

Clinical characteristics of children with airway malacia complicated by pneumonia

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Abstract

Objective

To summarize the pathogens and clinical presentation of children with airway malacia complicated by pneumonia.

Methods

Children hospitalized with airway malacia complicated by pneumonia were eligible for enrollment from January 1, 2013 to December 31, 2019. Medical records of patients were reviewed for etiology, clinical characteristics, and laboratory examination results.

Results

A total of 164 pneumonia patients with airway malacia were admitted. The male-to-female ratio was 3:1. The age of patients ranged from 1 month to 4 years old. The median age was 6 (3–10) months. The most commonly detected pathogen were *Mycoplasma pneumoniae* (25/164, 15.24%), *Streptococcus pneumoniae* (18/164, 10.98%), and respiratory syncytial virus (16/164, 9.76%). Common signs among the 164 patients with confirmed airway malacia included cough (98.78%), wheezing (67.07%), fever (35.37%), intercostal retractions (23.17%), dyspnea (10.98%), cyanosis (11.11%), and crackles (50%). Compared with those without airway malacia, the incidence of premature delivery and mechanical ventilation was higher, and the duration of symptoms before admission (median, 13.5 d) and hospital stay (median 10.0 d) were longer. Of the children with pneumonia, 11.59% of those with airway malacia required supplemental oxygen compared with 4.88% of those without airway malacia ($p < 0.05$).

Conclusion

The median age of children with airway malacia was 6 months. The most common pathogen in patients with airway malacia complicated by pneumonia was *Mycoplasma pneumoniae*. Patients with airway malacia complicated by pneumonia often presented with a longer disease course, more severe symptoms, and had delayed recovery.

Introduction

Airway malacia is a disease referring to an excessive collapse of the airway, which is caused by disproportionate laxity of the posterior wall (pars membranacea) or compromised cartilage integrity [1]. This concept was first proposed by Baxter and Dunbar in 1963. Airway malacia could occur in isolation, or in association with other congenital or acquired conditions [2]. It is an important cause of noisy breathing, recurrent wheezing and respiratory infections, chronic coughing, and episodes of respiratory

distress in young children[3, 4]. In a study by Masters et al. [5], children with airway malacia had higher respiratory illness frequency, disease severity, likelihood of a significant cough, and tendency for a delayed recovery.

In a retrospective study, the incidence of airway malacia was at least 1/2100 [6]; however, at present, the exact incidence and prevalence of airway malacia remains uncertain. As the clinical manifestations of airway malacia—which cannot be diagnosed using routine examinations such as blood examination, imaging, or lung function tests—are not common and fiber optic bronchoscopy is limited in its application, many clinicians have insufficient understanding of this disease. This study aimed to summarize the pathogens and clinical presentation of pneumonia in children with airway malacia, and to compare these with those in children without airway malacia to provide a scientific basis for making early diagnoses and identifying reasonable treatments.

Materials And Methods

Patients

This prospective descriptive study was conducted in patients aged <4 years old with chronic respiratory symptoms or recurrent pneumonia who underwent fiber optic bronchoscopy and were admitted to the Department of Respiratory Medicine in the Children's Hospital of Soochow University between January 1, 2013 and December 2019. Chronic respiratory symptoms were defined as cough, stridor, or wheeze present for ≥ 3 weeks [5]; recurrent pneumonia was defined as at least two pneumonia episodes within the past 1 year [7]. The exclusion criteria for our study were: (1) patients with incomplete clinical data; (2) patients with heredity metabolic diseases, neurological disorders, congenital heart disease, and/or immunodeficiency; and (3) patients with evidence suggesting that wheezing was caused by non-infectious factors, such as bronchial foreign bodies and tuberculosis.

Patients with chronic respiratory symptoms or recurrent pneumonia who underwent fiberoptic bronchoscopy were classified into either the airway malacia group or no airway malacia group, and the ratio of the sizes of the two groups was 1:1. Airway malacia is weakness of the trachea and/or bronchial deformity at the end of expiration leading to a reduction in the diameter of the airway of more than 1/3. The airway malacia group consisted of patients with airway malacia seen on bronchoscopy. The no airway malacia group consisted of patients with no airway malacia seen on bronchoscopy. The study was approved by the Ethics Committee of Children's Hospital of Soochow University.

