Elevated Serum Levels of Herpes Virus Entry Mediator and IL-5 in Cough Variant Asthma Versus Classic Asthma Patients

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Abstract

Background

Cough variant asthma (CVA) is a special phenotype of asthma. We aimed to elucidate the differential inflammatory features in patients with CVA in contrast to patients with classic asthma (CA).

Methods

A total of 68 patients with persistent uncontrolled asthma (34 with CVA, 34 with CA) were enrolled. We collected the demographic data, pulmonary function test (PFT) parameters, hematological variables, and several serum biomarkers. The independent-samples *t* test was used for analyzing measurement data, and Chi-square test was for count data. Multivariate logistic regression analysis was used to determine the possibility of different phenotypes. Receiver operating characteristic (ROC) curves were generated to evaluate the values of biomarkers for distinguishing between CVA and CA. Linear correlation analysis was performed to assess the linear relationship between two variables.

Results

Compared with CA group, CVA group had a higher percentage of females, lower proportion of asthma family history, shorter disease course, and better pulmonary function (P all < 0.05). Increased levels of blood eosinophil count (P = 0.045), eosinophil percentage (P = 0.046), serum IL-5 (P = 0.011), and serum herpesvirus entry mediator (HVEM) (P = 0.002) were also found in CVA patients compared to those in CA patients compared to those in CA patients. The logistic analysis revealed that serum HVEM had a strong predictive power for CVA group (OR = 1.105, P = 0.015). The sensitivities and specificity of serum HVEM and IL-5 to distinguish between CVA and CA at optimal cut-offs were 85.0% and 61.1%; 85.0% and 61.1%, respectively. Area under the curves (AUCs) of serum HVEM and IL-5 were 0.789 and 0.739, respectively. Furthermore, serum HVEM and IL-5 had no correlation with PFT parameters in CVA group (P all > 0.05).

Conclusions

Elevated serum levels of HVEM and IL-5 are exhibited in CVA patients, which may indicate their important roles in the pathogenesis and progression of CVA.

Background

Asthma is a heterogeneous disease affecting 1–18% of the populations in different countries. [1, 2]. It is ordinarily characterized by persistent and chronic airway inflammation and can be identified by respiratory symptoms including wheezing, coughing, chest tightness and dyspnea.[2] Due to the interaction between genetic and environmental factors, many different phenotypes of asthma have been induced and appeared distinct clinical symptoms, therapeutic effects and outcomes.[3, 4] Cough variant asthma (CVA) is a specific phenotype of asthma presenting chronic cough as the sole or predominant symptom, characterized by airway hyper responsiveness.[5] CVA has been increasingly recognized as a pre-asthmatic state because nearly 30% of patients with CVA may develop into classic asthma (CA) within several years.[6, 7] However, a previous study has indicated that the pathophysiology is different between CVA and CA, and may be associated with the variant sensitivity of cough receptors located in the superficial layer of the airway wall.[6] Therefore, it is essential to explore the CVA biomarkers for risk prediction as well as providing new insights into the pathophysiological mechanisms of CVA.

Herpes virus entry mediator (HVEM) is one of the tumor necrosis factor superfamily (TNFSF) receptors, and highly expressed on the surface of many immune cells such as T cells, B cells, eosinophils, monocytes and dendritic cells.[8] We

have previously reported that TNFSF14 (TNFSF member 14) protein combining its receptor HVEM plays a critical role in exacerbating airway inflammation and the pathogenesis of airway remodeling,[9] and during asthma attack inhaled budesonide can reduce airway inflammation by down-regulating the expressions of TNFSF14 and HVEM in the lungs of asthmatic mice[10]. Furthermore, interleukin (IL)-5, the main cytokine involved in the growth and activation of eosinophils, is essential to the pathophysiology of type 2 inflammation in asthma. [11-13] Both HVEM and IL-5 appear to play important roles in the inflammatory processes of asthma. However, whether CVA patients and CA patients present similar inflammatory patterns remains unclear. Our study aimed to compare the serum levels of HVEM and IL-5 in patients with CVA and CA, and investigate the ability to distinguish between the two subtypes of asthma.

Methods

Patients and study design

A total of 68 adult patients with asthma admitted to Shenzhen People's Hospital (the Second Clinical Medical College of Jinan University, the First Affiliated Hospital of Southern University of Science and Technology) between August 2018 and May 2019 were enrolled in the study (34 with CVA, 34 with CA). All subjects were suffering from uncontrolled moderate to severe asthma.

All study patients were diagnosed according to the recommendations of the Global Initiative for Asthma (GINA) 2017. CVA patients had a clinical history of isolated chronic non-productive cough (longer than 8 weeks), and were absent of wheezing or dyspnea in contrast to CA. Patients were excluded if they had infectious conditions, other lung diseases [such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension, bronchiectasis, interstitial lung disease, eosinophilic bronchitis (EB), and allergic bronchopulmonary aspergillosis (ABPA)], severe renal or hepatic dysfunction, cardiac dysfunction, acute coronary syndrome, active malignancy, pregnancy, or have a recent history of surgery.

