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Factors associated with hospital admission in adult patients with asthma exacerbations: A systematic review

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ABSTRACT

Objectives: A variable proportion of patients presenting to the emergency department (ED) with acute asthma require admission to hospital. Previous studies have identified select factors associated with admission following ED presentation; however, no review has synthesized the evidence in this regard. This systematic review summarizes the evidence regarding factors associated with hospital admission following ED presentation. **Methods:** Searches were conducted in seven electronic databases and common sources of grey literature. Studies reporting disposition for adults after ED presentation were included. Admission proportions and factors associated with hospitalization that remained statistically significant in multivariable analyses ($p < 0.05$) were reported. **Results:** Out of an initial 5865 identified articles, 15 articles met full inclusion criteria and 11 were included in the analyses. Female sex ($n = 2$) and older age ($n = 2$) were individual factors associated with admission. Patient vital signs and severity followed by patient attributes were the two most frequent domains associated with admission. Admission proportions were analyzed in 10 studies at a median of ~20% with no clear change between 1996 and 2012. **Conclusions:** Factors such as patient demographics (e.g., female sex, older age), patient vital signs/severity, and history are associated with admission following ED presentation for acute asthma. These can be employed by ED clinicians to effectively discern patients at high risk for admission and lead to more evidence-based decision-making.

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Abbreviation list

aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
BMI	Body mass index
CI	Confidence interval
ED	Emergency department
HR	Hazard ratio
ICS	Inhaled corticosteroids
LABA	Long acting β -agonist
LTRA	Leukotriene receptor antagonist
NOS	Newcastle–Ottawa Scale
OCS	Oral corticosteroids
PFTs	Pulmonary function tests
ROB	Cochrane risk of bias tool
SABA	Short acting β -agonist
SCS	Systemic corticosteroids

Introduction

Asthma is a chronic inflammatory disease of the lungs that affects approximately 7% of the adult population of North America (1) and approximately 8.5% of the Canadian population over the age of 12 (2). In Canada, approximately 20% of the total annual costs for asthma are related to asthma exacerbations (3).

Typically, systemic corticosteroids (SCS), short-acting beta agonists (SABA), and short-acting anticholinergics (SAAC) are frontline treatments used to combat acute exacerbations (4); however, severe asthma attacks often require the administration of inhaled corticosteroids (ICS), intravenous magnesium sulfate, and non-invasive ventilation. Patients who frequently present to emergency departments (EDs) with asthma exacerbations may experience potentially serious complications of the disease;

approximately 13% of these patients will require admission to hospital in Canada (5). North American studies have reported 20% admission proportions; this variation could be explained by differences in practice of in the management of acute asthma and system factors (e.g., reimbursement). Evidently, tools to standardize ED management may be beneficial as guideline treatment adherence is associated with a lower risk of hospitalization (6).

Previous studies have identified a multitude of risk factors associated with increased hospital admission following ED presentation for acute asthma in adult patients (7–9). Such factors include, but are not limited to, female sex, age, patient attributes, medication profile, vital signs, severity, and pulmonary function tests (PFTs). Individual studies, although informative, investigate a select number of risk factors that may be unique or more prevalent in certain geographical regions. Currently, no review identifies these factors and examines commonalities across studies. This systematic review was conducted in an effort to identify factors associated with hospital admission worldwide following asthma exacerbations in adults presenting in the ED.

Methods

Protocol

A protocol was developed *a priori* to define the objectives, search strategy, eligibility criteria, outcomes, procedure for extracting and analyzing information from included studies, and data analysis. This systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (registration number: CRD42015023892)

Search strategy

A comprehensive search of electronic databases (MEDLINE, EBM Reviews, EMBASE, CINAHL, SCOPUS, Proquest Dissertations, and Theses) was completed for July 3, 2015, to database inception. The search strategy was configured by a health science librarian based on subject headings and keywords formatted accordingly to each database. There were no exclusions of articles based on date of publication, language, or publication status (i.e., report, abstract, manuscript, thesis, etc.). Grey literature searches included Google Scholar and hand searches of conference abstracts from the *Canadian Journal of Emergency Medicine* and the *Society of American Emergency Medicine* from 2005–2015. Bibliographies of retrieved articles and known reviews were also searched for relevant studies.

