Bronchodilator reversibility in the GAN severe asthma cohort

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Abstract

Background: Positive bronchodilator reversibility (BDR) is a diagnostic criterion for asthma. However, patients with asthma may exhibit negative BDR test.

Aim: To describe frequency of positive and negative BDR in patients with severe asthma and associations with phenotypic characteristics.

Methods: Positive BDR was defined as FEV1 increase > 200 ml AND > 12% upon testing with a short-acting beta-agonist (SABA).

Results: Out of 2013 patients included in the German Asthma Net (GAN) severe asthma registry, 793 had data on BDR. Hereof, 250 (31.5%) had a positive and 543 (68.5%) had a negative BDR test. Comorbidities significantly associated with negative BDR were gastro-esophageal reflux (GERD) (28.0% vs 40.0%, $p<0.01$) and EGPA (0.4% vs 3.0%; $p<0.05$), while smoking history (active: 2.8% vs 2.2%; ex: 40.0% vs 41.7%) and COPD comorbidity (5.2% vs 7.2%) were similar in both groups. Patients with positive BDR had worse asthma control (median ACQ-5 3.4 vs 3.0, $p<0.05$), reported dyspnea at rest (26.8% vs 16.4%, $p<0.001$) and chest tightness (36.4% vs 26.2%, $p<0.001$) more frequently, had more severe airway obstruction at baseline (FEV1% pred: 56 vs 64, $p<0.001$) and higher FeNO levels (41 vs 33 ppb, $p<0.05$), while diffusion capacity did not differ (DLCO-SB % pred. 70% vs 71%). Multivariate linear regression analysis identified association of lower baseline FEV1% ($p<0.001$) and chest tightness ($p<0.05$) with positive, and GERD ($p<0.05$) with negative BDR.

Conclusion: In this real-life setting the majority of patients with severe asthma exhibited negative BDR. Interestingly, this was not associated with smoking history or COPD, but with lower FeNO and presence of GERD.

Key Words

Bronchodilator responsiveness. Severe asthma. Real-life cohort. GERD. FeNO.

Resumen

Antecedentes: La reversibilidad broncodilatadora (RB) positiva es un criterio diagnóstico para el asma. Sin embargo, los pacientes con asma pueden presentar una prueba RB negativa.

Objetivos: Describir la frecuencia de RB positivas y negativas en pacientes con asma grave y sus asociaciones con características fenotípicas.

Métodos: La RB positiva se definió como un aumento del FEV1 > 200 ml y > 12 % tras la inhalación de un agonista beta de acción corta (SABA).

Resultados: De 2013 pacientes incluidos en el registro de asma grave del German Asthma Net (GAN), 793 tenían datos sobre RB. De estos, 250 (31,5%) tuvieron una prueba RB positiva y 543 (68,5%) negativa. Las comorbilidades significativamente asociadas con RB negativa fueron el reflujo gastroesofágico (ERGE) (28,0 % frente a 40,0 %, p<0,01) y EGPA (0,4 % frente a 3,0 %; p<0,05), mientras que el antecedente de tabaquismo (activo: 2,8 % frente a 2,2 % ; exfumador: 40,0% vs 41,7%) y la comorbilidad de la EPOC (5,2% vs 7,2%) fueron similares en ambos grupos. Los pacientes con RB positiva tenían peor control del asma (mediana ACQ-5 3,4 vs 3,0, p<0,05), mas disnea en reposo (26,8% vs 16,4%, p<0,001) y mayor opresión torácica (36,4% vs 26,2%, p<0,001), además presentaban una obstrucción de las vías respiratorias más grave al inicio del estudio (FEV1% pred: 56 frente a 64, p<0,001) y niveles más altos de FeNO (41 frente a 33 ppb, p<0,05), mientras que la capacidad de difusión fue similar (DLCO-SB % pred. 70% vs 71%). El análisis de regresión lineal multivariable identificó una asociación de FEV1% basal inferior (p<0,001) y opresión torácica (p<0,05) con RB positiva y ERGE (p<0,05) con RB negativa.

