FREQUENCY AND RISK FACTORS OF FREQUENT EXACERBATIONS OF ASTHMA IN PATIENTS IN A TERTIARY CARE HOSPITAL: A HOSPITAL-BASED COMPARATIVE STUDY

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ABSTRACT

Objective: To determine the frequency of recurrent exacerbations in asthma patients and compare the risk factors for frequent and non-frequent exacerbations.
Study Design: Cross-sectional study.
Place and Duration of Study: KRL Hospital Islamabad from Jun to Dec 2016.
Patients and Methods: Non-probability technique was used to sample two hundred and eighty one patients. Asthma exacerbations were defined by GINA guidelines. Frequent exacerbations were defined as two or more in the previous year. Data regarding demographics and risk factors were collected. Inhaler technique was checked. BMI and blood eosinophil levels were measured. SPSS 22 was used for data analysis.
Results: Out of total 281 patients, frequent asthma exacerbations were observed in 143 (50.9%) patients. Female gender (p=0.00) and lower education (p=0.02) led to frequent exacerbations. Patients education about disease or treatment (p=0.03), URTI (p=0.00), allergen exposure (p=0.00), drug history (p=0.04), treatment step-II (p=0.00), medication non-compliance (p=0.00), incorrect inhaler technique (p=0.01), anxiety (p=0.01), previous ICU admission (p=0.02) and blood eosinophilia (p=0.00) were significantly associated with frequent exacerbations. Of these, independent predictors were patient education (p=0.02), URTI (p=0.00), allergen exposure (p=0.00), drug history (p=0.00), treatment step-II (p=0.03), medication non-compliance (p=0.02), anxiety (p=0.01) and eosinophilia (p=0.00).
Conclusion: Majority of our patients underwent frequent exacerbations. Risk factors found to be associated with frequent exacerbations were female gender, lower education, patient unawareness, URTI, allergen and drug exposure, treatment step-II, medication non-compliance, anxiety and blood eosinophilia.

Keywords: Asthma, Anxiety, Blood eosinophilia, Exacerbation, Frequent, Risk factors**.**

INTRODUCTION

Asthma is one of the most chronic diseases in the world affecting more than 300 million people worldwide and a rise up to 400 million people affected is expected by 2025[1]. The prevalence in Asian countries is variable with Indian studiess howing prevalence from 1.9 to 10.3%[2]. The prevalence of asthma according to global initiative of asthma (GINA)in 2005 in central asia and Pakistan was 4.3%[3]. Around twenty million Pakistani adults suffer asthma complications[4]. Asthma exacerbations are distressing, leading to major economic losses. Data from Japan revealed huge economic burden of asthma exacerbations, accounting for annual cost of 3.4 billion dollars[5]. The prevalence data regarding exacerbation frequency in Pakistan are lacking. Patients with frequent asthma exacerbations are of more concern as they are at higher risk of morbidity. Studies have shown several risk factors associated with frequent exacerbations including smoking, hospitalization in the previous year, respiratory infections, gastroesophageal reflux disease (GERD), intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs), sinusitis, mental health disorders and higher eosinophil counts[6].

Due to limited data in Pakistan regarding the causes of frequent exacerbations and preventative measures, further exploration is required. The

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rationale for this study was to determine the frequency of recurrent exacerbations in a subset of patients presenting to tertiary care. In addition, we looked into the potential risk factors causing frequent and non-frequent asthma exacerbations.