Study selection

Studies including at least 80% adult patients (≥ 17 years) presenting to an ED or equivalent acute care setting with an uncomplicated exacerbation of asthma were considered for inclusion in the review. The primary outcome was all factors statistically associated with hospitalization in multivariate models following acute asthma exacerbation. Secondary outcomes included ED management protocols using SABA, SCS, SAAC agents; long-term management protocols using SCS, ICS, ICS/long-acting β -agonist (LABA); non-pharmacological care (smoking cessation, primary care provider, asthma action plan, education), and the proportion of patients who were hospitalized. There were no exclusion criteria based on study design; however, studies without methods (e.g., editorials, commentaries) and studies with no formal multivariate analysis were excluded. In the case of duplicate studies, including published abstracts, only the main publication was included.

The identification of studies from the search strategy involved a three-step process using two independent reviewers (NA and JH) and senior researchers (CVR, BHR). First, from the title, abstract, and descriptors, literature searches were screened to identify potentially relevant studies for full review. Any potential articles with insufficient information had the full manuscript retrieved. Second, from the full text and using specific criteria, potentially relevant studies were independently chosen for inclusion in the review. Standardized forms with predefined inclusion/exclusion criteria were used. Third, two senior researchers reviewed the potentially relevant articles independently. Disagreement in the second step was resolved by third party adjudication (CVR), disagreements between senior researchers were resolved by consensus; reasons for exclusion were documented.

Risk of bias assessment

Methodological quality of individual studies was assessed by two reviewers (NA and JH); discrepancies were discussed with a senior researcher (CVR). Observational cohort studies were evaluated using the Newcastle–Ottawa Scale (NOS), an eight-item tool that appraises the methods of participants' selection, and comparability between cohorts and outcomes (10).

Data extraction and analysis

Three reviewers (NA, JH and MH) extracted information from included studies on to data extraction forms. Disagreements and reliability were checked by an external reviewer (CVR). An evidence table was constructed to report information on each article's source, country, study

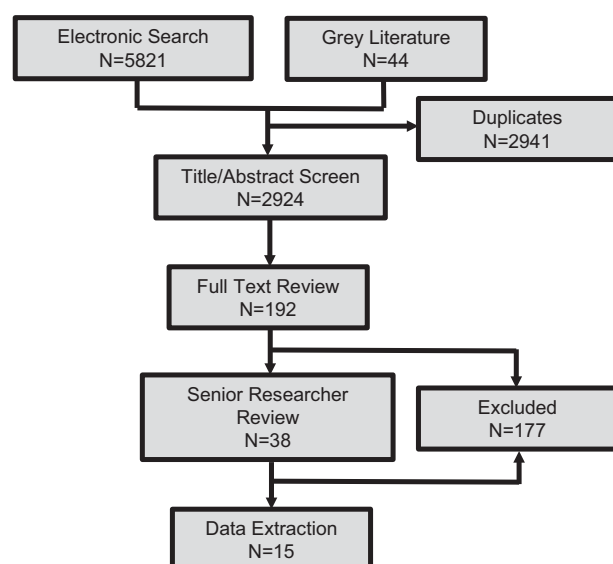


Figure 1. PRISMA flowchart of systematic searches for a systematic review of factors associated with hospital admission following asthma exacerbations. Top 3 reasons for exclusion: No multivariate analysis ($n = 86$, 49%); hospital admission not from ED ($n = 38$, 22%); pediatric population ($n = 10$, 6%).

design, study analysis, inclusion/exclusion criteria of participants, demographic characteristics of participants, admission proportions, and factors associated with admission by multivariate analysis. Effect estimates from individual studies were presented as adjusted risk ratios (aRRs) or odds ratios (aORs) with 95% confidence intervals (CIs) when possible. Factors associated with admission at a statistical significance level ($p < 0.05$) included individual factors (e.g., female sex, age) or were categorized into four domains (e.g., patient attributes, medication profile, vitals/severity, and PFTs) based on common themes and presented in a table format. The proportions of hospital admissions over time were graphically displayed and their correlation was evaluated through the Spearman's rank correlation coefficient (r_s). Figures were

generated using GraphPad Prism version 6.07 for Windows (Graph Pad Software, La Jolla, California, USA).