Data collection

Patient demographic data (eg. age, gender, smoking status, family history of asthma, allergy history, and comorbidities) and the asthma control test (ACT) scores were collected. The following determinations were performed: 1) fractional exhaled nitric oxide (FeNO) test, 2) pulmonary function test (PFT), 3) serum levels of HVEM and IL-5, 4) routine blood tests, and 5) induced sputum cell analysis test. Blood and sputum samples were obtained within 2 hours of admission to the hospital.

Statistical Evaluation

Statistical Package for Social Sciences (SPSS) version 13.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Measurement data from normal distribution were expressed as the mean ± standard deviation and the independent-samples *t* test was used to assess significant differences. Non-normally distributed continuous data were expressed as the median (interquartile range, IQR), and a two-sample Wilcoxon Rank Sum test was used to analyze. Chi-square test or Fisher's exact test was for categorical variables. Multivariate logistic regression analysis was used to check the independent correlation factors. Receiver operating characteristic (ROC) curves were generated to evaluate the biomarkers for distinguishing CVA and CA. The Youden index was used to determine the optimal cutoffs of variables including HVEM, IL-5 and eosinophils. Linear regression was used to analyze the correlation between two numerical variables A P value of less than 0.05 ($P < 0.05$) was considered as a statistically significant difference.

Results

Baseline characteristics of the study population

The present study included 34 patients of CVA and 34 of CA, and 42 of them (65.63%) were women. The mean age was years, and mean disease duration was months. The baseline characteristics of both groups are shown in Table 1. Overall, compared

with patients with CA, patients with CVA were more common in females (73.5 vs. 50%, $P = 0.046$), had a shorter duration of asthma [12.0 (4.8, 39) vs. 96.0 (48.0, 240.0) months, $P < 0.001$], and less likely to have a family history of asthma (5.9 vs. 29.4%, $P = 0.011$). However, here was no significant difference in age, body mass index (BMI), length of hospital stay, smoking status, history of glucocorticoid medication, and ACT scores between the two groups ($P = 0.425$, 0.271, 0.847, 0.085, 0.323, 0.134, respectively). Furthermore, the CVA group presented better lung function than CA group, with higher levels of FEV1 (2.32 ± 0.61 vs. 1.91 ± 0.72 L, $P = 0.014$), FEV1%pred (94.16 ± 16.22 vs. 69.43 ± 20.28%, $P < 0.001$), FVC%pred (104.91 ± 18.02 vs. 90.70 ± 17.14%, $P = 0.002$), FEV1/FVC (75.02 ± 4.83 vs. 62.68 ± 10.65%, $P < 0.001$), MEF25% (43.82 ± 12.72 vs. 27.98 ± 17.52%, $P < 0.001$), MEF50% (64.44 ± 16.52 vs. 34.92 ± 20.60%, $P < 0.001$), and MEF75/25% (55.51 ± 13.91 vs. 31.66 ± 19.48%, $P < 0.001$).

Table 1
Comparison of general conditions between CVA and CA groups

	CVA (n = 34)	CA (n = 34)	$\chi^2/t/Z$	*P*
Sex				
Male, n (%)	9 (26.5)	17 (50)	3.985	0.046*
Female, n (%)	25 (73.5)	17 (50)		
Age, (years), Mean ± SD	52.65 ± 14.45	50.06 ± 12.03	2.323	0.425
BMI, (kg/m^2), Mean ± SD	23.90 ± 3.14	23.06 ± 3.08	0.440	0.271
Length of hospital stay, (days), Mean ± SD	7.00 ± 2.67	6.88 ± 2.32	0.351	0.847
Asthma duration, (months), Median(Q1,Q3)	12.0 (4.8,39)	96.0 (48.0,240.0)	4.369	0.000*
Smoking history				
Yes, no quit, n (%)	4 (11.8)	6 (17.6)	4.932	0.085
Yes, quit, n (%)	1 (2.9)	6 (17.6)		
No, n (%)	29 (85.3)	22 (64.7)		
Hormone medication history, n (%)	4 (11.8)	7 (20.6)	0.976	0.323
Family history of asthma, n (%)	2 (5.9)	10 (29.4)	6.476	0.011*
ACT score, Median(Q1,Q3)	17.0(14.0,19.0)	16.0(13.0,18.3)	1.500	0.134
Lung function				
FEV_1,(L), Mean ± SD	2.32 ± 0.61	1.91 ± 0.72	2.525	0.014*
FEV_1%pred, Mean ± SD	94.16 ± 16.22	69.43 ± 20.28	5.520	0.000*
FVC%pred, Mean ± SD	104.91 ± 18.02	90.70 ± 17.14	3.309	0.002*
FEV_1/FVC, (%), Mean ± SD	75.02 ± 4.83	62.68 ± 10.65	6.140	0.000*
MEF50%, Mean ± SD	64.44 ± 16.52	34.92 ± 20.60	6.460	0.000*
MEF25%, Mean ± SD	43.83 ± 12.72	27.98 ± 17.52	4.226	0.000*
MMEF75/25%, Mean ± SD	55.51 ± 13.91	31.66 ± 19.48	5.750	0.000*

