

Immunoglobulin deficiency in patients with chronic rhinosinusitis: Systematic review of the literature and meta-analysis

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Background: Several studies have shown a high prevalence of immunoglobulin deficiencies in patients with chronic rhinosinusitis (CRS).

Objective: We sought to perform a systematic review and meta-analysis to estimate this prevalence more precisely and to identify patients who need substitution treatment.

Methods: All case series published after 1990 describing patients with CRS, which was defined as symptomatic rhinosinusitis for more than 12 weeks and documented immunoglobulin deficiencies (including deficiencies of IgG with subclasses, IgA, and IgM; specific antibody deficiencies; and potential common variable immunodeficiency), were retrieved.

A meta-analysis of the proportion of any combination of common variable immunodeficiency, IgG deficiency, IgA deficiency, and IgM deficiency in patients with CRS was performed by using logit transformation of the prevalence. Recurrent CRS was defined as rhinosinusitis not controlled by appropriate conservative management for 4 months, and difficult-to-treat CRS was defined as noncontrollable rhinosinusitis despite successful sinus surgery and appropriate conservative management for at least 1 year.

Results: The meta-analysis revealed a prevalence of pooled IgG, IgA, and IgM deficiencies in 13% of patients with recurrent CRS and 23% of patients with difficult-to-treat CRS. The prevalence of IgG subclass deficiency (5% to 50%) and specific antibody deficiency (8% to 34%) was increased in patients with CRS, as was the prevalence of respiratory allergies in patients with recurrent CRS (31% to 72%).

Conclusion: Immunoglobulin deficiency is a frequent condition in patients with CRS. An even higher prevalence of atopy was observed in patients with recurrent CRS. Therefore immunoglobulin titers and accurate allergy diagnostic workups

are strongly recommended in these patients to provide specific treatments for symptom alleviation. However, there is a need for larger prospective studies addressing the effect of specific therapeutic interventions for CRS. (*J Allergy Clin Immunol* 2015;■■■:■■■-■■■.)

Key words: Sinusitis, rhinitis, chronic, recurrence, respiratory tract infections, immunoglobulins, immune deficiency syndromes, IgG deficiency, common variable immunodeficiency, hypersensitivity

Although chronic rhinosinusitis (CRS) is not linked to increased mortality, both morbidity¹ and socioeconomic effect² are substantial. The reported prevalence of CRS in industrialized countries is 11% to 14%,³⁻⁵ whereas the prevalence seems to be as high as 30% in developing countries.⁶⁻⁸ CRS is a complex disease with multiple causes, including allergies, rhinosinonasal anatomic malformations, and local secretory or systemic immunoglobulin deficiencies.³ The most frequent immunoglobulin deficiencies are IgG subclass deficiencies, with an estimated prevalence of 2% to 20%^{9,10}; vaccine specific antibody deficiencies (SADs), with an estimated prevalence of 5% to 11%^{11,12}; selective IgA deficiency, with a frequency of 0.2% to 0.3%^{9,13}; unselected IgG deficiency¹⁴; rare selective IgM deficiencies^{10,14}; and common variable immunodeficiency (CVID), with an estimated prevalence of 0.004%.^{9,13} Other immune deficiencies, such as complement factor deficiency, were not considered in this study.

For symptomatic immunoglobulin deficiencies (eg, SAD, IgG subclass deficiency, and CVID), early antibiotic treatment and preventive intravenous or subcutaneous immunoglobulin substitution therapy are available.^{15,16} However, in current clinical practice immunoglobulin deficiencies might not be sufficiently taken into consideration as a cause of CRS.¹⁷ Patients with untreated immunoglobulin deficiency can present with persistent symptomatic CRS despite proper conservative and surgical management.¹⁸ In contrast, patients without evidence of immunoglobulin deficiency have a good prognosis after sinus surgery, with a low rate of recurrence of 22% after 3 years.¹⁹

The worldwide recognized European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) consensus on CRS published in 2012 did not gather a sufficient amount of evidence-based data to provide clear guidelines on the importance and management of immunoglobulin deficiencies in patients with CRS.³ Thus the aim of the present study was to systematically review the available literature and perform a meta-analysis of the prevalence of the most frequent and clinically relevant deficiencies, in particular IgG, IgG subclass, IgA, and IgM deficiencies and CVID, in patients with CRS.

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Abbreviations used

CRS: Chronic rhinosinusitis
 CVID: Common variable immunodeficiency
 EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps
 IgAGMD: Combination of CVID, selective IgA deficiency, unspecified IgG deficiency, and selective IgM deficiency
 IgG1-3D: Combination of IgG₁, IgG₂, and IgG₃ deficiency
 SAD: Specific antibody deficiency

METHODS**Literature search strategy and selection criteria**

According to the EPOS consensus, CRS is defined as the presence of 2 or more of the 4 following symptoms for 12 or more weeks: A, nasal blockage/obstruction/congestion; B, nasal discharge (anterior/posterior nasal drip); C, facial pain/pressure; and D, reduction or loss of smell. Either symptoms A or B should be present.³ Recurrent CRS was diagnosed when the disease was not controlled by appropriate conservative management (ie, nasal saline irrigation, topical corticosteroids, antibiotic therapy, and eventually sinus surgery). If not further specified, we assumed that appropriate conservative management was established before surgery was considered or when an ear, nose, and throat specialist, allergist, or immunologist was in charge of the patient. Difficult-to-treat CRS was defined as noncontrollable rhinosinusitis despite successful sinus surgery and appropriate conservative management for at least 1 year.³ Drug-resistant CRS was defined as recurrent CRS that did not fulfill the criteria of difficult-to-treat CRS.

