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Factors for poor prognosis of near-fatal asthma after recovery from a life-threatening asthma attack

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Background/Aims: The aim of this study was to investigate poor prognostic factors associated with a near-fatal asthma attack following patient recovery.

Methods: We enrolled 68 patients who suffered near-fatal asthma attacks and were admitted to the intensive care units of five university hospitals. The patients were divided into two groups. The first group was comprised of patients who discontinued oral corticosteroids within 6 months after being discharged from the hospital and who maintained a forced expiratory volume in 1 s (FEV_1) $\geq$60% of the maximum or estimated values of the corresponding patients. The second group included patients who continued on oral corticosteroids for $\geq$6 months or who maintained a FEV_1 $<$60%.

Results: In patients with near-fatal asthma, factors for a poor prognosis included older age [48.47$\pm$3.53 vs. 64.69$\pm$2.59 years, $p<0.05$], chronic severe asthma, high values for inflammation-related laboratory markers (ESR, 8.75$\pm$2.05 vs. 23.88$\pm$4.40 mm/h, p=0.004; CRP, 1.72$\pm$0.46 vs. 6.68$\pm$9.36 mg/dL, $p<0.05$), asthma exacerbated by pneumonia (28.1 vs. 52.8%, $p<0.05$), and relatively low nutritional status (albumin, 4.00$\pm$0.14 vs. 3.51$\pm$0.10 g/dL, $p<0.05$).

Conclusions: These prognostic factors may induce irreversible obstruction of the airways with subsequent acute exacerbation of asthma or the need for continual oral corticosteroids after being discharged from the hospital. Patients with these factors should be treated appropriately, under close surveillance.

Key Words: Status asthmaticus; Intensive care unit; Mechanical ventilation; Glucocorticoids; Prognosis

INTRODUCTION

Asthma is a serious worldwide public health concern[1]. Some asthmatic patients present with complicating conditions such as hypercapnea ($PaCO_2$, $\geq$45 mmHg), and some require mechanical ventilation assistance. This type of asthma exacerbation is commonly referred to as near-fatal asthma (NFA), severe life-threatening asthma, or acute severe asthma. The classification system established by the Global Initiative for Asthma categorizes NFA as acute severe asthma and imminent respiratory arrest; the British Thoracic Society (BTS) classifies NFA as acute severe asthma and life threatening asthma[2, 3]. According to one study comparing patients who visited an emergency department due to asthma during 1996-2000 and those who were admitted during 2001-2003, the proportion of patients with NFA has increased over time[4].

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Table 1. Demographic features and past history of the enrolled patients

Characteristic	All (n=68)	Group 1† (n=32)	Group 2‡ (n=36)	*p* value§
Age, yr	56.94±2.37	48.47±3.53	64.69±2.59	<0.001
Sex, M:F	35:33 (51.5:48.5)	14:18 (43.8:56.3)	21:15 (58.3:41.7)	NS
Smoking status				
Never smoked	43 (63.2)	20 (62.5)	23 (63.9)	NS
Ex-smoker	12 (17.6)	4 (12.5)	8 (22.2)	
Current smoker	13 (19.1)	8 (25.0)	5 (13.9)	
Atopy	28 (41.2)	14 (43.8)	14 (38.9)	NS
Duration of diagnosed asthma				
>10 yr	21 (30.9)	7 (21.9)	14 (38.9)	0.082
5-10 yr	19 (27.9)	11 (34.3)	8 (22.2)	
1-5 yr	18 (26.5)	8 (25.0)	10 (27.8)	
<1 yr	7 (10.3)	4 (12.5)	3 (8.3)	
First asthma attack	3 (4.4)	2 (6.3)	1 (2.8)	
Hospital admissions for asthma	38 (55.9)	16 (50.0)	22 (61.1)	NS
ICU	10 (14.7)	4 (12.5)	6 (16.7)	NS
General ward	34 (50.0)	15 (46.9)	19 (52.8)	NS
General ward within 1yr	16 (23.5)	7 (21.9)	9 (25.0)	NS
Administration of anti-inflammatory agent without interruption	23 (33.8)	6 (18.8)	17 (47.2)	0.016
During 3 mo before admission				
Oral corticosteroid	16 (24.2)	3 (9.4)	13 (36.1)	0.009
Inhaled corticosteroid	23 (34.8)	10 (31.3)	13 (36.1)	NS
Beta-agonist	37 (56.1)	17 (53.1)	20 (55.6)	NS
Theophylline	21 (31.8)	6 (18.8)	15 (41.7)	0.041
During 2 wk before admission				
Oral corticosteroid	15 (22.7)	4 (12.5)	11 (30.6)	0.073
Inhaled corticosteroid	18 (27.3)	5 (15.6)	14 (38.9)	0.033
Beta-agonist	35 (51.5)	16 (50.0)	19 (52.8)	NS
Theophylline	20 (29.4)	6 (18.8)	14 (38.9)	0.069

