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Review Article

Chlorine gas exposure and evolutive patterns of reactive airways dysfunction syndrome: a systematic review

Exposição ao gás cloro e padrões evolutivos da síndrome da disfunção reativa das vias aéreas: uma revisão sistemática

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Abstract

Introduction: chlorine is the most irritant gas to which people are commonly exposed to daily. One of its toxic effects is reactive airway dysfunction syndrome (RADS). *Objective:* this study aims to summarize the evidence from the evolutive patterns of RADS. *Methods:* this systematic review study was conducted using the databases of the University of São Paulo repository, BVS/LILACS, PubMed/Medline, and SciELO. Studies from September 1985 to July 2021 with "chlorine" and "occupational asthma" as descriptors, associated with "reactive airway dysfunction syndrome" or "irritant-induced asthma," were included. These articles were assessed by two independent reviewers. The study's quality was assessed using the Joanna Briggs checklist. *Results:* a total of 22 studies were retrieved, including 11 case series, 8 case reports, and 3 cross-sectional studies. The selected studies covered 1.335 participants from 11 countries, and only 170 had a diagnosis of RADS with documented evolution. Of these, 115 (65%) were due to occupational exposure. The most frequent RADS evolutive pattern was the long-term persistence of symptoms, spirometric alterations, and/or bronchial hyperresponsiveness, mainly in the occupational setting. A lack of standardization of adequate information reporting was found. *Conclusions:* chronicity was the most frequent RADS evolutive pattern.

Keywords: chlorine; occupational asthma; humans; systematic review; occupational health.

Resumo

Introdução: *o cloro é o gás irritante a que as pessoas estão comumente expostas no cotidiano. Um dos seus efeitos tóxicos é a síndrome da disfunção reativa das vias aéreas (SDRA).* Objetivo: *resumir as principais evidências dos padrões evolutivos da SDRA.* Métodos: *Revisão sistemática da literatura de artigos publicados entre setembro de 1985 e julho de 2021 no repositório da Universidade de São Paulo (USP) e nas bases BVS/LILACS, PubMed/Medline e SciELO. Foram utilizados os descritores "cloro" e "asma ocupacional" associados à "síndrome da disfunção reativa das vias aéreas" ou "asma induzida por irritantes". Dois revisores independentes selecionaram e avaliaram a qualidade dos estudos, com apoio do* checklist *do Instituto Joanna Briggs.* Resultados: *selecionaram-se 22 estudos: 11 séries de casos, oito relatos de caso e três estudos transversais. Os estudos selecionados abrangeram 1.335 participantes de 11 países, e apenas 170 tiveram diagnóstico de SDRA com evolução documentada. Destes, 115 (65%) foram devido à exposição ocupacional. Os padrões evolutivos mais frequentes foram persistência prolongada dos sintomas, alterações espirométricas e/ou hiper-responsividade brônquica, principalmente no ambiente ocupacional. Observou-se falta de padronização no relato de informações adequadas.* Conclusões: *a cronicidade foi o padrão evolutivo da SDRA mais frequente. Houve falta de informação apropriada que impediu uma análise adequada dos resultados.*

Palavras-chave: *cloro; asma ocupacional; humanos; revisão sistemática; saúde do trabalhador.*

Introduction

Chlorine is a greenish-yellow poisonous gas classified as a toxic respiratory irritant. It can cause acute damage to the upper and lower respiratory tract due to its high reactivity and intermediate solubility in water[1,2].

It is a critical chemical used in various industrial processes, including pesticides, plastics, solvents, bleach in paper and cloth, detergents, drinking water, and swimming pool treatment. Workers exposed to gases, particularly chlorine, are at greater risk of respiratory diseases[3]. Among the occupational diseases, those affecting the respiratory system are the most common with an increasing trend, accounting for 17% of all occupational deaths[3,4]. Furthermore, the general population may be exposed to chlorine by two means: people who use chemicals inadequately for domestic cleaning purposes, such as mixing household products to clean more or better (e.g., toilet cleaner with bleach) and people near an industrial plant or transport accidental release, such as a leak from a chlorine tank[1]. It is the most irritating gas to which people are commonly exposed daily. Additionally, it usually occurs in poorly ventilated environments without adequate personal protection, requiring frequent emergency care[5].

Chlorine presents a strong and pungent odor, with threshold values ranging from 0.1 to 0.3 ppm[2]. At workplaces, exposure limits vary according to the regulatory and scientific agencies. For example, up to an 8-hour time-weighted average (TWA), the U.S. Occupational Safety and Health Administration (OSHA) sets a permissible exposure limit of 1 ppm, whereas the U.S. American Conference of Governmental Industrial Hygienists (ACGIH) sets a threshold limit value of 0.5 ppm[6]. However, the air monitoring strategies do not eliminate the risk of exposure caused by accidental emission[7].

Its toxic effects are felt mainly in the airways. They depend on the dose and duration of exposure, ranging from mild cases with transient mucosa irritation to more severe cases involving the tracheobronchial tree (chronic bronchitis), lung parenchyma (pulmonary edema, acute respiratory distress syndrome), and, eventually, death[8]. In addition, some individuals can develop a variant form of occupational asthma, known as reactive airway dysfunction syndrome (RADS), which progresses with long-term asthmatic signs and symptoms after the end of exposure[8,9]. Chlorine is one of the main irritant agents that trigger this syndrome, although this causal relationship has been questioned for many years[9,10].