Bronchoscopy and BALF collection

The fiberoptic bronchoscopy and BALF collection procedure has been described previously [8]. The collected BALF was used for respiratory pathogen analysis (10 types of viruses and bacteria including *Mycoplasma pneumoniae* [MP]).

According to the part of airway with malacia on bronchoscopy, airway malacia was classified into tracheomalacia, bronchomalacia, or tracheobronchomalacia. Tracheomalacia refers to a weakness of the trachea that could make the airway softer and more susceptible to collapse with changes in pressure. Bronchomalacia is the isolated weakness and collapsibility of one or both of the mainstem bronchi and/or their respective divisions at the lobar or segmental level without tracheal involvement. Tracheobronchomalacia is the appearance of a deformity including the whole or segments of the trachea and one or both of the mainstem bronchi.

According to the degree of malacia, the severity of malacia was divided into mild (one-third to one-half invagination), moderate (one-half to three-quarters invagination), and severe (more than three-quarters invagination)[9].

Detection of respiratory pathogens analysis

Direct immunofluorescence was used to detect respiratory syncytial virus infection (RSV), influenza virus A (IVA), influenza virus B (IVB), parainfluenza virus (PIV) I, PIV II, PIV III, adenovirus (ADV), and MP. Human metapneumovirus (HMPV), human bocavirus (HBoV), and human rhinovirus (HRV) were detected using reverse transcription polymerase chain reaction.

Bacteria were identified using quantitative analysis by inoculating BALF onto elected media for 18–24 h. Bacterial growth $>10^3$ colony-forming units/mL was considered significant.

Data collection

Data regarding personal history, demographics, clinical characteristics, and laboratory examination results were documented after admission. Demographic and clinical characteristics included age, sex, length of hospital stay, and requirement for supplemental oxygen. Laboratory examination results including white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP) level, and detection of common viruses were recorded.

Statistical analyses

Statistical analyses were conducted using SPSS 26.0 (IBM, SPSS, Chicago, IL, USA).

Data are shown as mean \pm standard deviation or median (interquartile range). Comparison of quantitative variables between the three age groups was performed using one-way analysis of variance or the Kruskal–Wallis test where appropriate. Comparison of the frequency distribution was performed using the chi-square test; $p < 0.05$ was considered as significant.

Results

Demographic characteristics

A total of 164 patients with airway malacia complicated by pneumonia were recruited to the study (Table 1). Of these 164 patients, 123 (75%) were male and 41 (25%) were female. The male-to-female ratio was 3:1. The age of the patients ranged from 1 month to 4 years old. Ninety (54.88%) patients were aged \leq 6 months, 42 (25.61%) patients were aged 6–12 months, and 32 (19.51%) patients were aged \geq 12 months, The median age was 6 (3–10) months.

There were 34 (20.73%), 88 (53.66%), and 42 (25.61%) patients with tracheomalacia, bronchomalacia, and tracheobronchomalacia, respectively. Of the 88 children with bronchomalacia, 44 (50%) had right-sided disease, 25 (28.41%) had left-sided disease, and 19 (21.59%) had bilateral disease. In all cases of pneumonia with airway malacia, 24/164 (14.63%) were complicated by other airway dysplasia, most frequently laryngomalacia (12/24, 50%), followed by bronchial stenosis (6/24, 25%), abnormal opening of the bronchus (4/24, 16.67%), and tracheal bronchus (2/24, 8.33%); 40.85% (67/164) of patients had mild airway malacia, 43.29% (71/164) of patients had moderate airway malacia, and 15.86% (26/164) of patients had severe airway malacia.

Table 1
Airway malacia in patients with CAP

Patient characteristics	Case
sex(Male/Female)	123/41
Mean age (months)	6(3 ~ 10)
Age group n (%)	
≤6 months	90(54.88%)
6 ~ 12 months	42(25.61%)
≥12 months	32(19.51%)
Part of malacia	
tracheomalacia	34(20.73%)
bronchiomalacia	88(53.66%)
racheobronchiomalacia	42(25.61%)
Degree of malacia	
mild malacia	67(40.85%)
moderate malacia	71(43.29%)
severe malacia	26(15.86%)
Range of malacia	
single malacia	95(57.93%)
double malacia	37(53.62%)
multiple malacia(≥3)	32(46.38%)

Pathogens

Overall, because more than one pathogen could be detected in a patient, a total of 119 different pathogens were detected (Fig. 1). The most commonly detected pathogen was MP (25/164, 15.24%). Meanwhile, among the detected viruses, RSV (16/164, 9.76%) was the most common, followed by PIV3 (7/164, 4.27%), HBoV (7/164, 4.27%), ADV (2/164, 1.22%), PIV 1 (1/164, 0.61%), and hMPV (1/164, 0.61%).

