REVIEW ARTICLE

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Infectious Complications Reporting in Common Variable Immunodeficiency: A Systematic Review and Meta-analysis

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ABSTRACT

Objectives: Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by hypogammaglobulinemia and increased susceptibility to recurrent infections. ***Methods***: We searched PubMed, Web of Science, and Scopus databases to find eligible studies from the earliest available date to January 2018 with standard keywords. Pooled estimates of the infection prevalence and the corresponding 95% confidence intervals were calculated using random-effects models. ***Results:*** We found that pneumonia (67.7%) was the most prevalent infection followed by upper respiratory tract (59.0%) and gastrointestinal infections (36.3%). Furthermore, bacterial complications (41.7%) were higher in CVID patients compared to viral (25.4%), parasitic (18.8%), or fungal (3.4%) infections. Patients with longer age at diagnosis presented with fewer disease comorbidities. There was an inverse correlation between T lymphocyte count and viral infections. Moreover, we found that immunoglobulin M (IgM) serum level was inversely correlated with hepatitis C and gastrointestinal infections, and IgG serum level was inversely correlated with infectious arthritis. Higher numbers of CD4 and CD8 T cells were associated with the lower frequencies of otitis media. CVID patients with infections had significantly lower percentages of CD3 T cells. In contrast, higher percentages of CD19 lymphocytes were found in CVID patients who had a history of infections. ***Conclusions:*** Our findings demonstrated that in addition to hypogammaglobulinemia, patients with CVID have an imbalance in the frequency of T lymphocytes, which is in parallel with the higher frequency of infectious complications.

Common variable immunodeficiency (CVID) is a heterogeneous category and the most common clinically significant primary immunodeficiency (PID) disorder characterized by impaired B cell differentiation to memory B cell and plasma cell.[1] Diagnosis of CVID is done by a marked reduction of at least two immunoglobulin (Ig) isotypes: IgG with IgA and/or IgM, and impaired specific antibody production against protein or polysaccharide antigens and vaccines.[2,3] Likewise, T-cell dysfunctions are reported in approximately one-third of CVID patients and contribute to the more variable clinical manifestations of the disease such as the development of opportunistic or unusual infections.[2,4–6] Several reports proposed that CVID represents a heterogeneous disease spectrum with a variety of clinical presentations including

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autoimmune disorders (AID), lymphoproliferative disease, enteropathy, malignancy, and recurrent bacterial and viral infections.[7,8]

Recurrent infections are among the first and the most common clinical manifestation of the disease. Acute and chronic infections are a leading cause of morbidity in patients with CVID.[7] Approximately, all CVID patients presented with recurrent upper and/or lower respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonia.[6,9,10] Recurrent infections especially respiratory tract infections (20–96%) and gastrointestinal infections (30–88%) are associated with a low subset of B cells, specifically reduced isotype-switched memory B cells and reduced immunoglobin levels.[5,11–14]

In this review, we sought to evaluate the existing evidence for rates of infectious complications, and performed a cumulative analysis of all studies reporting these complications. To the best of our knowledge, this is the first systematic review examining the infectious findings in CVID.

METHODS

This systematic review and meta-analysis is carried out based on PRISMA statement guidelines.[15]

Our search strategy composed of three components: (1) comprehensive searching of international and national electronic databases for published documents, (2) hand-searching of the reference section of the retrieved scientific documents, and (3) contacting experts in the field in order to assess unavailable papers.

We performed a comprehensive search using the Scopus, PubMed, and Web of Science databases to gather English articles published up to January 2018. Search strategy keywords and MeSH terms were categorized in two groups and combined: (1) 'CVID', 'common variable immunodeficiency', 'hypogammaglobulinemia', 'primary antibody deficiency'; and (2) 'infection', 'pneumonia', 'sinusitis', 'otitis', 'meningitis', 'diarrhea', 'hepatitis C', 'skin infection', 'gastrointestinal infection', 'candidiasis', 'upper respiratory tract infection', 'tonsillitis', 'pharyngitis', 'abscess', 'conjunctivitis', 'CNS infection', 'sepsis', 'septic arthritis', 'osteomyelitis', 'bacterial infection', 'viral infection' 'parasitic infection', or 'fungal infection'.

Screening of the gathered documents was done in two steps. We first screened by title and abstract to exclude all irrelevant studies, and then assessed the full texts for eligibility criteria. The inclusion criteria were: (1) English-language studies; (2) study design as prospective or retrospective cohort, cross-sectional, case series, or case-control studies; (3) studies conducted on human subjects; (4) the targeted population were those who met the international (PAGID and/or European Society for Immunodeficiency (ESID) diagnostic criteria for diagnoses of CVID; (5) their subject of the evaluation was the epidemiological, clinical, and immunological features of patients; and (6) their primary or alternative outcome of interest was infection incidence or prevalence.

Additionally, to gain further insight into the characteristics of CVID patients who developed infections, data from all studies which describe in detail the characterization of CVID patients either with infections or without infections was obtained. Review articles, studies using animal models, and studies regarding other types of PID than CVID were all excluded. For studies with overlapping data, only the study with the largest patient cohort was included. Both the steps were done independently by two reviewers, and discrepancies between the reviewers were resolved by the third reviewer.

Two authors extracted data independently from the included studies based on title and abstracts in a standardized Microsoft Excel spreadsheet. Any disagreements were resolved by discussing and consensus with a third author. The following data were collected from all identified studies: name of the first author, published year, the country of origin of the study, study design, the population characteristics, demographics, clinical, and immunologic data. The medical records of all papers were gathered if a case was reported in more than one study.

Aggregated data analysis was done with simple pooled data to provide an overall summary of subgroup data or data from a number of related studies. Data were combined without being weighted, and the analysis was performed as if the data were derived from a single sample. Central and descriptive statistics were reported for quantitative data. For variables with skewed distribution, median and interquartile range (IQR) were reported as the index of data dispersion. Analytical analyses was performed using Mann-Whitney U, chi-square, and Fisher's exact tests.

Meta-analysis was performed for the prevalence data on infections and various types of infections