The first mention of RADS in the scientific literature occurred in 1981, when Brooks and Lockey reported 13 cases of a non-immunological airway hyperreactivity disease following exposure to high levels of an irritating agent[11]. Four years later, Brooks et al.[12] proposed its diagnostic criteria. Since then, subsequent reports have modified these criteria, including cases with delayed onset of asthma after one or more high-level exposures[13]. According to the American College of Chest Physicians, these cases should be subsumed under "irritant-induced asthma"[14]. **Table 1** lists the original and the modified diagnostic criteria for RADS.

Table 1 Reactive airways dysfunction syndrome diagnostic criteria

Original criteria[d]	*Modified criteria[e]*
– New-onset symptoms simulating asthma	– New-onset symptoms simulating asthma or recurrence of childhood asthma
– The onset of symptoms occurred after a single exposure incident or accident	– Symptom onset related to one or more high-level exposures
– Onset of symptoms ≤24 hours after exposure	– Symptoms can begin >24 hours after exposure
– Exposure to a gas, smoke, fume, or vapor in very high concentrations and with irritant qualities to its nature	– Any high-level exposure to gas, fume, vapor, sprays, or even dust
– Symptoms persistent for ≥3 months	– No mention
– Pulmonary function tests may show airflow obstruction	– No mention
– Methacholine challenge test was positive	– No mention
– Other types of pulmonary diseases were ruled out	– Difficulty in excluding previous airway disease associated with smoking or atopy may occur

Adapted by the authors from Brooks et al.[12(d)] and Tarlo et al.[14(e)].

There is some evidence that concentration and duration of exposure to the irritant agent may substantially impact the development and persistence of symptoms. Other predisposing factors to airway irritation and history of current smoking may contribute to its development, although there is some controversy about the latter. On the other hand, there is a consensus that atopy is not associated with maintenance of RADS symptoms[15,16].

So far, the RADS evolutive patterns comprise complete resolution, chronicity, and death[8,12,17]. However, few studies focused on outcomes assessment at different follow-up times using different tools, such as clinical evaluation, lung function, and/or bronchoprovocation test. This lack of a standard approach for reporting RADS outcomes undoubtedly impairs the complete understanding of the reason for the differences in evolutive patterns[10,18].

Thus, this study aims to summarize the main evidence from the evolutive patterns of RADS.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct and report this review[19]. In addition, the study protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) and approved on October 3rd, 2021, under registration number CRD42021276622.

Search strategy

A search strategy was developed in three electronic databases (BVS/LILACS, PubMed/Medline, and SciELO) and one digital dissertation and thesis library (University of São Paulo, Brazil) in July 2021. The study adopted various combinations of descriptors associated with the text words: "chlorine," AND "reactive airway dysfunction syndrome," OR "irritant-induced asthma," OR "occupational asthma".

Eligibility criteria

Articles were considered for inclusion based on *PICOS* systematic search strategy. *P*articipants: people presenting RADS cases; *I*ntervention: unique exposure to high chlorine concentrations; *C*omparison: not applicable; *O*utcome: the report of RADS cases follow-up for at least three months; *S*tudy design: original observational articles in Spanish, English, or Portuguese published from September 1985 to July 2021.

All articles with RADS cases reported by the authors were accepted independently of the proposed diagnostic criteria. Then, participants who fulfilled the criteria were included, and their characteristics were analyzed. Single exposure to high concentration criteria was adopted since the concentration and duration of exposure to the irritants may substantially impact the outcome[16]. Cases with exposure to other irritants (single or mixture) and less than three months of follow-up were excluded[12]. Moreover, editorial articles, authors' opinions, books, experimental studies (*in vivo* and *in vitro*), and reviews were excluded. The PubMed database was the reference database for cases of duplicate articles.

September 1985 was selected as the initial period for evaluating the articles since the original diagnostic criteria were reported at that time, with a later extension of their definition[12,13,14].

Selection of studies

Two reviewers (ACB and FAC) independently assessed the entire study selection process. Any disagreements about study selection were discussed and, if necessary, a third reviewer (ASV) was consulted. The flowchart starts by analyzing the titles, followed by the abstract, and, then full text. Finally, the reference lists of eligible papers were checked to find additional relevant studies.

Data extraction

ACB extracted the data from the eligible studies using a form that included: 1. Study characteristics: name of the first author, year of publication, country of study; 2. Methods: study design, sample size, and exposure site; 3. RADS cases: number of cases, age, sex, complementary exams (spirometry and bronchial provocation test with results), evolutive pattern (resolution, chronicity, death); and 4. Quality score, which was reviewed by ASV.

Methodological quality assessment

Two reviewers (ACB, ASV) independently assessed the quality of each eligible study following the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (University of Adelaide, Australia), which is valid for cross-sectional, case-series, and case report studies[20]. This checklist contains questions for each study category (eight for cross-sectional and case report, and ten for case-series), comprising reporting, methodology design, execution, and tools for results analysis. The available answers for each item were "yes," "no," and "not applicable." In the end,

an overall score for each article was achieved, and a cut-off of 50% of checklist answers was considered for rating the risk of bias as high (>50%), moderate (=50%), or low (<50%).