A positive BALF culture was obtained in all children with airway malacia; 26.83% (44/164) BALF samples had a positive bacterial culture: 10.98% (18/164) *Streptococcus pneumoniae* (SP), 7.93% (13/164) *Haemophilus influenzae* (HI), 1.83% (3/164) *Escherichia coli*, 1.22% (2/164) *Staphylococcus aureus*,

1.22% (2/164) *Enterobacter aerogenes*, 1.22% (2/164) *Klebsiella pneumoniae*, 0.61% (1/164) coagulase-negative staphylococci, 0.61% (1/164) *Acinetobacter baumannii*, 0.61% (1/164) *Moraxella catarrhalis*, and 0.61% (1/164) *Acinetobacter*. Patients with a positive BALF culture had a higher median neutrophil percentage in the BALF (Fig. 2); however, this difference was not statistically significant.

In patients (n = 90) aged ≤ 6 months, 61 pathogens were detected; the most commonly detected viral pathogens were HRV (10/61, 16.39%), RSV (9/61, 14.75%), and PIV3 (7/61, 11.48%). In patients aged 6–12 months (n = 42) and ≥ 12 months (n = 32), the most commonly detected viral pathogens were RSV (3/28, 10.71% and 4/30, 13.33%, respectively), HRV (4/28, 14.29% and 2/30, 6.67%, respectively), and HBoV (3/28, 10.71% and 4/30, 13.33%, respectively). The main bacterial pathogens in children of all ages were SP and HI.

In the airway malacia group, the incidence of premature delivery and mechanical ventilation was higher than that in the non-airway malacia group. Children with pneumonia with airway malacia had a longer duration of symptoms before admission (median, 13.5 d) and longer hospital stay (median, 10.0 d) than children with pneumonia without airway malacia. A greater proportion of children with pneumonia with airway malacia required supplemental oxygen than children with pneumonia without airway malacia (11.59% vs. 4.88%, respectively, $p < 0.05$). Children with pneumonia with airway malacia were significantly more likely to have wheezing (67.07%), laryngeal stridor (32.93%), dyspnea (10.98%), cyanosis (11.11%), and intercostal retraction (23.17%); all of these were statistically different between the two groups (all $p < 0.05$). Children with airway malacia had a higher neutrophil count than children without airway malacia, while there was no significant difference between the two groups with respect to the WBC count or CRP level ($p > 0.05$).

Table 3
Clinical features of CAP children hospitalized with or without airway malacia

Clinical features	airway malacia (n = 164)	Non-airway malacia (n = 164)	<i>P</i>
Personal history			
premature delivery n(%)	27(16.46)	11(6.71)	0.006
mechanical ventilation n(%)	10(6.10)	2(1.22)	0.019
Length of stay(day)	10(7.25 ~ 15)	7(6 ~ 8)	< 0.001
Symptom duration prior to admission(day)	13.5(4 ~ 30)	6.5(4 ~ 10)	< 0.001
requirement for supplemental oxygen(%)	19(11.59)	8(4.88)	0.027
Clinic presentation			
cough	162(98.78)	163(99.39)	1.000
wheezing	110(67.07)	79(48.17)	< 0.001
fever	58(35.37)	63(38.41)	0.567
laryngeal stridor	54(32.93)	17(10.37)	< 0.001
Dyspnea	18(10.98)	8(4.88)	0.041
Cyanosis	11(11.11)	2(1.22)	0.011
Retractions	38(23.17)	6(3.66)	< 0.001
Crackles n (%)	82(50.00)	90(54.88)	0.376
Laboratory findings			
WBC count($\times 10^9/L$)	10.55(7.61 ~ 14.99)	10.34(7.56 ~ 12.89)	0.212
N count($\times 10^9/L$)	3.67(2.32 ~ 5.58)	3.06(1.86 ~ 5.01)	0.013
CRP count > 8mg/L[n(%)]	24(14.63)	31(18.90)	0.301
pathogens			
virus	60(36.59)	64(39.02)	0.649
bacteria	66(40.24)	62(37.80)	0.651
MP	21(12.80)	15(9.15)	0.289