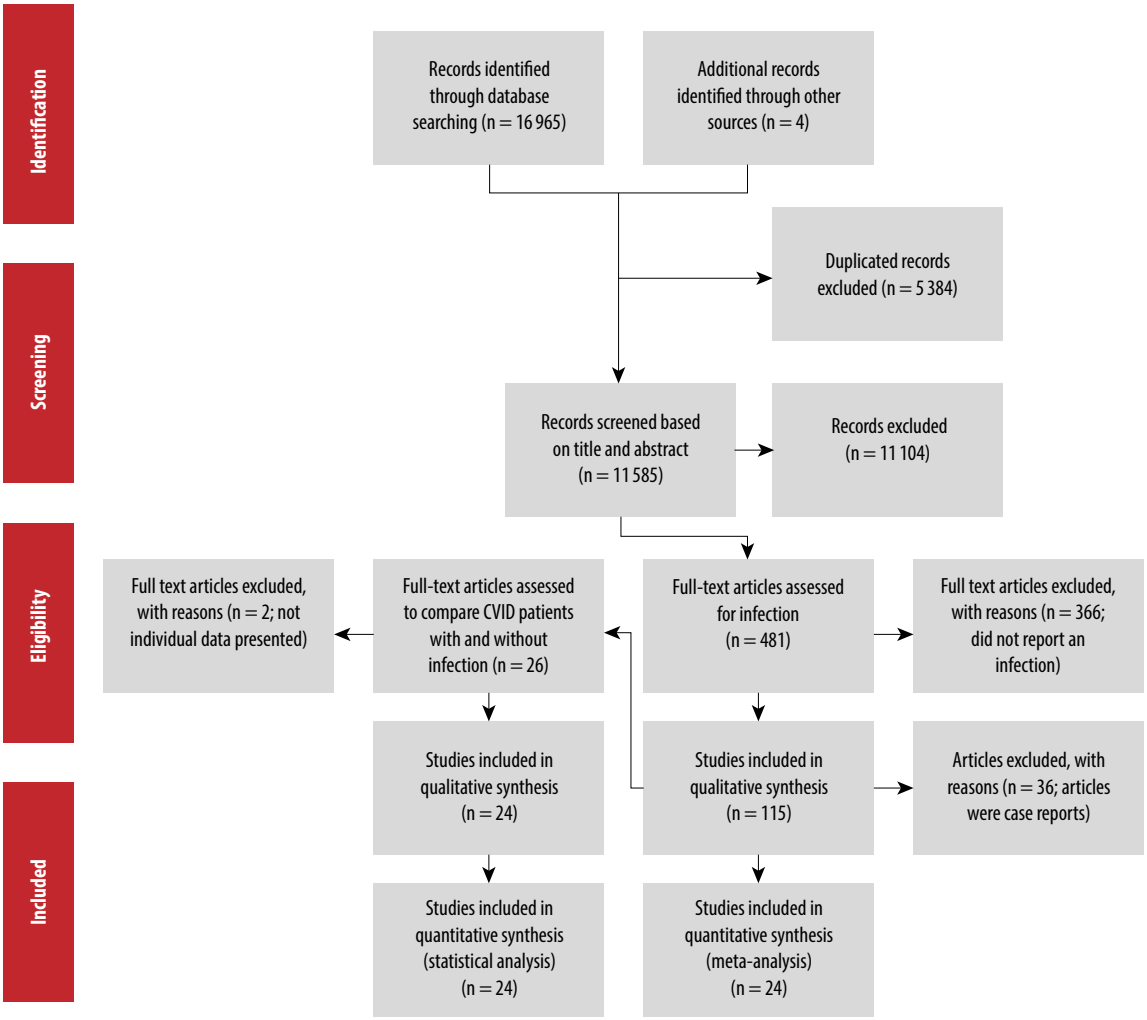

Figure 1: Flow diagram of the systematic review and meta-analysis for infections in CVID.

in the studies of CVID. Given the expected heterogeneity between studies, a meta-analysis was performed using a random-effects model to account for inter-study variation. Heterogeneity was assessed using the I-square (I^2) statistic, which describes the percentage of variation between studies that is due to heterogeneity rather than chance. Data analysis was conducted STATA v.14 software (Stata-Crop, College Station, TX).

RESULTS

The results of the literature search and selection process are shown in Figure 1. A total of 16 969 articles were retrieved from the initial search from which 5384 were duplicated studies. After screening 11 585 studies for titles and abstracts, 481 articles were selected, and the full texts were assessed. Of the 481 studies, 366 studies did not meet the eligibility criteria, from which most did not present the data of infections independently, and 36 case reports were excluded. Finally, 79 studies met the inclusion criteria and were analyzed.[4–14,16–83] The characteristics of the included studies in this systematic review are depicted in Table 1. The sample sizes of CVID patients varied from 4 to 2212 in a study from the ESID. The studies were conducted in 19 countries with most originating from the US (n = 11), Iran (n = 12), and France (n = 9). The oldest study was carried out in 1972 and the latest in 2018.

Our findings showed that respiratory tract infection was the most frequent infectious complications in patients with CVID. Pneumonia prevalence was between 19.1% and 100%, and based on random effect model, the pooled prevalence was 67.7% (95% confidence intervals: 61.5–74.0; I^2 = 94.8) and it was the most prevalent infection [Figure 2], followed by upper respiratory tract infections (URTIs) with a prevalence of 59.0%. Sinusitis, otitis media, and tonsillitis showed higher

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.

First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Desjardins, M. (2018)	Canada	Case-control	McGill University Health Centre and Centre Hospitalier Universitaire de Québec	42 (M = 14, F = 28)	Mean age of onset = 18.1 Mean age of diagnosis = 32.1	26 (61.9) (45.6–76.4)				URTI: 33 (78.6) (64.1–88.3) Sepsis: 2 (4.8) (0.6–16.2) CNS infection: 2 (4.8) (0.6–16.2)
Erazo-Borrás, L. (2017)	Colombia	Case-control	-	22 (M = 12, F = 10)	Age of onset median = 5 (0.5-42) Median age at diagnosis = 26 (6–49) Median current age = 37 (13–63)	16 (72.7) (49.8–89.3)	10 (45.5) (24.4–67.8)	11 (50.0) (28.2–71.8)	7 (31.8) (13.9–54.9)	SI: 8 (36.4) (17.2–59.3) Pharyngitis: 7 (31.8) (13.9–54.9) Tonsillitis: 7 (31.8) (13.9–54.9)
Azizi, G. (2018)	Iran	Case-control	National registry of PID Children's Medical Center affiliated to Tehran University of Medical Sciences	72 (M = 41, F = 31)	Median current age = 24 (33.5–16.25) Median age of onset = 4.0 (11.0–1.0) Median age of diagnosis = 13.50 (28.75–7.0)	52 (72.2) (60.4–82.1)	35 (48.6) (36.7–60.7)	44 (61.1) (48.9–72.4)		Conjunctivitis: 10 (13.9) (6.9–24.1) CNS infection: 8 (11.1) (4.9–20.7)
Azzu, V. (2017)	UK	Case series		4 (M = 3, F = 1)	Average age at diagnosis = 26	1 (25.0) (4.6–69.9)				URTI: 1 (25.0) (4.6–69.9) Abscess: 2 (50.0) (15.0–85.0)
Sanchez, L. (2017)	US	Cohort	United States Immunodeficiency Network (USIDNET) database	349 (M = 190, F = 159)	Age range: 3–91 Early onset (2–10) = 110 patients Adolescent onset (11–17) = 83 patients Adult onset (> 18) = 264 patients Age of diagnosis range: 2–76.9	299 (65.4) (60.9–69.8)	205 (44.9) (40.2–49.5)	357 (78.1) (74.0–81.8)	86 (18.8) (15.3–22.7)	Candida: 68 (14.9) (11.7–18.5) SI: 86 (18.8) (15.3–22.7) Sepsis: 38 (8.3) (6.0–11.2) Abscess: 36 (7.9) (5.6–10.7) Osteomyelitis: 4 (0.9) (0.2–2.2) Conjunctivitis: 54 (11.8) (9.0–15.1) Pharyngitis: 73 (16.0) (12.7–19.7) Tonsillitis: 23(5.0) (3.2–7.5) CNS infection: 29 (6.3) (4.3–9.0)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Valizadeh, A. (2017)	Iran	Cohort	Children's Medical Center Hospital, Pediatrics Center of Excellence	120 (M = 67, F = 53)	Median age, year (IQR) = 20 (14–28) Age of onset = 2 (0.6–6) Age of diagnosis median (IQR) = 9 (4–15.7)	42 (35.0) (26.5–44.2)				SI:24 (20.0) (13.3–28.3) URTI: 39 (32.5) (24.8–41.3) Abscess: 3 (2.5) (0.5–7.1) Conjunctivitis: 36 (30.0) (22.0–39.0) Septic arthritis: 10 (8.3) (4.1–14.8) CNS infection: 4 (3.3) (0.9–8.3)
Friedmann, D. (2017)	Germany	Case-control	-	58 (M = 24, F = 34)	Age range: 19–75				25 (43.1) (30.2–56.8)	
Selenius, J. (2017)	Finland	Cross-sectional	Hospital District of Helsinki and Uusimaa Adult Immunodeficiency Unit of Helsinki University Hospital clinics in Kymenlaakso Social and Health Services (Carea) and South Karelia Social and Health Care District (Eksote)	132 (M = 67, F = 65)	Age range at diagnosis: 9–74 Age range at the time of study: 20–84	13 (50.0) (29.9–70.1)				
Çalişkaner, A. (2016)	Turkey	Cohort	Adult immunology clinic in the Central Anatolia region of Turkey,	25 (M = 12, F = 13)	Mean age = 36.6 ± 13.4 Delay in diagnosis was 107 ± 95.6 months	19 (76.0) (54.9–90.6)		3 (12.0) (4.2–30.0)	2 (8.0) (1.0–26.0)	URTI: 3 (12.0) (4.2–30.0)
Furudoï, A. (2016)	France	Cohort	10 patients were registered in the French DEFI cohort and seven patients were followed up in the Department of Internal Medicine, Haut-Le vve ˆque Hospital	17 (M = 8, F = 9)	Age of onset mean = 20.1 Age of diagnosis mean = 34.9	11 (68.8) (41.3–89.0)	7 (43.8) (19.8–70.1)	1 (6.3) (0.2–30.2)		CNS infection: 3 (18.8) (4.0–45.6)