Abbreviations: CVA: Cough variant asthma; CA: Classic asthma; BMI: Body mass index; ACT: Asthma control test; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; MEF: Maximum expiratory flow; MMEF: Maximal mid-expiratory flow.

*: $P < 0.05$.

Levels of inflammatory biomarkers

Patients with CVA had a higher serum HVEM [128.53(100.89, 204.83) vs. 90.71(37.05, 108.08) pg/mL, $P = 0.002$], higher serum IL-5 [104.19 (89.03, 199.66) vs. 84.57(26.87, 103.58) ng/L, $P = 0.011$], higher blood eosinophil percentage [6.3(3.0, 9.8) vs. 4.4(0.2, 8.4) %, $P = 0.046$], and higher blood eosinophil count [0.35(0.13, 0.94) vs. 0.34(0.01, 0.53) $X10^9$/L, $P = 0.045$] compared with CA. While white blood cell (WBC) count (6.11 ± 1.83 vs. 7.61 ± 2.41 $X10^9$/L, $P = 0.005$) and blood neutrophil count (3.25 ± 1.01 vs. 4.94 ± 2.63 X 10^9/L, $P = 0.001$) were significantly lower in CVA compared with CA. However, there were no differences in serum IL-17, sputum neutrophil percent, sputum eosinophil percent, and FeNO levels between the two groups ($P = 0.897$,

0.622, 0.311, 0.499, respectively). The comparison of inflammatory biomarker levels between patients with CVA and CA was shown in Table 2, Fig. 1 and Fig. 2.

Table 2
Comparison of inflammatory biomarker levels between CVA and CA groups

	CVA(n = 32)	CA(n = 32)	*t*/*Z*	*P*
Peripheral blood				
WBC, (10^9/L), Mean ± SD	6.11 ± 1.83	7.61 ± 2.41	2.890	0.005*
Neu, (10^9/L), Mean ± SD	3.25 ± 1.01	4.94 ± 2.63	3.487	0.001*
Eos%, Median(Q1,Q3)	6.3(3.0,9.8)	4.4(0.2,8.4)	1.994	0.046*
Eos, (10^9/L),Median(Q1,Q3)	0.35(0.13,0.94)	0.34(0.01,0.53)	2.006	0.045*
IL-5, (ng/L),Median(Q1,Q3)	104.19(89.03,199.66)	84.57(26.87,103.58)	2.514	0.011*
IL-17, (ng/L),Median(Q1,Q3)	44.27(20.82,51.12)	44.75(18.07,54.14)	0.146	0.897
HVEM, (pg/L), Median(Q1,Q3)	128.53(100.89,204.83)	90.71(37.05,108.08)	3.040	0.002*
Induced sputum				
Neu%, Mean ± SD	60.02 ± 27.27	56.02 ± 28.78	0.496	0.622
Eos%, Median(Q1,Q3)	6.8(0.6,28.1)	8.2(1.8,36.0)	1.013	0.311
FeNO(ppb), Median(Q1,Q3)	23.0 (13.8,61.5)	35.5 (17.3,50.3)	0.676	0.499
Abbreviations: CVA: Cough variant asthma; CA: Classic asthma; WBC: White blood cell; Neu: Neutrophil; Eos: Eosinophil; IL: Interleukin; HVEM: Herpes virus entry mediator; FeNO: Fractional exhaled nitric oxide.				
*: P < 0.05.				

Regression Analysis of inflammatory biomarkers

Univariate and multivariate logistic regression analysis were conducted to identify CVA related factors by the inflammatory biomarkers, including serum HVEM, serum IL-5, WBC count, blood neutrophil count, blood eosinophil count, and blood eosinophil percent. The result showed that serum HVEM [odds ratio (OR) = 1.105; 95% confidence interval (CI) 1.020–1.197; *P* = 0.015] had a strong predictive power for CVA group, indicating that serum HVEM is the independent risk factor for identifying CVA (Table 3). However, other variables including serum IL-5, WBC count, blood neutrophil count, blood eosinophil count, and blood eosinophil percent were not significant predictors.