The difference between the report (up to three cases) and the case series (more than three cases) was based on the number of participants described[21].

Variable description

From the clinical and functional respiratory point of view, the evolutive pattern was divided into four groups: rapid resolution (in three months); late resolution (from three to six months); chronicity of the condition, defined as the persistence of clinical and/or functional respiratory changes (after six months); and death[12,13,17].

Spirometry was used to classify the severity of obstruction according to the criteria by American Thoracic Society (ATS) and European Respiratory Society (ERS), which uses the percentage of forced expiratory volume in one second (FEV1): mild (>70%), moderate (60 to 69%), moderately severe (50 to 59%), severe (35 to 49%), and very severe (<35%)[22].

Results

Figure 1 displays a flowchart depicting the study selection process. Our search strategy retrieved 358 citations from electronic databases, of which 13 met the inclusion criteria. The reference list inspection added nine articles, totaling 22. Of these, 11 were case series, eight case reports, and three were cross-sectional studies; 21 were written in English and one in Spanish.

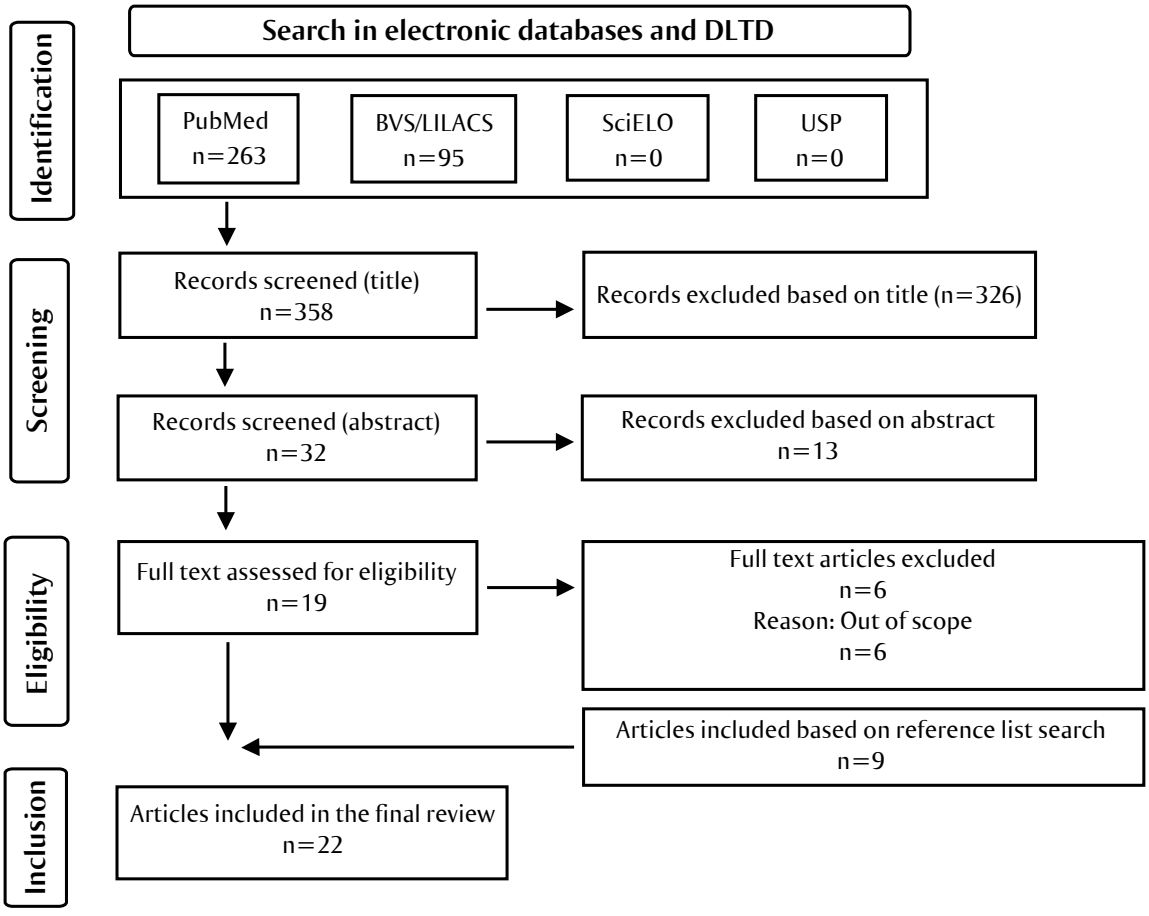

Figure 1 PRISMA flowchart of the study selection process

DLTD: Digital Library of Theses and Dissertations; BVS/LILACS: Biblioteca Virtual em Saúde/Literatura Latino-Americana e do Caribe em Ciências da Saúde; SciELO: Scientific Library Online; USP: Universidade de São Paulo.

This systematic review covered 1.335 participants from 11 countries, most of the studies conducted in North America (six in Canada and six in the USA). A total of 15 studies primarily involved occupational exposure (977 people), two reported an environmental accident (85 participants), two described accidents at home (56 participants), and three studies involved both occupational and environmental exposure (226 participants).