Because the current criteria for CVID,²⁰ including antibody responses to vaccines, exclusion of other causes of hypogammaglobulinemia (eg, long-term systemic corticosteroid use), and imaging studies showing bronchiectasis, were not reported in detail by the majority of the studies, the term potential CVID was used for our systematic review. A combination of CVID, selective IgA deficiency, unspecified IgG deficiency, and selective IgM deficiency (IgAGMD) was the main focus of this study. Isolated or combined IgG₁, IgG₂, and IgG₃ subclass deficiencies (IgG1-3D) in the absence of IgA, total IgG, and IgM deficiency were also analyzed as a group, representing the clinically significant IgG subclass deficiency. IgG₄ deficiency was excluded because of its limited clinical significance for CRS. SAD was defined as a poor antibody response to polysaccharide anti-pneumococcal vaccination with normal immunoglobulin levels.^{9,10} Laboratory reference ranges used for the determination of immunoglobulin deficiencies varied between studies (Table I). We considered laboratory reference ranges to be valid when immunoglobulin deficiencies were defined as 2 SDs or more below the mean range of the general population or when a discrepancy of less than 30% with generally accepted and published reference ranges was found.²¹⁻²³ When normal laboratory reference ranges were considered invalid (ie, too narrow and therefore leading to an overestimation of deficient values), the respective immunoglobulin deficiencies were reported with uncertainty by giving a range rather than exact values in Table II.

On January 15, 2014, the Cochrane Library, MEDLINE, EMBASE, and OVID databases were searched for studies on adult CRS that were published in English after 1990; pediatric reports were excluded. We aimed to identify all cross-sectional studies, both prospective and retrospective, that reported the prevalence of immunoglobulin deficiencies in patients with CRS. Healthy volunteer control groups are mentioned where available.

The databases were screened by using the following search algorithm: "rhinosinusitis" or "rhinitis" or "sinusitis" AND "immune deficiency" or "immunodeficiency" or "immune defect" or "immunoglobulin" or "IgG" or "IgA" or "IgM" or "specific antibody deficiency" or "SAD" or "common variable immunodeficiency" or "CVID". The literature search was completed by screening the reference lists of key review articles and relevant original articles.

To obtain additional information regarding the original data, in particular for studies in which cumulative results (ie, IgG and IgA deficiencies in the same patient) were not clearly reported and studies in which the definition of

the laboratory reference ranges of immunoglobulins were not clear, several corresponding authors were contacted by e-mail. Complementary data were obtained from Seppänen et al,²⁴ Chee et al,¹⁸ and Cui et al.²⁵ Seppänen et al²⁴ provided us with their original database, and therefore we could exactly determine which immune deficiency (combination) was present in each patient. For the studies by Chee et al¹⁸ and Cui et al,²⁵ the authors informed us of the exact number of patients having combined immunoglobulin deficiencies.

Meta-analysis: Data extraction, interpretation, and bias management

The meta-analysis was performed by using all studies on patients with recurrent CRS and IgAGMD who were identified based on the systematic literature review because the clinical significance of these deficiencies is well described in the literature.^{9,10,14} In contrast, IgG1-3D and SAD were not included because their clinical significance is controversial⁹; in addition, the systematic literature review did not provide data of sufficient quality on IgG1-3D and SAD to perform a secondary meta-analysis. Because the inclusion criteria for nonrecurrent CRS differed considerably between the studies, we focused our meta-analysis on recurrent CRS and performed the subgroup analysis on drug-resistant and difficult-to-treat CRS. The 3 studies with missing IgM values, Armenaka et al,²⁶ Hoover et al,²⁷ and Vanlerberghe et al,²⁸ were included in the analysis by estimating the IgM values as normal to avoid an overestimation of IgAGMD caused by selection bias.

Statistical analysis

IgAGMD prevalence was calculated by using a proportion meta-analysis with a LOGIT transformation method provided by R software (version 2.15.1) in the "meta" package (version 3.8-0). Depending on the I^2 statistic,²⁹ a fixed- or random-effect meta-analysis was performed. The threshold was set at 30% for the use of the random effect. A funnel plot was performed with the LOGIT transformation of proportions of interest and the corresponding study size to assess potential publication bias caused by small studies.³⁰

RESULTS**Study selection**

Our literature search identified 573 studies that were screened for immunoglobulin deficiencies in patients with CRS. From this screening, which was performed independently by 2 authors, 20 studies with a cross-sectional design (prospective or retrospective) that reported the prevalence of immunoglobulin deficiencies in patients with CRS were retained. Of these 20 studies, 7 had to be excluded because of missing sample size ($n = 1$), pediatric populations ($n = 3$), and CRS definitions that were not consistent with EPOS criteria ($n = 3$). Finally, 13 studies were retained for the systematic review. A meta-analysis was performed on 11 because the study by Carr et al³¹ reported only SAD and the study by May et al³² included patients with nonrecurrent CRS.