Table 3
Multivariable logistics regression analysis of CVA group

	OR	95%CI	*P*
IL-5	0.944	0.890 ~ 1.001	0.055
HVEM	1.105	1.020 ~ 1.197	0.015*
WBC	0.307	0.061 ~ 1.533	0.150
Neu (Peripheral blood)	5.440	0.631 ~ 46.879	0.123
Eos% (Peripheral blood)	1.018	0.534 ~ 1.939	0.957
Eos (Peripheral blood)	1.093	0.663 ~ 1.876	0.381
Abbreviations: CVA: Cough variant asthma; IL: Interleukin; HVEM: Herpes virus entry mediator; WBC: White blood cell; Neu: Neutrophil; Eos: Eosinophil.			
*: $P < 0.05$.			

We then used ROC curve analysis to the ability of inflammatory biomarkers to distinguish CVA from CA. The AUC of serum HVEM (AUC 0.789, 95% CI 0.646–0.931, $P = 0.002$) was much better than other single biomarkers. The optimal cut-off value for serum HVEM was 98.69 pg/ml, with sensitivity of 85.0% and specificity of 61.1%; 87.77ng/ml for IL-5 with 85.0% sensitivity and 61.1% specificity (AUC 0.739, 95% CI 0.578–0.899, $P = 0.012$). While combining serum HVEM with serum IL-5, the AUC and specificity can increase to 0.822 and 100%, respectively. Other biomarkers such as WBC count, blood neutrophil count, blood eosinophil count, and blood eosinophil percent did not show the ability to distinguish between CVA and CA ($P =$ 0.066, 0.062, 0.539, 0.350, respectively). The results of the ROC curve analysis were shown in Table 4 and Fig. 3.

Table 4
Ability of inflammatory biomarkers to distinguish CVA from CA

	AUC	95% CI	Cut-off	Sensitivity	Specificity	*P*
IL-5	0.739	0.578 ~ 0.899	87.77	0.850	0.611	0.012*
HVEM	0.789	0.646 ~ 0.931	98.69	0.850	0.611	0.002*
WBC	0.670	0.501 ~ 0.839	-	-	-	0.066
Neu	0.673	0.502 ~ 0.843	-	-	-	0.062
Eos%	0.589	0.398 ~ 0.780	-	-	-	0.350
Eos	0.558	0.366 ~ 0.750	-	-	-	0.539
Il-5 + HVEM	0.822	0.691 ~ 0.953	-	0.600	1.000	0.001*
Abbreviations: CVA: Cough variant asthma; CA: Classic asthma; IL: Interleukin; HVEM: Herpesvirus entry mediator; WBC: White blood cell; Neu: Neutrophil; Eos: Eosinophil.						
*: $P < 0.05$.						

Correlation Analysis between inflammatory biomarkers and PFT parameters

In the CVA group, there was no positive relationship between PFT parameters and inflammatory biomarkers including serum HVEM, serum IL-5, serum IL-17, WBC count, blood neutrophil count, blood eosinophil count, blood eosinophil percent, sputum eosinophil percent, sputum neutrophil percent, and FeNO levels (P all > 0.05). More details were shown in Table 5.

Table 5
Relationship between inflammatory biomarkers and PFT in the CVA group

	FEV_1%pred		FVC%pred		FEV_1/FVC		MEF50%		MEF25%		MMEF75/25%	
	r	P	r	P	r	P	r	P	r	P	r	P
Peripheral blood												
WBC	0.153	0.396	0.143	0.428	0.161	0.370	0.109	0.545	0.235	0.188	0.177	0.325
Neu	0.260	0.144	0.207	0.248	0.219	0.220	0.236	0.186	0.378	0.060	0.300	0.090
Eos%	-0.167	0.352	-0.247	0.167	0.255	0.152	0.027	0.883	0.037	0.839	0.072	0.689
Eos	-0.112	0.535	-0.162	0.369	0.073	0.686	-0.016	0.930	-0.071	0.696	-0.050	0.784
IL-5	-0.268	0.254	-0.284	0.226	0.224	0.342	0.218	0.356	0.161	0.497	0.144	0.544
IL-17	-0.141	0.553	-0.267	0.254	0.407	0.075	0.295	0.207	0.260	0.298	0.311	0.182
HVEM	-0.289	0.216	-0.263	0.262	0.115	0.630	0.189	0.424	0.190	0.422	0.135	0.570
Induced sputum												
Neu%	0.413	0.070	0.330	0.155	0.028	0.908	-0.184	0.438	0.078	0.745	-0.068	0.774
Eos%	-0.428	0.060	-0.288	0.215	0.293	0.211	0.438	0.053	0.269	0.252	0.384	0.095
FeNO	-0.227	0.236	-0.224	0.243	-0.010	0.961	0.084	0.665	0.011	0.953	0.086	0.657

Abbreviations: CVA: Cough variant asthma; PFT: Pulmonary Function Test; WBC: White blood cell; Neu: Neutrophil; Eos: Eosinophil; IL: Interleukin; HVEM: Herpesvirus entry mediator; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; MEF: Maximum expiratory flow; MMEF: Maximal mid-expiratory flow.