Out of the 1.335 participants, 177 (13,2%) had RADS diagnosed after chlorine gas exposure. Of these, 115 (65%) were due to occupational exposure, and 62 (34.8%) to environmental exposure. A total of 170 (96%) cases had their evolution reported: 48 (28.2%) had a rapid resolution, 14 (8.2%) late resolution, 97 (57.1%) developed a chronic condition, one (0.6%) evolved to death, and 10 (5.9%), had unknown evolution due to lack of follow-up information. Most of the chronic cases occurred at the workplace (90%).

Regarding participants' sex, 88 (51.8%) were male, 72 (42.4%) were female, and 10 (5.9%) were unknown due to lack of information. More RADS cases occurred among male workers in occupational settings (86; 50.6%) than with female (15; 8.8%). The opposite occurred in the environmental exposure, with 55 (32.4%) female and only two (1.2%) male. Moreover, 81 (47.6%) male and 16 (9.4%) female workers evolved to chronic persistent symptoms, whereas seven (4.1%) male and 49 (28.8%) female had a complete resolution. The mean age was 42.4 years. Patients with rapid resolution had a mean age of 33 years; those with a late resolution, 41.3 years of age; and those who evolved with a chronic condition; 42.9 years of age. There was no information about the age of the patient who died. A significant gap in the ethnicity report was observed, with only 26 (15.3%) cases: 17 Caucasians, six Latinos, two Afro-descendent, and one Oriental.

The length of exposure was described for 77 cases, ranging from a few minutes[8,12,23-30,40,41] to 24 hours[28], while the air measurement of chlorine gas occurred in eight (5.5%) cases: "doses below 0.30 ppm"[8], "readings of 0.36 ppm and 0.37 ppm"[8], and "intense dose"[27].

Smoking history was recorded in 161 (94.7%) RADS cases. Among these, 83 (48.8%) were non-smokers, 61 (35.9%) were current smokers, 17 (10%) were former smokers, and nine (5.3%) were unknown due to lack of information. The smoking burden was obtained in 21 cases[8,12,25,28-31], ranging from less than 0.5 packs/year to more than 28 packs/year, and it is not possible to correlate with the evolution of the case. Moreover, ten (5.9%) patients displayed an atopy status, whereas 75 (44.1%) did not, and 85 (50%) were unknown due to lack of information. For asthma, five (2.9%) had this diagnosis in childhood, 115 (67.6%) denied it, and 50 (29.4%) had unknown diagnosis due to lack of information.

The onset of symptoms within 24 hours was reported for 113 (66.4%) cases, whereas 57 (33.5%) cases lacked this information, despite being reported as RADS cases. The most common were cough (74.9%), dyspnea (62.8%), wheezing (57.1%), and chest tightness (50.3%). These symptoms persisted from three months[32] to 12 years after the inciting event[33].

A total of 106 (62.4%) patients were evaluated in the emergency room (ER). Afterward, there was no pattern of the medical follow-up, ranging from 24 hours to 22 years (Figure 2). The medical follow-up frequency was: once (32 participants)[12,27,28,29,30,34,35], twice (122 participants)[8,23,24,32,33,36,41,42], three times (five participants)[25,37,38], four times (nine participants)[39,40], five times (one participant)[26], and seven times (one participant)[31].

Complementary tests performed included chest X-ray (77; 45.3%), peak flow measurement (76; 44.7%), spirometry (107; 62.9%), bronchial provocation test (55; 32.4%), and arterial oxygen tension (PaO2) (59; 34.7%) measured in blood sample.

A total of 68 (88.3%) cases presented normal chest radiographs, four (5.2%) had abnormal findings (bilateral alveolar infiltrates in three and one suggestive of bronchiectasis), and five (6.5%) were unknown due to lack of information.

Concerning spirometry, two studies did not perform it (56 participants)[28,32], other two did not inform (seven participants)[,27,40], and one study partially conducted it (seven participants)[34]. Out of 107 patients that performed spirometry, 85 (79.4%) were obstructive, 13 (12.1%) were normal, three (2.8%) were restrictive, and six (5.6%) were unknown due to lack of information. Thus, most of the chronic cases (87; 89.7%) presented an obstructive pattern on spirometry; while the same characteristic was only present in 1.6% of the cases with resolution. The severity of the obstruction was only determined in 15 cases: six were mild[12,24,26,30,35,36], seven were moderate[29,31,35,37], one was moderately severe[29], and one was severe[23]. The mean value of the FEV1/FVC ratio was 75.1%.