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Janssen, W. (2017)	Netherlands	Cohort	Department of Pediatric Immunology and Infectious Diseases, Laboratory of Translational Immunology, Wilhelmina Children's Hospital	55 (M = 30, F = 25)	-	29 (43.6) (31.4–56.7)				URTI: 29 (43.6) (31.4–56.7)
Kutukculer, N. (2016)	Turkey	Case-control	Ege University Pediatric Immunology Department	20 (M = 17, F = 3) in case (CVID)	Mean age of onset = 7 Mean age of diagnosis = 8					
Mokhtari, M. (2016)	Iran	Retrospective Cohort	Children's Medical Center (Pediatrics Center of Excellence)	185 total 113 studied (M = 69, F = 44)	Mean age of onset = 5.9 ±4.7 Mean age of diagnosis = 12.7±11.3	93 (82.3) (74.0–88.8)		78 (69.0) (59.6–77.4)		CNS infection: 12 (10.6) (5.6–17.8)
Yazdani, R. (2016)	Iran	Case-control	Children's Medical Center (Pediatrics Center of Excellence)	30 (M = 20, F = 10)	Mean age = 23.43 ± 11.58 Mean age of onset = 6.32 ± 8.57 Mean diagnostic delay = 6.21 ± 5.43	23 (76.7) (57.7–90.1)	16 (53.3) (34.3–71.7)	19 (63.3) (43.9–80.1)		
Lin, L. (2015)	China		Five cases from Peking University First Hospital 35 cases from China National Knowledge Infrastructure and Wan Fang Database	40 (M = 30, F = 10)	Median age at onset = 11 (range: 4–51) Median age at diagnosis = 14.5 (range: 5–66). Average time of delay in diagnosis = 5.3 years (range: 1–41)	28 (70.0) (53.5–83.4)	7 (17.5) (7.3–32.8)	5 (12.5) (4.2–26.8)	12 (30.0) (16.6–46.5)	SI: 1 (2.5) (0.1–13.2) Abscess: 2 (5.0) (0.6–16.9) CNS infection: 1 (2.5) (0.1–13.2)
Lougaris, V. (2016)	Italy		Pediatrics Clinic, University of Brescia, Italy	15(M = 9, F = 6)	Mean age at diagnosis = 15 Mean age at the time the study = 27.3	8 (53.3) (26.6–78.7)				

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Musabak, U. (2017)	Turkey		-	31 (M = 19, F = 12)	Current age median = 28 Age at diagnosis median =23 Delay in diagnosis median = 14	20 (64.5) (45.4–80.8)	14 (45.2) (27.3–64.0)	26 (83.9) (66.3–94.5)	12 (38.7) (21.8–57.8)	Candida: 3 (9.7) (2.0–25.8) SI: 2 (6.5) (0.8–21.4) CNS infection: 2 (6.5) (0.8–21.4)
Arshi, S. (2016)	Iran	Retrospective Cohort	The Allergy and Clinical Immunology department of Rasol E Akram Hospital of Iran University of Medical sciences, Tehran, Iran	47 (M = 47, F = 0)	Mean age = 27 (range: 4–63) Mean follow-up time = 6.8 (range: 0.5–23). Mean age of onset = 11.2 (range: 1–32) Mean diagnostic delay = 9				12 (25.5) (13.9–40.3)	SI: 16 (34.0) (20.9–49.3) Abscess: 12 (25.5) (13.9–40.3) Osteomyelitis: 10 (21.3) (10.7–35.7) CNS infection: 6 (12.8) (4.8–25.7)
Dong, J. (2016)	China	Retrospective cohort	Inpatients or outpatients of the Affiliated Hospital(the largest tertiary referral center) of Qingdao University,	8 (M = 5, F = 3)	Mean age at onset = 32.5 ± 12.6 (range: 15–49) Mean age at diagnosis = 43 ± 13.7 year Mean diagnostic delay = 10.5	5 (62.5) (24–591.5)	1 (12.5) (0.3–52.7)			
Gathmann B. (2014)	European Society	Cohort	28 medical centers contributing to the European Society for Immunodeficiencies	2212 (M = 1081, F = 1131)	-	288 (31.9) (28.9–35.1)				CNS infection: 36 (4.0) (2.8–5.5)
Berrón-Ruiz, L. (2014)	Mexico	Cohort	Instituto Nacional de Pediatría and Centro Médico Nacional "La Raza" Instituto Mexicano del Seguro Social, Mexico City	16 (M = 6, F = 10)	Mean age at onset = 12.2 Mean age at diagnosis = 14.6	14 (87.5) (61.7–98.4)	7 (46.7) (21.3–73.4)	12 (75.0) (47.6–92.7)	12 (75.0) (47.6–92.7)	CNS infection: 16 (100) (79.4–100)

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Maglione, P. (2014)	US	Retrospective analysis	electronic medical records from Mount Sinai Hospital (New York, New York)	61 (M = 27, F = 34)	Median age of 47 years (range: 14–89)	33 (54.1) (40.8–66.9)				
Ramírez-Vargas, N. (2014)	Mexico	Cohort	Immunol ogy Division of seven different reference centres in Mexico	43 (M = 23, F = 20)	Age of onset median = 13.7 Age of diagnosis median = 19	36 (83.7) (69.3–93.2)	21 (48.8) (33.3, 64.5)	36 (83.7) (69.3–93.2)	30 (69.8) (53.9–82.8)	Candida: 2 (4.7) (0.6–15.8) Sepsis: 2 (4.7) (0.6–15.8) Abscess: 2 (4.7) (0.6–15.8) Osteomyelitis: 2 (4.7) (0.6–15.8) CNS infection: 7 (16.3) (6.8–30.7)
Agondi, R. (2013)	Brazil	Cross-sectional	Primary Immunodeficiency Outpatient Clinic of the Division of Clin- ical Immunology and Allergy, University of Sa ̃o Paulo, from January 2009 to December 2011	72 (M=35, F=37)	Mean age at onset = 13.8 ±10.7 Mean age at diagnosis = 28.6 ± 12.5 Mean time to diagnosis = 14.8 ± 12.0 years	53 (73.6) (61.9–83.3)		45 (62.5) (50.3–73.6)		CNS infection: 5 (6.9) (2.3–15.5)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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Mohammadinejad P. (2012)	Iran	Cohort	Children medical center affiliated to the Tehran university of medical science	69 (M=34, F=35)	Mean time of follow-up = 5.2 ± 4.3 years Mean diagnostic delay = 4.4 ± 3.6 years	53 (76.8) (65.1–86.1)	10 (14.5) (7.2–25.0)	41 (59.4) (46.9–71.1)	40 (58.0) (45.5–69.8)	SI: 10 (14.5) (7.2–25.0) URTI: 44 (63.8) (52.0–74.1) Sepsis: 2 (2.9) (0.4–10.1) Abscess: 14 (20.3) (11.6–31.7) Osteomyelitis: 1 (1.4) (0.0–7.8) Conjunctivitis: 17 (24.6) (15.1–36.5) Pharyngitis: 5 (7.2) (2.4–16.1) Septic arthritis: 10 (14.5) (7.2–25.0) CNS infection: 6 (8.7) (3.3–18.0)
Bayry, J. (2011)	France	Case-Control	-	10 (M = 8, F = 2)	Mean age = 32.5 (23–66)	3 (30.0) (6.7–65.2)	1 (10.0) (0.3– 44.5)	3 (30.0) (6.7–65.2)	1 (10.0) (0.3–44.5)	Candida: 3 (30.0) (6.7– 65.2) Conjunctivitis: 1 (10.0) (0.3–44.5)