*Values given as means±SE or No. (%), unless otherwise indicated. NS, not significant.
†Group 1: Patients who discontinued oral corticosteroids within 6 months after being discharged from the hospital and whose FEV1 was maintained ≥60% of the maximum or estimated values of the corresponding patients.
‡Group 2: Patients who continued oral corticosteroids for ≥6 months after discharge or whose FEV_1 was maintained at <60%.
§ Group 1 vs. Group 2

Numerous studies have concluded that NFA is a major risk factor for asthma-related deaths. A clinical follow-up study conducted in 1992 reported that the mortality rates of patients who required mechanical ventilation were 10.1% after 1 year, 14.4% after 3 years, and 22.6% after 6 years[5]. According to a more recent study, however, the mortality rate for asthma tended to decrease over time, and because many patients recover from NFA, it is important to analyze the prognostic factors that may affect the clinical outcomes in these patients after discharge from the hospital[6].

Several studies have been conducted on NFA risk factor determination, but few conclusive reports exist on NFA risk follow-up. The aim of this study was to identify prognostic factors related to NFA patient outcomes. We compared NFA patients who required continual oral corticosteroid administration or had irreversible airway obstructions and those who did not require prolonged steroid therapy or had reversible airflow obstructions.

MATERIALS AND METHODS

Study subjects

We enrolled and analyzed 68 asthmatic patients who were treated at the intensive care units (ICUs) of five university hospitals located in Seoul and Kyounggi Province. In accordance with the National Asthma Education and Prevention Program Expert Panel Report 2 of the U.S. National Institutes of Health and the criteria suggested by the BTS, severe asthma exacerbation was defined as an attack characterized by one of the following: absence of respiratory sounds, bradycardia, hypotension, loss of paradoxical pulse, $PaCO_2$ ≥45 mmHg,

Table 2. Clinical characteristics of the patients during hospitalization

	All	Group 1	Group 2	p value†
Duration of exacerbations				
〈4 h	14 (20.6)	5 (15.6)	9 (25.0)	NS
4-24 h	25 (36.8)	11 (34.4)	14 (38.9)	
1-7 days	24 (35.3)	14 (43.8)	10 (27.8)	
〉7 days	5 (7.4)	2 (6.3)	3 (8.3)	
Aggravating factors				
Infectious diseases	52 (76.5)	22 (68.8)	30 (83.3)	NS
Pneumonia	28 (41.2)	9 (28.1)	19 (52.8)	0.039
NSAIDs exposure	5 (7.4)	4 (12.5)	1 (2.8)	NS
Unknown	8 (11.8)	3 (9.4)	5 (13.9)	NS
Cardiac problems	12 (17.9)	3 (9.4)	9 (25.7)	0.081
Total duration of admission				
〈1 wk	18 (26.5)	10 (31.3)	8 (22.2)	0.020
1-2 wk	28 (41.2)	17 (53.1)	11 (30.6)	
〉2 wk	22 (32.4)	5 (15.6)	17 (47.2)	
ICU admission, days	5.60±0.88	3.78±0.47	7.22±1.57	0.042
Mechanical ventilation	43 (63.2)	18 (56.3)	25 (69.4)	NS
Duration, days	3.18±0.82	3.22±0.64	6.32±2.02	NS

