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Differences between asthmatics and nonasthmatics hospitalised with influenza A infection

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ABSTRACT: Asthmatics hospitalised because of influenza A infection are less likely to require intensive care or die compared with nonasthmatics. The reasons for this are unknown.

We performed a retrospective analysis of data on 1520 patients admitted to 75 UK hospitals with confirmed influenza A/H1N1 2009 infection. A multivariable model was used to investigate reasons for the association between asthma and severe outcomes (intensive care unit support or death).

Asthmatics were less likely than nonasthmatics to have severe outcome (11.2% *versus* 19.8%, unadjusted OR 0.51, 95% CI 0.36–0.72) despite a greater proportion requiring oxygen on admission (36.4% *versus* 26%, unadjusted OR 1.63) and similar rates of pneumonia (17.1% *versus* 16.6%, unadjusted OR 1.04). The results of multivariable logistic regression suggest the association of asthma with outcome (adjusted OR 0.62, 95% CI 0.36–1.05; p=0.075) are explained by pre-admission inhaled corticosteroid use (adjusted OR 0.34, 95% CI 0.18–0.66) and earlier admission (⩽4 days from symptom onset) (adjusted OR 0.60, 95% CI 0.38–0.94). In asthmatics, systemic corticosteroids were associated with a decreased likelihood of severe outcomes (adjusted OR 0.36, 95% CI 0.18–0.72).

Corticosteroid use and earlier hospital admission explained the association of asthma with less severe outcomes in hospitalised patients.

KEYWORDS: Asthma, corticosteroids, influenza, inhaled corticosteroid therapy, mortality in asthma, prognosis

Viral respiratory tract infections are the commonest cause of exacerbations of asthma, being implicated in ~80% of exacerbations in children and 50% of exacerbations in adults [1–3]. The most commonly identified virus associated with exacerbations of asthma is rhinovirus, followed by coronavirus, influenza, parainfluenza and respiratory syncytial virus [1, 4].

During the 2009–2010 influenza pandemic, asthma was noted to be the commonest comorbid illness of patients admitted to hospital with influenza A/H1N1 (H1N1pdm) infection, present in ~25% of patients [5–7]. It was further observed that asthmatics admitted to hospital with influenza infection were less likely to die or require admission to intensive care compared with nonasthmatics [6, 8, 9]. In contrast, the presence of virtually all other chronic medical conditions was associated with an increased risk of death following hospitalisation [9]. The reasons why a diagnosis of asthma should be associated with less severe outcomes in hospitalised patients have not been examined. Possible explanations suggested include: 1) a lower threshold for hospital referral and admission, hence a milder illness at time of admission compared with nonasthmatics; 2) the occurrence of treatable influenza-induced exacerbations of asthma rather than influenza-related pneumonia prompting admission; and 3) the tendency for asthma to be the dominant risk factor in younger age groups in whom the case-fatality rate due to influenza is lower [9, 10].

In May 2009, the UK Department of Health established the Influenza Clinical Information

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Network (FLU-CIN) to undertake clinical surveillance of hospitalised cases of H1N1pdm infection. The aim of this study was to provide rapid information on the admission of cases to hospital and to improve the management of influenza. We used the abundant information from this study to examine the risk factors and outcomes of persons with asthma.

METHODS

Between April 2009 and January 2010, FLU-CIN collected clinical, epidemiological and outcome data on patients admitted to 75 hospitals in 31 UK cities or towns with confirmed H1N1pdm infection. The details of data collection and the overall findings from the first wave of the 2009 pandemic have been described elsewhere [6], but the analysis described here is based on the full dataset from the first and second waves combined [11]. Briefly, H1N1pdm infection was diagnosed by a positive reverse transcriptase PCR result from respiratory samples obtained during the admission episode. A large dataset was collected by specifically trained data collectors, and included demography, pre-existing medical conditions, acute and long-term medications and clinical observations at the time of hospital admission.

A diagnosis of pneumonia was based on the criteria as previously described [12]: 1) admission chest radiograph report clearly suggestive of pneumonia; 2) admission chest radiograph report of acute infiltrates but no consolidation; and 3) no chest radiograph report available but admission radiograph documented in the clinical notes as being in keeping with pneumonia (n=24). Clinical observations were matched to criteria of the National Health Service Swine Flu Community Assessment Tool for adults and children aged <16 years (online supplementary table A) [13].

