includes hospitalization fee, laboratory tests, diagnostic imaging, drug administration, injections, and medical procedures, and excludes high-price procedures and medication refills at the time of discharge.²² According to the DPC/DPS system of Japan, the permitted length of hospital stay for asthma exacerbation that can be covered by the “comprehensive payment system” by government is 6 days. If total expenditure was higher than the amount of 6 days hospitalization defined by the DPC/DPS,²¹ patients were categorized into intensive medical recipients. The amount of expenditure for 6 days hospitalization during study periods are shown in [Supplementary Table 1](#), the average amount during the study period was 268,840 JPY.

Statistics

Data were analyzed using JMP 11.2.0 Start Statics (SAS Institute Inc., Cary, NC, USA), and were presented as median (ranges) or number (%). Comparisons of length of stay, recovery time from

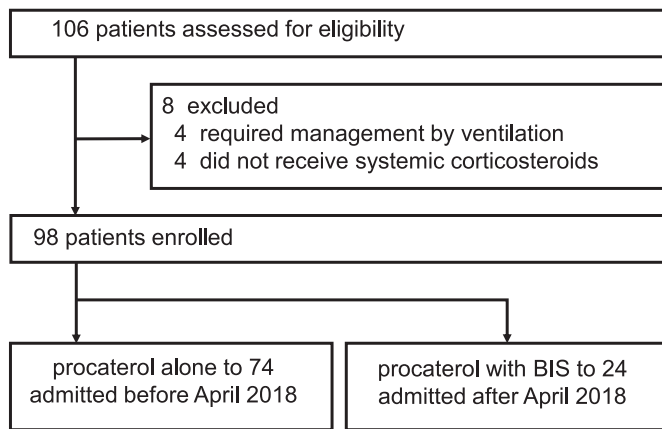


Fig. 1. The diagram of studied patients. BIS, budesonide inhalation suspension.

symptoms, and hospitalization costs between the 2 groups stratified according to the age (≥ 65 years-old),²³ smoking habits (never/ex-current), body temperature (≥ 37.5 °C; the infection law of Japan, https://www.mhlw.go.jp/web/t_doc?dataId=00tb9642&dataTy=1&pageNo=1), white blood cell count ($\geq 9000/\mu\text{L}$),²⁴ CRP (≥ 0.3 mg/dL),²⁵ and the use of ICSs, regular oral corticosteroids/biologics, BIS, ABx/anti-influenza viral drugs, and oxygen were performed using Wilcoxon rank-sum test. For dichotomous variables (early dischargers, well responders, and intensive medical recipients), Chi-square or Fischer exact tests were applied for the data analysis. An index with p of ≤ 0.15 by a comparison between the two groups were adopted in a logistic regression analysis to determine factors contributing to early dischargers, well responders, and intensive medical recipients. A p value < 0.05 was considered significant when α error was set at 5%.

Results

Patients characteristics

We selected 106 patients who were admitted to our hospital due to severe asthma exacerbation from database (Fig. 1). Among 106 patients, 4 required management of ventilation and 4 did not receive SCSs but only ABx with and procaterol inhalation during their hospitalization periods. Thus, 98 patients were eligible for this study, comprised of 24 patients in the BIS+ group and 74 in the procaterol alone BIS- group.

Baseline characteristics between the two treatment groups and treatment steps according to the GINA 2015 guideline at hospitalization are presented in Table 1 and Figure 2, respectively. Sixty-four patients were routinely managed by clinicians, 50 of which were treated by our group. Of these, 54 have received moderate or high doses of ICSs and additional long-acting β_2 agonists ($n = 54$), leukotriene receptor antagonists ($n = 42$), oral corticosteroids ($n = 5$), and biologic agents ($n = 10$). On the contrary, two were prescribed short-acting β_2 agonists only and 32 were not taking any treatments against asthma by any clinicians. The 2 treatment groups were similar, with no clinically relevant differences in baseline characteristics such as sex, smoking habit, temperature, white blood cell count, CRP, the use of ABx and oxygen, and the presence of phlegm.

ABx or peramivir, an intravenous anti-influenza viral agent, were commenced in 55 patients (56%) at the time of hospitalization and they were classified into ABx/peramivir+ group, and the remaining 43 patients into ABx/peramivir- groups. The breakdown of types of ABx/peramivir are as follows; intravenous 3rd

Table 1

Characteristics of the patients at the time of hospitalization.