*Values given as means±SE or No. (%), unless otherwise indicated. NSAIDs, nonsteroidal anti-inflammatory drugs; NS, not significant.
†Group 1 vs. Group 2

respiratory arrest, or the need for tracheal intubation[3, 7]. All patients had regular follow-up examinations for at least 6 months following hospital discharge. Patients with a smoking history of more than 10 pack-years and those with pulmonary emphysema confirmed by chest radiography or computed tomography were excluded from this study owing to the possibility of underlying chronic obstructive pulmonary disease.

The patients were divided into two groups. For the patients in Group 1, oral corticosteroids were discontinued within 6 months after hospital discharge and the forced expiratory volume in 1 s (FEV_1) was maintained ≥60% of the maximum or estimated values of the corresponding patients. For the patients in Group 2, oral corticosteroids were administered for ≥6 months or the FEV_1 was maintained at 〈60%.

Data collection

We analyzed the patients' medical records to collect data on demographic characteristics, previous asthma history, atopy, smoking status, clinical features during hospitalization, and outpatient clinic follow-ups after hospital discharge. Asthma history included the duration of asthma, previous asthma-related hospitalizations, and a list of administered anti-asthmatic agents. Hospitalization for asthma was categorized as admission to the ICU or to the general ward. We documented the types of anti-asthmatic agents that were administered at 3 months and 2 weeks prior to the asthma-related hospitalizations.

Atopy was assessed in patients with a history of allergic rhinitis or atopic dermatitis, as determined by a positive reaction on a skin prick test or the presence of serum specific IgE. To analyze the clinical characteristics, we examined the duration of dyspnea before hospitalization, potential aggravating factors, length of the hospital or ICU stay, duration of mechanical ventilation assistance, and vital signs at the time of admission. Laboratory findings and chest radiographs at the initial visit were analyzed. Follow-up duration, post-discharge duration of oral corticosteroid administration, and asthma-related rehospitalizations were assessed for each patient.

Statistical analysis

The data are expressed as means±standard error (SE). The statistical analyses were performed using SPSS software, version 12.0 (SPSS Inc., Chicago, IL, USA). For continuous variables, we compared the independent groups using Student's t-test. The relationship between categorical variables was assessed using χ^2 analysis. A value of p〈0.05 was considered to be statistically significant.

RESULTS

Demographic characteristics and past history

Table 1 shows the patients' demographic features and histories. The mean age differed significantly between the two groups (Group 1 vs. Group 2: 48.47±3.53 vs. 64.69±2.59 years; p〈0.05).

The patients in Group 2 had asthma for a longer time than

Table 3. Physical examination and laboratory findings

	All	Group 1	Group 2	p value†
Physical examination				
sBP, mmHg	137.92±5.06	137.19±6.08	138.59±8.02	NS
dBP, mmHg	82.42±3.08	82.29±3.90	82.53±4.76	NS
PR, /min	112.85±3.43	114.10±3.18	111.71±5.94	NS
RR, /min	28.03±1.18	27.52±1.49	28.50±1.82	NS
Laboratory findings				
Arterial pH	7.25±0.02	7.224±0.031	7.277±0.031	NS
$PaCO_2$, mmHg	59.14±3.88	62.10±6.67	56.45±4.30	NS
PaO_2, mmHg	71.20±4.67	71.28±4.95	71.14±7.79	NS
WBC, cells/	14571±808	13863±831	15200±1340	NS
ESR, mm/h	17.98±3.01	8.75±2.05	23.88±4.40	0.004
CRP, mg/dL	4.64±1.03	1.72±0.46	6.68±9.36	0.006
Albumin, g/dL	3.74±0.09	4.00±0.14	3.51±0.10	0.005