*: $P < 0.05$.

Discussion

In the current study, we have shown for the first time higher HVEM and IL-5 serum levels in CVA patients compared to CA patients. Although CVA patients with chronic cough as the only respiratory symptom can be distinguished from CA patients,[2] our finding is still important in presenting features of particular inflammatory mediators such as HVEM and IL-5 in CVA. It has been suggested that HVEM and IL-5 are significantly associated with persistent airway inflammation in asthma. Therefore, our study has implied IL-5-induced eosinophilia and HVEM-related inflammation may be responsible for the pathogenesis of CVA.

The present study assessed 64 adult patients who had persistent uncontrolled asthma by the GINA-defined criteria. The CVA group had a higher prevalence of female patients and a shorter duration of disease compared to the CA group, and the results are consistent with the earlier report.[14] Meanwhile, we also found noticed the routine PFT parameters for evaluating mechanical properties of the large, medium-sized, and small airways in CVA group were significantly greater than those in CA group. It may suggest that the decline of pulmonary function is relatively milder in CVA patients. However, previous studies found that the values of MEF50% and MEF25% in CVA patients were lower compared with CA patients, and suggested that CVA is mainly characterized by dysfunctions of small airways [15, 16]. The discrepancy in results may be explained by the different enrolled subjects. Moreover, we still need to monitor the changes of PFT parameters and levels of airway inflammation to prevent CVA from developing into CA.

It has been reported that eosinophilic inflammation may be an underlying mechanism of CVA, [5] and a blood eosinophil count of > 300 cells/ul was considered an eosinophilic phenotype of asthma in the previous year.[5, 17, 18] In our study, the median

blood eosinophil count of two groups were both greater than 300 cells/ul, while blood eosinophil count and eosinophil percent were significantly higher in CVA group compared to those in CA group. We also found that the serum IL-5 level was significantly increased in CVA patients. IL-5 is a major cytokine responsible for the growth and differentiation of eosinophils, and its binding of IL-5 receptor promotes adhesion of eosinophils to airway mucosa, which is a key contributor to airway inflammation in asthma. [13, 19] Therefore, the results indicate that the IL-5/eosinophil pathway may play a pathogenetic role in CVA, and anti-IL-5 therapy may provide an alternative approach for patients with uncontrolled CVA. However, there was no significant difference in FeNO levels between the two groups. Although FeNO could be a useful biomarker for eosinophilic inflammation, [5] it is highly susceptible to various factors such as atopy, smoking status, pulmonary function and so on. Thus, the FeNO levels between the two groups should be comprehensively evaluated.

HVEM has been implicated to play in airway inflammation and airway remodeling of asthma by combining with TNFSF14.[9] Our study showed that the level of serum HVEM in CVA group was significantly higher than those in CA group. Furthermore, the multivariate logistic regression analysis revealed that HVEM is an independent risk factor for identifying CVA (OR = 1.105, P = 0.015). It may suggest that HVEM-mediated inflammation is uniquely important for the pathogenesis of CVA, but whether this network may also participate in the IL-5/eosinophil pathway of CVA patients is not known. These results provide a new way to explore the pathogenesis of CVA. In addition, the results of ROC curve analysis showed that serum IL-5 and serum HVEM can be used to distinguish CVA from CA. In both biomarkers, HVEM had a higher AUC value of 0.789, and the sensitivity and specificity were 85.0% and 61.1%, respectively, at a better cut-off value of 98.69 pg/ml. Moreover, the combination of serum HVEM and serum IL-5 can improve the AUC value to 0.822 with a specificity of 100%, indicating this combination might be useful to identify the CVA phenotype. While in clinical practice, it would not be commonly used because CVA patients are easy to be identified from CA patients by symptoms. Therefore, increased serum levels of HVEM and IL-5 may implicate elevated airway inflammation in CVA patients and need selected anti-inflammatory drugs to control clinical symptoms. Whereas, this still needs to be confirmed in further studies. Besides, the results of correlation analysis showed that no significant correlation was found between the laboratory indicators (e.g. serum IL-5, serum HVEM, and FeNO) and PFT parameters, suggesting high levels of these inflammatory biomarkers were not associated with the pulmonary function of CVA patients.

There were some limitations in our study. First, our study was from a single center and the sample size was limited, future multicenter studies should be performed to further prove the result. Second, we did not detect the levels of sputum IL-5 and sputum HVEM between the two groups, whether the levels of these inflammatory biomarkers in airways have similar changes are not evaluated. Finally, we did not investigate the mechanisms of HVEM and IL-5/eosinophil pathway in CVA phenotype, and further studies are needed to verify them.