Conclusión: En este entorno en vida real, la mayoría de los pacientes con asma grave tuvieron una RB negativa. Curiosamente, esto no se asoció con antecedentes de tabaquismo o EPOC, sino con FeNO más bajo y presencia de ERGE.

Palabras clave: Respuesta a broncodilatadores. Asma grave. Cohorte de vida real. ERGE. FeNO.

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Introduction

Severe asthma is prevalent in around 5-10% of asthma patients and causes high morbidity, healthcare resource use and cost [1,2]. It is currently diagnosed when high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic steroids are required to prevent asthma from becoming uncontrolled or which remains uncontrolled despite this therapy [1]. The Severe Asthma registry of the German Asthma Net (GAN) is a large multicentric registry in Germany and Austria with > 2000 patients included as of January 1, 2021. It records baseline and long-term follow-up of patients with severe asthma in order to describe disease presentation, course and care situation [3].

Bronchodilator reversibility (BDR) testing is recommended in the diagnostic workup of asthma by national [4,5] and international guidelines [6]. After halting inhaled and other interfering treatments, spirometry is performed before and following inhalation of short-acting beta-agonist (SABA). A positive BDR test is currently defined as an increase of FEV1 of >12% and >200 ml. Positive BDR is regarded as a characteristic of asthma, whereas negative BDR favors a diagnosis of COPD [6]. However, BDR testing may also be negative in patients with asthma for various reasons including beta2-receptor downregulation due to high frequency SABA use [7] or airway remodeling in long-standing disease [6,8]. Such characteristics are frequently found in patients with severe uncontrolled asthma. Still, a positive BDR test has generally been used as an inclusion criterion for asthma trials, also in recent randomized controlled trials in severe asthma [9–11]. Further, so called “irreversible airway obstruction” may lead to a premature diagnosis of COPD, possibly leading to suboptimal treatment if indeed severe asthma is the underlying disease.

Aims of the present analyses are therefore to describe the frequency of positive and negative BDR in a large real-life cohort of patients with severe asthma and associations with other disease parameters and symptoms.

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Methods

The GAN Severe Asthma Registry is prospectively collecting routine clinical parameters of patients with severe asthma at baseline and annual follow-ups [3,12]. All patients fulfill the criteria of severe asthma as per assessment of a specialized pulmonologist based on the ERS/ATS definition [1]. Parameters include demographics, comorbidities, medications, pulmonary function tests and symptoms. All patients provided written informed consent prior to participation in the registry, which was approved by the ethics committee of the University of Mainz as well as local IRBs at each institution and is being performed in accordance with the principles of the Declaration of Helsinki. Like all other registry data, BDR test was performed in the participating centers as part of clinical routine. Following recommendations patients were advised to withhold inhaled and other interfering treatments before testing [12,13]. A positive BDR test was defined as an increase in FEV1 of > 12% and 200 ml after inhalation of 200-400 µg of SABA, otherwise patients were classified as having negative test. The present analyses include the baseline visits of all registry patients as of January 1, 2021. Firstly, we selected patients with data on BDR test available. Then patients were stratified in positive and negative BDR test. Fraction of exhaled nitric oxide (FeNO) was measured with any available device [14]. In case of displayed value of " <5 ppb", we calculated with a value of 0.

Statistics

Statistical analyses were performed using the statistical software SAS® 9.4 (TS1M6) for Microsoft Windows. To compare frequency of parameters between positive and negative BDRT groups, we used a Chi-Square test or U-test for dichotomous or continuous variables respectively. All statistical tests were two-sided with a significance level (alpha) of 0.05. Test results of $p<0.05$ are considered 'significant'.

Next, for the parameters with significant differences between BDR positive and negative groups, we performed further analyses on FEV1 reversibility [%]. For dichotomous parameters we performed a t-test to test whether there is a significant difference in FEV1 reversibility [%] when stratifying for the dichotomous parameter. For the continuous parameters, we performed univariate linear regression analysis performed with the target variable FEV1 reversibility [%] and the continuous variable as the independent parameter. Then, we performed multiple linear regression analysis with the target variable FEV1 reversibility [%] and the significant parameter of the univariate linear regression analysis or t-test. Due to missing information, 83 out of 793 (10.5 %) cases were excluded from the multiple regression analysis, which was carried out for 710 patients.