	All patients (n = 98)	BIS- (n = 74)	BIS+ (n = 24)	p value
Age, yrs	61 (22–92)	59 (22–92)	69 (35–90)	0.095
Sex, females, n (%)	65 (66)	47 (64)	18 (75)	0.33
Smoking, never/ex/current, n (%)	51 (52)/35 (36)/12 (12)	37 (50)/28 (38)/9 (12)	14 (58)/7 (29)/3 (13)	0.73
Body temperature, °C	36.9 (35.6–39.9)	36.9 (35.6–39.9)	37.0 (35.9–38.8)	0.80
Febrile (≥ 37.5 °C), n (%)	72 (73)	18 (24)	8 (33)	0.43
WBC, μL	8800 (3800–18,200)	9300 (3800–18,200)	7950 (4300–15,500)	0.09
WBC $\geq 9000/\mu\text{L}$, n (%)	47 (48)	38 (51)	9 (38)	0.25
CRP, mg/dL	0.82 (0.03–24.4)	0.81 (0.03–24.4)	1.54 (0.03–14.8)	0.58
CRP ≥ 0.3 mg/dL, n (%)	69 (71)	50 (69)	19 (79)	0.44
SpO ₂ at admission, %	94 (79–100)	95 (84–100)	94 (79–98)	0.24
Phlegm, n (%)	20 (20)	16 (22)	4 (17)	0.77
Daily treatments for asthma				
ICSs use, n (%)	62 (63)	45 (61)	17 (71)	0.47
Doses, μg daily [†]	640 (160–1800)	640 (160–1800)	640 (500–1000)	0.66
LABAs use, n (%)	57 (58)	41 (55)	16 (67)	0.35
LTRAs use, n (%)	42 (43)	30 (41)	12 (50)	0.42
OCSs use, n (%)	5 (5)	4 (4)	2 (8)	0.59
Biologics, n (%)	10 (10)	7 (9)	3 (13)	0.70
Treatments for severe asthma exacerbation				
Procaterol use, n (%)	98 (100)	74 (100)	24 (100)	–
BIS use, n (%)	24 (24)	0 (0)	24 (100)	–
Systemic corticosteroids, (PSL equivalent) mg/day	60 (30–120)	60 (30–120)	60 (40–80)	0.48
ABx/peramivir use, n (%)	55 (56)	43 (58)	12 (50)	0.49
ABx/peramivir, combination, n (%)	8 (15)	6 (14)	2 (17)	> 0.99
Oxygen, n (%)	41 (42)	29 (39)	12 (50)	0.35

WBC, white blood cell count; CRP, C-reactive protein; ICSs, inhaled corticosteroids; LABAs, long-acting β_2 agonists; LTRAs, leukotriene receptor antagonists; OCSs, oral corticosteroids; BIS, budesonide inhalation suspension; PSL, prednisolone; ABx, antibiotics.

[†] n = 62 for all, n = 45 for BIS-, n = 17 for BIS+, n = 8 for all, n = 6 for BIS-, n = 2 for BIS+.

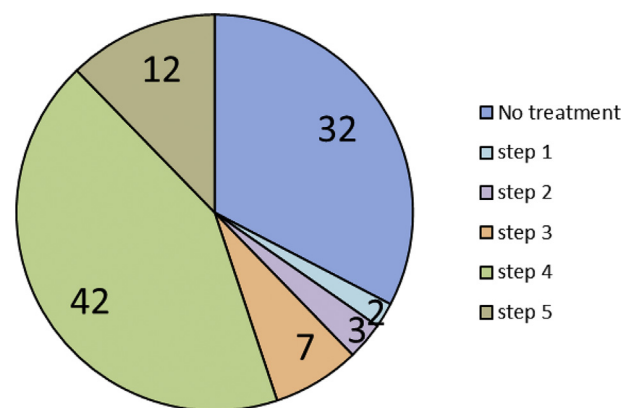


Fig. 2. Treatment steps at the time of hospitalization according to the GINA 2015 guideline.

generation β -lactam ($n = 29$, sulbactam/ampicillin or ceftriaxone), intravenous 4th generation β -lactam ($n = 5$, tazobactam/piperacillin) oral macrolides ($n = 12$, clarithromycin or azithromycin), oral quinolones ($n = 13$, levofloxacin or garenoxacin), and peramivir ($n = 4$). Eight patients had received combination therapies of ABx/peramivir (3rd generation β -lactam/oral macrolides; $n = 4$, 3rd generation β -lactam/quinolones; $n = 1$, 3rd generation β -lactam/peramivir; $n = 2$, and 4th generation β -lactam/oral quinolones;

$n = 1$). **Supplementary Table 2** shows the clinical characteristics at baseline of patients in the ABx/peramivir+ and ABx/peramivir– groups. ABx/peramivir+ group had higher body temperature and CRP levels, and lower values of SpO₂ at admission than ABx/peramivir– group. This demonstrates, as expected, that ABx/peramivir+ groups had more signs of respiratory infection than ABx/peramivir– group. Although 8 patients had received combination therapies of ABx/peramivir, the proportion of such patients did not differ between BIS+ and BIS– groups (**Table 1**).

The efficacy of BIS for severe asthma exacerbation in terms of length of stay, recovery time from symptoms, and hospitalization costs

Figure 3 depicts frequency distribution of patients with the two treatment groups regarding length of stay, recovery time from symptoms, and hospitalization costs. The median (ranges) length of stay and recovery time from symptoms of all patients were 8 (3–19) and 5 (1–12) days, respectively. Almost one-third of patients were categorized into early dischargers ($n = 33$, 34%) and well responders ($n = 34$, 35%). Expenditure for hospitalization costed 307,490 (28,040–1,130,510) JPY. Sixty patients (61%) were considered as intensive medical recipients arbitrarily defined according to the DPS/DPS.