Results

Search results

The search strategy initially identified 5865 articles. After removing duplicates, title and abstract screening and full text review, 38 studies advanced to the senior researcher review. The two senior researchers selected 15 articles (5,8,9,11–22) for inclusion ($\kappa = 0.89$; 95% CI: 0.75 to 1.0) all of which progressed to data extraction (Figure 1). The primary reasons for exclusion were: no multivariate analysis ($n = 86$, 49%), hospital admission not from ED ($n = 38$, 22%), and pediatric population ($n = 10$, 6%). From these 15 articles, 8 studies (8,9,11,12,14,17,20,22) were derived from the Multicenter Airway Research Collaboration (MARC) databases: 5 sub-analyses (8,9,12,17,20) between 1996 and 1998, one sub-analysis (11) between 1999 and 2002, and 2 sub-analyses (14,22) between 2011 and 2012. Only one article (8) was chosen from the 1996–1998 time period to avoid counting data twice. The systematic review evidence is based on 11 studies (5,8,11,13–16,18,19,21,22) (Table 1).

Study characteristics

Included studies were all observational ($n = 11$) and provided data on aforementioned outcomes. Studies included populations exclusively from the United States ($n = 5$) (14,18,19,21,22) Canada ($n = 1$) (5), Japan ($n = 2$) (13,16), Israel ($n = 1$) (15). Two studies (8,11) reported combined data from the United States and Canada (Table 1). All studies were published in peer-reviewed journals.

Overall, the sample sizes of the individual studies ranged from 83¹⁶ to 2738²¹ patients (median = 1228;

Table 1. Study characteristics of manuscripts that met full inclusion criteria.

Publication year	Author	Country of origin	Enrolment dates	Number of subjects	Admission proportion (%)
1996	Kunitoh (16)	JPN	U/K	83	19
1999	[§] Singh (20)	USA	1996–1997	1228	18.9
2000	Stanford (21)	USA	1996–1997	2738	28
2002	Weber (8)	CAN/USA	1996–1998	1805	20.1
2003	[§] Boudreaux (12)	CAN/USA	1996–1998	1800	20
2005	[§] Clark (9)	CAN/USA	1996–1998	1193	29.3
2006	Banerji (11)	CAN/USA	1999–2002	2064	16.8
2010	[§] Liao (17)	CAN/USA	1996–2001	2236	22
2010	Rowe (5)	CAN	2004–2005	695	13.1
2012	Mancuso (18)	USA	2005–2009	296	62.1
2013	Dankner (15)	ISR	2000–2001	723	36.5
2013	Hasegawa (13)	JPN	2009–2011	1380	11
2014	Hasegawa (22)	USA	2011–2012	1227	19.2
2014	Schneider (19)	USA	2009–2012	175	37.1
2015	Chasm (14)	USA	2011–2012	2000	16.6

Note. [§] denotes studies that were not included in analyses (see Discussion); JPN= Japan; USA = United States of America; CAN= Canada; ISR= Israel; U/K= unknown.

Table 2. Summary of evidence table for systematic review of factors associated with hospital admission following asthma exacerbations.

Included studies for analysis		Individuals factors		Domains			
Publication year	Author	Female sex	Age	Patient attributes	Medication profile	Vitals/ severity	PFTs
1996	Kunitoh (16)					✓	
2000	Stanford (21)			✓			
2002	Weber (8)	✓		✓	✓	✓	✓
2006	Banerji (11)		✓				
2010	Rowe (5)		✓	✓ ED _{2Y}	✓ SABAA ₂₄	✓ Tr, RR, SaO ₂	
2012	Mancuso (18)			✓			
2013	Dankner (15)					✓	
2013	Hasegawa (13)					✓	
2014	Hasegawa (22)			✓			
2014	Schneider (19)				✓	✓	
2015	Chasm (14)	✓					
TOTALS	11 (100%)	2 (18%)	2 (18%)	5 (41%)	3 (27%)	6 (54%)	1 (9%)

Note. PFTs = Pulmonary function tests; ✓ = statistically significant factors identified in multi-variable adjusted analyses; Tr = triage; RR = respiratory rate; SaO₂ = oxygen saturation; SABAA₂₄ = use of short-acting beta-agonists in 24 hours; ED_{2Y} = emergency department visits in the past two years.