Conclusion

We have shown that CVA patients exhibit a distinct inflammatory profile with increased serum levels of IL-5 and HVEM, not associated with pulmonary functions, which appears to be strikingly different from the CA patients. These findings imply that IL-5 and HVEM may play an important role in the pathogenesis and progression of CVA; in addition, anti-inflammatory therapy to inhibit HVEM or IL-5/eosinophil pathway may become a new treatment option for patients with uncontrolled CVA. Future studies are necessary to verify and confirm the results.

List Of Abbreviations

CVA
Cough variant asthma; CA:classic asthma; PFT:Pulmonary function test; ROC:Receiver operating characteristic; HVEM:Herpes virus entry mediator; TNFSF:Tumor necrosis factor superfamily; IL:Interleukin; GINA:Global Initiative for Asthma; COPD:Chronic obstructive pulmonary disease; EB:Eosinophilic bronchitis; ABPA:Allergic bronchopulmonary aspergillosis; ACT:Asthma control test; FeNO:Fractional exhaled nitric oxide; SPSS:Statistical Package for Social Sciences; IQR:Interquartile range; OR:Odds ratio; CI:Confidence interval; AUC:Area under the curves.

Declarations

Ethics approval

This study was approved by the Ethics Committee of Shenzhen People's Hospital (LL-KY-201712012), and informed consent was obtained from each subject before inclusion in the study. All methods were performed in accordance with the relevant guidelines, regulations and Declaration of Helsinki.

Consent to participate

Not applicable.

Availability of data and material

Some or all data, or code generated or used during the study are available from the corresponding author by request.

Competing interests

The author(s) declare no competing interests.

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Authors' contributions

Conceptualization: CY, ZY, DC and FS. Methodology: CY, ZY, FS and RC. Formal analysis: CY. Writing - Original Draft: CY. Writing - Review & Editing: ZY, DC, FS and RC. Investigation: DC, WF, YZ, BL and SL. Software:DC, WF and YZ. Data curation: WF, YZ, BL and SL. Data curation: YZ, BL and SL. Visualization: BL and FS. Supervision: FS and RC.