FLU-CIN was a public health surveillance project for which the Ethics and Confidentiality Committee of the National Information Governance Board for Health and Social Care in England reviewed procedures and approved the collection, storage and use of personal data for surveillance purposes without the need for individual participant consent. This report represents a secondary analysis of the entire FLU-CIN database that includes data on 1520 patients from both spring/summer 2009 (n=601) and autumn/winter 2009/2010 (n=919) pandemic waves.

Analyses and statistical methods

Descriptive analyses were performed comparing patients with and without asthma. The diagnosis of asthma was based on records in the medical case notes at the time of hospital admission and did not require documentation of confirmatory spirometry. These analyses were also performed separately for children (aged <16 years) and adults; p-values were calculated using the Chi-squared test for categorical exposure variables.

A nested case–control analysis of the surveillance cohort was used to investigate the association between a diagnosis of asthma and severe outcome from H1N1pdm 2009 infection, the latter being defined as death or the need for level 2 (high dependency unit) or level 3 (intensive care unit) care while in hospital. Patients with ''severe outcomes'' constituted ''cases''. Potential confounding variables in the multivariable logistic regression were identified from both our previous work investigating risk factors for severe outcomes in the same cohort [11] and an *a priori* conceptual framework based on the descriptive analyses. The effect of the following covariates on the relationship between asthma and severe outcomes was independently assessed by introducing them separately, in turn, into the original model: age; comorbidities (using the Charlson index, excluding asthma cases) [14]; immune compromise; season of admission; severity of illness at admission (severe respiratory distress; increased respiratory rate; oxygen saturation ⩽92%; respiratory exhaustion; severe clinical dehydration or shock; altered consciousness; dyspnoea and C-reactive protein levels); pre-admission inhaled steroid use; time to hospital admission (from symptom onset); in-hospital antiviral use; in-hospital antibiotic use; and in-hospital oral/intravenous corticosteroid use. Any covariate that modified the original unadjusted odds ratio by at least 10% towards a null association was then included in the final multivariable logistic regression model. If the association of asthma with less severe outcomes was fully explained by associated comorbidities or treatments, then the adjusted odds ratio of asthma with severe outcomes would be expected to approximate one in the final multivariate model.

By way of a further check on the robustness of our findings, an expanded multivariable analysis was also performed including all covariates that were independently associated with both exposure (asthma) and outcome. Results are presented as adjusted odds ratios and 95% confidence intervals. A p-value of <0.05 was taken to be statistically significant. STATA (release 11; StataCorp, College Station, TX, USA) was used for all statistical analyses.

RESULTS

The study cohort comprised 1520 patients; 720 (47.4%) were male and of median age 26 years (interquartile range 9–44.4), of whom 480 (31.6%) were children aged <16 years. Asthma was the commonest comorbid illness, present in 385 (25.3%) patients. Patients with asthma were more likely to be on regular inhaled corticosteroids than patients without asthma (52.7% *versus* 4.5%).

Tables 1 and 2 compare the demographic, clinical and treatment/management characteristics of asthmatic and non-asthmatic patients. Patients with asthma were significantly less likely to die or require intensive care support while in hospital compared with nonasthmatics (11.2% *versus* 19.8%; OR 0.51, 95% CI 0.36–0.72). Conversely, asthmatics were significantly more likely than nonasthmatics to exhibit features of severe respiratory compromise at the time of hospital admission, meeting the following triage criteria: severe respiratory distress, oxygen saturation ⩽92%, respiratory exhaustion and severe clinical dehydration or clinical shock (table 1). Consistent with these findings, asthmatics reported significantly more dyspnoea at the time of admission (58.4% *versus* 30.8%; unadjusted OR 3.15, 95% CI 2.48–4.0) and were significantly more likely to receive supplemental oxygen (36.4% *versus* 26%; unadjusted OR 1.63, 95% CI 1.27–2.08). These differences were similar when children and adults were analysed separately (online supplementary tables B and C).