*Values given as means±SE. sBP, systolic blood pressure; dBP, diastolic blood pressure; PR, pulse rate; RR, respiratory rate; ABGA, arterial blood gas analysis; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NS, not significant.
†Group 1 vs. Group 2

Table 4. Clinical outcome and prognosis of discharged patients

	All	Group 1	Group 2	p value†
Follow up, mo	30.21±3.38	28.88±4.96	31.92±4.46	NS
Readmission	21 (36.2)	8 (23.5)	13 (54.2)	NS
ED, GW 〈3 days	5 (8.6)	3 (8.8)	2 (8.3)	NS
GW 〉3 days	15 (25.9)	5 (14.7)	10 (41.7)	0.021
ICU	5 (8.6)	0 (0)	5 (20.8)	0.005
OCS dosage after discharge, mg/day				
〈1 wk	19.43±2.29	20.10±3.28	18.53±3.15	NS
1 wk to 1 mo	9.47±1.19	8.05±1.52	11.35±1.85	NS
1 mo to 3 mo	4.39±0.96	1.27±0.37	7.76±1.73	0.001
3 mo to 6 mo	5.22±1.29	2.03±1.89	8.27±7.84	0.014
Average	5.32±0.80	2.84±0.78	8.39±1.29	0.001

*Values given as means±SE or No. (%), unless otherwise indicated. ED, emergency department; GW, general ward; ICU, intensive care unit; OCS, oral corticosteroid; NS, not significant.
†Group 1 vs. Group 2

those in Group 1 (〉10 years in Group 2), but the difference was not statistically significant (Group 1 vs. Group 2: 21.9 vs. 38.9%, p 〉0.05). Compared with Group 1, Group 2 was treated more frequently with anti-inflammatory agents before ICU admission (Group 1 vs. Group 2: 18.8 vs. 47.2%, p〈0.05), especially with respect to oral corticosteroids during the 3 months before admission and inhaled corticosteroids during the 2 weeks before admission (Group 1 vs. Group 2: 9.4 vs. 36.1%, p=0.009; and 15.6 vs. 38.9%, p〈0.05, respectively). In Group 1, five of the nine patients who had received inhaled corticosteroids for 3 months before hospitalization stopped taking the drugs 2 weeks before hospitalization. Both study groups used β-agonists with similar frequency.

Clinical characteristics during hospitalization

The clinical characteristics of the study patients during hospitalization are summarized in Table 2, and the physical findings and laboratory test results are reported in Table 3. Based on chest radiography, pneumonia occurred more frequently in Group 2 than in Group 1 (Group 1 vs. Group 2: 28.1 vs. 52.8%, p〈0.05), with concomitantly longer hospital (≥2 weeks) and ICU stays by the Group 2 patients (Group 1 vs. Group 2: 15.6 vs. 47.2%, p〈0.05; and 3.78±0.47 vs. 7.22±1.59 days, p〈0.05, respectively). There was no difference in the degree of hypercapnia between the two groups. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were significantly higher in Group 2 than in Group 1 (Group 1 vs. Group 2: 8.18±2.05 vs. 23.88±4.40 mm/h, p〈0.05; 1.72±0.14 vs. 6.68±1.71, p〈0.05, respectively), and the mean serum albumin level was significantly lower in Group 2 than in Group 1 (Group 1 vs. Group 2: 4.00±0.14 vs. 3.51±0.10 g/dL, p〈0.05).

Follow-up results

Table 4 presents the data on patient rehospitalization and use of oral corticosteroids. Compared with the patients in Group 1, more patients in Group 2 were readmitted to the ICU or general hospital ward for longer than 3 days (41.7%, $p<0.05$; or 20.8%, $p<0.05$, respectively). There was no significant difference in the oral corticosteroid dosage between the two groups during the first month following hospital discharge, but the dosage differed significantly between the groups at the 3- and 6-month follow-up visits (Group 1 vs. Group 2: at 3 months, 1.27 ± 0.37 vs. 7.76 ± 1.73 mg/day, $p<0.05$; at 6 months, 2.03 ± 1.89 vs. 8.27 ± 7.84 mg/day, $p<0.05$).