Length of stay, recovery time from symptoms, and hospitalization costs were compared between BIS+ and BIS– groups (**Table 2**). As expected, BIS+ group showed shorter length of stay and recovered faster from exacerbated symptoms than BIS– group (6.0 days vs 8.5 days and $p = 0.01$, and 2.5 days vs 5.0 days and $p < 0.001$). Expenditure for hospitalization in BIS+ group showed 25% reduction as compared to that in BIS– group (258,260 JPY vs 343,350 JPY and $p = 0.045$).

The number of early dischargers, well responders, and intensive medical recipients were also compared between the 2 groups (**Table 3**). In BIS+ groups, more than half patients were considered as early dischargers ($n = 13$, 54%) and well responders ($n = 14$, 58%), respectively. Meanwhile, only less than 30% of patients met criteria of early dischargers and well responders ($n = 20$, 27% for both) in BIS– group. There are significant differences in the number of early dischargers and well responders between the 2 groups (**Table 3**).

However, the number of intensive medical recipients were only marginally different between BIS+ and BIS– groups (**Table 3**).

These finding indicate that BIS in combination with procaterol was useful in terms of the shortened hospitalization periods, fastened recover time from symptoms, and reduced hospitalization costs in patients with asthma.

Other factors associated with length of stay, recovery time from symptoms, and hospitalization costs

We sought to identify whether other clinical factors were associated with length of stay, recovery time from symptoms, and hospitalization costs (**Table 2, 3**). High CRP (≥ 0.3 mg/dL) and the ABx/peramivir+ groups required longer time until symptoms relief than the counterpart group. They were also associated with higher expenditure for hospitalization together with the presence of phlegm and the use of oxygen (**Table 2, 3**). Early dischargers were less prevalent in the ABx/peramivir+ group than in the ABx/peramivir– group (**Table 3**).

Meanwhile, age of ≥ 65 years, sex, smoking habit, and the use of ICSs and oral corticosteroids/biologics were unrelated to either length of stay, recovery time from symptoms, or hospitalization costs (**Table 2**).

Contributing factors for length of stay, recovery time from symptoms, and hospitalization costs

Lastly, logistic regression analysis was performed using indices with p of < 0.15 to determine factors contributing to early dischargers, well responders and intensive medical recipients (**Table 4**). We found that the use of BIS contributed to early dischargers, well responders, and less intensive medical recipients, along with signs of respiratory infection such as the use of ABx/peramivir, high CRP, and the presence of phlegm (**Table 4**). This indicates that BIS is effective to shorten length of stay and to reduce symptoms and medical expenditure irrespective of the presence or absence of signs of respiratory infection.

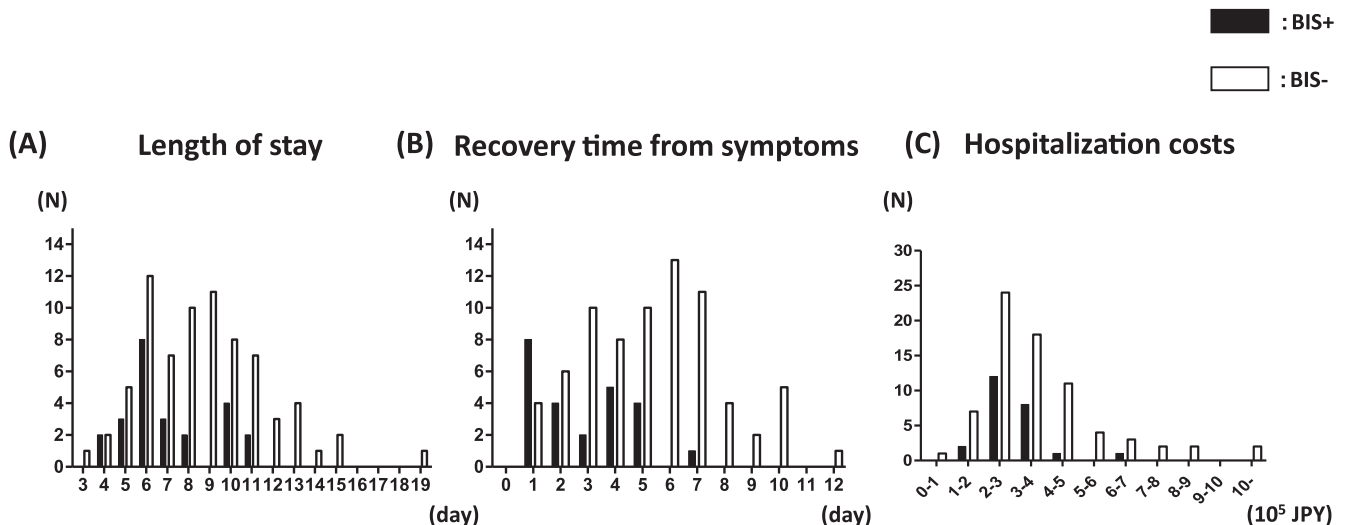


Fig. 3. The distribution of length of hospital stay (A), recovery time from symptoms (B), and hospitalization costs (C). Length until resolution of wheezes was adopted as an index of recovery time from symptoms.

