

# Lung damage caused by electronic cigarettes in non-smokers, a Systematic Review

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## ABSTRACT

**Background:** The use of electronic cigarette by non-smokers is increasing under the belief that these are a harmless alternative to tobacco. It has been evidenced that the use of electronic cigarette causes damage to systemic health, but no systematic review has been carried out on how “vaping” affects non-smokers’ health. The objective of this study is to conduct a systematic review of the available evidence to determine the lung damage that electronic cigarettes cause in non-smokers’ health. **Material and methods:** We conducted a research of the available evidence on different online searching engines such as PubMed based on the MeSH terms. We selected studies which met the inclusion and exclusion criteria. We collected data from clinical trials to show electronic cigarette’s acute effects on non-smokers after one vaping session and cross-sectional studies to analyze vaping effects on regular users. **Results:** 14 articles were included, of those 7 were clinical trials and 7 were cross-sectional studies. None of the patients were former or current smokers. Clinical trials included 139 patients, mean age was 28 years, 57% of them were male. Dizziness was the most common symptom associated with a vaping session (51,5%). Mean FEV1/FVC was 81,3% and average FeNO was 16,6 ppb. The total of patients included in cross-sectional studies was 2501 with an average age of 27 years old, 53% were female. The most common symptom in this group was dyspnea (28,4%). Medium FEV1/FVC found on the spirometry was 83,4% and medium FeNO was 19 ppb. **Conclusion:** Even though measured variables do not show severe respiratory damage associated with vaping in non-smokers, electronic cigarettes’ safety cannot be assured due to the lack of available evidence.

## KEYWORDS

Electronic nicotine delivery systems, Vaping, Lung injury, Lung diseases, Non-smokers

## Daño pulmonar por uso de cigarrillo electrónico en pacientes no tabaquistas, una Revisión Sistemática

## RESUMEN

**Introducción:** El uso del cigarrillo electrónico en personas no fumadoras se encuentra en aumento bajo la creencia de que son una alternativa inocua ante el tabaco. Ha sido comprobado que su uso produce daños sistémicos en la salud, pero no se ha realizado hasta el momento una revisión sistemática sobre como el “vapeo”

afecta a las personas no tabaquistas. El objetivo de este trabajo es revisar la literatura disponible en búsqueda de determinar el daño pulmonar que causa el uso de cigarrillo electrónico en personas que no fuman ni han fumado cigarrillos convencionales. **Materiales y métodos:** Se realizó una búsqueda de la evidencia disponible en diferentes motores online como PubMed en base a los términos MeSH. Se seleccionaron los artículos que cumplían con los criterios de inclusión y exclusión. Se utilizaron los ensayos clínicos para demostrar los efectos agudos de una sesión de vapeo en no usuarios de cigarrillo electrónico y los estudios transversales para observar los efectos a largo plazo de vapeadores regulares. **Resultados:** Se encontraron 14 artículos, de los cuales 7 fueron ensayos clínicos y 7 estudios transversales. Ningún paciente era ex o actual tabaquista. Los ensayos clínicos incluyeron un total de 139 pacientes cuya edad media fue 28 años y de sexo femenino en un 57%. El síntoma más común asociado a una sesión de vapeo fueron mareos (51,5%), la relación VEF1/CVF media fue de 81,3% y el promedio de FeNO fue de 16,6 ppb. Los estudios transversales sumaron un total de 2501 pacientes, con una edad media de 27 años y de sexo femenino en un 53%. El síntoma más frecuente en este grupo fue disnea (24,8%), la relación VEF1/CVF media fue de 83,4% y el promedio de FeNO fue 19 ppb. **Conclusión:** A pesar de que las variables medidas no demuestran graves daños a nivel respiratorio por el uso del cigarrillo electrónico en pacientes no tabaquistas, no se puede asegurar su inocuidad debido a la escasa evidencia disponible.