DISCUSSION

Only a few studies have analyzed the disease course and prognosis of NFA. In the present study, our aim was to establish risk factors that may influence the prognosis of NFA following patient discharge from the ICU.

We categorized the patients with a poor prognosis (Group 2) as those with irreversible airflow obstruction or those receiving oral corticosteroids >6 months post-discharge to maintain pulmonary function. For two-thirds of the patients in Group 2, this admission to the ICU was their first visit to that university hospital, making it difficult to compare clinical data before and after hospitalization because of a lack of baseline statistics.

The patients in Group 2 also exhibited older age, high ESR and CRP values on admission, exacerbation of asthma by pneumonia as confirmed by chest radiography, and serum albumin levels at the lower normal limit. The high ESR and CRP values indicate a state of inflammation, and the low albumin suggests poor nutrition; thus severe inflammation and relatively poor nutrition may have a negative impact on the NFA prognosis. Although the mechanisms through which acute inflammation may influences a negative asthma outcome are not entirely clear, a Severe Asthma Research Program study found that two-thirds of severe chronic asthmatic patients had a history of pneumonia and concluded that pneumonia is the highest risk factor for the development and poor prognosis of NFA[8]. One study assessing comorbid diseases related to asthma exacerbation in patients with difficult-to-treat asthma reported an odds ratio of 6.9 for repeated respiratory tract infections, which is in agreement with our results[9]. Patients with a poor prognosis used anti-inflammatory drugs more frequently before hospitalization, suggesting that they had suffered from severe chronic asthma. Although it was not a statistically significant finding, patients in our study with a poor prognosis were likely to have had asthma for ≥10 years. This suggests that the severity and chronicity of asthma may be important prognostic factors for NFA.

In contrast, the smoking status and presence of atopy had no effect on the NFA prognosis. Additionally, there was no significant difference between Groups 1 and 2 regarding a history of general hospital or ICU admission within the recent year, although hospital and ICU admissions are known to be major risk factors for asthma-related deaths. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is a characteristic of severe asthma, and previous studies have suggested that NSAIDs also act as etiologic agents for NFA[10]. In the present study, the asthma symptoms in five patients were exacerbated after NSAID administration; one patient in the poor prognosis group (Group 2) suffered from NSAID-induced asthma aggravation. This result suggests that hypersensitivity to NSAIDs may be a risk factor for severe asthma exacerbation but may not be prognostic for NFA.

Prognosis was not significantly correlated with hypercapnea or degree of respiratory acidosis at the initial visit. In one study on patients with severe asthma exacerbation, 12 patients with $PaCO_2$ ≥100 mmHg and 27 with $PaCO_2$ <100 mmHg were followed for 12 years, and hypercapnea was shown to not be a factor influencing patient prognosis[11]. Although one study reported that increases in $PaCO_2$ and acidity were risk factor for death, the patients in that study died of septicemia or the failure of organs other than the lungs[12].

A previous 6-year follow-up study on 145 asthma patients with severe asthma exacerbation, who died during or after hospitalization, suggested that old age is an important NFA risk factor, whereas hypersensitivity to NSAIDs and smoking are ~~is~~ not[6]. This result is similar to our findings.

In a study based on a cohort of the European Network for Understanding Mechanisms of Severe Asthma, researchers compared patients who had developed NFA within 5 years prior to study entry with those who had experienced no near-fatal asthma attack within the same period. In this comparative study, the NFA patients used more β-agonists and fewer inhaled corticosteroids, suggesting that patient compliance with the anti-inflammatory drug prescription is an important prognostic factor[13].

In summary, in NFA patients, old age, severe inflammation, asthma exacerbation by pneumonia, relatively low nutritional status, and chronic severe asthma may be factors indicating a poor prognosis for irreversible obstruction of the airways with subsequent acute exacerbation of asthma and suggesting the need for regular oral corticosteroids following hospital discharge. It is recommended that patients with these risk factors be treated appropriately, under close surveillance.

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