There was no significant difference in the proportions of asthmatic patients with pneumonia compared with nonasthmatics (asthma 17.1% *versus* 16.6%; OR 1.04, 95% CI 0.77–1.42). As asthmatics were more likely to have a chest radiograph

TABLE 1 Demographics and clinical characteristics in patients with and without asthma[#]

Patient characteristics	Asthmatics	Nonasthmatics	Unadjusted OR (95% CI)	p-value
Total patients	385 (25.3)	1135 (74.7)		
Age years[¶]				
Mean±SD	31.58±17.55	27.52±22.16		
<1	3 (0.8)	118 (10.4)	0.07 (0.02–0.21)	<0.001
1–4	11 (2.9)	127 (11.2)	0.23 (0.12–0.44)	<0.001
5–15	57 (14.8)	164 (14.5)	1.03 (0.74–1.43)	0.864
16–25	81 (21.0)	164 (14.5)	1.56 (1.17–2.08)	0.003
26–35	80 (20.8)	162 (14.3)	1.60 (1.18–2.17)	0.003
36–45	67 (17.4)	128 (11.3)	1.66 (1.20–2.29)	0.002
46–55	51 (13.3)	117 (10.3)	1.32 (0.93–1.87)	0.125
56–65	22 (5.7)	93 (8.2)	0.67 (0.42–1.08)	0.103
66–75	10 (2.6)	45 (4.0)	0.68 (0.34–1.36)	0.274
76–85	1 (0.3)	16 (1.4)	0.18 (0.02–1.38)	0.099
>85	2 (0.5)	1 (0.1)	5.92 (0.54–65.49)	0.147
Number of comorbidities				
0	298 (77.4)	838 (73.8)	1.00	
1	56 (14.6)	211 (18.6)	0.75 (0.54–1.03)	0.076
⩾2	31 (8.0)	86 (7.6)	1.01 (0.66–1.56)	0.951
Charlson index score				
0	296 (79.9)	843 (74.3)	1.00	
1–2	79 (20.5)	236 (20.8)	0.95 (0.72–1.27)	0.744
3–5	10 (2.6)	53 (4.7)	0.54 (0.27–1.07)	0.077
>5	0 (0.0)	3 (0.3)	NA[§]	
COPD	21 (5.5)	62 (5.5)	1.00 (0.60–1.66)	0.995
Chronic pulmonary conditions excluding asthma or COPD	10 (2.6%)	26 (2.3)	1.14 (0.54–2.38)	0.733
Neurological disorders	16 (4.2)	71 (6.3)	0.65 (0.37–1.13)	0.128
Hepatic disease	3 (0.8)	22 (1.9)	0.40 (0.12–1.33)	0.135
Cardiovascular disease	45 (11.7)	143 (12.6)	0.92 (0.64–1.31)	0.639
Obesity	16 (4.2)	33 (2.9)	1.45 (0.79–2.66)	0.233
Diabetes	25 (6.5)	77 (6.8)	0.95 (0.60–1.52)	0.844
Hypertension	27 (7.0)	89 (7.8)	0.89 (0.57–1.39)	0.597
Immunocompromised status	2 (0.5)	40 (3.5)	0.14 (0.03–0.59)	0.007
Cerebrovascular disease	29 (7.5)	94 (8.3)	0.90 (0.58–1.39)	0.641
Triage criteria[+]				
A: severe respiratory distress	263 (68.3)	399 (35.2)	3.98 (3.11–5.09)	<0.001
B: increased respiratory rate	91 (23.6)	341 (30.0)	0.72 (0.55–0.94)	0.016
C: oxygen saturation ⩽92%	173 (44.9)	378 (33.3)	1.63 (1.29–2.07)	<0.001
D: respiratory exhaustion	12 (3.1)	12 (1.1)	3.01 (1.34–6.76)	0.008
E: severe clinical dehydration or clinical shock	59 (15.3)	123 (10.8)	1.49 (1.07–2.08)	0.020
F: altered consciousness	17 (4.4)	88 (7.6)	0.55 (0.32–0.94)	0.028
G: other clinical concern	38 (9.9)	103 (9.1)	1.10 (0.74–1.62)	0.642
Dyspnoea	225 (58.4)	350 (30.8)	3.15 (2.48–4.00)	<0.001
C-reactive protein mg·L^{-1}				
⩽30	114 (29.6)	279 (24.6)	1.00	
31–99	79 (20.5)	183 (16.1)	1.06 (0.75–1.49)	0.753
>100	38 (9.9)	124 (10.9)	0.75 (0.49–1.15)	0.183
Missing	154 (40.0)	549 (48.4)		
Admission ⩽4 days after symptom onset	254 (66.0)	602 (53.0)	1.46 (1.03–2.05)	0.033
Admission <2 days after symptom onset	185 (48.3)	447 (39.4)	1.16 (0.88–1.52)	0.289