Table 2

Comparisons of length of stay, recovery time from symptoms, and hospitalization costs between the two groups stratified according to age, sex, smoking habit, signs of respiratory infection, and the use of inhaled corticosteroids, oral corticosteroids/biologics, BIS, antibiotics, and oxygen.

Clinical factors	Length of stay			Recovery time from symptoms			Hospitalization costs [†]		
			p value			p value			p value
Age	≥65 yrs	<65 yrs		≥65 yrs	<65 yrs		≥65 yrs	<65 yrs	
	7.5 (4–15)	8.0 (3–19)	0.92	5.0 (1–10)	5.0 (1–12)	0.36	3.1 (1.0–11.3)	3.1 (0.3–10.5)	0.60
Sex	Females	males		Females	males		Females	males	
	8.0 (3–14)	8.0 (4–19)	0.87	5.0 (1–10)	5.0 (1–12)	0.96	3.0 (1.0–10.5)	3.2 (0.3–11.3)	0.46
Smoking	Never	ex/current		never	ex/current		Never	ex/current	
	8.0 (3–14)	8.0 (4–19)	0.73	5.0 (1–10)	4.0 (1–12)	0.94	3.0 (1.0–7.0)	3.2 (0.3–11.3)	0.53
Body temperature	≥37.5 °C	<37.5 °C		≥37.5 °C	<37.5 °C		≥37.5 °C	<37.5 °C	
	8 (4–15)	8 (3–19)	0.56	5.0 (1–10)	4.5 (1–12)	0.40	3.2 (2.0–11.3)	3.0 (0.3–10.5)	0.21
WBC	≥9000/μL	<9000/μL		≥9000/μL	<9000/μL		≥9000/μL	<9000/μL	
	9 (3–19)	7 (4–15)	0.16	5.0 (1–10)	4.0 (1–12)	0.28	3.4 (0.3–8.9)	3.0 (1.0–11.3)	0.49
CRP	≥0.3 mg/dL	<0.3 mg/dL		≥0.3 mg/dL	<0.3 mg/dL		≥0.3 mg/dL	<0.3 mg/dL	
	8.0 (3–19)	7.5 (4–13)	0.58	5.0 (1–12)	3.0 (1–10)	0.02	3.2 (0.3–11.3)	2.5 (1.0–8.3)	0.01
Phlegm	+	–		+	–		+	–	
	9.0 (6–15)	7.5 (3–19)	0.11	5.0 (2–9)	4.0 (1–12)	0.30	3.9 (0.3–8.9)	2.9 (1.0–11.3)	0.02
ICSs	+	–		+	–		+	–	
	8.0 (3–19)	7.0 (4–15)	0.38	4.0 (1–10)	5.0 (1–12)	0.24	3.1 (1.0–10.5)	3.1 (0.3–11.3)	0.87
OCSs/biologics	+	–		+	–		+	–	
	7.5 (4–13)	8.0 (3–19)	0.93	4.5 (1–10)	5.0 (1–12)	0.85	3.8 (2.0–8.9)	3.0 (0.3–11.3)	0.24
BIS	+	–		+	–		+	–	
	6.0 (4–11)	8.5 (3–19)	0.01	2.5 (1–7)	5.0 (1–12)	<0.0001	2.6 (1.0–6.6)	3.4 (0.3–11.3)	0.045
ABx/peramivir	+	–		+	–		+	–	
	8.0 (3–19)	7.0 (4–13)	0.12	5.0 (1–10)	4.0 (1–12)	0.04	3.7 (1.8–11.3)	2.5 (0.3–10.5)	0.008
Oxygen	+	–		+	–		+	–	
	8.0 (3–19)	8.0 (4–15)	0.39	5.0 (1–10)	4.0 (1–12)	0.28	3.7 (2.0–10.5)	2.8 (0.3–11.3)	0.004

WBC, white blood cell count; CRP, C-reactive protein; BIS, budesonide inhalation suspension; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ABx, antibiotics.

[†] Hospitalization costs were noted in $\times 10^5$ JPY.

Discussion

Nowadays, asthmatic patients are imposed on substantial socioeconomic burden worldwide.^{26,27} Although management of asthma by ICSs can reduce the risk of hospitalization due to severe asthma exacerbation,²⁸ some patients still have to be admitted to hospital because of poor knowledge for asthma self-management and its severity.^{29,30} For pediatric asthma, although theophylline fails to shorten length of stay by severe asthma exacerbation in several reports,^{31,32} an additional 2 mg of BIS daily to standard management reduces hospitalization periods.³³ In the present study, we have demonstrated for the first time that an additional 1 mg of BIS daily in combination with procaterol and intravenous systemic corticosteroids is effective in adult asthma who are admitted to hospital in terms of length of stay, recovery time from symptoms, and hospitalization costs. The present findings provide clinicians with a novel treatment recommendation for severe asthma exacerbation requiring hospitalization.