IQR: 695, 2000). The average ages of the cohorts were between 23.6 ($\pm$ 5.0) (15) and 44 ($\pm$ 13) (18), with females comprising between 51.3% (15) and 72.0% (18). Between 25% (18) and 34.8% (8) of asthmatic patients enrolled in the studies were smokers and 18.2% (15) to 45.6% (11) reported using ICS at baseline. Black/non-white Hispanic ethnicity was the most common (n = 5) (8,11,14,19,22), with Caucasian patients a close second (n = 3) (5,18,21). Pulmonary functions were reported in 10 studies and varied in the measures employed.

Methodological quality of the studies

All of the cohort studies had a low risk of bias and were assessed as being of high methodological quality according to the NOS scale. One study (18) scored 7/8 with all remaining studies scoring 8/8.

Outcomes

Individual factors significantly associated with admission

Female sex was an individual factor associated with hospitalization in two of the 11 studies considered in the analyses (Figure 2A/Appendix) (8,14). The reported aORs were 1.92 (95% CI: 1.48 to 2.48) (14) and 2.1 (95% CI: 1.3 to 3.6) (8); one study reported a non-significant association

between female sex and hospital admission (aOR 1.0; 95% CI: 0.6 to 1.6) (5). Two of the 11 studies considered in the analyses reported older age (using different categories) to be an individual factor associated with hospitalization (Figure 2B/Appendix) (5,11). Two studies included age as an adjusting factor in the multivariate analyses (13,15) and one study (11) analyzed patients $\geq$ 55 years old and found these older patients to be associated with admission (aOR 2.0; 95% CI: 1.2 to 3.4); however, the latter association was eliminated when changes in peak expiratory flow (PEF) were controlled for (aOR 0.9; 95% CI: 0.4 to 2.1).

Factors associated with admission as domains

While all studies used multivariable analyses, their methods and statistical approaches (mostly multiple logistic/linear regressions) varied. Some studies assessed predictors for hospital admission; (5,8,16) others were interested in evaluating the predictive role of specific factors (11,13,14,15,18,19,21,22). Table 2 presents factors associated with admission in the following four domains (with individual factors): patient attributes (ethnicity, previous admission, body mass index [BMI], insurance status), medication profile (SABA, LABA, ICS, OCS, leukotriene receptor antagonist [LTRA], anti-histamine, or theophylline pre- or post-index use), vitals/severity

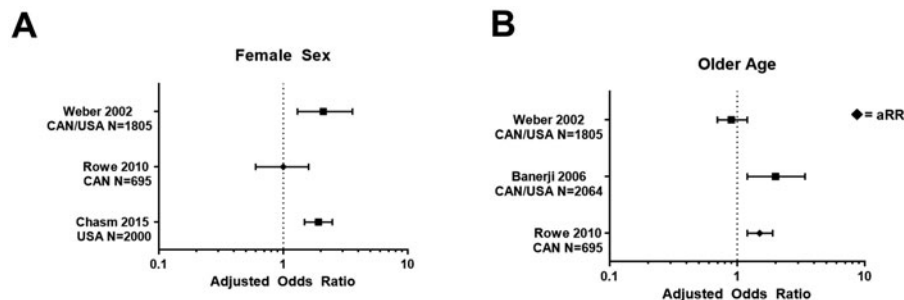


Figure 2. Forest plots of individual factors associated with hospital admission following asthma exacerbations. A. Female sex as an individual factor for admission. B. Older age as an individual factor for admission.

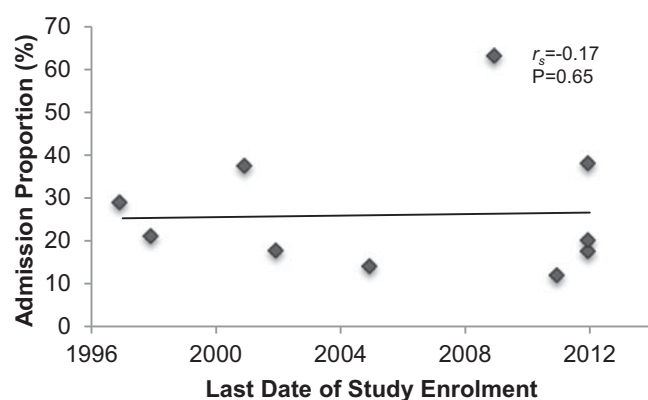


Figure 3. Admission proportions based on last date of patient enrollment from studies included in factors associated with hospital admission following asthma exacerbations.