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Results

Baseline characteristics

Out of 2013 patients with severe asthma included in the GAN registry, 793 had data on BDR. Herof, 250 (31.5%) had positive BDR test, while 543 (68.5%) were classified as negative. The mean age of the patients was 49.9 (SD 16.3) years and 6.2% were children (Table 1). The asthma phenotype classified according to the current ICD-10 was predominantly allergic in 42.4%, non-allergic in 31.4% and mixed in 26.2%. 41.2% of the patients were former smokers with a median of 10 packyears and 6.6% had a diagnosis of comorbid COPD. Regarding these baseline characteristics there were no significant differences between patients with positive and negative BDR test. Grouped comparisons for all parameters assessed in the registry can be found in Supplementary Table S1 .

Pulmonary function testing (PFT)

Pulmonary function testing showed more severe airway obstruction in patients with positive BDR test with lower FEV1%, FVC%, FEV1/FVC, PEF, MEF75, MEF50, MEF25, and higher residual volume (RV) and resistance (R) (Figure 1, $p<0.01$ for all parameters). In contrast, diffusion capacity for carbon monoxide (DLCO) was similar (70% versus 71% of pred., $p=0.51$, figure 1).

Median FeNO was higher in patients with positive BDR (41 ppb vs 33 ppb, $p=0.012$, table 2), while in the total population blood eosinophils counts (BEC) did not significantly differ between groups (median BEC 276.5/µl vs 243.3/µl, figure 1). Looking only at a subgroup of patients later initiated with biologics for eosinophilic asthma (mepolizumab, benralizumab, reslizumab, dupilumab, n=135), in whom BEC values were available before the initiation of the biologic, these were higher than in the total population, but similar when comparing patients with positive and negative BDR (median BEC /µl 450 vs 530, $p=0.15$).

Next, we analyzed asthma control and quality of life measured by ACT, ACQ-5 and AQLQ. Patients with positive BDR had higher median ACQ-5 (3.4 vs 3.0, $p<0.01$, figure 1) reporting dyspnea at rest (26.8% vs 16.4%, $p=0.0006$) and chest tightness more frequently (36.4% vs 26.2%, $p=0.0034$, table 2) whereas differences were not significant for ACT and AQLQ (Supplementary table S1).

Regarding systemic treatments, patients with positive BDR were more often currently treated with OCS but without biologic compared to those with negative BDR (32.8% vs 25.6%),

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while patients with negative BDR received biologic without OCS more frequently (14.0% vs. 23.4%, p=0.0130, table 2).

Comorbidities significantly associated with negative BDR were gastro-esophageal reflux and eosinophilic granulomatosis (EGPA) with polyangiitis ($p<0.05$, table 2) while history of chronic sinusitis (42% vs 47.9%) and nasal polyps (34.7 vs 36.3%) were similar (Table 2).

For the aforementioned parameters with significant frequency differences between patients with positive and negative BDR, we performed further analyses. For dichotomous parameters, FEV1 reversibility in % between the two groups of the dichotomous parameter was compared. Here, we found significant differences in FEV1 reversibility (%) when stratifying the patients for presence of resting dyspnea, chest pain, GERD and EGPA as well as current use of OCS and biologics (Table 3). For the continuous parameters we performed a univariate linear regression analysis with the target variable FEV1 reversibility (%) and the continuous variable as the independent parameter (Table 4). Here, higher ACQ-5 and lower FEV1% at baseline were significantly associated with FEV1 reversibility (%). Further, using multiple regression analysis, we found that chest tightness and lower FEV1 % at baseline were positively associated and GERD was negatively associated with FEV1 reversibility % (Table 5).

Discussion

In the present large real-life severe asthma cohort the majority of patients had a negative BDR suggesting that this parameter is of limited value for diagnosis and differentiation from COPD in severe uncontrolled patients. The prevalence of comorbid COPD in our cohort was low and even though 41.2% of patients stated to have smoked in the past, the median exposition of 10 packyears was only moderate. Further, diffusion capacity was only mildly reduced (DLCO-SB 70% pred.) at mean, and did not differ between patients with positive and negative BDR. In sum, these characteristics suggest that smoking history and consequent COPD likely do not explain negative BDR in the majority of patients with severe asthma.