MATERIAL AND METHODS

This cross sectional study was conducted from Jun to Dec 2016 at KRL Hospital Islamabad. The study was approved by hospital ethics committee and informed consent was obtained from all patients. Sample size estimated was two hundred and eighty one using 95% confidence level, with prevalence of risk factors causing frequent exacerbations being 4.8%[7]. Sampling was by convenient non-probability technique. Patients with diagnosed asthma, aged eighteen to eighty years, either gender and presenting with an exacerbation were recruited. Patients with parenchymal lung diseases, pulmonary tuberculosis, chronic obstructive pulmonary disease, malignancy and illnesses like chronic kidney disease or congestive cardiac failure were excluded. All information was recorded by investigators in the study pro forma. Patients' characteristics like age, gender, education, body mass index (BMI) and duration since diagnosis were documented. BMI was calculated by dividing weight with height squared (kg/m^2). Patients' inhaler technique was checked. A blood sample was taken to check for blood eosinophils. Blood investigation was carried out according to standard laboratory biochemical methods at KRL Hospital. An exacerbation was defined as an episode with worsening symptoms requiring urgent treatment as per GINA guidelines[8]. Frequent exacerbations were defined as two or more exacerbations in the past year. We took cut off of two exacerbations as some patients have one exacerbation at the most in a year compared to multiple exacerbations in others, similar to previous studies[6]. Information was collected regarding potential factors causing frequent exacerbation including patient education about disease and treatment, upper respiratory tract infections (URTI), allergen exposure, drug history, treatment step, medication compliance, inhaler technique, emotions, exercise, hormonal influences, recent hospital and previous ICU admission, afterhours' hospital visit, smoking, diabetes mellitus (DM), sinusitis, GERD, obesity, obstructive sleep apnea(OSA) and depression. Drug history encompassed use of NSAIDs or aspirin. Treatment steps were categorized according to guidelines[9]. Emotion was reported as anger, excitement and anxiety. Hormonal influences were taken as premenstrual phase, pregnancy or menopause. Hospital admissions within last year and previous ICU admission ever due to exacerbation were noted. Frequent after hours' hospital visits indicated number of visits. Diabetes was pre-diagnosed by guidelines[10]. Sinusitis, GERD, OSA and depression were diagnosed by respective specialists. Obesity entailed BMI greater than 30 kg/m^2. Eosinophilia was defined as an absolute eosinophil count of >350 cells per microliter. Statistical analysis was performed using statistical package for social sciences (SPSS) version 22. Frequency and percentages were calculated for qualitative variables including gender, education, diagnosis duration, inhaler technique and risk factors. Mean was calculated for age and BMI. Demographic data was compared between frequent and non-frequent exacerbations by chi-square test. Odds ratio (OR) for patients with frequent versus one exacerbation was obtained by logistic regression analyses. Multiple regression analysis was performed to assess significant independent predictors of frequent exacerbations. A p-value ≤0.05 was statistically significant.

RESULTS

Out of total 281 exacerbation patients, 146 (52%) were male and 135 (48%) female. Frequent exacerbations were observed in 143 (50.9%) patients, being more common in females 80 (59.3%) compared to males 63 (43.2%). Mean age of patients was 45.18 ± 12.52 years. Mean BMI was 22.52 ± 2.96 kg/m^2. The duration of diagnosis was 5 to 10 years in most of the patients i.e. 163 (58%), and majority patients i.e. 112 (39.9%) were at treatment step-III. On comparing

demographics between patients with frequent and infrequent exacerbations, only gender (p=0.00) and education (p=0.02) were significantly different, indicating that females and those with lower education underwent frequent exacerbations (table-I). Univariate analysis showed that patient education about disease or treatment (p=0.03), URTI (p=0.00), allergen exposure (p=0.00), drug history (p=0.04), treatment step-II (p=0.00), medication non-compliance (p=0.00), incorrect inhaler technique (p=0.01), anxiety (p=0.01), previous ICU admission (p=0.02) and blood eosinophilia (p=0.00) had a higher odds of developing frequent exacerbations (table-II). When the risk factors associated with frequent exacerbations were examined using multiple regression analysis, patient unawareness regarding asthma disease or treatment (p=0.02), URTI (p=0.00), allergen exposure (p=0.00), drug exposure (p=0.00), treatment step-II (p=0.03), medication non-compliance (p=0.02), anxiety (p=0.01) and blood eosinophilia (p=0.00) independently increased the risk (table-III). Incorrect inhaler technique and previous ICU admission did not independently increase risk of frequent exacerbation.

Table-I: Comparison of demographic characteristics of the patients (n=281).