The efficacy of BIS for asthma is mainly reported in a field of pediatric asthma. It can improve not only asthma-related symptoms including wheezes^{13–17} but also pulmonary function in acute asthma.^{13,14,17} Nebulized BIS using a jet nebulizer is rapidly absorbed throughout the lungs, and its plasma concentration reaches to maximum within 30 min, with a terminal elimination half-life of within 3 h.³⁴ In adults, 58%–70% of the dose of nebulized BIS is deposited into the lung.³⁵ Good pharmacokinetics and pharmacodynamics of BIS may offer preferable outcomes for length of stay, recovery time from symptoms, and hospitalization costs as reported in the present study as well as in previous studies.^{13–17}

In this study, length of hospital stay is longer than that of previous reports from the United States (ranging 2–4 days).^{6,38} One possible reason may be our meticulous educational intervention by pharmacists. Educational intervention focusing on inhalation technique and medication adherence by pharmacists can improve not only asthma-related symptoms³⁹ but also future asthma control in outpatients.^{20,40} Counseling during hospitalization by

pharmacist reduces emergency department visits and hospitalization due to asthma attack after discharge, with the enhancement of medication adherence.⁴¹ Time may be too limited to implement asthma education if most of patients discharged within 4 days. Although either the use of ICS or oral maintenance corticosteroids/biologics did not relate to the length of stay, recovery time from symptoms, or hospitalization costs, our cohort included 54 patients (55%) undergoing treatment step 4/5 according to the GINA 2015 guideline, who are considered to have severe asthma. Of these, 50 were routinely managed for asthma in our hospital, a tertiary care department for asthma. Thus, characteristics of patients with asthma may be different from those of previous reports and other general hospitals. Although there is no report of an association between hospitalization and severity of asthma as far as we have searched, more severe nature of our cohort might have prolonged the length of stay and increased expenditure for asthma hospitalization.

Additionally, comorbid respiratory infection such as acute bronchitis and influenza virus infection would also affect the severity of exacerbation, leading to prolonged length of stay and higher medical expenditure. Respiratory infection is well known trigger of asthma exacerbation not only in children but also in adults.^{42,43} Human rhinovirus,⁴² followed by influenza virus,⁴² *Chlamydia pneumoniae*,^{44–46} *Mycoplasma pneumoniae*,^{42,46} *Haemophilus influenzae*,⁴⁷ and *Streptococcus pneumoniae*⁴⁸ are the commonest causative microorganisms for asthma exacerbation or hospitalization. In children, bacterial infection was independently associated with acute wheezing episode up to three years, together with viral infection.⁴⁹ Ikura *et al.* has demonstrated that approximately 70% of adult patients with asthma hospitalization have either or both viral and bacterial infection.⁴⁸ Nowadays, hospitalization length that can be covered comprehensively by government is defined by the average length of hospitalization of whole Japan; that is six days. However, it remains unclear whether this is long enough to treat severe asthma exacerbation, or comprehensive health care fees for the hospitalization (average 268,840 JPY from

Table 3
Comparisons of early dischargers, well responders, and intensive medical recipients in patients who were admitted to hospital between the 2 groups stratified according to age, sex, smoking habit, signs of respiratory infection, and the use of inhaled corticosteroids, oral corticosteroids/biologics, BIS, antibiotics and oxygen.

Clinical factors, n (%)	Early dischargers			Well responders			Intensive medical recipients		
			p value			p value			p value
Age	≥65 yrs	<65 yrs		≥65 yrs	<65 yrs		≥65 yrs	<65 yrs	
	18 (32)	15 (36)	0.71	16 (38)	18 (32)	0.54	24 (57)	36 (64)	0.47
Sex	Females	males		Females	males		Females	males	
	20 (31)	13 (39)	0.39	24 (37)	10 (30)	0.52	38 (58)	22 (67)	0.43
Smoking	Never	ex/current		never	ex/current		Never	ex/current	
	16 (31)	17 (36)	0.62	18 (35)	16 (34)	0.90	32 (63)	28 (60)	0.75
Body temperature	≥37.5 °C	<37.5 °C		≥37.5 °C	<37.5 °C		≥37.5 °C	<37.5 °C	
	10 (38)	23 (32)	0.55	5 (19)	29 (40)	0.06	19 (73)	41 (57)	0.17
WBC	≥9000/μL	<9000/μL		≥9000/μL	<9000/μL		≥9000/μL	<9000/μL	
	12 (26)	21 (41)	0.10	14 (30)	20 (39)	0.33	31 (66)	29 (57)	0.36
CRP	≥0.3 mg/dL	<0.3 mg/dL		≥0.3 mg/dL	<0.3 mg/dL		≥0.3 mg/dL	<0.3 mg/dL	
	21 (30)	11 (39)	0.40	17 (25)	16 (57)	0.002	49 (71)	11 (39)	0.004
Phlegm	+	–		+	–		+	–	
	4 (20)	29 (37)	0.19	4 (20)	30 (38)	0.19	18 (90)	42 (53)	0.003
ICSs	+	–		+	–		+	–	
	20 (32)	13 (36)	0.70	26 (42)	8 (22)	0.052	39 (63)	21 (58)	0.65
OCSs/biologics	+	–		+	–		+	–	
	7 (50)	26 (31)	0.22	6 (43)	28 (33)	0.55	10 (71)	50 (60)	0.39
BIS	+	–		+	–		+	–	
	13 (54)	20 (27)	0.01	14 (58)	20 (27)	0.005	11 (46)	49 (66)	0.08
ABx/peramivir	+	–		+	–		+	–	
	13 (24)	20 (47)	0.02	13 (24)	21 (49)	0.009	40 (73)	20 (47)	0.008
Oxygen	+	–		+	–		+	–	
	15 (37)	18 (32)	0.60	10 (24)	24 (42)	0.07	31 (76)	29 (51)	0.01