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Al-Herz, W. (2011)	Kuwait	Cohort	Allergy and Clinical Immunology Unit, Department of Pediatrics (Al-Sabah Hospital), and the Pediatric Dermatology Unit of the National Dermatology Center between January 2004 and December 2009	128 (5 cvid)	Mean age at onset = 0.89 ± 1.34 Mean age at diagnosis = 3.16 ± 3.48					SI: 1 (20.0) (0.57–1.6)
Malamut, G. 2010	France	Retrospective cohort	Ten referral centers in France (six gastroenterology departments, two internal medicine departments, one hematology department, one clinical immunology department), between January 1962 and July 2004	50 (M=26, F=24)	Mean age at onset = 34.5 ± 14.3 Mean age at diagnosis = 36.8 ± 15.6					
Aghamohammadi, A. (2010)	Iran	Retrospective	The Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences	76 (M = 43, F = 33)	Age at study = 17 (2–59) Age of onset = 2 (0.5–46) Age of diagnosis =9 (2–54) Diagnostic delay = 5 (1–32) years	59 (77.6) (66.6–86.4)				
Ardeniz, O. (2010)	Turkey	Cohort	Ege University Medical Faculty Internal Medicine Division of Allergy and Clinical Immunology	23(M = 13, F = 10)	Median age of onset = (F: 12.5 and M: 15) Median age of diagnosis = (F: 33 and M: 28)	14 (60.9) (38.5–80.3)	21 (91.3) (72.0–98.9)	21 (91.3) (72.0–98.9)		Hep C: 1 (4.3) (0.1–21.9) Sepsis: 1 (4.3) (0.1–21.9) CNS infection: 2 (8.7) (1.1–28.0)

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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Carvalho, K. (2010)	Brazil	Case-control	Division of Pediatric Clinical Immunology located at the Federal University of Sao Paulo	17 (M = 7, F = 10)	Median age at diagnosis (IGR) = 22 (IQR = 13.26) Median age at first symptoms (IQR) = 12 (3.16)	15 (88.2) (63.6–98.5)	6 (35.3) (14.2–61.7)	11 (64.7) (38.3–85.8)		
Salehzadeh, M. (2010)	Iran	Cohort	Division of Allergy and Clinical Immunology of Children's Medical Center Hospital	24 (M = 17, F = 7)	Median age at diagnosis (IQR) = 102.5 months (2–43 years) Median diagnostic delay (IQR) = 63.5 months (3–477 months)	21 (87.5) (67.6–97.3)	16 (66.7) (44.7–84.4)	19 (79.2) (57.8–92.9)	21 (87.5) (67.6–97.3)	Candida: 5 (20.8) (7.1–42.2) SI: 8 (33.3) (15.6–55.3) Abscess: 5 (20.8) (7.1–42.2) Conjunctivitis: 8 (33.3) (15.6–55.3) Septic arthritis: 5 (20.8) (7.1–42.2)
Van de ven, A. (2010)	Netherlands	Cohort	Thirty-eight pediatric CVID patients of the Wilhelmina 'Children's Hospital in Utrecht, The Netherlands, were included	38 (M = 32, F = 6) 9	Mean age at diagnosis = 5.5 ± 2.5	2 (22.2) (2.8–60.0)			2 (22.2) (2.8–60.0)	URTI: 7 (77.8) (45.3–93.7) Sepsis: 2 (22.2) (2.8–60.0) CNS infection: 1 (11.1) (0.3–48.2)
Yong, P. (2010)	US	Cohort	Childrens Hospital of Philadelphia	24 (M = 14, F = 10)	Age of onset ≥ 2 Median age of diagnosis = 84	11 (45.8) (25.6–67.2)	12 (50.0) (29.1–70.9)	12 (50.0) (29.1–70.9)		Sepsis: 3 (12.5) (2.7–32.4) CNS infection: 1 (4.2) (0.1–21.1)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Mamishi, S. (2010)	Iran	Retrospective cohort	Children's Medical Center Hospital	26 (M = 15, F = 11)	Mean age = 6.87 ± 4.15	16 (61.5) (40.6–79.8)	20 (76.9) (56.4–91.0)		20 (76.9) (56.4–91.0)	Hep C: 1 Sepsis: 3 (11.5) (2.4–30.2) Septic arthritis: 2 (7.7) (0.9–25.1)
Huck, K. (2009)	Germany	Case-control	Pediatric immunodeficiency clinic in Düsseldorf, Germany (From 1997–2007)	16 (M = 8, F = 8)	Mean age at diagnosis = 9 years and 9 months, Mean age at onset = 4 years and 8 months Diagnostic delay = 5 years	10 (90.9) (58.7–99.8)	7 (43.8) (19.8–70.1)	6 (37.5) (15.2–64.6)	3 (27.3) (6.0–61.0)	SI: 1 (9.1) (1.6–37.7) Osteomyelitis: 2 (18.2) (2.3–51.8) Conjunctivitis: 1 (9.1) (0.2–41.3) Tonsillitis: 2 (18.2) (2.3–51.8) Septic arthritis: 1 (9.1) (0.2–41.3)
Llobet, M. (2009)	Spain	Retrospective cohort	The University ChildrenÕs Hospital Vall dÕHeb- ron, Barcelona	22 (M = 15, F = 7)	Median age at diagnosis = 7.8 (Range: 2.5–16 years)	15 (68.2) (45.1–86.1)			8 (36.4) (17.2–59.3)	SI: 5 (22.7) (7.8–45.4) URTI: 11 (50.0) (30.7–69.3) Sepsis: 2 (9.1) (1.1–29.2)
Urschel, S. (2009)	Germany	Retrospe ctive cohort	Pediatric Immunology and Infectious Diseases, University Children's Hospital, Ludwig Maximilians University	32 (M = 15, F = 17)	Median age at diagnosis = 10.4	25 (78.1) (60.0–90.7)	22 (68.8) (50.0–83.9)	25 (78.1) (60.0–90.7)	10 (31.3) (16.1–50.0)	SI: 7 (15.9) (6.6–30.1) Sepsis: 5 (15.6) (5.3–32.8) Conjunctivitis: 3 (9.4) (2.0–25.0) CNS infection: 8 (25.0) (11.5–43.4)
Yu, G. (2009)	USA	Case-control	Stanford Hospital and Clinics and Lucile Packard Children's Hospita	14 (M = 8, F = 6)	Mean age = 32 (range: 6–67)	1 (7.1) (0.2–33.9)				