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease. [#]: all ages (n=1520); [¶]: all comparisons with all other age groups, for example, were asthmatics more likely to be in the <1-year age group as compared with any other age group; [+]: National Health Service Swine Flu Community Assessment Tool criteria [8]; [§]: could not be calculated due to insufficient data.

performed on admission (OR 1.57, 95% CI 1.17–2.11; p=0.003), sensitivity analysis investigating the association between pneumonia and asthma including only patients with a definite chest radiograph record was performed; no significant difference between asthmatics and nonasthmatics was found (OR 0.85, 95% CI 0.62–1.18; p=0.329).

Antivirals (319 (82.9%) out of 385 cases using oseltamivir and nine (2.3%) out of 385 cases using zanamivir), antibiotics and systemic corticosteroids were prescribed upon hospital admission in significantly more patients with asthma compared with nonasthmatics (table 2).

Data relating to the time to admission from symptom onset were available for 1083 (71.3%) patients in the study cohort. Of these patients, those with asthma were significantly more likely to be admitted to hospital within 4 days of symptom onset compared with nonasthmatics (254 (65.2%) out of 385 *versus* 602 (53.0%) out of 1135; OR 1.46, 95% CI 1.04–2.07). Median (interquartile range) time from symptom onset to

TABLE 2 Treatments and clinical outcomes in patients with and without asthma[#]

	Asthmatics	Nonasthmatics	Unadjusted OR (95% CI)	p-value
Total patients	385 (25.3)	1135 (74.7)		
Treatments				
Pre-admission antibiotics	78 (20.3)	202 (17.8)	1.17 (0.87–1.57)	0.282
Pre-admission antivirals	44 (11.4)	128 (11.3)	1.02 (0.71–1.46)	0.936
Pre-admission inhaled corticosteroids	203 (52.7)	51 (4.5)	23.70 (16.79–33.47)	<0.001
Required supplemental oxygen on admission	140 (36.4)	295 (26.0)	1.63 (1.27–2.08)	<0.001
i.v. fluid replacement on admission	88 (22.9)	302 (26.6)	0.82 (0.62–1.07)	0.146
In-hospital antivirals	323 (83.9)	800 (70.5)	2.18 (1.62–2.95)	<0.001
In-hospital antibiotics	334 (86.8)	921 (81.2)	1.52 (1.09–2.12)	0.013
In-hospital oral/*i.v.* corticosteroids	177 (46.0)	125 (11.0)	6.88 (5.23–9.04)	<0.001
Clinical outcomes				
Pneumonia	66 (17.1)	188 (16.6)	1.04 (0.77–1.42)	0.792
Length of hospital stay				
<2 days	71 (18.4)	218 (19.2)	1.00	
⩾2 days	290 (75.3)	755 (66.5)	1.18 (0.87–1.59)	0.281
Missing	24 (6.2)	162 (14.3)		
Severe outcomes[¶]	43 (11.2)	225 (19.8)	0.51 (0.36–0.72)	<0.001

Data are presented as n (%), unless otherwsie stated. [#]: all ages (n=1520); [¶]: death or requiring level 2 or 3 care in hospital.

hospital admission was the same for asthmatics (2 (1–3) days) as for nonasthmatics (2 (1–4) days; p=0.28).