Systematic review

The basic clinical characteristics of 1418 patients reported in the 13 selected studies, as well as the study design (ie, retrospective vs prospective), are shown in Table III. Data originated from 7 different countries during the time period of 1991 to 2009; however, some patients might have been recruited before 1991 in the studies by Lund and Scadding,³³ Armenaka et al,²⁶ and Scadding et al.³⁴ The mean age of all patients reported in the 9 studies reporting age was 43 years, and a male proportion of 51% was reported in 11 studies. The study by May et al³² reported nonrecurrent CRS (ie, CRS managed with antibiotics but not necessarily with nasal saline irrigation and topical steroids

TABLE I. Laboratory ranges

Studies	IgA	IgM	IgG	IgG ₁	IgG ₂	IgG ₃	IgG ₄	SAD
Laboratory ranges for selected studies								
Alqudah et al ³⁵	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD
Armenaka et al ²⁶	57–362	46–317	603–1688	422–1292	117–747	41–129	Undetectable	—
Carr et al ³¹	—	—	—	—	—	—	—	–2 SD
Chee et al ¹⁸	–2 SD	–2 SD	–2 SD	—	—	—	—	—
Cui et al ²¹	70–500	40–230	700–1600	490–1140	150–640	20–110	8–140	—
Hoover et al ²⁷	100–498	—	740–1624	305–1480	35–1477	10–105	4–158	—
Jiang and Hsu ³⁶	100–350	50–250	700–1600	280–1020	60–790	14–240	11–330	—
Lund and Scadding ³³	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	—
May et al ³²	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD
Safdarian and Ferguson ³⁷	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD
Scadding et al ³⁴	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	–2 SD	—
Seppänen et al ²⁴	M: 88–484 F: 52–402	M: 36–259 F: 47–284	680–1500	490–1140	150–640	20–110	8–140	—
Vanlerberghe et al ²⁸	–2 SD	—	–2 SD	—	–2 SD	–2 SD	—	—
Reference laboratory ranges								
Dati et al ²¹	70–400	40–230	700–1600	—	—	—	—	—
Lepage et al ²²	—	—	—	390–1000	102–450	14–102	6–185	—
Schauer et al ²³	—	—	—	280–800	115–700	24–125	5–125	—
Siemens Biotechnology	—	—	—	410–1010	170–790	11–85	3–201	—

Laboratory ranges for immunoglobulin levels are described in milligrams per deciliter. Values considered to be significant bias inductors are shown in boldface. IgG₄ was considered deficient in the study by Armenaka et al²⁶ when undetectable. Lepage et al²² defined normal immunoglobulin ranges based on a 12- to 18-year-old control population. Siemens Biotechnology defined normal immunoglobulin ranges based on a white population of 279 adults (unpublished data).

F, Female; M, male; –2 SD, Less than 2 SDs.

or sinus surgery). Of the 12 studies reporting recurrent CRS, 8 reported drug-resistant CRS and 4 reported difficult-to-treat CRS. In 9 studies patients with secondary causes of CRS (ie, cystic fibrosis, primary ciliary dyskinesia, HIV infection, and fungus ball) were excluded. Five studies stated that patients with systemic corticosteroid treatment were excluded, whereas 1 study reported that such patients were included. A total of 5 studies had a retrospective design, whereas 8 studies were prospective. The prevalence of asthma varied from 15% to 68%, with 5 missing values; the prevalence of nasal polyposis varied from 13% to 60%, with 7 missing values; and the prevalence of respiratory allergy varied from 31% to 72%, with 5 missing values. Respiratory allergy was investigated by using skin prick tests with aeroallergens in all studies, except the study by Hoover et al,²⁷ in which both total and specific IgE levels were determined. We also planned to analyze aspirin intolerance, but this condition was only reported in the study by Alqudah et al,³⁵ in which 7 (10%) of the patients had aspirin intolerance.

The prevalence of the different immunoglobulin deficiencies, as defined in the Methods section, is listed in Table II. Potential CVID was present in 0% to 10% of patients; unspecified IgG deficiency was present in 0% to 16% of patients, selective IgA deficiency was present in 0% to 6.8% of patients, and selective IgM deficiency was present in 0% to 10% of patients. In several studies IgG1–3 deficiency, SAD, and combinations of immunoglobulin deficiencies were reported with uncertainty. First, some deficiencies were not evaluated in all patients, as in the studies by Alqudah et al³⁵ and Vanlerberghe et al²⁸: Alqudah et al³⁵ assessed IgG subclass deficiencies in 31 of 67 patients and SAD in 51 of 67 patients, and Vanlerberghe et al²⁸ reported only IgG₂ and IgG₃ subclass deficiency. Second, laboratory standard values were too high for IgG₃ in the study by Armenaka et al²⁶ and too low for

IgG₂ in the studies by Jiang and Hsu³⁶ and Hoover et al.²⁷ Third, concomitant deficiencies were not always reported. Overall, IgG1–3D was reported inadequately in 7 studies and adequately in only 4 studies, with a prevalence ranging from 3.2% to 50%. SAD was reported inadequately in 2 studies and adequately in 1 study, with a prevalence of 8.1%. Despite its limited clinical significance, IgG₄ deficiency was reported inadequately in 2 studies and adequately in 9 studies, with a prevalence ranging from 0% to 15%. IgAGMD was calculated exactly on the base of individual immunoglobulin deficiencies in 8 studies, with a prevalence ranging from 5.4% to 23%. Association between IgAGMD and IgG1–3D was calculated exactly in 4 studies, with a prevalence ranging from 11% to 73%. Combination of IgAGMD, IgG1–3D, and SAD was calculated exactly only in the study by Safdarian and Ferguson,³⁷ with a total immunoglobulin deficiency prevalence of 35%. These results are summarized in Fig 1.