(vital signs, O_2 saturation, dyspnea score, Canadian Triage Acuity Scale [CTAS]) and PFTs. Vitals/severity was the most common domain associated with hospital admission. Five manuscripts reported attributes to be significantly associated with admission with only one manuscript reporting a risk estimate for PFTs.

Admissions

All 11 studies reported admission proportions (median = 20%; IQR: 16.8, 29.3); however, only 10 (5,8,11,13–15,18,19,21,22) were plotted according to their corresponding final date of patient enrollment period (Figure 3). One study (16) did not report patient enrollment dates and was not plotted. Two studies (8,21) had final-date admission proportions reported between 1996 and 1999, four studies (5,11,15,18) between 2000 and 2009, and four studies (13,14, 19, 22) from 2010 to 2012. Overall, a line of best fit shows no trend in hospitalizations over time, with an average proportion of 25% ($r_s = -0.17$; $P = 0.65$).

Discussion

This systematic review summarized evidence from 11 observational studies that provide evidence on factors associated with hospital admission following presentation by adults for asthma exacerbation in the ED. Our results suggest that advancing age is an individual factor significantly and consistently associated with hospitalization. Unlike the systematic review on factors associated with relapse following discharge for acute asthma (23), female sex was only identified as an individual factor significantly associated with hospitalization in two papers. Vital signs and severity and patient attributes were the most frequently reported domains ($n = 6$ and $n = 5$, respectively) of associative factors with PFTs ($n = 1$) being the least. Furthermore, admission proportions have not changed dramatically from the late 1990's to 2010's (median of ~20%).

Of our 15 included studies, eight were a part of the MARC series. This network is a collaborative research initiative in EDs within both the United States and Canada that share common datasets. In order to avoid double counting data, we stratified the datasets based patient enrolment date. From the 1996–1998 dataset, only the article by Weber *et al.* was considered in our analyses, as it was the only manuscript that reported using a full logistic regression model for hospital admissions. The remaining four reported adjusted models considering individual variables of specific interest.

Factors associated with admission are diverse within the literature and can be heterogeneous in their exact context. Thus, in order to manageably report each included study's outcomes in a systematized manner, reported factors were categorized into domains. Each domain acts as a practical and unified descriptor of factors that share a common element. Patient attributes pertains to elements that solely relate to the patient and can be quickly identified on initial presentation or during triage. Medication profile describes both medications used chronically and during the ED visit and is readily identifiable during the ED admission history. Vital signs and severity and PFTs can be easily established during the ED work-up. Readily available factors which earlier studies have shown to be significantly associated with hospitalizations, such as female sex and age can be quickly obtained by clinicians and applied when making clinical management decisions (24,25). Current risk stratification trees, such as CHOP (change [C] in peak expiratory flow severity category, ever hospitalization [H] for asthma, oxygen [O] saturation on room air, and initial peak expiratory flow [P]), contain factors we classified in our domains; which lends credence to our grouping of factors into domains (26). Because all four of our domains cover a comprehensive array of factors, they have the potential to be used as a pre-screening tool to quickly identify high-risk patients for admission. The use of domains could further be integrated in to current management (e.g., assistance determining the need for consultations) and disposition approaches (e.g., assistance determining individualized outpatient care needs), and enhance both the breadth and appropriateness of candidate patients hospitalized. Ultimately, quickly identifying patients at risk for admission or increasing the ability to properly admit or discharge could contribute to decreasing ED crowding and improved resource use, quality, and efficiency.

Strengths and limitations

One of the main strengths of this systematic review is the underlying search strategy. We were unable to formally assess the potential for publication bias due to the small number of studies for each individual factor that