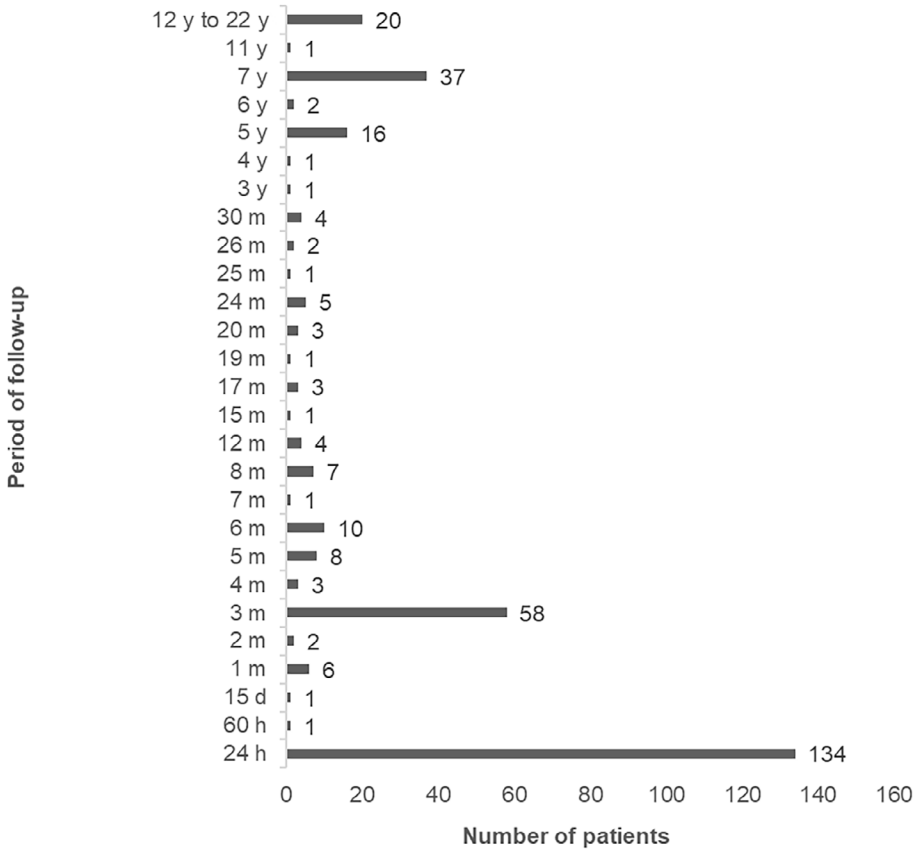

Figure 2 Period of follow-up since the accident. h: hour; d: day; m: month; y: year

Moreover, of the 107 individuals that underwent spirometry, 38 were assessed once and 69 serially. For the latter, the pulmonary function evolution included maintenance of normality (1)[41], maintenance of obstruction (60)[24,33,37,38,42], improvement to normal (4)[26,39], worsening to a combined ventilatory impairment (both obstruction and restriction) (1)[31], and worsening to a mild restriction (3)[25].

Bronchial provocation tests were performed in 55 (32.4%) participants, of which 45 (81.8%) had positive results, seven (12.7%) negative, and three (5.5%) borderlines. A total of 65 (38.2%) participants did not underwent it, and there was no information on 50 (29.4%).

Only two studies comprising 56 participants, measured PaO2 just after the exposure[32,41]. Gorguner et al.[32] reported it as mean (65±13 mmHg), and Kim et al.[41] reported the individual result (91.4 mmHg). The other two studies, which comprised three participants, measured it during follow-up (four months and five years), and all were below the normal reference value[23,25].

The therapy instituted in the ER room for the 106 patients included inhaled bronchodilators, cough suppressants, inhaled and intravenous corticosteroids, intravenous methylxanthine, and supplemental oxygen therapy. There was no information about this topic in the remaining 64 (37.6%). Among 106 patients who received immediate treatment, 53 (50%) had complete resolution and 46 (43.4%) evolved to a chronic case. However, 37 of the 46 patients who developed chronicity received only cough suppressants and oxygen. At follow-up, there were 103 (60.6%) treatment reports including inhaled bronchodilator and corticosteroids. A total of 53 (31.2%) cases evolved with complete resolution, and 50 (29.4%) developed chronicity.

A total of 11 studies achieved an overall high risk of bias (50%), three were considered moderate risk (9.1%), and eight were low risk (40.9%). The main failures in the report were the demographic description of the patient (all), identification of confounding factors and their management (all cross-sectional studies), description of clinical information (5 out of 11 case series), description of site/clinic demographic information (9 out of 11 case series), and detail of statistical analysis (20 out of 22) (**Table 2**).

Table 2 Results of the methodological quality assessment

CASE REPORT

Author (s)	Study patient description	Patient history description	Patient clinical condition description	Diagnostic test description	Patient treatment description	Post-treatment description	Adverse events identification	Summary of lessons learned	Overall classification (risk)
Donnelly and FitzGerald[37]	**No**	Yes	Yes	**No**	Yes	Yes	**No**	Yes	Low
Moore and Sherman[23]	**No**	**No**	**No**	**No**	Yes	Yes	**No**	Yes	**High**
Deschamps et al.[24]	**No**	Yes	**No**	Yes	Yes	**No**	**No**	Yes	Moderate
Schönhofer et al.[25]	**No**	Yes	Yes	Yes	Yes	Yes	**No**	Yes	Low
Lemière et al.[26]	**No**	Yes	**No**	Yes	Yes	Yes	**No**	Yes	Low
Williams[27]	**No**	**No**	**No**	**No**	**No**	**No**	**No**	Yes	**High**
Solà et al.[35]	**No**	**No**	**No**	**No**	**No**	**No**	**No**	Yes	**High**
Hannu et al.[31]	**No**	Yes	**No**	Yes	Yes	Yes	**No**	Yes	Low