Meta-analysis

The meta-analysis revealed an IgAGMD prevalence of 12.7% (95% CI, 8.6% to 18.3%; $I^2 = 79\%$) in patients with recurrent CRS (Fig 2, A). A subgroup analysis showed an IgAGMD proportion of 9.8% (95% CI, 6.5% to 14.7%; $I^2 = 71\%$) for patients with drug-resistant CRS (Fig 2, B) and an IgAGMD proportion of 22.8% (95% CI, 17.5% to 29.3%; $I^2 = 0\%$) for patients with difficult-to-treat CRS (Fig 2, C). The visual analysis of the funnel plot showed an asymmetry, possibly indicating publication bias (Fig 3).

DISCUSSION

Systematic review

The analysis of 11 published studies revealed a surprisingly high prevalence of immunoglobulin deficiencies in patients

TABLE II. Immunoglobulin deficiencies and their corresponding prevalence in selected studies

Studies	No.	Potential CVID	IgA deficiency	IgG deficiency	IgM deficiency	IgG ₁₋₃ deficiency	IgG ₄ deficiency	SAD	IgAGMD	IgAGMD + IgG ₁₋₃ deficiency	IgAGMD + IgG ₁₋₃ deficiency + SAD
Alqudah et al ³⁵	67	1 (1.5%)	1 (1.5%)	5 (7.5%)	7 (10%)	≥1† (≥3.2%)	≥3† (≥3.7%)	≥23† (≥34%)	14 (20%)	≥15† (≥22%)	≥38† (≥57%)
Armenaka et al ²⁶	60	0	2 (3.3%)	2 (3.3%)	—	8-29*‡ (13% to 48%)	0-9* (0% to 15%)	—	≥4† (≥6.7%)	≥12*‡‡ (20% to 55%)	≥12*‡‡ (≥20%)
Armenaka et al, healthy	30	0	0	0	—	6-11*‡ (20% to 37%)	0-3* (0% to 10%)	—	0	≥6*‡‡ (≥20%)	≥6*‡‡ (≥20%)
Carr et al ³¹	105	—	—	—	—	—	—	0-15* (0% to 14%)	—	—	≥15† (≥14%)
Chee et al ¹⁸	79	8 (10%)	5 (6.3%)	6 (7.6%)	0	—	—	—	19 (22%)	≥19† (≥24%)	≥19† (≥24%)
Cui et al ²¹	167	0	4 (2.4%)	1 (0.6%)	4 (2.4%)	9 (5.4%)	2 (1.2%)	—	9 (5.4%)	18 (11%)	≥18† (≥11%)
Cui et al, healthy	110	0	0	0	1 (0.9%)	3 (2.7%)	0	—	1 (2.7%)	4 (3.6%)	≥5† (≥4.5%)
Hoover et al ²⁷	83	1 (1.2%)	5 (6.0%)	0	—	≥3‡ (≥3.6%)	—	—	≥6† (≥7.2%)	≥9†‡ (≥11%)	≥9†‡ (≥11%)
Jiang and Hsu ³⁶	145	2 (1.4%)	5 (4.1%)	0	9 (6.9%)	≥1‡ (≥0.7%)	0-8‡ (0% to 5.5%)	—	16 (11%)	≥17‡ (≥12%)	≥17‡‡ (≥12%)
Lund and Scadding ³³	47	0	3 (6.4%)	0	3 (6.4%)	12 (26%)	0 (0%)	—	6 (13%)	18 (38%)	≥18† (≥38%)
May et al ³²	245	0-5* (0% to 2.0%)	—	0-5* (0% to 2.0%)	—	16 (6.6%)	1 (0.4%)	—	≥5† (≥2.0%)	≥21† (≥8.6%)	≥21† (≥8.6%)
Safdarian and Ferguson ³⁷	37	1 (2.7%)	0	6 (16%)	1 (2.7%)	2 (5.4%)	0 (0%)	3 (8.1%)	8 (22%)	10 (27%)	13 (35%)
Scadding ³⁴	74	0	5 (6.8%)	4 (5.4%)	5 (6.8%)	8-22* (11% to 30%)	0-2* (0% to 2.7%)	—	14 (19%)	22-36* (30% to 49%)	≥22*† (≥30%)
Seppänen et al ²⁴	48	5 (10%)	3 (6.3%)	2 (4.2%)	1 (2.1%)	24 (50%)	0 (0%)	—	11 (23%)	35 (73%)	≥35† (≥73%)
Seppänen et al, healthy	198	0	5 (2.5%)	0	3 (1.5%)	44 (22%)	8 (4.0%)	—	8 (4.0%)	52 (26%)	≥52† (≥26%)
Vanlerberghe et al ²⁸	261	0	3 (1.1%)	10 (3.8%)	—	≥44† (≥17%)	—	—	≥13† (≥5.0%)	≥57† (≥22%)	≥57† (≥22%)

Boldface values indicate values reported exactly. Italic values indicate healthy control groups.