Variables		Exacerbations		*p*-value
	Total n (%)	≥2 [n=143]	1 [n=138]	
Age Group (Years)				
18-30	29 (10.3%)	14 (48.3%)	15 (51.7%)	
31-40	85 (30.2%)	45 (52.9%)	40 (47.1%)	
41-50	84 (29.9%)	41 (48.8%)	43 (51.2%)	0.87
51-60	45 (16%)	21 (46.7%)	24 (53.3%)	
61-70	24 (8.5%)	13 (54.2%)	11 (45.8%)	
>70	14 (5%)	9 (64.3%)	5 (35.7%)	
Gender				
Male	146 (52%)	63 (43.2%)	83 (56.8%)	0.007*
Female	135 (48%)	80 (59.3%)	55 (40.7%)	
Education				
None	19 (6.8%)	15 (78.9%)	4 (21.1%)	
Primary School	29 (10.3%)	17 (58.6%)	12 (41.4%)	
Secondary School	32 (11.4%)	22 (68.8%)	10 (31.3%)	
College	55 (19.6%)	23 (41.8%)	32 (58.2%)	0.026*
Bachelor's Degree	76 (27%)	32 (42.1%)	44 (57.9%)	
Master's Degree	42 (14.9%)	19 (45.2%)	23 (54.8%)	
Professional Degree	8 (2.8%)	5 (62.5%)	3 (37.5%)	
Technical School	20 (7.1%)	10 (50%)	10 (50%)	
BMI Underweight (BMI<18.5)	32 (11.4%)	16 (50 %)	16 (50 %)	
Normal (BMI 18.5-24.9)	205 (73%)	98 (47.8%)	107 (52.2%)	0.13
Overweight BMI 25-29.9	38 (13.5%)	24 (63.2%)	14 (36.8%)	
Obese BMI >30	6 (2.1%)	5 (83.3%)	1 (16.7%)	
Diagnosis duration				
<5 Years	99 (35.2%)	47 (47.5%)	52 (52.5%)	0.626
5-10 Years	163 (58%)	85 (52.1%)	78 (47.9%)	
>10 Years	19 (6.8%)	11 (57.9%)	8 (42.1%)	

DISCUSSION

Asthma exacerbations are common cause of morbidity and mortality, in Pakistan and worldwide. The results of our study have shown that frequent exacerbations occur quite commonly. Overall females under went more exacerbations, similar to studies by Ahmed et al[11]

and Bilal et al[12]. The mean age of our study population was 45 years. Ahmed et al[11] reported mean age of 64 years for females. Bilal et al[12] reported a mean age of 47.1 years. These results suggest diverse age presentation and a nationwide study would be required for comparison. We also found that lower education led to more exacerbations similar to prior

Table-II: Potential risk factors associated with frequent exacerbations (n=281).