CROSS-SECTIONAL STUDY

Author (s)	Clear inclusion criteria	Study subjects and environment description	Exposure measurement	Condition measurement criteria	Confounding factors identification	Confounding factors strategies	Outcome measurement	Appropriate statistical analysis	Overall classification (risk)
Salisbury et al.[42]	Yes	**No**	**No**	Yes	**No**	**No**	Yes	Yes	Moderate
Gautrin et al. [30]	Yes	**No**	**No**	Yes	**No**	**No**	Yes	**No**	**High**
CDC[40]	Yes	**No**	**No**	Yes	**No**	**No**	Yes	**No**	**High**

CASE SERIES

Author (s)	Clear inclusion criteria	Condition measurement	Methods for condition identification	Consecutive inclusion	Total inclusion of participants	Study patients description	Clinical information description	Reporting of follow-up results	Site information description	Appropriate statistical analysis	Overall classification (risk)
Brooks et al. [12]	Yes	Yes	Yes	Yes	Yes	**No**	Yes	Yes	Yes	**No**	Low
Boulet[36]	Yes	Yes	Yes	**No**	**No**	**No**	Yes	Yes	**No**	**No**	Moderate
Meggs et al.[34]	Yes	**No**	Yes	**No**	**No**	**No**	Yes	**No**	**No**	**No**	**High**
Chatkin et al.[28]	**No**	**No**	**No**	Yes	Yes	**No**	Yes	Yes	**No**	**No**	**High**
Hickmann et al.[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**No**	**No**	Low
Gorguner et al.[32]	**No**	Yes	**No**	Yes	Yes	**No**	**No**	**No**	**No**	Yes	**High**
Malo et al.[33]	Yes	Yes	Yes	Yes	Yes	**No**	**No**	Yes	Yes	**No**	Low
Mohan et al.[39]	**No**	Yes	**No**	Yes	Yes	**No**	**No**	Yes	**No**	**No**	**High**
Patel et al. [29]	**No**	Yes	**No**	Yes	Yes	**No**	**No**	Yes	**No**	**No**	**High**
Chierakul et al.[38]	Yes	Yes	Yes	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**High**
Kim et al.[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**No**	**No**	Low

Adapted from the *Joanna Briggs Institute Critical Appraisal tool*.

Table 3 summarizes the characteristics of the selected studies.

Table 3 Characteristics of the selected studies

Author, year, country	*Study characteristics (design; number; exposure site)*	*Cases of RADS due to chlorine gas*				*Complementary exams*		*Evolution pattern*
		Number with documented evolution	*Age (years)*	*Sex*	*Ethnicity*	*Spirometry (result)*	*Methacholine bronchial challenge test (result)*	
Brooks et al., 1985, United States[12]	CS; n=10; Environmental/ Occupational	1 (Occup)	34	1 F	1 NI	1 (obstruction)	1 (positive)	1 Chronic
Boulet, 1988, Canada[36]	CS; n=5; Environmental/ Occupational	1 (Occup)	69	1 M	1 NI	1 (obstruction)	1 (positive)	1 Chronic
Donnelly and FitzGerald, 1990, Ireland[37]	CR; n=1; Occupational	1	30	1 M	1 NI	1 (obstruction)	1 (not done)	1 Chronic
Moore and Sherman, 1991, United States[23]	CR; n=1; Occupational	1	25	1 M	1 NI	1 (obstruction)	1 (not done)	1 Chronic
Salisbury et al., 1991, Canada[42]	Cross-sect; n=174; Occupational	37	37 NI	37 M	37 NI	37 (obstruction)	37 (NI)	37 Chronic
Deschamps et al., 1994, France[24]	CR; n=1; Environmental	1	39	1 F	1 NI	Obstruction	1 (positive)	1 Chronic
Gautrin et al., 1994, Canada[30]	Cross-sect; n= 45; Occupational	5	35;36;52; 56;56	5 M	5 NI	5 (obstruction)	5 (positive)	5 Chronic
Meggs et al., 1996, United States[34]	CS; n=13; Occupational	13	30-61 (mean 48)	1 M; 12 F	13 Cauc	7 (obstruction); 6 (NI)	7 (positive); 6 (NI)	13 Chronic
Schönhofer et al., 1996, Germany[25]	CR; n=3; Occupational	3	31;42;54	3 M	3 NI	3 (obstruction [2]; normal [1])	3 (positive)	3 Chronic
Lemière et al., 1997, Canada[26]	CR; n=1; Occupational	1	36	1 M	1 NI	1 (obstruction)	1 (positive)	1 Late resolution
Williams, 1997, United States[27]	CR; n=3; Occupational	2	41;53	2 M	2 NI	1 (normal); 1 (NI)	2 (NI)	2 Chronic
Chatkin et al., 1999, Canada[28]	CS; n= 89; Occupational	1	40	1 M	1 NI	1 (not done)	1 (positive)	1 Chronic
Hickmann et al., 2001, United States[8]	CS; n=20; Occupational	6	35;39;42; 47;52	5 M; 1 F	4 Cauc; 2 Afrodesc	6 (normal)	6 (negative)	6 Late resolution

(Continue)

Tabela 3 Continued...