*Might be associated with other deficiencies.

†Deficiency not adequately measured.

‡Laboratory ranges differ significantly (see Table I).

with recurrent CRS, in particular up to 10% for potential CVID (Table II).³⁸ However, most studies used CVID based on low immunoglobulin levels, except the study by Alqudah et al,³⁵ who defined CVID in accordance to the criteria for primary immunodeficiencies.²⁰ These criteria include diminished serum IgG, IgA, or IgM levels of 2 or more SDs less than the respective means for age; absent isohemagglutinins or poor specific antibody responses to vaccines; and exclusion of other causes of hypogammaglobulinemia, but international consensus is lacking.^{39,40} To improve the diagnostic accuracy of our review, several authors were contacted, and some provided us with their original databases and complementary information. Nevertheless, for most potential CVID cases, data on the infection and immunodeficiency workup were incomplete. For all these reasons, we used the term “potential CVID.” Even if the prevalence of potential CVID in patients with CRS is overestimated by our results and keeping in

mind that the reported prevalence of CVID in the general population is 1:25,000^{9,13} and the reported prevalence of CRS is around 10%,⁴ CVID is either underdiagnosed in the general population⁴¹ or recurrent CRS represents a rare subgroup of patients with CRS and a particularly high prevalence of CVID.

Reported prevalences of major immunoglobulin class deficiencies in patients with CRS were as high as 6.8% for IgA, 16% for IgG, and 10% for IgM. Moreover, analysis of the 3 studies using control groups of healthy volunteers²⁴⁻²⁶ suggested that pooled IgG1-3D is significantly associated with recurrent CRS. Looking at the individual studies, Armenaka et al²⁶ reported a higher prevalence of isolated IgG₃ deficiency of 45% in a cohort of 60 patients with CRS compared with 17% in the 30 control subjects, whereas their pooled IgG1-3D data were not interpretable because the laboratory reference ranges were too narrow. Cui et al²⁵ found a prevalence of 5.4% of IgG1-3D in 167 patients with CRS, whereas their control group

TABLE III. Study characteristics

Studies	No.	Age (y)	Sex (male)	Inclusion criteria	Recruitment year	Country	Allergy	Asthma	Polyps	Sec RSC excl	Systemic corticoids excluded	Study design
Alqudah et al ³⁵	67	22-77 (mean, 50)	24 (36%)	DTT CRS	2001-2009	United States	28 (42%)	27 (40%)	19 (28%)	Yes	Yes	Retrospective
Armenaka et al ²⁶	60	16-75 (mean, 40)	18 (30%)	DR CRS	≤1994	United States	23 (38%)	22 (37%)	8 (13%)	Yes	Yes	Prospective
Carr et al ³¹	105	>18 (mean, 48)	39 (37%)	DTT CRS	2002-2010	United States	76 (72%)	72 (68%)	47 (44%)	Yes	—	Retrospective
Chee et al ¹⁸	79	(mean, 44)	—	DTT CRS	1991-1997	United States	40 (51%)	28 (35%)	—	Yes	—	Retrospective
Cui et al ²¹	167	(median, 34)	88 (53%)	DR CRS	≤2009	China	74 (44%)	26 (18%)	95 (57%)	Yes	Yes	Prospective
Hoover et al ²⁷	83	18-76 (mean, 43)	36 (43%)	DR CRS	1991-1995	United States	31 (37%)	28 (34%)	—	Yes	Yes	Prospective
Jiang and Hsu ³⁶	145	16-84 (mean, 41)	101 (70%)	DR CRS	1997-1999	Taiwan	—	—	75 (52%)	—	Yes	Prospective
Lund and Scadding ³³	47	15-60	21 (45%)	DR CRS	≤1992	United Kingdom	—	—	—	Yes	—	Prospective
May et al ³²	245	4-79 (mean, 44)	176 (72%)	CRS	1993-1998	Germany	—	—	—	—	—	Prospective
Safdarian and Fergusson ³⁷	37	>18	—	DR CRS	2003-2008	United States	—	—	—	—	—	Retrospective
Scadding et al ³⁴	74	15-60 (mean, 38)	30 (41%)	DR CRS	≤1995	United Kingdom	42 (57%)	11 (15%)	—	Yes	—	Prospective
Seppänen et al ²⁴	48	20-68 (mean, 41)	15 (31%)	DTT CRS	1996-2001	Finland	15 (31%)	27 (56%)	29 (60%)	Yes	—	Prospective
Vanlerberghe et al ²⁹	261	>18	110 (42%)	DR CRS	2002-2004	Belgium	—	—	—	No	No	Retrospective

Allergy, Respiratory allergy prevalence; Asthma, asthma prevalence; DR CRS, Drug-resistant CRS; DTT CRS, EPOS-defined difficult-to-treat CRS; Polyps, nasal polyposis prevalence; Sec RSC excl, secondary causes of rhinosinusitis excluded.

of 110 patients had a prevalence of 2.7% of IgG1-3D, a difference that did not reach statistical significance. Finally, Seppänen et al²⁴ reported a significantly higher prevalence of isolated IgG₁ and IgG₃ deficiencies in 48 patients with CRS