WBC, white blood cell count; CRP, C-reactive protein; ICS, inhaled corticosteroids; OCS, oral corticosteroids; BIS, budesonide inhalation suspension; ABx, antibiotics.

Table 4
Factors contributing to early dischargers, well responders, and intensive medical recipients in patients who were admitted to hospital.

	Early dischargers			Well responders			Intensive medical recipients		
	Odds ratio	95% C.I.	p value	Odds ratio	95% C.I.	p value	Odds ratio	95% C.I.	p value
Body temperature, ≥37.5 °C	–	–	–	0.57	0.16; 2.10	0.40	–	–	–
WBC, ≥9000/μL	0.59	0.24; 1.48	0.26	–	–	–	–	–	–
CRP, ≥0.3 mg/dL	–	–	–	0.28	0.09; 0.92	0.04	2.70	0.87; 8.36	0.09
The presence of phlegm	–	–	–	–	–	–	6.61	1.23; 35.6	0.03
The use of ICS	–	–	–	1.75	0.57; 5.41	0.33	–	–	–
The use of BIS	2.99	1.11; 8.06	0.03	6.58	2.03; 21.3	0.002	0.29	0.10; 0.85	0.02
The use of ABx/peramivir	0.38	0.16; 0.94	0.03	0.67	0.23; 1.93	0.46	1.74	0.63; 4.85	0.29
The use of oxygen	–	–	–	0.53	0.19; 1.52	0.24	2.45	0.89; 6.74	0.08

95% C.I., A 95% confidence intervals; WBC, white blood cell; CRP, C-reactive protein; ICS, inhaled corticosteroids; OCS, oral corticosteroids; BIS, budesonide inhalation suspension; ABx, antibiotics.

2014 to 2018) are properly defined. Although we did not evaluate causative pathogens in all patients with respiratory infection in the present study, additional length of stay and cost for asthma hospitalization should be reconsidered hereafter when comorbid respiratory infection is suspected from physical and laboratory findings [i.e. fever (≥37.5 °C), elevated CRP levels, and the presence of phlegm]. Meanwhile, ABx should not be used routinely unless respiratory infection is strongly suspected because a Cochrane Database review show limited effect of ABx on asthma exacerbation.⁵⁰

There are a number of limitations in our study. First, this was a retrospective study conducted in a single tertiary asthma care center involving small sample size (n = 98), including a historical control group. Also, patients who required management of ventilation were excluded. Indeed, the decision of discharge and the evaluation of symptoms relief might have differed among attending physicians, leading to bias of length of stay, recovery time from symptoms, and hospitalization costs. Therefore, the present findings may not be applicable to clinical practice in general. Also, several reports have already demonstrated the efficacy of BIS for acute asthma exacerbation.^{13–17} However, little is known regarding clinical factors contributing to prolonged length of stay, persistent asthma-related

symptoms and increased hospitalization costs. Our study is novel in that we have evaluated factors associated with not only hospitalization periods but also with recovery time from symptoms and hospitalization costs in detail. There was no difference in our patients' background between the active treatment group with BIS and the historical control group (Table 1). Second, we did not evaluate adverse events caused by BIS. According to the medical records, none of the participants experienced any obvious serious adverse events. However, we should prospectively evaluate the safety and tolerability of BIS as well as ABx. Third, asthma-related symptoms other than wheezes could not be evaluated. To determine associations between asthma-related symptoms and the use of BIS, we need to quantify or semiquantify symptoms by using such as visual analogue scales in future studies. Albeit there remain these concerns, the present findings would lead to reconsideration of treatment strategy for asthma hospitalization. To build new evidence of BIS as a treatment option for asthma exacerbation, however, multicenter, randomized, blinded, prospective studies are necessary.