Association with severe outcomes

The association of asthma with severe outcomes (unadjusted OR 0.51, 95% CI 0.36–0.72) was unaffected by age (adjusted OR 0.49, 95% CI 0.35–0.70), presence of comorbidities as measured by the Charlson score (adjusted OR 0.51, 95% CI 0.36–0.72), immune compromise (adjusted OR 0.51, 95% CI 0.36–0.72), in-hospital antiviral use (adjusted OR 0.49, 95% 0.34–0.69), in-hospital antibiotic use (adjusted OR 0.49, 95% CI 0.35–0.70) or season (spring *versus* autumn/winter and first *versus* second pandemic wave) of admission (adjusted OR 0.51, 95% CI 0.36–0.72). In a further analysis to avoid linear assumptions regarding age and based on differences in age between asthmatics and nonasthmatics (table 1), the association of asthma with severe outcomes was adjusted for age <5 years (adjusted OR 0.50, 95% CI 0.35–0.71) and age 16–45 years (adjusted OR 0.52, 95% CI 0.36–0.74).

In contrast, point estimates of the association of asthma with severe outcome were reduced by >10% when adjusted independently for pre-admission inhaled corticosteroid use (adjusted OR 0.63, 95% CI 0.42–0.94) and ''admission ⩽4 days from symptom onset'' (adjusted OR 0.64, 95% CI 0.43–0.95) (further results are given in online supplementary table D). In a multivariate model including both these covariates (pre-admission inhaled corticosteroids and admission ⩽4 days from symptom onset), the association of asthma with a decreased likelihood of severe outcomes then failed to maintain statistical significance (adjusted OR 0.73, 95% CI 0.45–1.17) (table 3). In the multivariate model including all covariates independently associated with both exposure (asthma) and outcome, the association of asthma with a decreased likelihood of severe outcomes was again nonsignificant (adjusted OR 0.62, 95% CI 0.36–1.05; p=0.075), but pre-admission inhaled corticosteroids appeared protective (adjusted OR 0.34, 95% CI 0.18–0.66; p=0.001) as was early hospital admission (adjusted OR 0.60, 95% CI 0.38–0.94; p=0.025) (table 4).

The impact of in-hospital systemic (oral/*i.v.*) corticosteroid use on the association of asthma with severe outcomes was complex. An interaction between asthma status and the association of systemic corticosteroids with severe outcomes was observed; in asthmatics, systemic corticosteroids were associated with a decreased likelihood of severe outcomes (OR 0.36 adjusted for pre-admission inhaled corticosteroids and admission ⩽4 days from symptom onset, 95% CI 0.18–0.72; p=0.004), while in nonasthmatics, systemic corticosteroids were associated with an increased likelihood of severe outcomes (OR 3.53 adjusted for pre-admission inhaled corticosteroids and admission ⩽4 days from symptom onset, 95% CI 2.16–5.78; p<0.001).

Post-hoc analysis of asthmatics on pre-admission inhaled corticosteroids compared with asthmatics not on pre-admission inhaled corticosteroids did not demonstrate any significant differences between the two groups in relation to the

TABLE 3 Multivariable model: asthma, delayed admission (4-day threshold) and inhaled corticosteroids in relation to severe outcomes

Covariate	Adjusted OR[#] (95% CI)	p-value
Asthma	0.73 (0.45–1.17)	0.195
Admission ⩽4 days after symptom onset	0.62 (0.42–0.91)	0.013
Pre-admission inhaled corticosteroids	0.72 (0.40–1.30)	0.276

[#]: adjusted for all other covariates in the model.

TABLE 4 Multivariable model of all covariates independently associated with both exposure (asthma) and severe outcomes

Covariate	Adjusted OR# (95% CI)	p-value
Asthma	0.62 (0.36–1.05)	0.075
Triage criteria¶		
A: severe respiratory distress	1.41 (0.64–3.13)	0.395
B: increased respiratory rate	2.05 (1.35–3.09)	0.001
C: oxygen saturation ⩽ 92%	3.05 (1.46–6.35)	0.003
D: respiratory exhaustion	5.57 (1.76–17.57)	0.003
E: severe clinical dehydration or clinical shock	4.57 (2.78–7.52)	<0.001
F: altered consciousness	5.92 (3.31–10.57)	<0.001
Dyspnoea	0.83 (0.38–1.79)	0.633
Admission ⩽4 days after symptom onset	0.60 (0.38–0.94)	0.025
Pre-admission inhaled corticosteroids	0.34 (0.18–0.66)	0.001
Required supplemental oxygen on admission	2.08 (1.03–4.19)	0.041
In-hospital antibiotics	4.22 (1.03–17.24)	0.045
In-hospital oral/*i.v.* corticosteroids	1.31 (0.80–2.14)	0.275