was identified; however, a comprehensive search of the published and grey literature was conducted without restrictions on publication status or language of publication. It is very likely that all literature pertaining to factors leading to admission during asthma exacerbation were identified during our search. Moreover, the involvement of two independent reviewers, a three-step process, and the use of rigorous/standardized methods during the identification and data extraction of relevant studies should minimize the risk of selection bias. A prevailing limitation of the study conclusions is their reliance on the results of observational studies. We synthesized a considerable amount of data, which individually may have been daunting to utilize for ED physicians; the categorization of factors into domains provides a practical method by which physicians can easily discern and identify high-risk admission patients. It is important to note that alternative domains could be created or combined based on differing criteria to group factors associated with hospitalization. The review of these manuscripts and the identification of factors most strongly associated with admission is an important “first step” in developing a valid decision aid for clinicians; however, more research is required to validate this. In addition, studies included were from various countries that may have differing healthcare systems, policies and management strategies. As such, our domains must be interpreted with caution in certain contexts and the commonalities between them and specific factors associated with admission identified. Variable factors were recorded in each study, and while demographics were reported universally, behaviors (e.g., adherence to medication, action plans, etc.) were not. Admission decisions in all studies were made at the discretion of the treating physicians and multiple factors may be involved (e.g., distance from home, unrecorded socio-economic issues, health system capacity, insurance status, etc.), which could not be standardized. This variation, likely, underestimates the role of some factors and suggests that additional comprehensive research remains valued. Finally, we were also unable to perform any meta-analysis due to the diversity of statistical measurements used among the studies.

Conclusions

Identifying factors associated with hospitalization during asthma exacerbations provides valuable information that may be used to effectively identify patients at high risk for admission at an early stage. These results suggest that these risk factors should be reported in future acute asthma studies and efforts to stratify patients by risk for admission (e.g., pathways, algorithms) should be encouraged. Overall, the goal of this program of research should

be to identify more efficient discharge and admission decisions and ultimately more favorable outcomes for patients. Given the paucity of studies, their variation and the desire on the part of many health care systems to reduce practice variation (e.g., hospital admission) more research in this field would be beneficial. Further research is required to validate these findings, elucidate the additive effect of these factors on decision-making and to determine how this knowledge can be translated to acute clinical settings (e.g., decision support systems).

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Conflicts of interest

The authors have no conflicts of interest to declare related to this topic. Dr. Rowe (BHR) was the primary author in one included study; however, BHR was excluded from the selection of potentially eligible manuscripts and final inclusion/exclusion decisions.

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Appendix

Age, sex, and pulmonary function details from included studies.

Publication year	Author	Female sex	Age	PFTs
1996	Kunitoh (16)	No	No	No
1999	Singh (20)	Yes*, sig (aOR 2.2; 95% CI: 1.3–4.0)	Yes**	Yes**, sig. Initial peak flow (aOR 2.1; 95% CI: 1.5–3.0) Change in peak flow (aOR 3.4; 95% CI: 2.2–5.3)
2000	Stanford (21)	Yes**	Yes**	No
2002	Weber (8)	Yes, sig (aOR 2.1; 95% CI: 1.3–3.6)	Yes, non-sig Per 10-year increase (aOR 0.9; 95% CI: 0.7–1.2)	Yes, sig. Initial peak flow (aOR 1.4; 95% CI: 1.2–1.7) Final peak flow (aOR 2.6; 95% CI: 2.2–3.1)
2003	Boudreaux (12)	Yes**	Yes**	Yes**
2005	Clark (9)	Yes**	Yes**	Yes**
2006	Banerji (11)	Yes**	Yes*, sig ≥ 55 (aOR 2.0; 95% CI: 1.2–3.4)	Yes**, non-sig. Change in peak flow ≥ 55 (aOR 0.9; 95% CI: 0.4–2.1)
2010	Liao (17)	Yes**	Yes**	Yes**
2010	Rowe (5)	Yes, non-sig (aRR 1.0; 95% CI: 0.6–1.6)	Yes, sig (aRR 1.5; 95% CI: 1.2–1.9)	Yes**
2012	Mancuso (18)	Yes**	Yes**	No
2013	Dankner (15)	Yes**	Yes**	No+
2013	Hasegawa (13)	Yes**	Yes**	No
2014	Hasegawa (22)	Yes**	Yes**	Yes**
2014	Schneider (19)	Yes**	Yes**	Yes**
2015	Chasm (14)	Yes* sig (aOR 1.92; 95% CI: 1.48–2.48)	Yes**	Yes**
Total	15 studies	4 studies individually assessed this factor.	3 studies individually assessed this factor.	3 studies adjusted for this factor.

Note. PFTs = Pulmonary function tests; aOR = adjusted odds ratio; aRR = adjusted risk ratio; CI = confidence interval; No = No evidence in the paper that factor was collected; Yes = Factor collected; variable included in MV analysis (*main independent variable; **adjusting factor); Sig = significant association with hospital admission in MV analysis; Non-sig = non-significant association with hospital admission in MV analysis.