## PALABRAS CLAVE

Dispositivos electrónicos de liberación de nicotina, Vapeo, Daño pulmonar, Alteraciones pulmonares, No tabaquistas

## BACKGROUND

Cigarette smoking is the main cause of non-communicable disease and preventable death in Argentina, therefore, a great amount of smokers attempt to quit (1). This desire comes associated with a search for alternatives to tobacco, such as electronic cigarettes (2) despite its lack of available evidence as a smoking cessation tool (3).

Electronic nicotine delivery systems, popularly known as electronic cigarettes, administer such substance by producing an aerosol (badly known as vapor) without the tobacco combustion produced in cigarette smoking. Each device is formed by a battery which provides the energy for the contained liquid (usually propylene glycol or glycerin as solvents, flavorings, distilled water and may or may not contain nicotine) to be aerosolized and aspired or “vaped” (4). Electronic cigarettes are popularly known as a harmless alternative to conventional cigarettes (5), however, these can cause health effects in the short term: increased risk of acute myocardial infarction, facial injuries from battery explosion, psychosocial effects due to addiction, and electronic cigarette or vaping-associated lung injury (EVALI) (6). Up to 2020, a total of 2807 cases and 68 deaths related to EVALI had been reported in USA (7). In Argentina,

the National Food, Drug and Medical Administration (ANMAT) has banned by the 3226 act the importation, distribution, commercialization and publicity or any form of promotion of the electronic cigarette in 2011 owing to insufficient evidence on long- efficacy and safety. Nonetheless, this resolution does not prohibit its use or possession. In spite of these findings, in 2019, Argentina also reported the first case of EVALI, thereupon, the Health Ministry declared it an epidemic. (9).

Electronic cigarette’s utilization is a growing tendency in young, non-smoker population. Even though in Argentina the main reason for vaping remains to be the attempt to quit smoking, 39,8 % of the surveyed vapers are motivated by the belief of its safety opposed to tobacco smoking (10). This can be seen worldwide: there is a high prevalence of electronic cigarette use in young, non-smokers patients under the belief that these are a harmless alternative to tobacco (11). Moreover, young people who vape have an increased risk to initiate cigarette smoking compared to non-vapers (12).

Extensive studies have been published on electronic cigarette’s use as a tool of smoking cessation, its ineffectiveness, and adverse effects, but no systematic review has been carried out on its consequences in patients who have never smoked conventional cigarettes.

These findings bring us the need to review the available evidence following the hypothesis that electronic cigarette's use in non-smoker population does not come without hazards to respiratory health.

## MATERIALS AND METHODS

### DESIGN

We conducted a systematic review of the available evidence on the pulmonary effects that electronic cigarettes could cause in never-smokers on different platforms: PubMed, Google Scholar, Cochrane, Trip, EBSCO and Ovid. We performed this investigation according to the PRISMA items: Preferred Reporting Items for Systematic reviews and Meta-Analysis (13), in order to reduce the risk of bias.

### POPULATION

The search was conducted by using the following MeSH terms: "Electronic Nicotine Delivery Systems", "Vaping", "Lung Injury", "Lung diseases", "Non-Smokers". Words were looked up separately and with boolean language "AND". No filter was established as to the year of publication or language, but the results were chronologically ordered showing newest studies first and then eliminating duplicates. Simultaneously, the "related articles" section in PubMed was used to collect additional relevant articles that may have gone missing in the primary searching strategy, along with the reference lists of the selected articles.

### INCLUSION CRITERIA

- Systematic reviews, reviews, clinical trials, and observational studies.
- Articles analyzing respiratory effects of the electronic cigarette.
- Studies performed in never-smokers.

### EXCLUSION CRITERIA

- Duplicated articles.

- Studies on electronic cigarette's use prevalence, opinions, components, effectiveness on smoking cessation, passive exposure, and environmental pollution.
- Studies performed in-vitro and on animals.
- Studies investigating former or current tobacco smokers.

### INVESTIGATION FIELD

This study was carried out as part of the final degree project in the medical career at Universidad Abierta Interamericana, (UAI), Buenos Aires, Argentina.