#: adjusted for all other covariates in the model; ¶: National Health Service Swine Flu Community Assessment Tool criteria [8].

number of other (nonasthma) comorbid illnesses and presenting features, except that asthmatics on inhaled corticosteroids were significantly more likely to complain of dyspnoea (64.5% *versus* 51.7%, unadjusted OR 1.7, 95% CI 1.13–2.56) and to meet triage criteria for severe respiratory distress (73.9% *versus* 62.1%, unadjusted OR 1.73, 95% CI 1.12–2.67) (table 5). Asthmatics on inhaled corticosteroids were significantly less likely to suffer a severe outcome compared with asthmatics not on inhaled steroids (7.4% *versus* 15.4%, unadjusted OR 0.44, 95% CI 0.23–0.85). Of the 254 patients on pre-admission inhaled corticosteroids, 51 (20.1%) patients were designated nonasthmatics. There was no evidence of benefit from pre-admission inhaled corticosteroids in nonasthmatics (unadjusted OR 0.99, 95% CI 0.49–2.00; p=0.968).

DISCUSSION

Asthma was the commonest comorbid illness in the FLU-CIN cohort, as observed consistently in other national and international cohorts [5, 7, 8]. In keeping with previous studies [5, 7, 8], a striking reduction in the likelihood of dying or requiring intensive care level support in asthmatics compared with nonasthmatics was noted. However, we found no evidence to suggest that asthmatics had a milder illness at the time of hospital admission to explain the lower rates of intensive care unit admission and death. Instead, the proportions of patients with radiologically confirmed pneumonia were very similar in asthmatics and nonasthmatics (17% *versus* 16.6%). In addition, compared with nonasthmatics, asthmatics had features indicative of greater respiratory compromise at the time of hospital admission; the latter being reflected in higher rates of dyspnoea, severe respiratory distress, respiratory exhaustion, oxygen saturations ⩽92% and need for supplemental oxygen. These features suggest that a lower threshold for hospital referral and admission in patients with asthma is an unlikely explanation for the observed association of asthma with less severe outcomes in hospitalised patients.

Interestingly, nonasthmatics were significantly more likely to be immunocompromised (n=40) compared with asthmatics (n=2). A Canadian cohort study comparing hospitalised solid organ transplant recipients and nonimmunocompromised patients with pandemic H1N1pdm infection also found that asthma was more common in nonimmunocompromised patients [15]. The reasons behind these observations warrant future investigation.

Although patients with asthma were more likely to receive antiviral and antibiotic treatment following admission to hospital, the association of asthma with less severe clinical outcomes was not influenced by in-patient antiviral use, antibiotic use, or by differences in age. Instead, factors related to the management of asthma were found to be more relevant; specifically the use of pre-admission inhaled corticosteroids, earlier admission to hospital (within 4 days of symptom onset) and in-hospital systemic (oral or intravenous) corticosteroid use.

Limitations of this study were that diagnoses of asthma recorded in case notes were not verified by reference to baseline spirometric data; in addition, the severity of airflow obstruction at the time of hospital admission, as measured by peak expiratory flow rates, was not captured in the FLU-CIN database. However, the lack of peak flow data would not have affected the main analysis comparing asthmatics *versus* nonasthmatics. The effect of comorbidities on the association of asthma with severe outcomes was adjusted for using the Deyo adaptation of the Charlson index score, which is a weighted measure using International Classifiaction of Diseases-10 classification. However, no comorbidity score is perfect and residual confounding cannot be completely excluded in this observational dataset. Data on time from symptom onset to hospital admission were available in 1,083 (71.3%) patients. There was no systematic reason for missing data and patients with missing data were similar to other patients. Therefore, given the overall size of the FLU-CIN cohort and the strength of the associations examined, it is unlikely that the missing data resulted in significantly altered results. Pandemic influenza vaccination status was not reliably recorded in the medical notes for all patients in the FLU-CIN cohort. Asthmatics, being in the target group for vaccination in the UK, may have been more