However, we found other comorbidities that were significantly associated with BDR. GERD was more frequent in patients with negative BDR, and also showed significant associations in the multivariate regression analysis. Association of asthma and GERD is well-known and represents a bidirectional epidemiological association, as recently reconfirmed in a large Korean cohort study [15]. Pathophysiologically, bidirectional associations are also assumed with acid reflux causing cough, vagal stimulation and airway inflammation whereas hyperinflation induced by severe asthma may predispose to GERD [16]. Specifically, GERD may lead to small airway inflammation, mucus plugging and fibrosis [16]. Our results support

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the hypothesis that association of asthma with GERD may relate to a specific asthma phenotype characterized by negative BDR. Recently, Enriques-Matas et al. found that GERD negatively affected quality of life especially in elderly patients with asthma [17] and more generally increased comorbidities are associated with exacerbations [18].

EGPA was also significantly associated with negative BDR, however the prevalence of this comorbidity (2.1%) was low in our cohort. Patients with EGPA may have lung manifestations beyond asthma that may play a role in the mechanisms underlying BDR. Similarly, Berti et al recently found in a study of 89 EGPA patients that PFTs did not improve at long-term follow-up regardless of ICS or OCS therapy [19].

FeNO reflects the level of local type-2 inflammation in the airways and predicts the response to inhaled and systemic steroids [20,21]. Here, we found an association of higher FeNO levels with positive BDR. Similarly, Janson et al. found that higher FeNO levels correlated with larger BDR in patients with asthma in large population based studies [22]. Additionally, Nerpin et al described that this was not only true for patients with asthma but even in non-asthmatic subjects [23]. We have previously shown that FeNO is associated with disease burden in severe asthma [24], which is also supported by the findings presented here.

Interestingly, in contrast to FeNO, BEC did not differ between patients with positive and negative BDR in the present analysis, neither in the total cohort nor in patients later treated with biologics. In this line, Caminati et al. found that increased FeNO, but not BEC was associated with markers of disease severity [25]. Still, these findings might be influenced by treatments as BEC are lowered by both systemic and, to a lesser degree, inhaled corticosteroids [26,27].

With regard to systemic treatments we found interesting associations showing patients with positive BDR received OCS without biologics more frequently, whereas patients with negative BDR received biologics without OCS more frequently. However, due to the observational, cross-sectional design of the study it is not possible to elucidate whether there is a causal relationship to the drugs or whether differences in treatment reflect different patient characteristics. It is possible that patients in the positive BDR group were more frequently treated with OCS due to severity of disease with worse lung function.

On the other hand, a pulmonary function improvement in response to OCS can also be used as a diagnostic test when BDR is negative in suspected asthma [4] and OCS treatment improves pulmonary function in asthma, irrespective of initial BDR [28].

Anti-IL5(R) and anti-IL4R biologics also improve pulmonary function, but it is not known whether this impacts on BDR. Of note, patients with negative BDR were excluded from

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licensing trials of biologics and thus the reported FEV1 increases of around 100-160 ml following anti-IL5/R and anti-IL4R treatment reflect patients with positive BDR only [9–11]. Interestingly, it was recently shown that the new anti-TSLP biologic tezepelumab reduces airway hyperresponsiveness provoked by mannitol inhalation [29], suggesting that the degree of variability of airway obstruction might be influenced by targeting specific components of type-2 inflammation.

Moreover, we found asthma control measured by ACQ-5 was worse in patients with positive BDR and specific symptoms of resting dyspnea and chest tightness showed highly significant associations to positive BDR. This higher symptom load might in part be explained by more severe PFT impairments at baseline found in this group. Yet, in multivariate regression analysis in addition to FEV1%, chest tightness was independently associated with BDR suggesting that this could be a symptom with a certain specificity for pronounced variability of airway obstruction.