### VARIABLES

The dependent variable in our study is lung damage caused by electronic cigarettes in never-smokers. Independent variables were classified as qualitative and quantitative.

Quantitative considered variables are: age (measured in years), blood pressure (measured in mercury millimeters, mmHg), heart rate (measured in beats per minute), oxygen saturation (measured in percentage), spirometry (analyzing FEV1/FVC measured in percentage), fractional exhaled nitric oxide (FeNO, measured in particles per billion, ppb) and bronchoscopy with bronchoalveolar lavage (measuring the number in percentage of macrophages, neutrophils, lymphocytes and eosinophils contained in the sample).

Sex (indicated by "male" and "female"), and signs and symptoms associated to vaping (indicated as "cough", "dyspnea", "expectoration", "palpitations", "dizziness", "pleasure", "sore throat" and "nausea") are the selected qualitative variables.

### STATISTICAL ANALYSIS

All studies were analyzed on the whole and then separated into clinical trials and cross-sectionals. The results of the relevant variables were displayed into Microsoft Word boards that are to be shown later in the results section. Based on that, we obtained mean results for quantitative variables and percentages for qualitative ones using Microsoft Excel.

## RESULTS

5.396 articles were found on PubMed in the initial search, the rest of the searching engines did not show any useful results. After excluding duplicated articles (423), we read titles and/or abstracts of the remaining 4.973. Out of those, 4.628 articles did not meet the determined criteria and were ruled out. Ultimately, we read the 345 left articles full text. In [figure 1](#) the search's flow diagram is displayed. The final selection included 14 studies, 7 clinical trials and 7 cross-sectional. In order to reduce biases, we present the results of the two different types of studies separately, since clinical trials assess variables in never-smokers and

never-vapers after a session of electronic cigarette usage, and cross-sectional evaluate their variables in never-smokers who already have a vaping habit with no intervention in the investigation whatsoever. The characteristics of the selected studies are presented at [table 1](#). 2.640 patients were included in total. The population's mean age was 28 years old. 54% were female and 46% male. Employed variables were blood pressure, heart rate, oxygen saturation, vaping associated symptoms, fractional exhaled nitric oxide and bronchoalveolar lavage obtained by bronchoscopy. Each study's complete results are detailed in [table 2](#), [3](#) y [4](#).