Potential Risk Factors	Number of Cases	Frequent Exacerbations ≥2		*p*-value	OR	[95% CI]
		n	Percentage (%)			
Patient Awareness						
Unaware	120	70	58.3%	0.03*	1.68	1.04 to 2.72
Aware	161	73	45.3%			
URTI						
Yes	163	10142	62.0%	0.00*	2.94	1.80 to 4.82
No	118		35.6%			
Allergen exposure						
Yes	191	115	60.2%	0.00*	3.35	1.96 to 5.70
No	90	28	31.1%			
Drug History						
Yes	36	24	66.7%	0.04*	2.11	1.01 to 4.42
No	245	119	48.6%			
Treatment Step						
Step-I	52	23	44.2%	0.28	1.38	0.75 to 2.54
Step-II	68	25	36.8%	0.00*	2.13	1.21 to 3.74
Step-III	112	64	57.1%	0.08	0.65	0.40 to 1.06
Step-IV	27	17	63%	0.19	0.57	0.25 to 1.31
Step V/VI	5	4	80%	0.22	0.25	0.02 to 2.29
Medication Compliance						
No	105	66	62.9%	0.00*	2.17	1.32 to 3.57
Yes`	176	77	43.8%			
Inhaler Techniques						
Incorrect	99	60	60.6%	0.01*	1.83	1.11 to 3.01
Correct	182	83	45.6%			
Emotion						
Anger	27	10	37%	0.13	1.86	0.82 to 4.23
Excitement	25	15	60%	0.34	0.66	0.28 to 1.53
Anxiety	54	36	66.7%	0.01*	0.44	0.23 to 0.83
Exercise						
Yes	44	22	50%	0.89	0.95	0.50 to 1.82
No	237	121	51.1%			
Hormonal influences (#=135)						
Premenstrual	19	13	68.4%	0.42	1.52	0.54 to 4.30
Menopausal	9	7	77.8%	0.27	2.45	0.49 to12.31
Pregnancy	23	12	52.2%	0.40	0.68	0.27 to 1.67
Recent Hospital Admission						
Yes	87	48	0.33		1.28	0.77 to 2.13
No	194	95				
Previous ICU Admission						
Yes	38	26	68.4%	0.02*	2.33	1.12 to 4.83
No	243	117	48.1%			
Afterhours hospital visit						
Yes	86	43	50%	0.84	0.95	0.57 to 1.57
No	195	100	51.3%			
Smoker						
Yes	109	59	54.1%	0.38	1.23	0.76 to 2.0
No	172	84	48.8%			
Co-Morbidities						
Diabetes	63	29	46%	0.38	0.77	0.44 to 1.36
Sinusitis	141	75	53.2%	0.43	1.20	0.75 to 1.92
GERD	78	37	47.4%	0.47	0.82	0.49 to 1.39
Obesity	6	5	83.3%	0.14	4.96	0.57 to 43.04
Obstructive Sleep Apnea	3	3	100%	0.99	NA	
Depression	160	82	51.2%	0.89	1.03	0.64 to 1.65
Blood Eosinophilia	38	29	76.3%	0.00*	3.64	1.65 to 8.02

#: Number for females=135, NA: Not applicable

reports[13]. We found no association of increased exacerbation in smokers, as seen previously[7]. As regards diagnosis duration, previous studies[14] revealed longer duration predisposed to recurrent exacerbations. However our results did not corroborate, which may be due to underestimation of disease duration by our patients as a part of reduced disease awareness. Our study clearly shows that frequent exacerbations occur due to multiple underlying factors. Unawareness regarding disease and management was one of the most important factorsincreasing risk of frequent exacerbations independently. Previous studies in Pakistan[12] and multiple international trials[15] revealed similar results. To counter this, a greater input is required from health care staff to improve patient education. Also patient support care systems would be of great help. Poor medication compliance and incorrect inhaler techniques are well-known to increase exacerbation frequency and our study was in accordance with previous studies[16]. Poor compliance was one of the independent predictors in our patients as well. This again points to lack of awareness, and launching an educational campaign to improve awareness would greatly benefit patients suffering multiple exacerbations.

Previous ICU[17] and hospital admissions in the past year[14] increase exacerbation risk. We also found previous ICU admissions to increase risk of exacerbations; however this lost significance when multiple variables were analyzed. However in our patients, previous hospital admissions or after hours' visit did not affect exacerbations frequency. This is likely due to patient practices i.e. short of life threatening exacerbation leading to ICU admission, patients preferably get treatment from local practitioners instead of hospital presentation. Hence although they may be exacerbating frequently, overall hospital visits are low. We also found that patients at treatment step-II i.e. on inhaled steroids alone in comparison to combination therapies under-went frequent exacerbations. Makela et al[16] have reported improved outcomes with combination inhaler compared to steroid inhaler. It's likely thatour patients choose to remain on inhaled steroids (step-II). compared to combination inhalers (step-III or higher), due to cost effectiveness, hence end up having frequent exacerbations. However this needs to be looked into with further studies. Viral infections and allergen exposure commonly increase frequent exacerbation risk[18]. The present study identified both URTI and allergens as independent risk factors for frequent exacerbations. Hence improved measures to avoid allergen contact and guarded exposure to patients with URTI may help reduce exacerbation frequency.