In patients with severe uncontrolled asthma several factors may be present that render obstruction non-reversible upon application of bronchodilators. Firstly, frequent use of SABA may lead to beta-receptor down-regulation and therefore reduce the effect of SABA [7]. Secondly, airway remodeling with not only muscular hypertrophy but also subepithelial fibrosis may occur, especially in long-standing disease [30,31]. We also found that in patients with positive BDR, PFT parameters showed more severe obstructive defects at baseline. Also, Heffler et al showed that positive BDR is a marker of poor asthma control even when BDR testing was performed without pausing asthma medications except for LABAs [32]. Our findings are in line with results from the severe asthma research program (SARP), that found highest reversibility in the cluster with worst baseline lung function. This cluster had also the highest FeNO levels and symptom load [33]. When comparing high-reversibility to low-reversibility in non-severe asthmatics, similar observations with worse pulmonary function and less well-controlled disease in the high reversibility group were made [34].

This may partially be due to the current definition of BDR that includes an increase in FEV1 of >12% which can be reached more easily when baseline values are low. Thus, the current FEV1% related definition has become a matter of debate in recent years. Even in the general population and asthmatics of unselected severities, Janson found that only 17% of asthmatics fulfilled the current criteria for positive BDR [22]. Our data further corroborate this notion for severe asthma with 2/3 of patients in this large real-life cohort being BDR negative. Interestingly, Janson et al suggested that a volume-related assessment of BDR by

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measurement of FVC instead of flow-related definition of FEV1 might be more relevant [22] and this is supported by data of Quanjer et al. for severe obstruction [35]. Indeed, evidence is growing that small airway dysfunction (SAD) may be more relevant for symptoms in asthma than FEV1 and SAD as well as its response to bronchodilators might be better captured by oscillometry in addition to mean expiratory flow (MEF) values [36,37] or using plethysmographic measures of airtrapping like RV [38]. Moreover, using improvement in z-scores may circumvent some of the limitations associated with the FEV1% based definition of BDR [39]. Here, for BDR we only had the standard parameter FEV1 % and FEV1 in ml available, however in the future GAN registry will collect more comprehensive pulmonary function data during BDR for a more detailed exploration.

Additionally, similar to other pulmonary function parameters, BDR may show variations over time and while some patients may continously exhibit positive BDR , a larger proportion has positive BDR only intermittently [40,41]. Thus, longitudinal observation may provide additional insights, but such longitudinal data on BDR was not available here.

Limitations of the study include the real-life setting of data acquisition and BDR. Thus, less than half of the patients included in the registry had data on BDR available at baseline. Further, even though patients were advised to withhold inhaled and other interfering treatments prior to BDR testing as requested by guidelines, this might be difficult for patients with severe uncontrolled asthma. Additionally, the 2019 update on ATS/ERS guidelines on standardization of spirometry [12], recommends longer bronchodilator withholding times than the previous version [13]. Yet, reflection of the real-life setting is also a strength of our data and highlights the issue faced in clinical practice, in that the BDR is often negative in severe asthma. Without thorough evaluation in a specialist setting this finding might be misinterpreted as COPD. Moreover, the use of the current FEV1 based definition of positive BDR as an inclusion criterion for RCTs in severe asthma should be revisited as it excludes the majority of the patients seen in real-life.

In summary, negative BDR was highly prevalent in this real-life cohort of patients with severe asthma and not associated with smoking history and COPD, questioning the relevance of BDR for diagnosis or differentiation of asthma from COPD. Parameters independently associated with positive BDR were lower FEV1% at baseline and chest tightness, while GERD comorbidity was associated with negative BDR.

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Conflicts of interest

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Table 1. Clinical characteristics of patients with severe asthma and positive or negative bronchodilator responsiveness (BDR) test

	Table 1: Baseline characteristics (N=793)				
			Bronchodilator responsiveness		
Item		**Total N=793**	**Positive N=250**	**Negative N=543**	**p-value pos. vs. neg.**
Sex- Female	n (%)	432 (54.5%)	129 (51.6%)	303 (55.8%)	0.27
Age – years	Mean (SD)	49.9 (16.3)	49.6 (15.6)	50.0 (16.5)	0.64
Age group - Children	n (%)	49 (6.2%)	15 (6.0%)	34 (6.3%)	0.88
BMI- kg/m²	Mean (SD)	27.4 (6.3)	27.2 (6.2)	27.5 (6.4)	0.68
Duration of asthma -years	Median	18.0 (0;80)	18.0 (0;72)	18.0 (0;80)	
Age at onset- years	Median	31.0	32.5 (0;69)	30.0 (0;84)	0.52
Age group at onset	Early (<12 years)	224 (28.4%)	62 (24.8%)	162 (30.0%)	0.13
	Late (> 12 years)	566 (71.6%)	188 (75.2%)	378 (70.0%)	