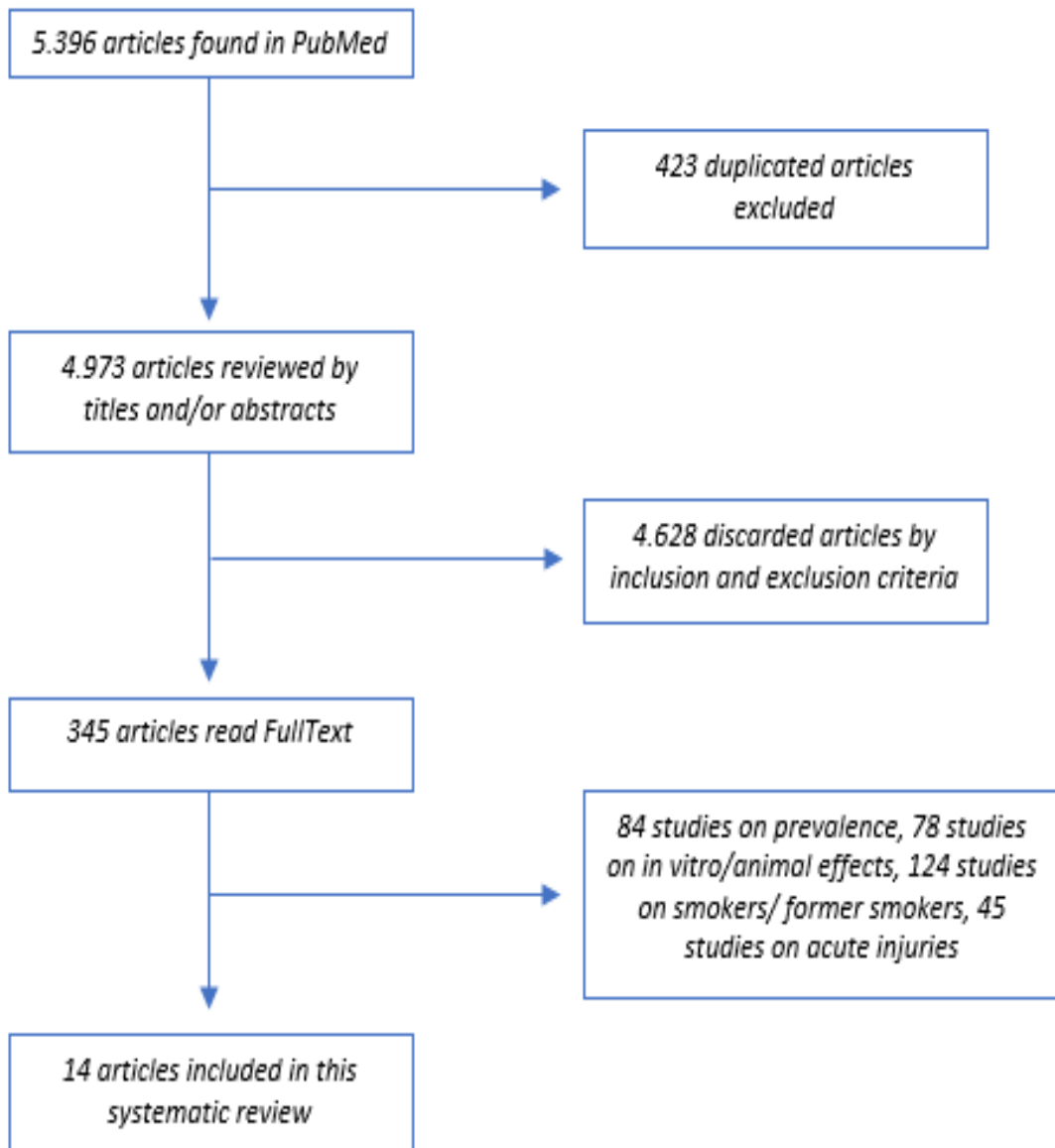


FIGURE 1. FLOW DIAGRAM OF THE PERFORMED SEARCH.

## CROSS-SECTIONAL STUDIES

Cross-sectional studies included 2501 patients. Spirometry was performed in 61 patients, mean FEV1/FVC was 83,4%. Mean fractional exhaled nitric oxide (FeNO) was 19 ppb in 39 patients. Vaping associated symptoms were inquired in 2440 patients: 11,5% revealed cough, 12% expectoration, 13% palpitations and 28,4% dyspnea.

## CLINICAL TRIALS

139 patients participated in the clinical trials. 70 of them were evaluated through spirometry, mean FEV1/FVC was 81,3%. Average FeNO in 81 patients was 16,6 ppb. Electronic cigarette's associated symptoms after one vaping session were gathered in 66 of these patients. 15,1% manifested cough, 51,5% dizziness, 18,1% nausea, 7,6% palpitations, 21,2% sore throat and 31,8% pleasure. Bronchoalveolar lavage by bronchoscopy was carried out after vaping in 23 patients, obtaining a mean result of 91% macrophages, 6,4% lymphocytes, 0,75% neutrophils and 0,1% eosinophils.

## DISCUSSION

In this systematic review we analyze clinical trials to discover acute respiratory effects on never-smokers after a vaping session and cross-sectional studies to determine chronic side effects in regular electronic cigarette's users. To remark this difference, we evaluate clinical trials and cross-sectional studies separately.