Table-III: Multiple logistic regression analysis for frequent exacerbations (n=281).

Potential Risk Factors	AOR	[95%CI]	*p*-value
Disease or treatment Unawareness	1.92	[1.08 to 3.39]	0.02*
URTI	2.70	[1.51 to 4.82]	0.00*
Allergen exposure	3.02	[1.62 to 5.64]	0.00*
Drug Exposure	3.25	[1.36 to 7.75]	0.00*
Treatment Step 2	1.99	[1.03 to 3.85]	0.03*
Medication non-compliance	1.96	[1.08 to 3.55]	0.02*
Emotion:Anxiety	0.41	[0.19 to 0.86]	0.01*
Blood Eosinophilia	3.60	[1.50 to 8.68]	0.00*

AOR: Adjusted Odds Ratio

According to Rajan et al[19], aspirin and NSAIDs are associated with morbid asthma events. Similarly, we found drug exposure to be independent predictor of frequent exacerbation. This is an important finding as NSAIDs are used extensively over the counter. They are

easily overlooked as precipitating factor in exacerbations, and have much more serious consequences than expected by patients. Psychosocial factors have been linked to poor asthma control and increased hospital visits as reported by Brinke et al[7]. We did not find depressionto increase tendency of frequent exacerbations. However when asked specifically about emotional stress like anxiety noted to precipitate exacerbation, there was a significant positive response. As mental health disorders have taboo attached to the diagnosis and seeking help is difficult, patients underreport these symptoms. Hence these are easily over looked as exacerbation triggers and should be diagnosed in timely manner. Contrary to our study, exercise induced exacerbations are common entity[20]. Hormonal influences did not increase frequency of exacerbations in our patients as seen in previous studies[7]. The comorbidities including DM, sinusitis, GERD, obesity, OSA and depression, although previously proven, were found insignificant in our study. The relationship between GERD and exacerbations is notable[21] however our findings were contrary. We diagnosed GERD by symptoms, however asymptomatic GERD occurs quite commonly[22]. Hence there is a possibility of underdiagnosing GERD in patients with frequent exacerbations. Sinusitis is common in asthmatics, and its severity has been linked to increased exacerbation risk[7,14]. Surprisingly we did not find this expected link. Also, we did not find obesity to cause increased exacerbations as found previously[23]. Similarly OSA is associated with frequent exacerbation[23]; however our study did not find this association. These variations maybe due to smaller number of patients with OSA and obesity. Blood eosinophilia was found to bean independent predictor for frequent exacerbations as reported previously[6]. It's quantifiableand can be easily performed in patients; hence these patients need to be informed regarding higher risk and careful monitoring. We successfully identified risk factors for the subgroup prone to frequent exacerbations. We recommend improving patient awareness regarding disease and medication compliance as well as optimizing treatment to reduce risk of exacerbations. We also emphasize on avoiding allergen contact and drugs triggering exacerbations. Therapeutic interventions aimed at correcting these factors are likely to reduce morbidity and expenditure in these patients. Despite our efforts to investigate using a systematic protocol, there are few limitations. First our study represents a small population subset in the city of Islamabad only, so it does not perfectly represent the whole population. Second, certain conditions like GERD, OSA and sinusitis were clinically diagnosed instead of investigative diagnosis. This could lead to underestimation of these conditions and hence lack of association. Third, the effects of treating modifiable risk factors on frequent asthma exacerbation were not studied. Therefore, these must be evaluated in a prospective study.

CONCLUSION

We found a huge number of our patients undergoing frequent asthma exacerbations which was surprising. The risk factors identified for frequent exacerbations were female gender, lower education level, patient unawareness, URTI, allergen exposure, drug exposure, treatment step-II, medication non-compliance, anxietyand blood eosinophilia.

RECOMMENDATION

We recommend improving awareness regarding risk factors especially amongst females and patients with lower education. Tailoring management around risk factors will result in fewer exacerbations, greatly improving patients' quality of life.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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