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Figures

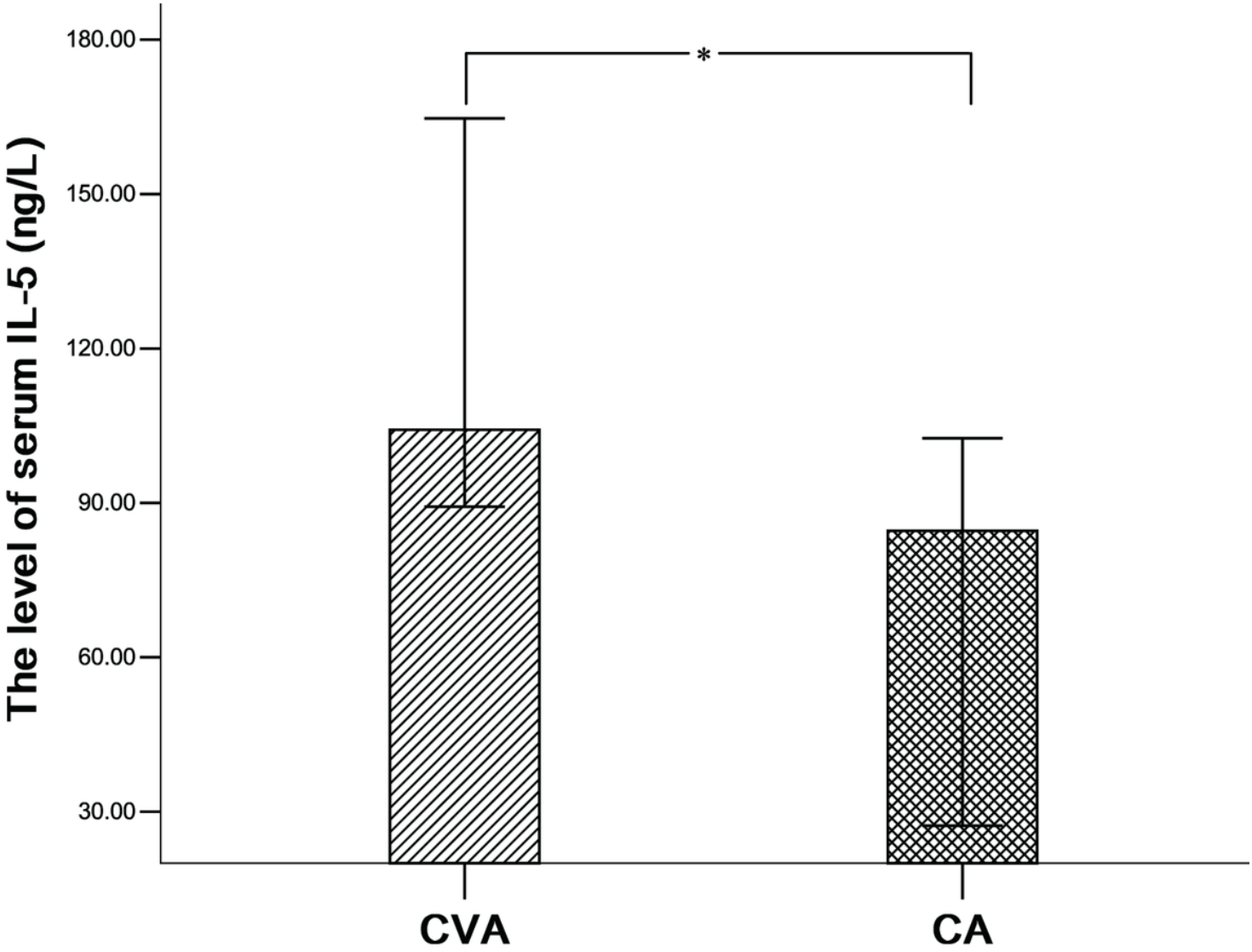

Figure 1

Differences of serum IL-5 levels between cough variant asthma (CVA) group and classic asthma (CA) group.