## CLINICAL TRIALS

Within clinical trials most patients are young adults (mean age 28 years), male (57%). No alterations in blood pressure, heart rate, respiratory rate and oxygen saturation were detected, all patients had normal values after a vaping session in this cohort. The most common symptom associated to acute exposition to electronic cigarettes is dizziness, followed by cough. Vaping brings pleasure to 67,7% of the patients who were asked, which is consistent with its addiction rate. In contrast, spirometry does not show abnormal results (normal: FEV1/FVC >75% (14)) in any of the studies. Found FeNO is normal in every patient (5-25

ppb) (15).

Even when selected variables prove to be normal, we selected some features of certain studies as highlights. Gonzalez et al. (16) found that a 10 minute vaping session increases mean arterial pressure (while remaining within normal range) and stimulates peripheral sympathetic nervous response evaluated through microneurography, equating this to the produced arterial response of smoking a regular cigarette (17), which can be a red flag in non-smokers. In this line of thought, Palamidis et al. (18) demonstrates lung functions alteration over plethysmography, where an increased airway resistance (Raw) and specific airway conductance (sGaw) can be seen in vapers. For the first time, Brozek et al. (19) investigates exhaled air temperature after using an electronic cigarette, results show it rises after the vaping session. This measuring is a recent and feasible method used to detect respiratory inflammatory processes. Bronchoscopy's cytology performed in 23 patients turned out quantitatively normal. Still, Staudt et al. (20) notes acute exposition to a vaping session alters lung cells function beyond numbers: specially, small airway epithelia, the place where tobacco-induced damage begins, and alveolar macrophages, first line of defense against different pathogens.

## CROSS-SECTIONAL STUDIES

Studies show most patients are female (53%) and mean is age 27 years old (53%). Although this results do not differ from normal, similar to what occurred in clinical trials, analyzing cross-sectional investigations could suggest some results on prevalence, being the participants regular electronic cigarette users: Hedman et al. (21) and Wang et al. (22) discover 1 in 5 vapers have never smoked conventional cigarettes, a number that comes into account considering electronic cigarette is a gateway to tobacco usage. Moreover, Wang et al. compares prevalence of cardiovascular events in smokers and vapers: this last group presents greater prevalence of chest pain, palpitations, coronary disease and arrhythmia, which could be due to the longer exposition these patients have to nicotine, since vaping does not come with the habit of "finishing a cigarette", but the electronic cigarette is left "on" for an indefinite amount of time, "ad libitum", most likely associated to the popular belief of its innocuity to

human health.. McConnell et al. (23) and Alnajem et al. (24) point that the tendency to vape to vape among adolescents rises in those with asthma, McConnell et al. associates it to teenagers opting for it instead of a conventional cigarette due to their pre-existing condition, which leads them to seek for a healthier alternative to tobacco use initiation. Polosa et al. (25) did not demonstrate any alterations on the variables used for his study. This research is the first prospective study in this selection of patients, an investigation that follows vapers over 4 years. The authors do not correlate its results with electronic cigarettes' safety and rather associate it to the length of the study. 4 years may not be conclusive, especially in young and healthy patients where we would not expect to find any lung alterations produced by tobacco smoking in that period either. In this cohort the main symptom associated to vaping is dyspnea (28,4%), this variation with clinical trials could be due to these patients having certain chronicity and habituation to electronic cigarettes.

Another study (26) demonstrates suppression of the cough-reflex sensitivity after a vaping session in non-smokers, which guides us to consider the loss of this important defense mechanism.

This study has a strength: it is the first systematic review to evaluate electronic cigarette's effects purely on never-smokers' patients. It is important to encourage investigations in this area since studies analyzing vaping indistinctly in smokers and non-smokers could be biased by previous lung damage produced by tobacco.

Even when this investigation brings us new knowledge, some interrogates are still unanswered. Further research is needed to create a standardized evaluation protocol for vapers' health similar as the one performed by Manzoli et al. (27). These should be based on using the same electronic cigarette, with the same liquid contained in each one. As Singh et al. (28), suggests, certain cytokines and interleukins can be

used as inflammatory markers in plasma and urine and could be reliable non-invasive markers on electronic cigarettes' effects.