(ie, 38% and 38%, respectively) compared with their 198 control subjects (ie, 8% and 15%, respectively). A particularly high proportion of pooled IgG1-3D (50%) was found in patients with difficult-to-treat CRS. Concerning SAD, a higher prevalence was observed in patients with difficult-to-treat CRS in the study by Alqudah et al,³⁵ whereas the results of Carr et al³¹ could not be considered because other immunodeficiencies were not analyzed. IgG₄ deficiency, which is not believed to be of clinical significance for CRS, was not associated with CRS. In summary, the prevalence of IgG1-3D/SAD seems to be higher in patients with CRS, in particular in those with difficult-to-treat CRS; however, this issue remains a matter of debate because these deficiencies are frequent in the general population and can be induced by corticosteroids.⁹⁻¹²

A large European study (the Global Allergy and Asthma European Network [GA²LEN]) has demonstrated a higher prevalence of asthma in patients with CRS,⁴ whereas the question of whether allergies represent a risk factor for CRS remains controversial.^{3,42} Reliable population-based data on the prevalence of asthma and respiratory allergies are scarce.⁴³ In addition, these data should be interpreted with caution because (1) the respiratory diagnoses were solely based on symptoms and not on skin prick test responses and (2) the patients could have consulted their physicians, more often leading to a referral bias.³ In the current review we found an increased prevalence of asthma and respiratory allergies in most CRS reports, with the exception of 1 study (Table IV).³⁴ These findings suggest that respiratory allergies are also linked to CRS; however, this question needs to be addressed specifically in the future because our review was not primarily designed to study allergies.

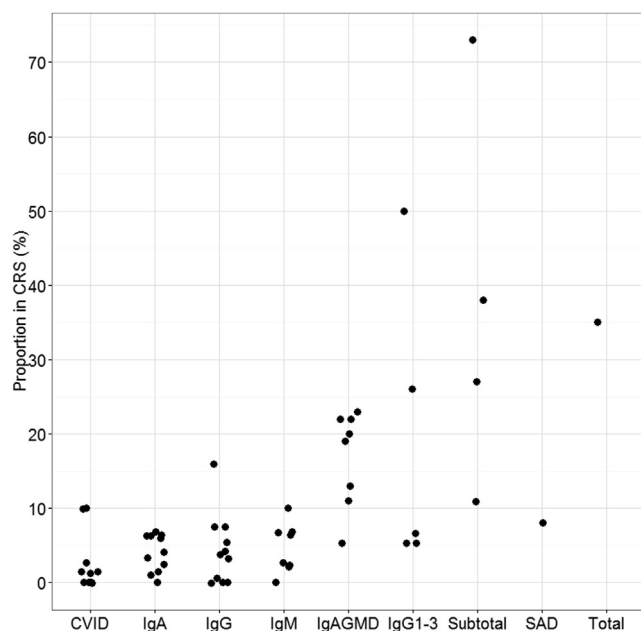


FIG 1. Prevalence of CRS in patients with immunoglobulin deficiencies and their combinations. Only immunoglobulin deficiency proportions considered as exact are depicted. CVID, Potential CVID; Subtotal, combination of IgAGMD and IgG1-3; Total, combination of IgAGMD, IgG1-3, and SAD.