Author, year, country	Study characteristics (design; number; exposure site)	Cases of RADS due to chlorine gas				Complementary exams		Evolution pattern
		Number with documented evolution	Age (years)	Sex	Ethnicity	Spirometry (result)	Methacholine bronchial challenge test (result)	
Gorguner et al., 2004, Turkey[32]	CS; n=55; Environmental	55	33 ± 11.3	55 F	55 NI	55 (not done)	55 (not done)	48 Rapid resolution; 1 death; 6 ND
Solà et al., 2005, Spain[35]	CR; n=18; Occupational	5	35;36;40; 42;56	3 M; 2 F	5 NI	5 (obstruction)	5 (not done)	5 Chronic
Malo et al., 2009, Canada[33]	CS; n=35; Occupational	20	20 NI	20 M	20 NI	20 (obstruction)	20 (positive)	20 Chronic
Mohan et al., 2010, India[39]	CS; n=64; Environmental	3	3 NI	3 NI	3 NI	3 (altered)	3 (not done)	3 Late resolution
Hannu et al., 2012, Finland[31]	CR; n=1; Occupational	1	43	1 M	1 NI	1 (obstruction)	1 (positive)	1 Chronic
Patel et al., 2012, India[29]	CS; n=19; Occupational	5	27;33;47; 50;52	5 M	5 NI	5 (obstruction)	5 (NI)	5 Chronic
CDC, 2012, United States[40]	Cross-sect; n=545; Occupational	6	6 NI	6 NI	6 Latino	6 (NI)	6 (3 positive; 3 borderline)	3 Late resolution; 3 ND
Chierakul et al., 2013, Thailand[38]	CS; n=21; Environmental	1	1 NI	1 NI	1 NI	1 (obstruction)	1 (positive)	1 ND
Kim et al., 2014, South Korea[41]	CS; n=211; Environmental/ Occupational	1 (Envir)	38	1 M	1 Asian	1 (normal)	1 (negative)	1 Late resolution

RADS: Reactive Airways Dysfunction Syndrome; CR: case report; SC: case series; cross-sect: cross-sectional; occup: occupational; envir: environmental; M: male; F: female; Cauc: Caucasian; Afrodesc: Afrodescendant; NI: not informed; ND: not determined.

Discussion

A total of 22 observational studies on RADS evolutive patterns were included in this systematic review. The most frequent finding was the long-term persistence of clinical symptomatology, pulmonary function abnormal values, and/or bronchial hyperresponsiveness (57.1%). These chronic cases had a profile that comprised occupational setting, male, older age, and smoking habit (current or past). In addition, most of them presented a sustained obstructive pattern on spirometry (89.7%), probably reflecting the pathological characteristics reported in RADS cases, including airway epithelial destruction, lymphocytic inflammatory infiltrate, thickening of the basement membrane, and airway wall subepithelial fibrosis[24,26,43]. However, this finding may be also related to smoking habit, either due to its additive effect, which reduces the parameters of airway function, or as a confounding factor in the diagnosis of smoking-related lung disease[13,33,44,45].

For a long time, there was a belief that chlorine inhalation was not associated with long-term effects[25,27]. However, since its first published criteria[12], a growing body of evidence has pointed out that RADS cases may follow distinctive courses: complete resolution at different times or chronicity[17,35,44,46-48]. The reason for the differences is still unknown[16,46,47]. In general, patients with RADS continue symptomatic and persist with bronchial hyperresponsiveness for years after the accident[12,49]. In addition, it has been suggested that if the symptoms do not clear within six months, they will probably persist for several years[13].

The host and environmental factors involved in the initiation, resolution, or persistence of

RADS need clarification[16]. There is some evidence that age, concentration, and duration of exposure may substantially impact the development and persistence of this syndrome[15,16,33]. Moreover, following toxic inhalation, the presenting PaO2 has been related to the likelihood of developing chronic symptoms[46]. On the other hand, there has been some debate about the role of smoking habit as predisposing factor[13,15,16,33,44,50], whereas atopy seems to not be associated[15,16]. In our analysis, site of exposure, age, sex, smoking history, and PaO2 were the primary variables related to how RADS cases evolved.

The main site of exposure observed in this review was the workplace, reflecting the extensive use of chlorine in a variety of industrial activities. Besides, most cases that evolved chronically (90%) had their exposure in this setting. One possible justification for this finding could be related to workers' daily exposure to the irritating agent at low doses, which are considered safe by labor legislation. However, this kind of exposure could lead, over time, to subclinical inflammatory respiratory changes, contributing to long-term effects after exposure to high concentrations[7,13,15,17]. We highlight that, although most cases were reported in an occupational environment, the only death occurred at home due to chlorine-based cleaning products[32]. The range of chlorine odor threshold is quite broad, and one should be cautious in relying on odor alone as a warning of hazardous exposure[2]. Besides, the non-mandatory use of personal protective equipment at home, the lack of information about the products and their hazardous combination, in addition to the lack of training in an accident situation could be possible explanations[5].

Regarding the age group, we observed that the mean age of patients who progressed chronically was higher (42.9 years) than those who evolved with rapid resolution (33 years) or late resolution (41.7 years). Malo et al. suggested that being older (i.e., the fact that these subjects are older when they stop the exposure) exert a deleterious effect on recovery[33].