TABLE 5 Comparison of 385 patients with asthma (all ages) by pre-admission inhaled corticosteroid use

Patient characteristics/clinical features	Pre-admission inhaled corticosteroids	No pre-admission inhaled corticosteroids	Unadjusted OR (95% CI)	p-value
Patients	203 (52.7)	182 (47.3)		
Number of comorbidities				
0	149 (73.4)	149 (81.9)	1.00	
1	34 (16.8)	22 (12.1)	1.55 (0.86–2.77)	0.143
⩾2	20 (9.9)	11 (6.0)	1.82 (0.84–3.93)	0.128
Charlson index score				
0	153 (75.4)	143 (78.6)	1.00	
1–2	44 (21.7)	35 (19.2)	1.17 (0.71–1.94)	0.527
3–5	6 (3.0)	4 (2.2)	1.40 (0.39–5.07)	0.606
>5	0 (0.0)	0 (0.0)		
COPD	12 (5.9)	9 (5.0)	1.21 (0.50–2.94)	0.677
Chronic pulmonary conditions excluding asthma or COPD	7 (3.5)	3 (1.7)	2.13 (0.54–8.37)	0.278
Neurological disorders	10 (4.9)	6 (3.3)	1.52 (0.54–4.27)	0.427
Hepatic disease	1 (0.5)	2 (1.1)	0.46 (0.04–4.95)	0.511
Cardiovascular disease	27 (13.3)	18 (9.9)	1.40 (0.74–2.63)	0.300
Diabetes	14 (6.9)	11 (6.0)	1.15 (0.51–2.60)	0.735
Hypertension	19 (9.4)	8 (4.4)	2.25 (0.96–5.26)	0.063
Immunocompromised status	0 (0.0)	2 (1.1)		
Cerebrovascular disease	20 (9.9)	9 (5.0)	2.10 (0.93–4.74)	0.074
Triage criteria[#]				
A: severe respiratory distress	150 (73.9)	113 (62.1)	1.73 (1.12–2.67)	0.013
B: increased respiratory rate	44 (21.7)	47 (25.8)	0.79 (0.50–1.27)	0.339
C: oxygen saturation ⩽92%	92 (45.3)	81 (44.5)	1.03 (0.69–1.55)	0.873
D: respiratory exhaustion	7 (3.5)	5 (2.8)	1.26 (0.39–4.06)	0.693
E: severe clinical dehydration	35 (17.2)	24 (13.2)	1.37 (0.78–2.41)	0.271
F: altered consciousness	10 (4.9)	7 (3.9)	1.30 (0.48–3.48)	0.607
G: other clinical concern	25 (12.3)	13 (7.1)	1.83 (0.90–3.69)	0.093
Dyspnoea	131 (64.5)	94 (51.7)	1.70 (1.13–2.56)	0.011
Pneumonia	28 (42.4)	175 (54.9)	0.61 (0.35–1.04)	0.066
Admission ⩽4 days symptom onset	23 (14.7)	28 (19.2)	0.73 (0.40–1.33)	0.305
In-hospital oral/*i.v.* corticosteroids	114 (56.2)	73 (40.0)	1.91 (1.27–2.87)	0.002
Severe outcomes[¶]	15 (7.4)	28 (15.4)	0.44 (0.23–0.85)	0.015

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease. [#]: National Health Service Swine Flu Community Assessment Tool criteria [8]; [¶]: death or requiring level 2 or 3 care in hospital.

likely to have been vaccinated compared with nonasthmatics. As all patients in this study had laboratory-confirmed H1N1pdm infection, if any patient had received the pandemic influenza vaccination, it had not prevented occurrence of infection. The possibility that vaccination of asthmatics may have attenuated the severity of illness remains. However, patients with other comorbid illnesses (who would have been equally likely to receive early vaccination) were not observed to have fewer severe outcomes, as had asthmatics. Therefore, a protective effect from pandemic influenza vaccination is unlikely to explain the findings of the current study.