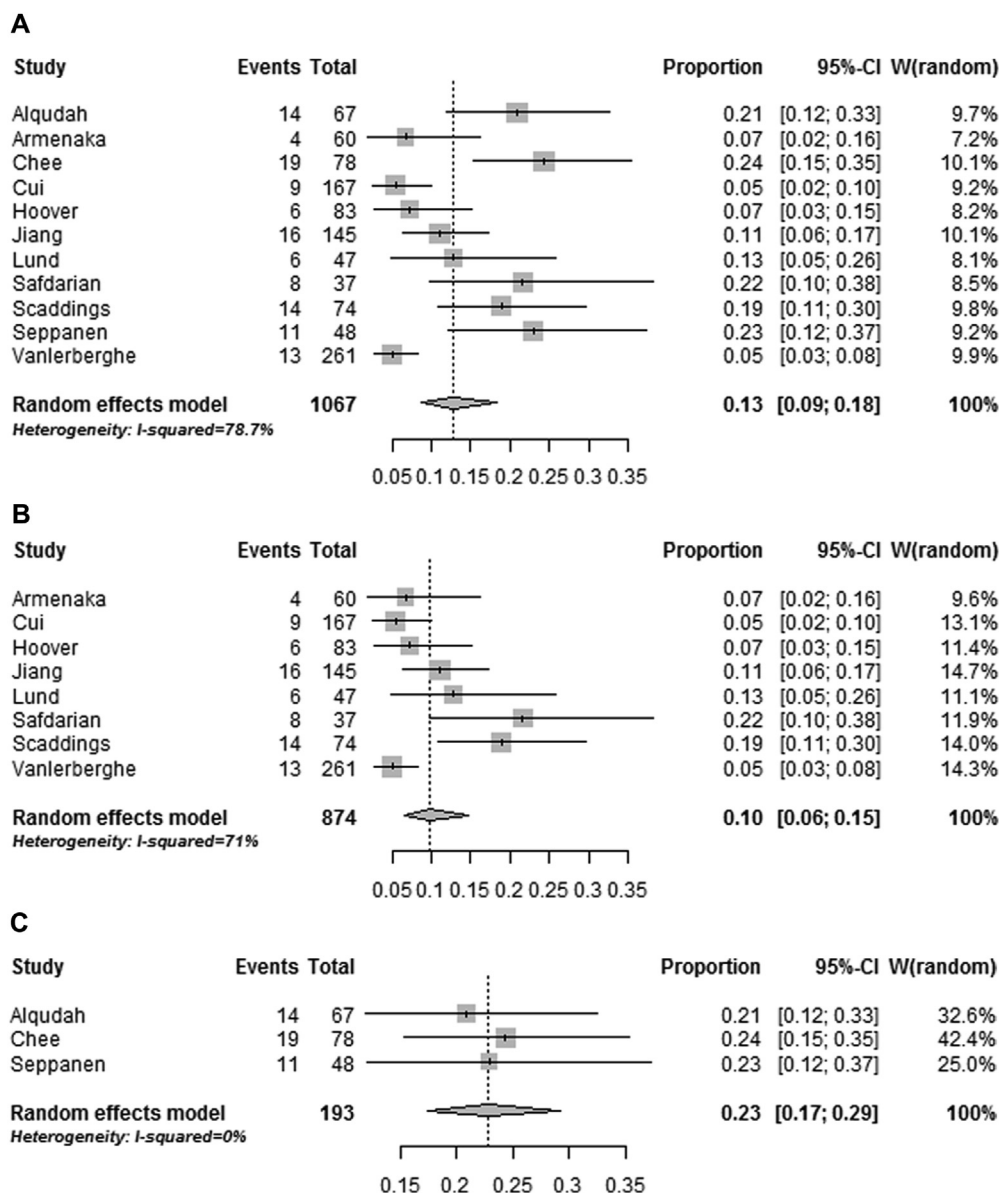


FIG 2. Proportion meta-analysis of selected immunoglobulin deficiencies. Proportions are represented by solid symbols, and 95% CIs are represented by lines. Diamonds represent the pooled proportion. *W*(random), Weights of different studies in meta-analysis by using random effects: **A**, recurrent CRS proportion meta-analysis; **B**, drug-resistant CRS proportion meta-analysis; and **C**, difficult-to-treat CRS proportion meta-analysis.

Meta-analysis

The results of the systematic review were corroborated by a meta-analysis showing an IgAGMD prevalence of 12.7% (95% CI, 8.6% to 18.3%) in patients with recurrent CRS compared with an estimated IgAGMD prevalence of less than 1% in the general population.^{9,10,13,14} A subgroup analysis revealed that the IgAGMD prevalence is significantly higher in patients with difficult-to-treat CRS (22.8%; 95% CI, 17.5% to 29.3%) compared with that in the drug-resistant subgroup (9.8%; 95% CI, 6.5% to 14.7%). As to the interpretation of the asymmetry of the funnel plot indicating a potential publication bias, it could reflect the fact that studies with patients with difficult-to-treat CRS showed higher rates of IgAGMD and had relatively small sample sizes. However, a publication bias seems improbable

because these studies revealed both low and high IgAGMD prevalences.

Nevertheless, the prevalence of immune deficiencies could have been underestimated for the following reasons. First, immunoglobulin deficiencies other than IgAGMD might not have been addressed or were excluded (ie, IgG1-3D, IgE deficiency, and SAD).^{44,45} Second, IgM deficiency was not reported in 3 studies, as mentioned above.²⁶⁻²⁸ Because we assumed for this meta-analysis that there was no IgM deficiency in these 3 studies, which only described drug-resistant CRS, the prevalence of IgAGMD could have been underestimated in the meta-analysis, particularly in the drug-resistant CRS subgroup but not in the difficult-to-treat CRS subgroup. A restricted meta-analysis on potential CVID, selective IgA deficiency, and

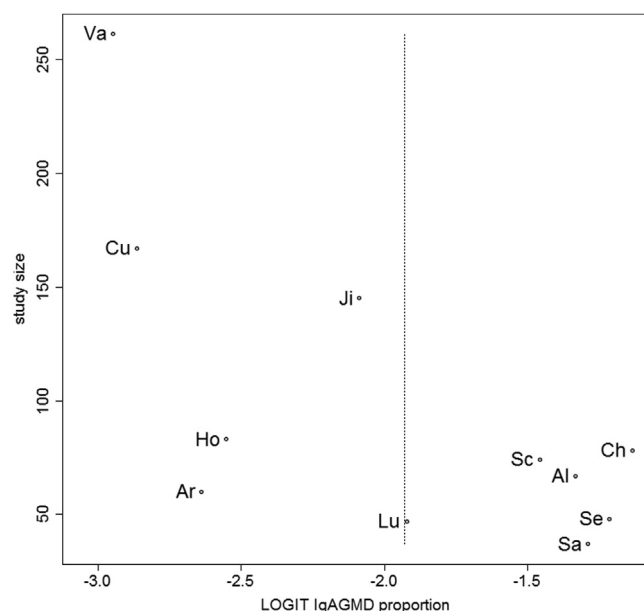


FIG 3. Funnel plots based on $1/SE$ and study size. Selected studies are represented by the first 2 letters of the first author's last name. Dotted line, LOGIT of the meta-analysis result with random effect.

unspecified IgG deficiency with subgroup analysis was performed to confirm whether the observed difference between the 2 subgroups was significant. This analysis showed a prevalence of combined potential CVID, IgA deficiency, and IgG deficiency of 9.4% for recurrent CRS (95% CI, 5.9% to 14.4%; $I^2 = 79\%$), of 18.6% for difficult-to-treat CRS (95% CI, 11.3% to 28.7%; $I^2 = 56\%$), and of 7.0% for drug-resistant CRS (95% CI, 4.6% to 10.5%; $I^2 = 58\%$). In summary, IgAGMD prevalence was significantly higher in the difficult-to-treat CRS subgroup than in the drug-resistant CRS subgroup, despite the lack of IgM assessment in some studies.