Clinical and laboratory characteristics of different age groups of children hospitalized with airway malacia complicated by pneumonia

To evaluate the difference among different age groups of children with airway malacia complicated by pneumonia, we divided the children into three age groups (Table 3). There was no significant difference in sex between the different age groups. The common characteristics among the 164 confirmed patients were cough (98.78%), wheezing (67.07%), fever (35.37%), retractions (23.17%), dyspnea (10.98%), cyanosis (11.11%), and crackles (50%); fever was more commonly detected in older children and wheezing was more commonly detected in children aged 6–12 months, while younger patients were more likely to have intercostal retractions. Other characteristics showed no significant difference among the three age groups ($p > 0.05$). Older children were more likely to have a higher neutrophil count than younger children ($p < 0.05$). The incidence of MP was higher among children aged > 6 months than among younger children and was highest among children aged ≥ 12 months. The incidence of different viruses and bacteria were similar across age groups.

Table 3
Clinical features of CAP children hospitalized with airway malacia in different age groups

Clinical features	≤ 6 months(n = 90)	6 ~ 12 months(n = 42)	≥ 12 months(n = 32)	<i>P</i>
	n(%)	n(%)	n(%)	
Female sex	26(28.89)	7(16.67)	8(25)	0.32
Clinic presentation				
cough	89(98.89)	41(97.62)	32(100)	0.703
wheezing	51(56.67)	36(85.71)	23(71.88)	0.003
fever	19(21.11)	19(45.24)	20(62.50)	< 0.01
Dyspnea	14(15.56)	3(7.14)	1(3.13)	0.075
Cyanosis	8(8.89)	1(2.38)	2(6.25)	0.320
Retractions	27(30.00)	9(21.43)	2(6.25)	0.023
Crackles	47(52.22)	19(45.24)	17(53.13)	0.719
Laboratory findings				
WBC count(x10 ⁹ /L)	9.98(7.23 ~ 15.92)	10.86(7.89 ~ 13.49)	12.06(8.36 ~ 15.26)	0.538
Neutrophils count(x10 ⁹ /L)	3.2(2.25 ~ 4.83)	4.14(2.15 ~ 6.46)	4.75(2.99 ~ 7.94)	0.024
CRP count > 8mg/L[n(%)]	10(11.11)	8(19.05)	6(18.75)	0.371
pathogens				
virus	29(32.22)	10(23.81)	11(34.38)	0.538
bacteria	23(25.56)	11(26.19)	10(31.25)	0.818
MP	9(10.00)	6(14.29)	10(31.25)	0.026

Discussion

Airway malacia refers to an excessive increase in compliance of the trachea, such that the airway is more susceptible to dynamic and/or static collapse. Jacobos IJ et al. reported that approximately 11–15% of children who undergo bronchoscopy have airway malacia [10], while the rate of occurrence in China is 16.7–22.1%[9, 11]. This study found that about 20% of children with long-term cough, wheezing, and recurrent infections who underwent bronchoscopy had airway malacia between January 2013 and November 2019, which is consistent with domestic research but higher than that reported in foreign research. The difference might be due to differences in diagnostic standards. In most foreign countries,

the diagnostic criterion is a reduction in the airway diameter of more than 1/2 [3], while in China the diagnostic criterion is a more than 1/3 reduction in airway diameter, which results in a higher diagnosis rate in China than in foreign countries. In addition, the wide application of bronchoscopy in China in recent years has led to increasing numbers of children being diagnosed early.

In the present study, 75% of children with airway malacia were male, which was consistent with reports that of children with airway malacia, 58–82% are male [9]; 80.49% of children with airway malacia were < 1 year old, and the median age was 6 months, which is consistent with Deacon et al. who reported that the median age of children with airway malacia was 6.8 months [12].

Airway malacia could be divided into primary and secondary malacia in origin.