In conclusion, additional BIS in combination with procaterol and intravenous SCSs may be useful for acute asthma hospitalizations in terms of length of stay, recovery time from symptoms, and hospitalization costs. The present findings may be useful for reduced

medical expenditure for asthma. To further determine the impact of BIS for asthma hospitalization in terms of the socio-economic burden, larger studies are necessary. Additionally, we should also investigate proper hospitalization periods for reducing risk of the recurrence of asthma exacerbations after discharge in the future studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.04.003>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KI contributed to the collection of data, the recruitment of patients, disease diagnosis and management, the acquisition and interpretation of data, and drafting the manuscript. YKa established the conception of the whole study, and contributed to the collection of data, the recruitment of patients, disease diagnosis and management, the acquisition and interpretation of data, and drafting the manuscript. KF, MT contributed to disease diagnosis and management. YIn, HN, SY, YKi contributed to disease management. RK, NT, SF, TU, OT, TT, HO, KM, YIt, and TO contributed to the collection of data, and the acquisition and interpretation of data. AN contributed to the interpretation of data, and revision of the manuscript.

References

- Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014;**7**:12.
- Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001;**107**:3–8.
- Cisternas MG, Blanc PD, Yen IH, Katz PP, Earnest G, Eisner MD, et al. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003;**111**:1212–8.
- Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;**9**:24.
- Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol* 2011;**127**:145–52.
- Kaur BP, Lahewala S, Arora S, Agnihotri K, Panaich SS, Secord E, et al. Asthma: hospitalization trends and predictors of in-hospital mortality and hospitalization costs in the USA (2001–2010). *Int Arch Allergy Immunol* 2015;**168**:71–8.
- Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;**361**:1071–6.
- O'Byrne PM, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest* 2006;**129**:1478–85.
- O'Byrne PM, Lamm CJ, Busse WW, Tan WC, Pedersen S, Group SI. The effects of inhaled budesonide on lung function in smokers and nonsmokers with mild persistent asthma. *Chest* 2009;**136**:1514–20.
- Geller DE. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. *Respir Care* 2005;**50**:1313–21. discussion 21–2.
- Thorsson L, Geller D. Factors guiding the choice of delivery device for inhaled corticosteroids in the long-term management of stable asthma and COPD: focus on budesonide. *Respir Med* 2005;**99**:836–49.
- Murphy K, Noonan M, Silkoff PE, Uryniak T. A 12-week, multicenter, randomized, partially blinded, active-controlled, parallel-group study of budesonide inhalation suspension in adolescents and adults with moderate to severe persistent asthma previously receiving inhaled corticosteroids with a metered-dose or dry powder inhaler. *Clin Ther* 2007;**29**:1013–26.
- Matthews EE, Curtis PD, McLain BI, Morris LS, Turbitt ML. Nebulized budesonide versus oral steroid in severe exacerbations of childhood asthma. *Acta Paediatr* 1999;**88**:841–3.
- Higenbottam TW, Britton J, Lawrence D, Connolly CK, Harrison NK, Eastham HM. Comparison of nebulised budesonide and prednisolone in severe asthma exacerbation in adults. *BioDrugs* 2000;**14**:247–54.
- Ediger D, Coşkun F, Kunt Uzlaşan E, Gürdal Yüksel E, Karadağ M, Ege E, et al. Clinical effectiveness of nebulised budesonide in the treatment of acute asthma attacks. *Tuberk Toraks* 2006;**54**:128–36.
- Singhi S, Banerjee S, Nanjundaswamy H. Inhaled budesonide in acute asthma. *J Paediatr Child Health* 1999;**35**:483–7.
- Chen AH, Zeng GQ, Chen RC, Zhan JY, Sun LH, Huang SK, et al. Effects of nebulized high-dose budesonide on moderate-to-severe acute exacerbation of asthma in children: a randomized, double-blind, placebo-controlled study. *Respirology* 2013;**18**(Suppl 3):47–52.
- Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;**43**:1130–9.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2015. Available at: <https://ginasthma.org>.
- Mehuys E, Van Bortel L, De Bolle L, Van Tongelen I, Annemans L, Remon JP, et al. Effectiveness of pharmacist intervention for asthma control improvement. *Eur Respir J* 2008;**31**:790–9.
- Ishii M. DRG/PPS and DPC/PDPS as prospective payment systems. *Jpn Med Assoc J* 2012;**55**:279–91.
- Ishikawa K, Yamamoto M, Kishi DT, Nabeshima T. New prospective payment system in Japan. *Am J Health Syst Pharm* 2005;**62**:1617–9.
- Inoue H, Niimi A, Takeda T, Matsumoto H, Ito I, Matsuoka H, et al. Pathophysiological characteristics of asthma in the elderly: a comprehensive study. *Ann Allergy Asthma Immunol* 2014;**113**:527–33.
- de Labry LO, Campion EW, Glynn RJ, Vokonas PS. White blood cell count as a predictor of mortality: results over 18 years from the Normative Aging Study. *J Clin Epidemiol* 1990;**43**:153–7.
- Hirakata Y, Yanagihara K, Kurihara S, Izumikawa K, Seki M, Miyazaki Y, et al. Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia. *Diagn Microbiol Infect Dis* 2008;**61**:170–4.
- Accordini S, Corsico A, Cerveri I, Gislason D, Gulsvik A, Janson C, et al. The socio-economic burden of asthma is substantial in Europe. *Allergy* 2008;**63**:116–24.
- Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. *Ann Am Thorac Soc* 2018;**15**:348–56.
- Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;**277**:887–91.
- Radeos MS, Leak LV, Lugo BP, Hanrahan JP, Clark S, Camargo CA, et al. Risk factors for lack of asthma self-management knowledge among ED patients not on inhaled steroids. *Am J Emerg Med* 2001;**19**:253–9.
- Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Respir Res* 2001;**2**:53–60.
- Strauss RE, Wertheim DL, Bonagura VR, Valacer DJ. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. *Pediatrics* 1994;**93**:205–10.
- Needleman JP, Kaifer MC, Nold JT, Shuster PE, Redding MM, Gladstein J. Theophylline does not shorten hospital stay for children admitted for asthma. *Arch Pediatr Adolesc Med* 1995;**149**:206–9.
- Razi CH, Akelma AZ, Harmanci K, Kocak M, Kuras Can Y. The addition of inhaled budesonide to standard therapy shortens the length of stay in hospital for asthmatic preschool children: a randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2015;**166**:297–303.
- Szefer SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. *J Allergy Clin Immunol* 1999;**104**:175–83.
- Szefer SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol* 2002;**109**:730–42.
- Stefan MS, Shieh MS, Spitzer KA, Pekow PS, Krishnan JA, Au DH, et al. Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids. *JAMA Intern Med* 2019;**179**:333–9.
- Diamond SA, Chapman KR. The impact of a nationally coordinated pharmacy-based asthma education intervention. *Can Respir J* 2001;**8**:261–5.
- García-Cárdenas V, Sabater-Hernández D, Kenny P, Martínez-Martínez F, Faus MJ, Benrimoj SI. Effect of a pharmacist intervention on asthma control. A cluster randomised trial. *Respir Med* 2013;**107**:1346–55.
- Stiegler KA, Yunker NS, Crouch MA. Effect of pharmacist counseling in patients hospitalized with acute exacerbation of asthma. *Am J Health Syst Pharm* 2003;**60**:473–6.
- Teichtahl H, Buckmaster N, Pertnikovs E. The incidence of respiratory tract infection in adults requiring hospitalization for asthma. *Chest* 1997;**112**:591–6.
- Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010;**376**:826–34.
- Miyashita N, Kubota Y, Nakajima M, Niki Y, Kawane H, Matsushima T. Chlamydia pneumoniae and exacerbations of asthma in adults. *Ann Allergy Asthma Immunol* 1998;**80**:405–9.
- Wark PA, Johnston SL, Simpson JL, Hensley MJ, Gibson PG. Chlamydia pneumoniae immunoglobulin A reactivation and airway inflammation in acute asthma. *Eur Respir J* 2002;**20**:834–40.
- Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB, et al. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006;**354**:1589–600.
- Wark PA, Tooze M, Powell H, Parsons K. Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission. *Respirology* 2013;**18**:996–1002.
- Ikura M, Hojo M, Koketsu R, Watanabe S, Sato A, Chino H, et al. The importance of bacterial and viral infections associated with adult asthma exacerbations in clinical practice. *PLoS One* 2015;**10**:e0123584.
- Bisgaard H, Hermansen MN, Bønnelykke K, Stokholm J, Baty F, Skytt NL, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ* 2010;**341**:c4978.
- Normansell R, Sayer B, Waterson S, Dennett EJ, Del Forno M, Dunleavy A. Antibiotics for exacerbations of asthma. *Cochrane Database Syst Rev* 2018;**6**:CD002741.