Current or past smokers evolved more frequently to chronicity (38.1%) than recovery (3.1%). Three studies reported the additive effect of smoking on the decrease in airway function parameters during RADS follow-up since tobacco substances lead to the inflammatory process and reduce respiratory secretion clearance[33,44,45]. However, it should be emphasized that smoking may also be a confounding factor in the diagnosis due to smoking-related lung disease[13].

We found male predominance among chronic cases (83.5%). This finding could reflect their considerable engagement in industrial activities involving chlorine since most male exposures occurred at workplaces[13]. Moreover, the associations between sex, occupation, exposure, and work-related asthma are complex. Surveillance systems in USA, UK, Canada, and France observed that males had more new-onset asthma, while females were more likely to have work-aggravated asthma[51].

The concentration and duration of exposure to irritants are two parameters probably related to the development and the persistence of respiratory functional abnormalities[16,47]. Bhérer et al.[52] reported a significant risk of persistent nonspecific bronchial hyperresponsiveness, a hallmark of RADS cases, related to the severity of incidents with exposure to high levels of chlorine. In general, there is lack of precise data about these two parameters. The accidental and non-warning characteristic of almost all cases precludes the accurate concentration gauge of the irritants[10,16,18,48,53]. In this review, despite 45% of studies reporting the length of exposure, only one study described a better response to therapy among those with shorter duration of the acute exposure (less than three hours)[32].

The PaO2 test is used to evaluate respiratory diseases, and lower values have been associated with chronic symptoms after exposure to inhaled toxins, probably reflecting more extensive damage to the airways and alveolar-capillary structures[25,43]. In our review, only two studies measured PaO2 initially, and both presented normal results with higher values and better outcome (complete resolution)[32,41].

In general, outcomes tend to be better when the diagnosis is established early, the exposure is stopped, and the specific treatment is started[8]. The short-term treatment of RADS usually includes systemic corticosteroids, supplemental oxygen if necessary, inhaled corticosteroids, and aerosolized bronchodilators, although the latter seems to be less effective in RADS patients[16,30,54]. Animal models have suggested that early treatment with parenteral corticosteroids (dexamethasone) may improve the prognosis; however, no human study showed efficacy of oral corticosteroids in the treatment of RADS cases[49]. However, duration, dose, and their effects in modifying the long-term outcome are still uncertain[16,49,54]. In our review, most cases that evolved with complete resolution underwent short and long-term treatment with corticosteroids, while only 5% of chronic cases underwent it.

To the best of our knowledge, this is the first review to focus on evolutive patterns of RADS due to chlorine gas exposure in a systematic manner. We have described five variables (site of exposure, age, sex, smoking history, and PaO2) related to how the RADS cases evolved. Some of those had already been described, and our review corroborated their importance as possible risk factors. However, we must acknowledge some limitations of this review. First, a considerable percentage (56.5%) of selected studies were classified as having moderate to high risk of bias, based on the lack of adequate information on characteristics of the subjects, clinical and exposure data, and description of diagnostic tests, mainly bronchial provocation tests and spirometry. Therefore, we should be cautious in generalizing these results. Secondly, there were few long-term follow-up studies and a significant lack of standard approach for reporting follow-up, which may have hindered the analyses of the factors involved in the prognosis of RADS.

Conclusion

RADS presents different evolutive patterns, ranging from complete resolution to chronicity. We found that long-term persistence of clinical symptomatology and/or spirometric alterations was the most frequent finding for RADS cases after a unique exposure to high chlorine concentration. In addition, we observed that occupational setting, male, older age, and smoking habit (current or past) were the profile related to this evolutive pattern. However, we recommend caution in generalizing these results due to the considerable percentage of moderate to high bias observed. Since the reasons for different RADS evolutive patterns are not fully understood, we suggest that future long-term follow-up studies should assess exposure characteristics and identify risk factors, along with developing a more structured approach to gathering information. By doing so, it will be possible to better understand the gaps in this subject.

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Authors' contribution

Vianna AS, Bhering ACPM, and da Silva FCA contributed to the conception and design of the study. Vianna AS, Bhering ACPM, da Silva FCA, Santos ASE, and Vianna RC contributed to the survey, analysis, interpretation of the data, in the elaboration and critical review of the manuscript, in the approval of the final version, and assume full responsibility for the study performed and published content.

Data availability

The entire dataset that supports the results of this study is available in Data Repository (SciELO Data) under DOI: https://doi.org/10.48331/scielodata.MBZK7S.

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Erratum

In the Review Article "**Chlorine gas exposure and evolutive patterns of reactive airways dysfunction syndrome: a systematic review**", with DOI: https://doi.org/10.1590/2317-6369/30021en2023v48e12**,** published on *Revista Brasileira de Saúde Ocupacional*, 48:e12, correct:

In the page 1/13, in the surname of the third author

Where it reads:

"Fernanda Antunes Cavalcante da Silva"

It should be read:

"Fernanda Cavalcante Antunes da Silva"

In the page 03/13, in "Selection of studies"

Where it reads:

"FAC"

It should be read:

"FCA"

In the page 13/13, in "Authors' contribution"

Where it reads:

"Cavalcante FAZ"

It should be read:

"da Silva FCA"