Primary airway malacia is related to premature delivery, malnutrition during pregnancy, and calcium deficiency. Hysinger EB et al. [13] reported that moderate or severe airway abnormalities were identified in 32/117 (27.3%) preterm infants.

In the present study, we found the incidence of premature delivery in children with airway malacia was 16.46%, which was higher than 6.71% of children without airway malacia. In premature infants, airway compliance is higher, the ratio of cartilage to airway smooth muscle is lower, tracheal muscular tension is low, and the smaller airway is easier to narrow.

The clinical symptoms associated with airway malacia are often atypical, mainly including recurrent wheezing, persistent or recurrent pneumonia, chronic cough, and dyspnea, among others. Holingert et al. [14] suggested that stridor and barking cough were the most common symptoms. Tan JZ et al. [4] indicated that reflex apnea is the most severe clinical symptoms. In mild airway malacia, a collapsed tracheobronchial wall during exhalation could prevent the effective clearance of secretions and cause occasional respiratory infections. In moderate airway malacia, wheezing is more frequently associated with lung respiratory tract infections. In severe malacia, the affected children could develop upper airway obstruction accompanied by cyanosis, expiratory stridor, and apnea. In the present study, symptom duration before admission and length of hospital stay were greater in children with airway malacia than those without airway malacia. This suggests that patients with pneumonia with airway malacia often present with slower disease progression. In addition, we also found that wheezing, laryngeal stridor, dyspnea, anhelation, cyanosis, and intercostal retractions were more common in patients with airway malacia. Furthermore, airway malacia was associated with increased severity relative to the disease in patients without airway malacia, which was consistent with a previous study where patients with airway malacia had a tendency for delayed recovery and more serious disease [5].

Previous reports on the etiology of pneumonia combined with airway malacia are very rare. Recognizing the pathogenic distribution of airway malacia complicated by pneumonia is of great significance to clinical treatment. In the present study, we found that the most common pathogen was MP, which is consistent with previous studies [15–17]. At the same time, we found that there was no significant difference in the detection rate of pathogens, including viruses, MP, and bacteria, in children with and

without airway malacia. This result differed from that of our previous report [15]. This may be due to differences in the inclusion criteria. In this study, patient enrollment was limited to those < 4 years old; in contrast, the study of Wang Yu-qing et al. did not limit the age of enrolled patients. Considering that the typical age of patients with airway malacia is < 4 years old, we only enrolled patients < 4 years old. Some studies [9, 18] have suggested that airway malacia could be improved or even eliminated when airway compression is removed or if inflammation is controlled promptly. Therefore, timely bronchoscopy and early identification of pathogens and timely treatment of infection are very important.

Our study has potential limitations. Some patients may have been treated with antibiotics before admission and the interval between fiberoptic bronchoscopy and admission varied among patients, which may have led to BALF specimens that were collected after different times with respect to antibiotic treatment and may have a certain effect on the results.

Conclusion

In conclusion, the median age of children with airway malacia was 6 months. Patients with airway malacia were more commonly male; bronchomalacia was the main type of disease, with malacia of the right bronchus being the most frequently reported subtype. Single airway malacia was more common than bilateral malacia. The most common pathogen was MP, and there was no significant difference in the detection rate of pathogens in children with and without airway malacia. Patients with pneumonia with airway malacia often present with slower disease progression, have a tendency for delayed recovery, and have more serious disease. Therefore, it is necessary to perform fiberoptic bronchoscopy in younger patients with pneumonia with a longer disease course, severe symptoms, and delayed recovery for confirmation of the diagnosis and to allow timely treatment.

Declarations

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Authors' contributions

Yongdong Yan and Wujun Jiang conceived of and designed the study, Ting Wang, Qiuyan Xu, Ge Dai contributed to writing, editing and submitting the manuscript. Yu Hong, Zhengrong Chen and Min Lu generated the figures and tables. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest, financial or otherwise.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figures