## LIMITATIONS

Our study does not come without limitations: there are ethical boundaries and difficulties on double blinding the clinical trials (a placebo equivalent to electronic cigarettes and its content has not been produced). In clinical trials vaping sessions have different lengths. In cross-sectional studies vapers have been users for diverse periods and frequencies. Available electronic cigarettes in the market do not inform or disinform its real content, liquids have been found where the reported nicotine percentage was less than the percentage contained (29), hence the results could not be generalized.

## CONCLUSION

As a final conclusion, although measured variables do not demonstrate alterations in respiratory health produced by electronic cigarettes in non-smokers both after acute consumption and regular use, we cannot generalize these results due to the lack of available information and the absence of a standardized health evaluation method for vapers. Besides, considering decades of tobacco usage are needed for patients to exhibit any associated diseases (30), we may not be able to see electronic cigarette's effects until the middle of this century. Nonetheless, this systematic review reinforces the fact that vaping is not an innocuous habit for never-smokers' health and should not be recommended by physicians as an effective smoking-cessation tool to smokers.

## CONFLICTS OF INTEREST

Author declare having no conflict of interest.

No.	Autor	Title	Year	Country	Design	N	Used N	Methodology	Used variables
1	Boulay, M. (31)	Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals	2017	Canada	Clinical trial	30	30	Evaluation of non-smokers non-vapers before and after a 10-minute vaping session	Age, HR, RR, O2 saturation, spirometry, FeNO
2	Palamidas, A. (18)	Acute effects of short term use of ecigarettes on Airways Physiology and Respiratory Symptoms in Smokers with and without Airway Obstructive Diseases and in Healthy non smokers	2017	Greece	Clinical trial	76	21	Evaluation of non-smokers non-vapers before and after a 10-minute vaping session	Gender, age, BMI, HR, O2 saturation, symptoms, FeNO
3	Cooke, W. (32)	Acute inhalation of vaporized nicotine increases arterial pressure in young non-smokers: a pilot study	2015	USA	Clinical trial	20	20	Evaluation of non-smokers non-vapers before and after a 10-minute vaping session	Age, gender, BMI, symptoms
4	Brożek, G. (19)	Acute respiratory responses to the use of e-cigarette: an intervention study	2019	Poland	Clinical trial	120	30	Evaluation of non-smokers vapers before and after a 5-minute vaping session	Age, gender, BMI, O2 saturation, spirometry, FeNO
5	Staudt, M. (20)	Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes	2018	USA	Clinical trial	10	10	Evaluation of non-smokers non-vapers before and after a 20 "puff" vaping session	Age, gender, BP, HR, RR, O2 saturation, BAL, symptoms
6	Song, M. (33)	Effects of electronic cigarette constituents on the human lung: A pilot clinical trial	2020	USA	Clinical trial	30	13	Evaluation of non-smokers non-vapers before and after a 60-minute session each day for 4 weeks	Age, BAL
7	Gonzalez, J. (16)	Acute effects of electronic cigarettes on arterial pressure and peripheral sympathetic activity in young nonsmokers Acute effects of electronic cigarettes on arterial pressure and peripheral sympathetic activity in young nonsmokers	2020	USA	Clinical trial	15	15	Evaluation of non-smokers non-vapers before and after a 10-minute vaping session	Age, gender, BMI, BP, symptoms
8	Hedman, L. (21)	Association of Electronic Cigarette Use with Smoking Habits, Demographic Factors, and Respiratory Symptoms	2018	Sweden	Cross-sectional	30.272	96	Evaluation of electronic cigarette's associated symptoms in vapers non-smokers	Gender, symptoms
9	Wang, J. (22)	Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study	2018	USA	Cross-sectional	39.747	573	Evaluation of electronic cigarette's associated symptoms in vapers non-smokers	Age, symptoms
10	McConnell, R. (23)	Electronic cigarette use and respiratory symptoms in adolescents	2017	USA	Cross-sectional	2086	1.693	Evaluation of electronic cigarette's associated symptoms in vapers non-smokers	Age, gender, symptoms
11	Meo, S. (34)	Electronic Cigarettes: Impact on Lung Function and Fractional Exhaled Nitric Oxide Among Healthy Adults	2019	Saudi Arabia	Cross-sectional	60	30	Health evaluation of vapers non-smokers	Age, gender, BMI, spirometry, FeNO
12	Polosa, R. (25)	Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked	2017	USA	Prospective	21	9	Health evaluation of vapers non-smokers through 4 years	Age, gender, BMI, BP, HR, spirometry, FeNO, BAL
13	Singh, K. (28)	Systemic biomarkers in electronic cigarette users: implications for noninvasive assessment of vaping-associated pulmonary injuries	2019	USA	Cross-sectional	48	22	Health evaluation of vapers non-smokers	Age, gender, BMI, spirometry
14	Alnajem, A. (24)	Use of electronic cigarettes and secondhand exposure to their aerosols are associated with asthma symptoms among adolescents: a cross-sectional study	2020	Kuwait	Cross-sectional	1565	78	Evaluation of electronic cigarette's associated symptoms in vapers non-smokers	Age, gender, symptoms