Supplementary materials

The impact of budesonide inhalation suspension for asthma hospitalization: In terms of length of stay, recovery time from symptoms, and hospitalization costs.

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Supplementary Table 1. The annual amount for asthma hospitalization expenditure in our hospital during study period

Fiscal year	2014	2015	2016	2017	2018
Amount, JPY	261730	271490	270530	270530	269930

Supplementary Table 2. Comparison of factors related to respiratory infection at admission between antibiotics (Abx)/peramivir + and ABx/peramivir – groups

	All patients (n = 98)	ABX/ peramivir + (n = 43)	ABX/ peramivir - (n = 55)	p value
Body temperature, °C	36.9 (35.6-39.9)	37.1 (35.6-39.9)	36.7 (35.9-38.5)	0.0005
Febrile (≥ 37.5 °C), n (%)	26 (27)	20 (36)	6 (14)	0.02
WBC, / μ L	8800 (3800-18200)	9200 (3800-18200)	8200 (4300-16300)	0.19
WBC ≥ 9000 / μ L, n (%)	47 (48)	30 (55)	17 (40)	0.14
CRP, mg/dL	0.82 (0.03-24.4)	1.91 (0.04-24.4)	0.28 (0.03-5.78)	<0.0001
CRP ≥ 0.3 mg/dL, n (%)	69 (71)	48 (87)	21 (50)	<0.0001
SpO ₂ at admission, %	94 (79-100)	93 (79-100)	95 (81-99)	0.03
Oxygen, required, n (%)	41 (42)	27 (49)	14 (33)	0.10
Phlegm, n (%)	20 (20)	14 (25)	6 (14)	0.21

ABx: antibiotics, peramivir: an intravenous anti-influenza viral agent