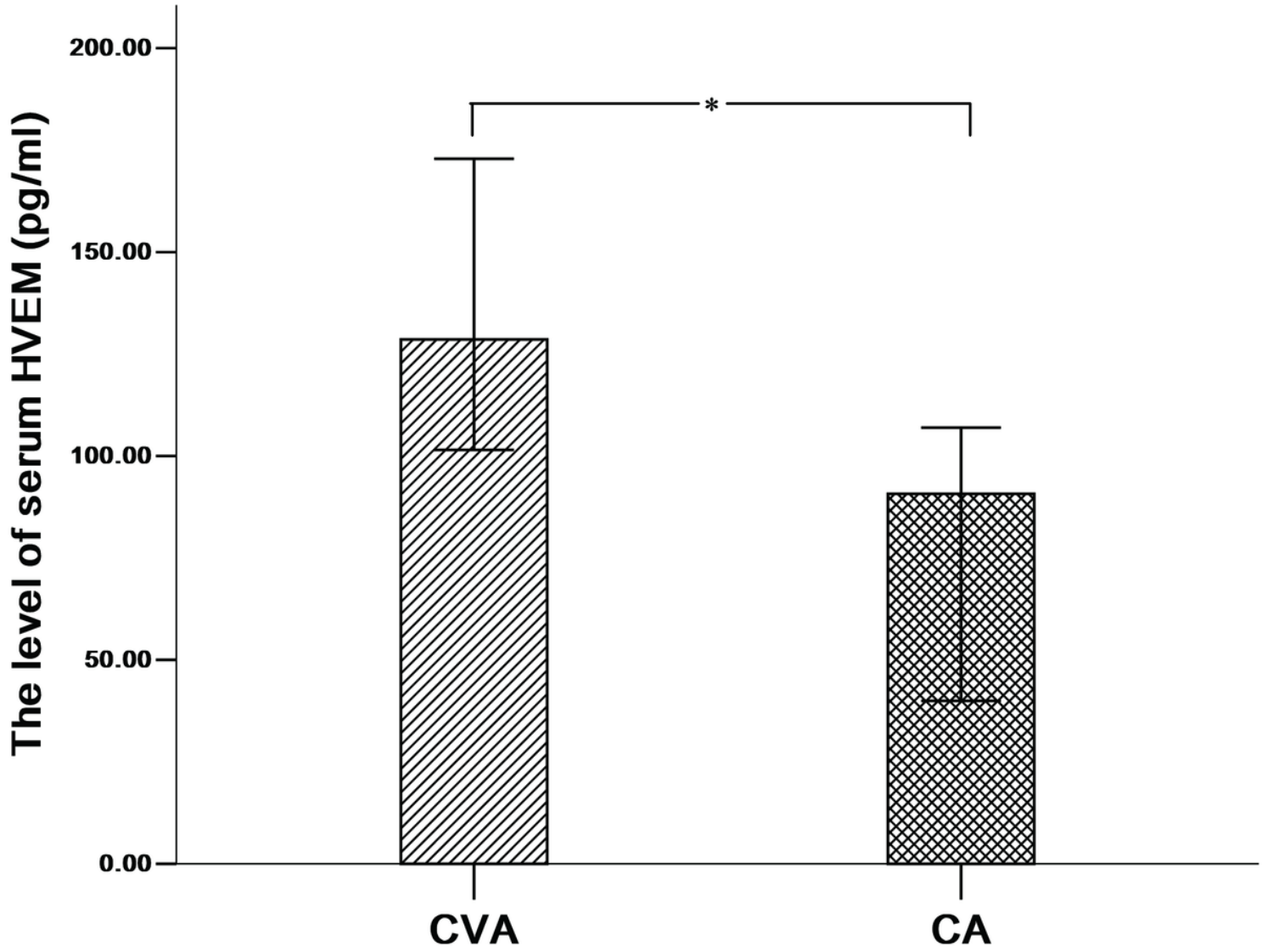

Figure 2

Differences of serum herpes virus entry mediator (HVEM) levels between cough variant asthma (CVA) group and classic asthma (CA) group.

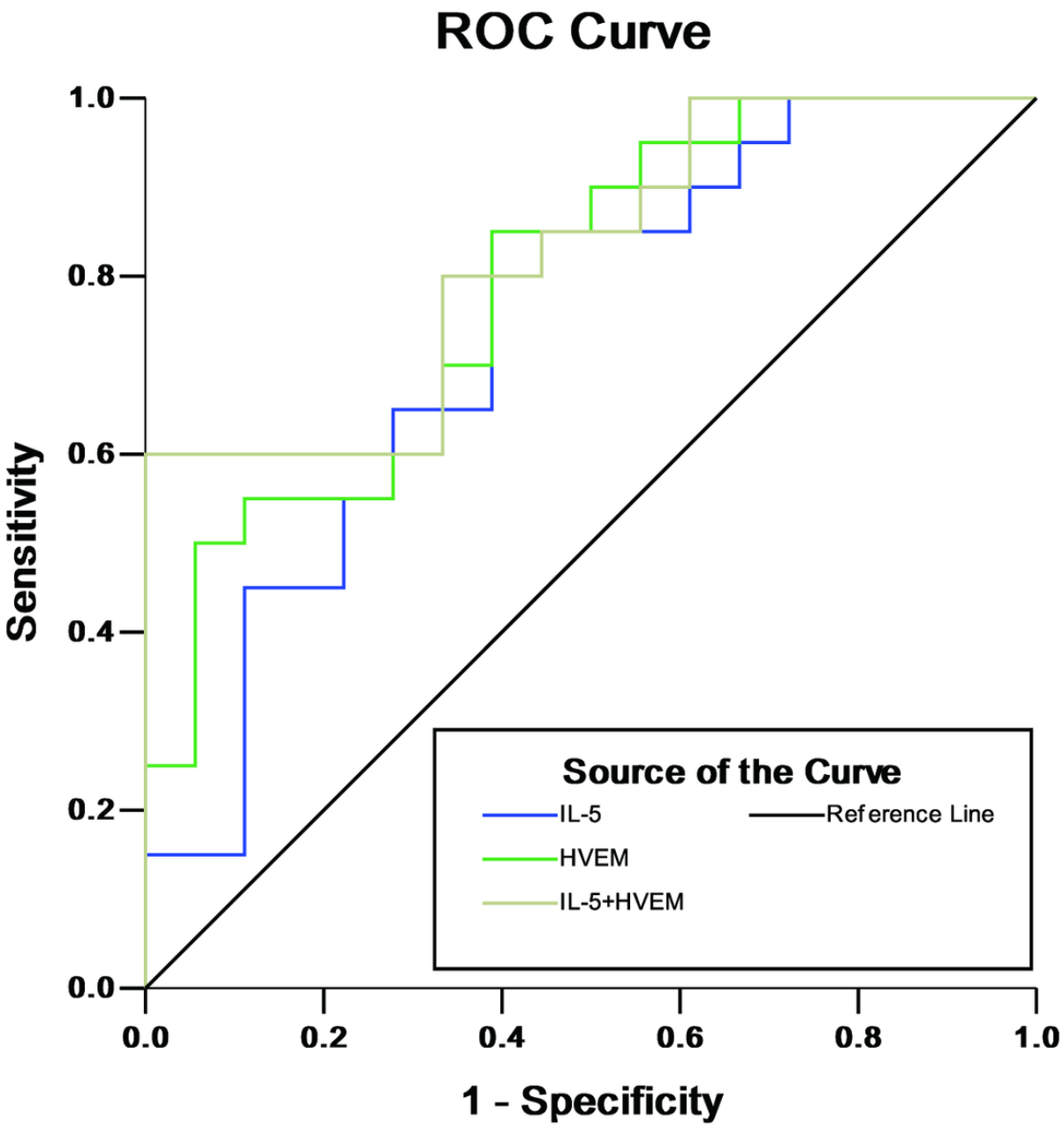

Figure 3

Receiver operating characteristic (ROC) curves for serum HVEM and IL-5 to differentiate between CVA and CA.