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Melo, K. M. (2009)	Brazil	Case-control	Recruited at the Division of Clinical Immunology at UNIFESP (Sao Paulo, Brazil)	16 (M = 6, F = 10)	Median age at diagnosis = 22 (IQR = 13–26) Median age of onset = 12 (IQR = 3–16) Median diagnostic delay = 9 (IQR = 4–12)	12 (75.0) (47.6–92.7)				
Malphettes, M. (2009)	France	Cohort	The French DEFI study (41 Centers)	313 (285 CVID +28 LOCID) 285CVID (M = 119, F = 166)	Median age of onset = 19					Candida: 3; 1.0 (0.2, 2.8) URTI: 258; 82.4 (77.8, 86.2)
Aydogan, M. (2008)	Turkey	Cohort	Division of Pediatric Allergy and Immunology at Marmara University Medical Faculty	10 (M = 6, F = 4)	Age of onset median = 4 Age of diagnosis median = 9.4	10 (100) (69.2–100.0)	7 (70.0) (34.8–93.3)	7 (70.0) (34.8–93.3)		
Oksenhendler, E. (2008)	France	Cohort	Department of Clinical Immunology, Hospital Saint-Louis in Paris	252 CVID= (M = 110, F = 142) + 89 other	Median age of onset = 19 Median age of diagnosis = 33.9	147 (58.3) (52.0–64.5)		160 (63.5) (57.2–69.4)	67 (26.6) (21.2–32.5)	Candida: 2; 0.8 (0.1, 2.8) Hep C: 3; 1.2 (0.2, 3.4) URTI: 175; 69.4 (63.5, 74.8) Sepsis: 33; 13.1 (9.2, 17.9) CNS infection: 20; 7.9 (4.9, 12.0)
Ramyar, A. (2008)	Iran	Retrospective analysis	Children Medical Center Hospital as the referral center for primary immunodeficiency disorders	7 (M = 5, F = 2)	-	5 (71.4) (29.0–96.3)	5 (71.4) (29.0, 96.3)	4 (57.1) (18.4–90.1)		Abscess: 7 (100) (64.6–100)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Rezaei, N. 2008	Iran		Iranian Primary Immunodeficiency Registry- recruited from among the medical personnel of the Children's Medical Center Hospital	25 (M = 18, F = 7)	Median age at onset = 13 months (range : 1–480) Median age at diagnosis = 97 months (range: 18–513) Median diagnostic delay = 45 months (2-452)	24 (96.0) (79.6–99.9)	17 (68.0) (46.5–85.1)	19 (76.0) (54.9–90.6)	13 (52.0) (31.3–72.2)	Candida: 6 (24.0) (9.4–45.1) Osteomyelitis: 1 (4.0) (0.1–20.4) Conjunctivitis: 9 (36.0) (18.0–57.5) Septic arthritis: 6(24.0) (9.4–45.1) CNS infection: 1 (4.0) (0.1–20.4)
Sève, P. (2008)	France	Retrospective cohort	Department of Internal Medicine, Hotel Dieu, 1 place de l'Hospital	18 (M = 9, F = 9) 14	Median age of onset = 27.5 years Median age of diagnosis = 6					URTI: 8 (57.1) (32.6–78.6)
Ward, C. (2008)	UK	Cohort	Department of Immunology at the Oxford Radcliffe Hospitals	108	-					Hep C: 6 (12.8) (4.8–25.7)
Johnston, D. T. (2007)	US	Retrospective analysis	Consecutive patients with CVID[9] who had attended the Adult Primary Immunodeficiency Clinic, University of Alabama at Birmingham	55 (M = 28, F = 27)	-	34 (61.8) (47.7–74.6)		41; 74.5 (61.0, 85.3)		
Quinti, I. (2007)	ITALY	Cohort	26 Italian Centers belonging to the Italian Primary Immunodeficiency Network	224 (M = 111, F = 1 13)	Mean age of onset = 26.6 Mean age of diagnosis = 8.9	110 (49.1) (42.4–55.9)	87 (38.8) (32.4–45.6)	121 (54.0) (47.3–60.7)		Candida:20 (8.9) (5.5–13.5) Hep C: 15 (34.9) (21.0–50.9) Sepsis: 5 (2.2) (0.7–5.1) Septic arthritis: 5 (2.2) (0.7–5.1) CNS infection: 3 (1.3) (0.3,–3.9)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Khodadad, A. 2007	Iran	Retrospective cohort	Iranian Primary Immunodeficiency Registry	39 (M = 24, F = 15)	Mean age = 16 ± 12					
Alachkar, H. (2006)	UK	Cohort	regional primary immunodeficiency clinics in Manchester, United Kingdom, in 2004—5	34	-	33 (97.1) (84.7–99.9)				
Ogershok, P.. (2006)	West Virginia	Cohort	children younger than 18 years who presented with CVID between the years of 1992 to 2005 to the West Virginia University immunology clinic after approval of the local institutional review board	12 (M = 8, F = 4)	Mean age of onset = 8 Mean age of diagnosis = 8.33	7 (58.3) (27.7–84.8)	8 (66.7) (34.9–90.1)	9 (75.0) (42.8–94.5)	3 (25.0) (5.5–57.2)	
Carbone, J. 2006	Spain	Case-control	-	14 (M = 8, F = 6)	Mean age = 37.4 (21–68)	11 (78.6) (49.2–95.3)	2 (14.3) (1.8–42.8)	5 (35.7) (12.8–64.9)	7 (50.0) (23.0–77.0)	Conjunctivitis: 2 (14.3) (1.8–42.8)
Viallard, J. 2006	France	Case-control	-	50 (M = 19, F = 31)	Median age = 38 (17–77)	23 (46.0 (31.8–60.7)	5 (10.0) (3.3–21.8)	40 (80.0) (66.3–90.0)	9 (18.0) (8.6–31.4)	Pharyngitis: 16 (32.0) (19.5–46.7)
Fevang, B. (2005)	Norway	Case-control	Section of Clinical Immunology and Infectious Diseases, Medical Department, Rikshospitalet University Hospital, Oslo	71 (M = 40, F = 31)	Median age = 44 (29–56) Median age of onset = 18 (6–35) Median age at diagnosis = 36 (20–49)	38 (53.5) (41.3–65.5)				URTI: 46 (64.8) (53.2–74.9)
Thickett, K. (2002)	Birmingham	Retrospective cohort	During 1997/1998, patients with CVID attending the regional immunology clinic	47 (M = 27, F = 20)	Median age (range) = 45.5 (22–81) Median age at diagnosis (range) = 35.0 (5–72) Median time from first symptoms to diagnosis (range) = 4.0 (0.8–45) years	9 (19.1) (9.1–33.3)		22 (46.8) (32.1–61.9)		