The value of early hospital referral of patients with exacerbations of asthma triggered by influenza infection may relate to the earlier administration of antivirals which, in large cohort and population-based studies, has been associated with improved outcomes [16]. Alternatively, this may reflect the importance of prompt appropriate treatment of asthma, including the administration of systemic corticosteroids, particularly in asthmatics not already on corticosteroid treatment.

Another view is that inhaled steroid use and early hospital admission might simply be markers of well-treated and confirmed asthma managed by well-informed doctors; and that asthmatics may have a different sort of illness from some nonasthmatics, this illness tending not to have such a severe ultimate outcome. The veracity of this view could not be explored within the current dataset. Patients with other chronic respiratory disorders, such as chronic obstructive pulmonary disease, typically managed with inhaled and systemic steroids and were not observed to have a lower likelihood of severe outcomes. This may reflect differences in the degree of response to treatment according to severity and chronicity of underlying lung disease, with asthma generally being more responsive than other chronic lung diseases [17].

The association between inhaled corticosteroid use in asthmatics and improved clinical outcomes is supported by findings from large epidemiological studies. Using the Saskatchewan Health databases and a cohort of 30 569 asthmatics, SUISSA *et al.* [18] demonstrated that regular use of low-dose inhaled steroids was associated with a decreased risk of death from asthma and with reductions of 31% in the rate of hospital admissions for asthma [19]. Likewise, low adherence rates to asthma medication, particularly inhaled corticosteroids, are associated with poorer asthma outcomes [20, 21]. The benefits from inhaled corticosteroids are thought to relate to their effects on airway inflammation and hyperresponsiveness and are not specific to any particular viral infection. Thus, although the current study focused on H1N1pdm infection, the observed benefit from inhaled corticosteroids on clinical outcomes in asthmatics would probably extend to other acute respiratory viral infections.

The relationship between asthma, in-hospital systemic corticosteroid use and clinical outcomes is more complicated. Some cohort studies of critically ill patients with H1N1pdm infection have reported an association of systemic corticosteroids with higher mortality or higher rates of hospital-acquired pneumonia [22–24], while other studies have not identified any association between systemic corticosteroid use and severe outcomes [25]. None of these studies differentiated between asthmatics and nonasthmatics. In the current study, systemic corticosteroids were associated with a lower likelihood of severe outcomes in asthmatics, while in nonasthmatics, there was an association with an increased likelihood of severe outcomes. This reflects the substantially different indications for administration of systemic corticosteroids in asthmatics compared with nonasthmatics. The benefit of systemic corticosteroids in the acute management of exacerbations of asthma is well described and rests on a large evidence base [26]. The findings from this study support the principles of acute asthma management, including the use of systemic corticosteroids for asthmatics hospitalised with influenza infection. In contradistinction, for nonasthmatics, the role of systemic corticosteroids in the management of severe influenza infections remains unclear and may even be harmful [27, 28]. In this study, corticosteroid use in nonasthmatics may have been more frequent in severely ill cases and, therefore, its use may merely be a marker for severe disease. However, this explanation alone does not account for the finding by HAN *et al.* [24] that patients with H1N1pdm infection who were treated prospectively with corticosteroids as a fever suppressant suffered worse outcomes. An adequately powered randomised controlled trial is required to inform the current debate, taking into account the possibility that different clinical groups may have different types of disease and may either benefit from or be harmed by steroid therapy.

Validation of our results in a separate cohort would be a desirable next step. In the meantime, the findings from this study emphasise the importance of compliance with regular inhaled corticosteroid use by asthmatics, especially in winter when respiratory viruses are circulating. This study also supports the use of systemic corticosteroids for asthmatics hospitalised with influenza infection, in accordance with the principles of acute asthma management [29].

In conclusion, we found that asthmatics admitted to hospital with influenza infection were half as likely as nonasthmatics to die or require intensive care support despite greater respiratory compromise at the time of hospital admission and similar rates of pneumonia. Pre-admission use of inhaled corticosteroids and earlier admission to hospital (within 4 days) explained most of the observed association of asthma with less severe outcomes. This is consistent with the interpretation that a proportion of asthmatics, compared with nonasthmatics, were admitted because of a condition triggered by viral infection (*i.e.* virus-induced asthma exacerbation) rather than because of the severity of the infection itself and for which hospital treatment was more effective.

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STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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