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	Table 1: Baseline characteristics (N=793)				
			Bronchodilator responsiveness		
Item		**Total N=793**	**Positive N=250**	**Negative N=543**	**p-value pos. vs. neg.**
Asthma phenotype ICD10	predominantly allergic asthma	336 (42.4%)	104 (41.6%)	232 (42.7%)	0.95
	non-allergic asthma	249 (31.4%)	80 (32.0%)	169 (31.1%)	
	mixed forms of asthma	208 (26.2%)	66 (26.4%)	142 (26.2%)	
Smoking habits	never-smoker	447 (56.4%)	143 (57.2%)	304 (56.1%)	0.81
	Active smoker	19 (2.4%)	7 (2.8%)	12 (2.2%)	
	former smoker	326 (41.2%)	100 (40.0%)	226 (41.7%)	
Former smoker: packyears	N	322	96	226	
	Median (range)	10.00 (0.5; 80)	9.00 (0.5;75)	10.00 (0.5; 80)	
Active Smoker: packyears	N	18	7	11	
	Median (range)	7.35	6.50 (0.5; 30)	12.00 (0;56)	
COPD	N	791	250	541	
	yes	52 (6.6%)	13 (5.2%)	39 (7.2%)	0.29
Incapacity for work	No	437 (55.2%)	131 (52.4%)	306 (56.5%)	0.61
	Yes	235 (29.7%)	82 (32.8%)	153 (28.2%)	
	Unknown	50 (6.3%)	16 (6.4%)	34 (6.3%)	
	not applicable	70 (8.8%)	21 (8.4%)	49 (9.0%)	

Table 2. Comparison of selected dichotomous parameters in positive vs. negative BDR.

Table 2:					
		Bronchodilator reversibility			
Item		**Total**	**Positive**	**Negative**	**p-value**
Resting dyspnea	N	792	250	542	
	yes	156 (19.7%)	67 (26.8%)	89 (16.4%)	0.0006*
Chest tightness / chest pain	N	792	250	542	
	yes	233 (29.4%)	91 (36.4%)	142 (26.2%)	0.0034*
Gastroesophageal reflux (GERD)	N	790	250	540	
	Yes	286 (36.2%)	70 (28.0%)	216 (40.0%)	0.0011*
Chronic sinusitis	N	791	250	541	
	Yes	364 (46.0%)	105 (42.0%)	259 (47.9%)	0.1233*
Nasal polyps	N	118	273	391	
	Yes	41 (34.7%)	99 (36.3%)	140 (35.8%)	0.77*
EGPA	N	791	250	541	
	Yes	17 (2.1%)	1 (0.4%)	16 (3.0%)	0.0211*
- Systemic therapies OCS – biologics	N	793	250	542	
	without OCS and without biologics	321 (40.5%)	105 (42.0%)	216 (39.9%)	0.0130*
	with OCS and without biologics	221 (27.9%)	82 (32.8%)	139 (25.6%)	
	without OCS and with biologics	162 (20.5%)	35 (14.0%)	127 (23.4%)	
	with OCS and with biologics	88 (11.1%)	28 (11.2%)	60 (11.1%)	

*p-value by Chi-square test, #p-value by U-test.