TABLE 1. CHARACTERISTICS OF THE SELECTED STUDIES

No.	Autor	Patients	Age	Sex (M/F)	BMI	HR (bpm)	BP (mmHg)	RR (rpm)	O2sat (%)	FEV1/FEV (%)	FeNO (ppb)
1	Boulay, M.	30	30	-	-	67,5	-	15	98	80	21
2	Palamidas, A.	21	34,5	12/9	27,1	85	-	-	97,8	-	12,75
3	Cooke, W.	20	23	10/10	22,59	-	-	-	-	-	-
4	Brożek, G.	30	22,2	19/11	24,39	-	-	-	97,7	83,09	15,93
5	Staudt, M.	10	42,2	5/5	-	72,2	111/65	14,35	98,95	81	-
6	Song, M.	13	25,5	-	-	-	-	-	-	-	-
7	Gonzalez, J.	15	21	9/6	25,76	-	126/72	-	-	-	-
8	Hedman, L.	96	-	61/35	-	-	-	-	-	-	-
9	Wang, J.	573	41,4	172/401	-	-	-	-	-	-	-
10	McConnell, R.	1693	17,3	853/840	-	-	-	-	-	-	-
11	Meo, S.	30	27,07	30/0	28,46	-	-	-	-	77,36	18
12	Polosa, R.	9	26,6	6/3	-	71	118/76	-	-	79,08	20
13	Singh, K.	22	35,54	10/12	27,39	-	-	-	-	95,50	-
14	Alnajem, A.	78	17	36/42	25,76	-	-	-	-	-	-

TABLE 2. RESULTS OF EACH STUDY.

No.	Autor	Patients	Macrophages	Lymphocytes	Neutrophils	Eosinophils
5	Staudt, M.	10	90%	7,8%	0,5%	0,2%
6	Song, M.	13	92%	5%	1%	0%

TABLE 3. RESULTS OF PERFORMED BRONCHOSCOPIES.

No.	Autor	Patients	Cough	Dizziness	Nausea	Palpitations	Sore throat	Dyspnea	Expectoration	Pleasure
2	Palamidas	21	10	-	8	5	10	-	-	11
3	Cooke, W.	20	-	19	3	-	-	-	-	-
5	Staudt, M.	10	-	4	1	-	-	-	-	10
7	Gonzalez, J.	15	-	11	-	-	4	-	-	-
8	Hedman, L.	96	11	-	-	-	-	13	24	-
9	Wang, J.	573	-	-	-	316	-	481	-	-
10	McConnell, R.	1693	271	-	-	-	-	176	271	-
14	Alnajem, A.	78	-	-	-	-	-	24	-	-

TABLE 4. RESULTS OF REPORTED SYMPTOMS.

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