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Cunningham-Rundles, C. 2002	US	Cohort	-	5 (M = 1, F = 4) or 248	Mean age at diagnosis = 33 (range: 13–46)	2 (40.0) (5.3–85.3)	1 (20.0) (0.5–71.6)			URTI: 1 (20.0) (3.6–62.4) Sepsis: 3 (1.2) (0.3–3.5) Abscess: 4 (1.6) (0.4–4.1) Osteomyelitis: 2 (0.8) (0.1–2.9) Septic arthritis: 2 (0.8) (0.1–2.9)
Guazzi, V. (2002)	Italy	Case-control	Seventeen patients affected by CVID and followed at the Division of Allergy and Clinical Immunology, University of Rome 'La Sapienza,' were included	17 (M=8, F=9)	Age range = 24–61 (mean = 47)					Hep C: 3 (17.6) (3.8–43.4)
Quinti, I. (2002)	16 countries	Cross-sectional	A questionnaire was sent to 125 clinical centers from 26 European countries	952	Mean age (range) = 47.8 (10–81)					Hep C: 50 (5.3) (3.9–6.9)
Kainulainen, L. (2001)	Finland	Cohort	The Finnish Social Insurance Institute maintains a central register of patients with primary hypogammaglobulinemia	97 (M = 54, F = 43) or 18	Median age = 33 years Median age at diagnosis = 32 (0.5–73.0) Duration of symptoms before diagnosis (median) = 5 years (0.2–37.0)	63 (66.3) (55.9–75.7)	28 (29.5) (20.6, 39.7)	57 (60.0) (49.4, 69.9)		Conjunctivitis: 9 (9.5) (4.4–17.2) CNS infection: 6 (6.3) (2.4–13.2)
Martinez Garcia, M. A. (2001)	Spain	Cross-sectional	Departments of Allergology, Internal Medicine, Pediatrics and Pneumology of hospital Universitario La Fe, Valencia, Spain	19 (M = 12, F = 7)	Mean age at onset = 14.7 Mean age at diagnosis = 23.2	14 (73.7) (48.8–90.9)	12 (63.2) (38.4–83.7)	12 (63.2) (38.4–83.7)		Candida: 8 (42.1) (20.3–66.5) URTI: 19 (100) (83.2–100.0)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Nijenhuis, T. (2001)	Netherlands	Case series	Starting with three affected family members (II:17, III:14 and IV:6; Fig. 1), we set out to analyze the pedigree	6 (M = 2, F = 4)	-	3 (50.0) (18.8–81.2)			1 (16.7) (0.4–64.1)	SI: 1 (16.7) (0.4–64.1) URTI: 3 (50.0) (18.8–81.2)
Bjóro, K. (1999)	Norway	Case-control	Section of Clinical Immunology and Infectious Disease, Department of Medicine, The National Hospital, Oslo	58	Median age = 44 (14–76)					Hep C: 6 (10.3) (3.9–21.2)
Aukrust, P. (1999)	Norway	Case-control	-	20 (M = 8, F = 12)	Median age =43 (25–63) years			6 (30.0) (11.9–54.3)		
Kainulainen, L. (1999)	Finland	Cohort	Turku University Hospital, Turku, Finland	18 (M = 8, F = 10)	Median age = 36 (7–69) Mean age at diagnosis = 31.5 Mean diagnostic delay = 6.3 years	14 (77.8) (52.4–93.6)	5 (29.5) (20.6–39.7)	10 (55.6) (30.8–78.5)		
Cunningham-Rundles, C. (1999)	US	Case series	Mount Sinai Medical Center at Memorial Hospital in New York City, from 1973 to 1986 and at Mount Sinai Medical Center from 1986 to 1999, over a 25-year period	248 (M = 102, F = 146)	Median age of onset = F:28 and M:23 Median age of diagnosis = F:29 and M:33	190 (76.6) (70.8–81.7)				Candida: 3 (1.2) (0.3–3.5) Hep C: 14 (5.6) (3.1–9.3) URTI: 243 (98.0) (95.4–99.3) CNS infection: 4 (1.6) (0.4–4.1)
Nordoy, I. (1998)	Norway	Case-control	Section of Clinical Immunology and Infectious Diseases, Rikshospitalet	31 (M = 13, F = 18)	-			7 (9.7) (2.0–25.8)		Hep C: 2 (6.5) (0.8–21.4)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Morris, A. (1998)	UK		Medical Research Council Immunodeficiency Clinic, Royal Free Hospital, London	77 (M = 41, F = 36)	Mean age = 46 Mean age at diagnosis = 26.6					Hep C: 3 (4.3) (0.9–12.2)
Aukrust, P. (1996)	Norway	Case-control	-	24 (M = 9, F = 15)	Median age = 38 (21–74)			9 (37.5) (18.8–59.4)		Hep C: 2 (8.3) (1.0–27.0)
Rump, J. A. (1995)	Germany	Case-control	-	15(M = 6, F = 9)	Mean age = 44.4±13.8					SI: 4 (30.8) (9.1–61.4)
Herbst, E. W. (1994)	Germany	Case-control	Institute of Pathology and *Department of Internal Medicine, University of Freiburg	17 (M = 7, F = 10) in case (CVID)	-			17 (100) (80.5–100.0)		Candida: 2 (11.8) (1.5–36.4) SI: 2 (11.8) (1.5–36.4) Conjunctivitis: 3 (17.6) (3.8–43.4) Tonsillitis: 17 (100) (80.5–100.0)
Singh, Y. (1994)	India	Retrospective cohort	Clinical Immunology Services of The All India Institute of Medical Sciences	14(M = 10, F = 4)	Mean age = 12.1 (range: 2–40)	12 (85.7) (57.2–98.2)				URTI: 6 (42.9) (17.7–71.1)
Aukrust, P. (1994)	Norway	Case-control	Medical Department A, University of Oslo, National Hospital, Rikshospitalet	25 (M = 9, F = 16) in case (CVID)	Age of onset = 2			8 (30) (11.9–54.3)		Hep C: 1;
Pandolfi, F. (1993)	USA	Case-control	Department of Allergy and Clinical Immunology, La Sapienza University of Rome	40 (M = 19, F = 21) 9	Mean age of onset = 28.5	8 (88.9) (51.8–99.7)		6 (66.7) (29.9–92.5)		Hep C: 1 (2.5) (0.1–13.2) URTI: 9 (100) (66.4–100.0)

Table 1: Main characteristics of the included studies on the prevalence of infection in common variable immunodeficiency patients.
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First author (year of publication)	Country	Study design	Recruitment setting and methods	Final sample size (male and female)	Age characteristics for total sample, years	Pneumonia n (%) (95% CI)	Otitis n (%) (95% CI)	Sinusitis n (%) (95% CI)	GI n (%) (95% CI)	Other infection n (%) (95% CI)
Sweinberg, S.. (1991)	USA	Retrospective	Immunology clinic at Children's Hospital of Philadelphia between 1975 and 1988	12 (M = 6, F = 6)	Mean age = 23.5±7.9 Mean age at onset = 8.5±9.8 years Mean age at diagnosis = 12.5±9.3 Mean diagnostic delay = 4.1±4.2 years	10 (83.3) (51.6–97.9)				
Lebranchu, Y. (1991)	France	Case-control	-	9 (M = 3. F = 6)	Mean age = 16–55 (range = 16–55)	7 (77.8) (40.0–97.2)		8 (88.9) (51.8–99.7)	1 (11.1) (0.3–48.2)	
Hansel, T. (1987)	UK	Retrospective cohort	The regional immunology laboratory in Birmingham	161 (M = 96, F = 65)	-	145 (90.1) (84.4–94.2)				URTI: 36 (22.4) (16.6–29.4) Sepsis: 27 (16.8) (11.4–23.5) Septic arthritis: 3 (1.9) (0.4–5.3) CNS infection: 8 (5.0) (2.2–9.6)
Conley, M.. (1986)	US	Case series	All patients followed at Children's Hospital of Philadelphia between 1980 and 1985. All patients followed at Children's Hospital of Philadelphia between 1980 and 1985	8 (M = 3, F = 5)	Mean age = 14.83 Mean age at onset = 1.78 Mean Age at diagnosis = 5.5	5 (62.5) (24.5–91.5)	8 (100) (63.1–100.0)	7 (87.5) (47.3–99.7)	5 (62.5) (24.5–91.5)	SI: 1 (12.5) (2.2–47.1) CNS infection: 1 (12.5) (0.3–52.7)
Gajl-Peczalska, K. (1973)	US	Case-control	-	9 (M = 6, F = 3)	Mean age = 29.6	8 (88.9) (51.8–99.7)	5 (55.6) (21.2–86.3)	5 (55.6) (21.2–86.3)		SI:1 (11.1) (2.0–43.5) Conjunctivitis: 1 (11.1) (0.3– 48.2)

PID: primary immunodeficiency; URTI: upper respiratory tract infection; CNS: central nervous system; SI: skin infection; IQR: interquartile range; CI: confidence interval.

prevalence among URTIs with 57.6%, 46.5%, and 38.9%, respectively. Figures 3 and 4 represent the forest plot and pooled prevalence of sinusitis and otitis media. Forest plot of prevalent infections did not show any trend of prevalence over time [Figures 2, 3, and 4]. Gastrointestinal infection with a prevalence of 36.3% was the second most infectious complications in CVID patients. In contrast, osteomyelitis was the least reported infection among patients with CVID. Additionally, bacterial infections were more reported in CVID patients compared with viral, parasitic, or fungal infections (41.7% vs. 25.4%, 18.8%, or 3.4%, respectively). Detailed information regarding the prevalence of infections are depicted in Table 2.