Table 3. FEV1 reversibility (%) for dichotomous parameters**.**

Table 3: FEV1 reversibility [%] (t-Tests)								
Item					**95% Conf. interval**		**t-test**	
		N	**Mean**	**SE**	**lower**	**upper**	**t-value**	**p value**
Resting dyspnea	No	636	10.53	0.72	9.12	11.94		
	Yes	156	17.54	2.65	12.30	22.77		
	Difference		-7.01	2.75	-12.43	-1.59	-2.55	0.0115
Chest tightness / chest pain	No	559	10.15	0.65	8.88	11.41		
	Yes	233	16.13	2.15	11.91	20.36		
	Difference		-5.99	2.24	-10.40	-1.58	-2.67	0.0080
Current use of OCS	No	483	10.51	0.78	8.97	12.05		
	Yes	309	14.09	1.59	10.97	17.21		
	Difference		-3.58	1.77	-7.05	-0.10	-2.02	0.0438
Current use of Biologics	No	542	12.97	0.98	11.04	14.91		
	Yes	250	9.59	1.26	7.11	12.08		
	Difference		3.38	1.60	0.24	6.52	2.11	0.0351
EGPA	No/ unknown	774	12.08	0.80	10.51	13.65		
	Yes	17	4.73	1.42	1.72	7.73		
	Difference		7.35	1.63	4.01	10.69	4.52	0.0001
GERD	No/ unknown	504	13.12	1.09	10.99	15.26		
	Yes	286	9.81	1.01	7.81	11.80		
	Difference		3.32	1.49	0.40	6.23	2.23	0.0259

For the dichotomous parameters, a t-test is performed to test whether there is a significant difference in FEV1 reversibility (%) between the two groups of the dichotomous parameter (Table 3).

Table 4. Univariate Linear Regression Analysis for continuous parameters

Table 4: Linear regression analysis (univariate)							
						95% Conf. interval	
Item	**Estimate**	**SE**	**t-value**	**p-value**	**Stand. Estimate**	**lower limit**	**upper limit**
ACQ-5	1.56707	0.46850	3.34	0.0009	0.12455	0.64725	2.48689
FEV1 [%]	-0.33624	0.03820	-8.80	<0.0001	-0.29938	-0.41123	-0.26126
FeNO at baseline [ppb]	0.02301	0.01519	1.51	0.1304	0.06331	-0.00683	0.05285

SE = standard error

For the continuous parameters, a univariate linear regression analysis is performed with the target variable FEV1 reversibility [%] and the continuous variable as the independent parameter .

Table 5. Multivariate linear regression analysis

Table 5: Linear regression analysis (multivariate)							
						95% CI	
Item	**Estimate**	**SE**	**t-value**	**p-value**	**Stand. Estimate**	**lower limit**	**upper limit**
ACQ-5	-0.00360	0.52822	-0.01	0.9946	-0.00029	-1.04067	1.03348
FEV1 [%]	-0.26397	0.03533	-7.47	<.0001	-0.28060	-0.33332	-0.19461
Resting dyspnea	2.67390	1.82865	1.46	0.1441	0.05570	-0.91638	6.26418
Chest tightness / chest pain	3.10083	1.54392	2.01	0.0450	0.07592	0.06957	6.13209
Systemic steroids	-0.52893	1.41514	-0.37	0.7087	-0.01391	-3.30735	2.24948
Biologics	-1.56801	1.45484	-1.08	0.2815	-0.03932	-4.42437	1.28835
EGPA	-5.24051	4.54253	-1.15	0.2490	-0.04202	-14.15910	3.67808
GERD	-3.03815	1.36898	-2.22	0.0268	-0.07957	-5.72595	-0.35036
Backward elimination p<0.150							
FEV1 [%]	-0.26522	0.03389	-7.83	<0.0001	-0.28194	-0.33177	-0.19868
Resting dyspnea	2.90417	1.74826	1.66	0.0971	0.06050	-0.52824	6.33658
Chest tightness / chest pain	3.15516	1.48983	2.12	0.0345	0.07725	0.23013	6.08019
GERD	3.08614	1.36311	-2.26	0.0239	0.08082	0.40989	5.76238

Multiple linear regression analysis with the target variable FEV1 reversibility [%] and the significant parameter of the univariate linear regression analysis or t-test
Due to missing information, 83 out of 793 (10.5 %) cases were excluded from the analysis.
Thus, the analysis is carried out for 710 patients.

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Figure 1. Comparison of selected parametric variables in patients with positive versus negative BDR test including pre-bronchodilator pulmonary function tests, ACQ-5, FeNO and blood eosinophil count. p-values by U-test. All n= 793 except for eosinophils before biologics n=134.