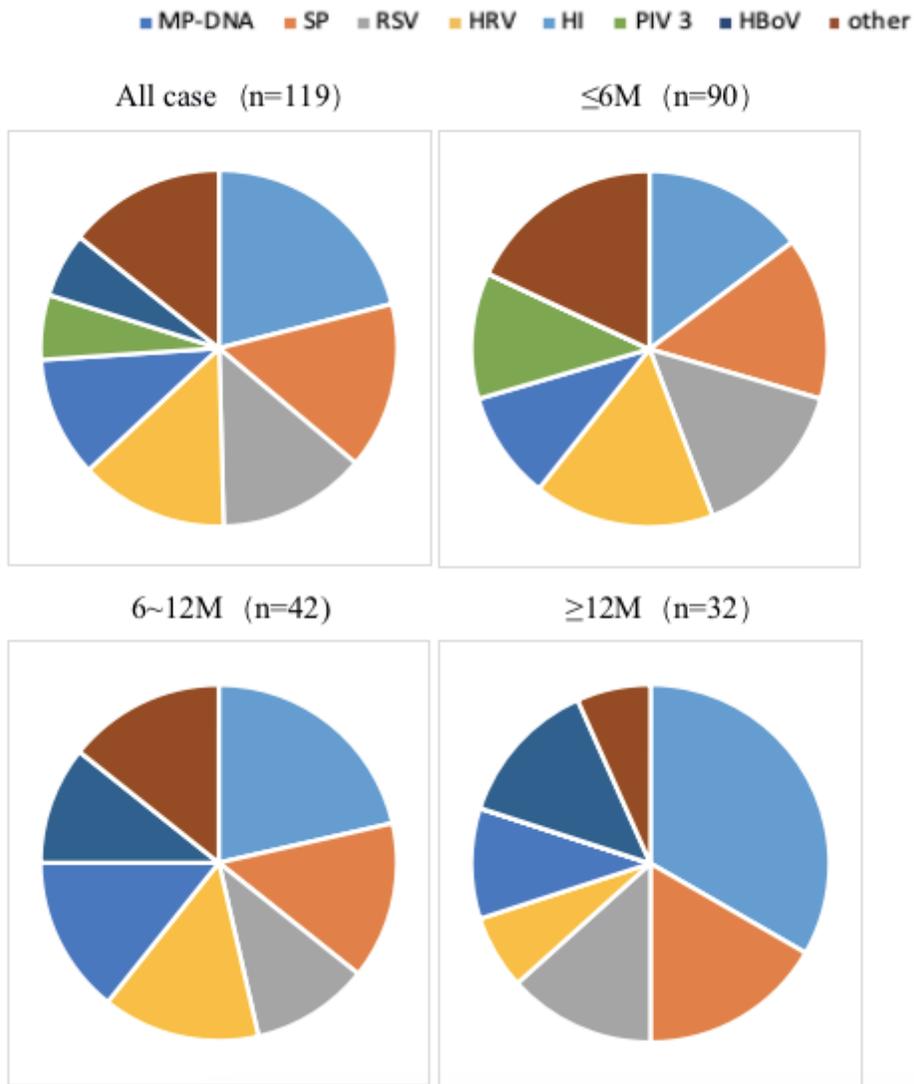


Figure 1

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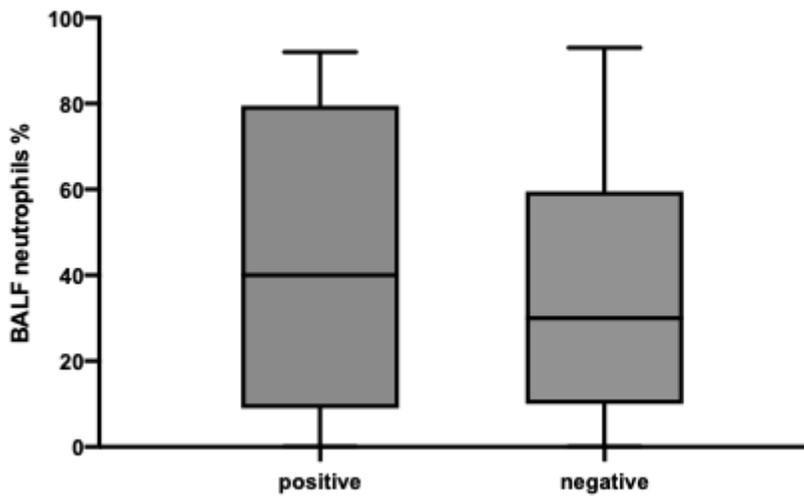


Figure 2

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