Based on meta-regression analyses, there were several significant immunological characteristics that explain the following types of infections prevalence. By increasing the diagnosis age by one year, there was a decrease in the prevalence of the said diseases, pneumonia by 1.2%, sinusitis by 2.5%, gastrointestinal infections by 1.6%, and infectious arthritis by 0.9% ($p = 0.009$, $p = 0.006$, $p = 0.016$, and $p = 0.018$, respectively). Moreover, per 100 mg/dL increase in IgM serum level, the prevalence of hepatitis C and gastrointestinal infections showed a decrease of 6.6% ($p = 0.006$) and 1.2% ($p = 0.090$), respectively. Also, per 100 mg/dL increase in IgG serum level, there was a decrease in prevalence of infectious arthritis by 4.4% ($p = 0.037$), and per 100 cell/mL increase in $CD3^+$ T cells, the prevalence of viral infections showed a decrease of 2.7% ($p = 0.016$).

In order to obtain more insight into the infectious characteristics of CVID patients, we compared demographic and corresponding immunologic data of CVID patients with and without infections in 24 completely defined studies. These studies comprised a total of 404 patients with CVID, of which 264 patients had a history of at least one known infection. CVID patients with infections showed significantly lower percentage of $CD3^+$ T cells compared to CVID patients without infections (478.0 (748.7) vs. 979.0 (678.1), $p = 0.013$). Also, the median (IQR) age at diagnosis for CVID patients with infection was 10.0 (13.9) years and was significantly lower than that of CVID patients without infection ($p = 0.003$). Moreover, the median (IQR) age at onset of symptoms, and IgA and IgM levels in CVID patients having infections were lower than that of patients without infection even though it was not statistically significant. CVID patients with a history of infection had lower percentages of CD4+ and CD8+ T cells compared to CVID patients without infections, although this was not statistically significant. In contrast, higher percentages of CD19+ lymphocytes (283.0 (294.0) vs. 146.0 (174.6), $p = 0.027$) were found in CVID patients with a history of infections compared to patients without this history. The detailed compared parameters are shown in Table 3.

DISCUSSION

Infections are the main characteristic findings and leading cause of morbidity and mortality in CVID patients. Although, over the past years early diagnosis and therapeutic strategies of CVID have been improved, yet there are accumulating results from epidemiological studies proving a high burden of infectious complications in these patients leading to a high incidence of deaths. Several studies have reported various prevalence rates of different infections; however, almost all of them are quite univocal to the fact that upper and/or lower respiratory infections are the most prevalent infectious complication among these patients. The highest and the lowest prevalence of upper respiratory infections were reported by Martínez García et al,[16] and Pandolfi et al,[17] at 100% and Çalişkaner et al,[18] at 12.0%, respectively. However, the results of meta-analysis showed that the pooled prevalence of URTIs was 59.0%.

Pneumonia is estimated to be the leading cause of lower respiratory infection, morbidity, and mortality globally in CVID patients.[84] There is a high prevalence of pneumonia among patients with CVID reported by large cohort studies conducted by Hansel et al,[19] Mokhtari et al,[20] and Cunningham-Rundles et al,[6] with frequencies of 90.1%, 82.3%, and 76.6%, respectively. In this study, pneumonia was assessed and reported in 58 studies, and based on the results of the random effect method, the pooled prevalence of pneumonia in total CVID patients was 67.7%. Therefore, we can conclude that pneumonia is one of the main complications of these patients and, in cases of mismanagement, could cause significant and everlasting further morbidities such as bronchiectasis, which is commonly reported in CVID patients.

We found that the cumulative infections attributable to bacterial etiologies were more frequent

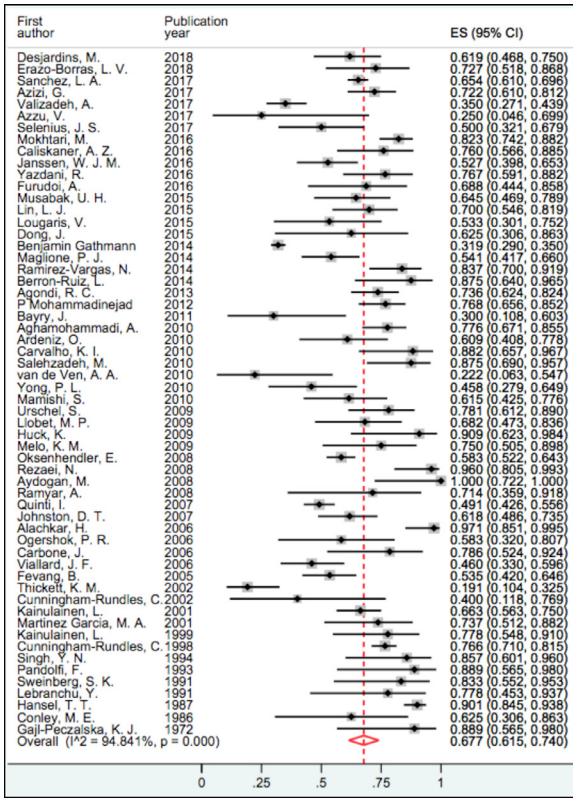

Figure 2: Forest plot and pooled prevalence of pneumonia.

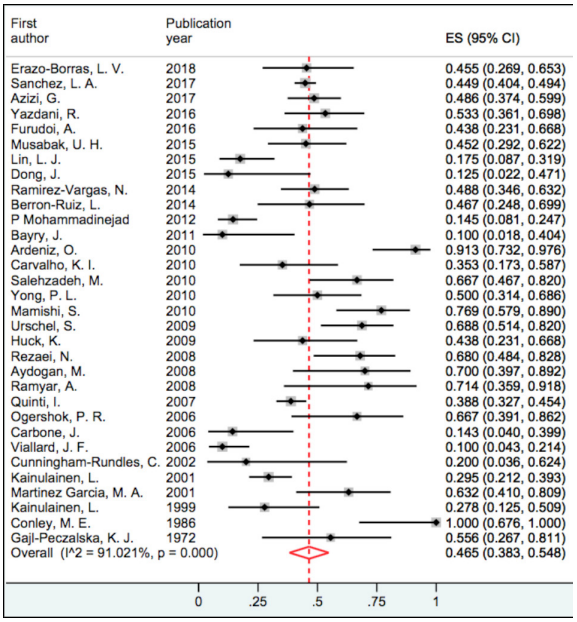

Figure 3: Forest plot and pooled prevalence of otitis media.

in CVID compared to viral or fungal infections (41.7% vs. 25.4% and 3.4%, respectively). Similarly, other studies reported a higher incidence of bacterial infections among CVID patients.[3,5,13] The higher prevalence of bacterial pathogens causing infections

Table 2: Pooled prevalence of various infections among the common variable immunodeficiency patients.