Limitations of the study

Our study has several limitations, as detailed below. The accuracy of our systematic review and meta-analysis depends on the quality of the published data and the supplementary information provided by the investigators on our request. Unfortunately, some of the immunoglobulin deficiencies of interest were not reported in sufficient detail. Furthermore, information about

secondary causes of hypogammaglobulinemia, such as systemic corticosteroid use, potentially leading to increased immunoglobulin catabolism and/or decreased immunoglobulin synthesis and IgG subclass deficiencies, was not always available.^{46,47} Moreover, the concentration of IgG subclasses is strongly age dependent, and most clinical laboratories rely on reference ranges made available by the manufacturer but not on published data. Hence standardization of IgG subclass determinations is still unsatisfactory, with no consensus regarding abnormal values.⁴⁸ Another caveat lies in the heterogeneity of the CRS study sample, potentially adding other confounding factors. The inclusion criteria varied across studies, as revealed by the I^2 statistic, especially between the drug-resistant and difficult-to-treat CRS subgroups but also within the drug-resistant CRS subgroup. Moreover, the study design might play a role because 3 of 4 retained retrospective studies showed higher IgAGMD prevalences.

Second, the diagnostic accuracy of CRS and CVID was difficult to determine. Details of the infection and immunodeficiency workups were incomplete, and radiologic evidence for bronchiectasis and CRS were not systematically reported. Nevertheless, the role of computed tomographic scanning in diagnosing CRS is controversial because it might lead to false-positive cases.^{49,50} On the other hand, the studies have been performed under the guidance of experts in the field assuming the ability to diagnose CRS and CVID properly. Finally, the majority of the 13 analyzed studies reported cohort data or case series and were not controlled.

Conclusions and clinical implications

By demonstrating a greater than 10-fold higher prevalence of immunoglobulin deficiencies in patients with recurrent CRS, especially those with difficult-to-treat CRS, the results of the present study are of relevance for both patients with CRS and the field of immune deficiency in total. Apart from treating the symptoms of CRS in a timely manner, it is important to evaluate patients with CRS for early diagnosis of CVID. In addition, immunoglobulin levels should be evaluated before eventual systemic corticosteroid treatment to avoid confusion with secondary immunoglobulin deficiencies. Early CVID diagnosis improves outcomes by allowing for more specific treatment approaches, including aggressive antibiotic therapy and IgG replacement, and by identifying and avoiding associated complications.^{15,16,38} Moreover, unnecessary and ineffective surgical procedures can be avoided because patients with difficult-to-

TABLE IV. Respiratory allergies and asthma prevalence in selected studies and in general population

Selected studies	Study country	Respiratory allergy prevalence in selected studies	Respiratory allergy prevalence in the general population*	Asthma prevalence in the selected studies	Asthma prevalence in the general population*
Alqudah et al ³⁵	United States	42% (30% to 54%)	18%	40% (29% to 52%)	21%
Armenaka et al ²⁶	United States	38% (26% to 51%)	18%	37% (24% to 49%)	21%
Carr et al ³¹	United States	72% (63% to 80%)	18%	68% (59% to 77%)	21%
Chee et al ¹⁸	United States	51% (40% to 62%)	18%	35% (25% to 46%)	21%
Cui et al ²¹	China	44% (37% to 52%)	8%	17% (11% to 22%)	5%
Hoover et al ²⁷	United States	35% (25% to 45%)	18%	34% (24% to 44%)	21%
Scadding et al ³⁴	United Kingdom	57% (45% to 68%)	18%	15% (7% to 23%)	32%
Seppänen et al ²⁴	Finland	31% (18% to 44%)	16%	56% (42% to 70%)	16%

Ninety-five percent CIs were calculated for selected studies.

*Prevalence of respiratory allergy and asthma symptoms reported in the general populations of the respective countries.³⁹

treat CRS have an average of 3 sinus surgeries before being assessed for humoral immune deficiency.¹⁸ However, introduction of IgG replacement therapy should depend on a careful evaluation by specialists.³⁹

Analysis of control groups of different ethnic backgrounds and ages by using standardized methods are needed to determine the prevalence of immunoglobulin deficiencies in the healthy population. In addition, large-scale prospective studies are warranted using strict inclusion criteria to explore the exact prevalence of immunoglobulin deficiencies in patients with CRS. These studies should carefully report infections; associated inflammatory, autoimmune, and lymphoproliferative disease; enteropathy; malignancies⁵¹; and use of medication, especially glucocorticoids.²⁴ Based on these findings, prospective randomized studies could be designed to evaluate the efficacy of specific treatments for immunoglobulin deficiencies in patients with recurrent CRS.

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Clinical implications: Immunoglobulin deficiencies can be detected in up to 23% of selected patients and should be investigated in patients with recurrent CRS because there are specific treatments available.

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