Infections	Frequency of study	Sum of sample size, sum of positive case	Prevalence range %	Pooled prevalence (95% CI)	I^2 %
Pneumonia	58	3937, 2294	19.1–100	67.7 (61.5–74.0)	94.8
URTI	20	1477, 978	12.0–100	59.0 (45.5–72.4)	98.1
Sinusitis	44	1339, 2187	6.3–100	57.6 (50.1–65.2)	93.7
Otitis media	32	1471, 628	10.0–100	46.5 (38.3–54.8)	91.0
Bacterial infection	19	950, 274	5.3–100	41.7 (18.8–64.6)	99.4
Tonsillitis	4	507, 49	5.0–100	38.9 (20.3–98.1)	99.5
Gastrointestinal infection	26	1635, 409	0–87.5	36.3 (26.5–46.2)	97.2
Viral infection	26	1837, 472	1.6–100	25.4 (13.0–37.7)	98.9
Parasitic infection	22	1344, 163	1.9–87.0	18.8 (13.5–24.0)	91.9
Pharyngitis	4	598, 101	7.2–32.0	18.8 (9.6–28.1)	81.2
Skin infection	17	938, 178	2.5–36.4	17.1 (11.9 - 22.4)	71.8
Abscess	11	1084, 91	1.6–100	16.9 (10.4–23.3)	94.4
Conjunctivitis	13	975, 154	9.1–36.0	16.9 (12.1–21.7)	64.7
CNS infection	25	3141, 192	1.3–100	11.2 (7.3–15.1)	96.1
Sepsis	14	1632, 128	1.2–22.2	7.3 (4.4–10.3)	83.0
Candidiasis	12	1367, 125	0.8–42.9	7.0 (5.8 –13.9)	90.3
Hepatitis C	14	1870, 108	1.2–34.9	5.7 (3.4–8.0)	72.8
Septic arthritis	9	908, 44	0.8–24.0	5.0 (2.3–7.7)	75.7
Fungal infection	11	1458, 51	1.1–46.9	3.4 (1.4–5.5)	75.1
Osteomyelitis	7	900, 22	0.8–12.0	1.9 (0.1–3.6)	62.2

URTI: upper respiratory tract infection; CNS: central nervous system; CI: confidence intarval; I^2: I-square.

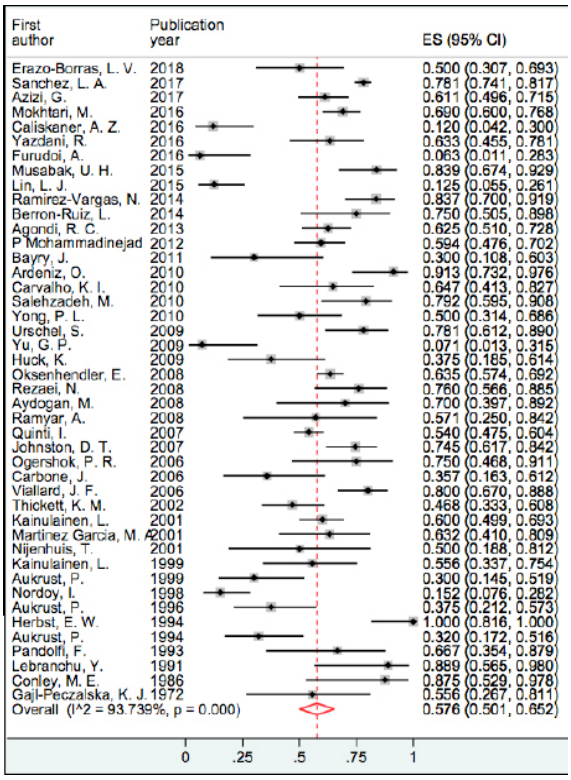

Figure 4: Forest plot and pooled prevalence of sinusitis.

in these patients can be interpreted as a result of impairment in antibody production by plasma cells. In contrast, cellular immunity is the effective defense mechanism against viral and fungal infections (it is already shown in the inverse correlation between the T lymphocyte count and the viral infections), hence infections caused by viral and fungal pathogens have lower prevalence as cellular immunity is less affected in patients with CVID.

CVID patients with infection had a significantly lower age at diagnosis compared to CVID patients without infection. It could be because the presentation of infection is one of the main characteristic features of the disease that could lead to earlier diagnosis for CVID. Unlike patients presenting with other manifestations of the disease, such as autoimmunity, allergy, and cancers, which are diagnosed in later stages of life.

There was a lower percentage of $CD3^+$ in CVID patients with infection compared to the group of CVID patients without infection. T cells, as well as B cells defect, are associated with more severe disease and higher infection rates in these patients.

Higher percentages of $CD19^+$ lymphocytes in patients with a history of infections might indicate that the primary defect is likely related to impairments of terminal stages of B cell differentiation.[85,86] Higher and/or normal numbers of $CD19^+$ does not necessarily indicate a better immune response. The impaired antibody production despite normal B cell counts in a study conducted by Ahn and Cunningham-Rundles.[85] Also suggests a defect in the differentiation of B cells into plasma and memory cells in many CVID patients. Several studies have

Table 3: Demographic and corresponding immunologic data of CVID patients with and without infection.

Parameters	Total (n = 404)	Patients with infection (n = 264)	Patients without infection (n = 140)	*p*-value
Sex ratio (M/F), n = 291	155/136	123/108	32/28	0.990
Consanguinity (Yes/No), n = 30	18/12	16/11	2/1	1.000
Age at onset, years median (IQR), n = 49	20.0 (20.0)	14.0 (21.0)	24.0 (18.2)	0.296
Age at diagnosis, years median (IQR), n = 96	12.0 (27.0)	10.0 (13.9)	28.0 (24.0)	0.003**
Diagnostic delay, years median (IQR), n = 30	4.0 (8.8)	2.1 (5.3)	4.0 (8.7)	0.343
IgG mg/dL, median (IQR), n = 193	276.0 (285.5)	272.5 (250.2)	280.0 (326.0)	0.406
IgA mg/dL, median (IQR), n = 149	9.0 (24.5)	6.0 (19.4)	10.0 (32.2)	0.129
IgM mg/dL, median (IQR), n = 149	10.0 (26.0)	17.0 (35.0)	10.0 (23.7)	0.051*
$CD3^+$ lymphocytes, cell/mL, n = 40	947.5 (832.7)	478.0 (748.7)	979.0 (678.1)	0.013**
$CD4^+$ T cells, cell/mL, n = 38	550.0 (274.5)	429.0 (NA)	550.0 (271.0)	0.626
$CD8^+$ T cells, cell/mL, n = 38	572.5 (482.7)	375.0 (NA)	580.0 (428.0)	0.570
$CD19^+$ lymphocytes, cell/mL, n = 65	232.0 (237.1)	283.0 (294.0)	146.0 (174.6)	0.027**
Lymphocyte, cell/mL, n = 29	1700.0 (963.0)	1700.0 (2912.0)	1722.0 (808.0)	0.981

CVID: common variable immunodeficiency; M: male; F: female; IQR: interquartile range; Ig: immunoglobulin.
Note: For age, age at onset, age at diagnosis, delay in diagnosis, the median is shown [with 25th and 75th percentiles]. Mann-Whitney U test for a numerical variable and the chi-square test or Fisher's exact test for the nominal variable was used.
**p-value is statistically significant < 0.050.*

pointed out the decreased level of class switch memory B cells ($CD19^+/CD27^+/IgD^-/IgM^-$), IgM memory B cells ($CD19^+/CD27^+$), and plasma cells in patients with CVID disease.[87–89] Furthermore, Unger et al,[90] reported that a subgroup of CVID patients manifests with the expansion of a special subset of B cells known as $CD21^{low}$ B cells, and it has been demonstrated that its expansion is linked with immune dysregulation in CVID patients.

A broad spectrum of T-cell abnormalities, including total numbers, percentages, surface markers, and function of various T-cell subpopulations have been reported in CVID patients. It has been shown a reduction of the total, naïve and memory $CD4^+$ T cells, recent thymic emigrants, and an increase in activated $CD4^+$ T cells. Some studies have demonstrated that CVID patients with a profound decrease in $CD4^+$ T-cell counts are more susceptible to develop autoimmunity and lymphoproliferative diseases, indicating that there is a strong correlation between the frequency of naïve T cells and clinical manifestations.[91,92] Similar to $CD4^+$ T cells, a decline in the frequency of $CD8^+$ T-cell subsets has been demonstrated. Naïve and effector memory $CD8^+$T-cell numbers are reduced whereas higher percentages of activated $CD8^+$ T cells have been reported.[61,93,94]

Disclosure
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