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# Malignancy in common variable immunodeficiency: a systematic review and meta-analysis

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**Abstract**

***Background****:* Common variable immunodeficiency (CVID) is the most common clinically significant primary immunodeficiency (PID) disorder characterized by variable clinical manifestations including recurrent infections, autoimmune disorders, enteropathy, lymphoproliferative disorders and malignancy. The aim of this study is to estimate the overall prevalence of malignancy in patients with CVID.

***Methods*****:** PubMed, Web of Science and Scopus were searched systemically to find eligible studies from the earliest available date to March 2019 with standard keywords. Pooled estimates of the malignancy prevalence and the corresponding 95% confidence intervals (CI) were calculated using random effects models.

***Results*****:** Forty-eight studies with a total of 8123 CVID patients met the inclusion criteria and were finally included in the meta-analysis. Overall prevalence of malignancy was 8.6% (95% CI: 7.1-10.0; $I^2$=79.2%). The prevalence of lymphoma, gastric cancer and breast cancer in CVID patients were 4.1% (95% CI: 3.3- 4.9; $I^2$=62.6%), 1.5% (95% CI: 0.78-2.2; $I^2$=68.9%), and 1.3% (95% CI: 0.64-1.9; $I^2$=54.9%), respectively. Moreover, autoimmunity and malabsorption were more frequent in patients with malignancy than those without malignancy.

***Conclusion*****:** The prevalence of malignancy has increased in CVID patients due to recent improvement in survival rate and the lymphoma is the most common type. This research highlighted the significance of malignancy screening and management in CVID patients.

**Keywords:** Malignancy; Lymphoma; Primary immunodeficiency; Common variable immunodeficiency

**Article Highlights**

• The most frequent malignancies in CVID patients are lymphoma, gastric cancer and breast cancer.

• The pooled prevalence of malignancy in CVID patients is 8.5% and from this prevalence of lymphoma is estimated 4.3%.



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• Malignancy in CVID patients may be concurrent with autoimmune disorder due to a dual effects of these phenotypes on uncontrolled inflammation and auto-antigen load after tissue destruction.

• CVID patients with malignancy have a higher immunoglobulin serum levels and CD8+ T cells than those without malignancy.

## 1. Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) disorder characterized by impaired differentiation of B cells to memory B cells and plasma cells (1). Diagnosis of CVID requires reduced levels of at least two immunoglobulin isotypes (IgG with IgA and/or IgM) and an impaired specific antibody (natural antibodies or response against new antigens) (2). Additionally, T-cell abnormalities and defects in other immune components are reported in approximately one-third of patients with CVID, and contribute to the more variable clinical presentations of the disease (2-4). CVID is a heterogeneous disease and presents variable clinical manifestations; the most common being recurrent bacterial infections. Besides infections, these patients have an increased tendency to develop the autoimmune disorder (AD), enteropathy, lymphoproliferative disease, and malignancy (5, 6).

Several studies report a variable frequency of malignancy in CVID patients (7-15). Generally, the reported incidence of cancer in these patients is around 10% (range 1.5-20.7%) and usually occurs during the 4th to 6th decade of life, with a risk 5-12 times higher than the general population (11, 16). Non-hodgkin lymphoma (NHL) (13, 17), gastric carcinoma (18, 19) and leukemia (20) are the most frequent reported malignancies in CVID patients.

However, due to heterogeneity of the results and lack of enough sample size in isolated studies, the complete picture is not yet illustrated. In this study, the authors aimed to systematically evaluate the existing evidence for the frequency of various types of malignancy in patients with CVID.



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## 2. Materials and Methods

### *2.1. Search strategy*

Our search strategy was 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.

### *2.2. Databases searched*

A comprehensive search was performed using the PubMed, Web of Science and Scopus databases for English articles. Search strategy terms were categorized in three groups and combined: 1) "CVID" or "common variable immunodeficiency" or "hypogammaglobulinemia"; or "primary antibody deficiency" 2) "clinical presentation" or "clinical feature" or "clinical manifestation"; 3) "malignancy" or "cancer" or "tumor" or "lymphoma" or "leukemia" or "carcinoma".

### *2.3. Screening process*

Screening of the derived documents was done in two stages: (1) screening of title and abstract to exclude all irrelevant studies, and (2) assessing full texts for eligibility criteria. Studies were included if: 1) they were written in English, 2) were designed as cohort, cross sectional, case series or case-control studies, 3) were conducted on human subjects, 4) their targeted population were those with CVID diagnosis, 5) their subject of evaluation was the epidemiological clinical and immunological features of patients, and 6) their main or alternative outcome of interest was malignancy incidence or prevalence.

Moreover, to gain further insight into the characteristics of CVID patients who develop cancer, data from all studies which describe in detail the characterization of CVID patients either with malignancy or without malignancy was obtained. Studies using animal models or reviews were all excluded. For studies with overlapping data, only the study with the largest data set was included. Both stages were done independently by two reviewers and discrepancies between the reviewers were resolved by the third reviewer.

### *2.4. Data extraction*



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Two authors independently extracted data from the included studies of first screening based on title and abstracts in a standardized Microsoft Excel spread sheet. Any disagreement was resolved by consensus with a third author person and discussion. The following data were collected from all identified studies: name of the first author, published year, number of participants, demographic, clinical, and immunologic data. The medical records of all papers were gathered if a case was reported in more than one study.

### *2.5. Statistical analysis*

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) was reported as the index of data dispersion. Analytical analyzes were performed using Mann-Whitney and Chi-square and Fisher exact tests.

Meta-analysis was performed for the prevalence data on malignancy and various types of malignancy in the studies of CVID. Given the expected heterogeneity between studies, a meta-analysis was performed using the 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 in Stata v.14 (StataCorp, College Station, TX).

## 3. Results

### *3.1. Study Selection and studies' characteristics*

The results of the literature search and selection process based on the PRISMA flow chart for systematic reviews are shows in **Figure 1**. A total of 16969 articles were retrieved from the initial search in different databases, from which 5388 were duplicated studies. After screening of 11581 studies for titles and abstracts, 421 articles were selected and the full-texts were assessed. 365 out of 421 articles did not meet the eligibility criteria, of which most did not



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present the data of malignancy independently (**Figure 1**). Furthermore, eight case reports were excluded.

The characteristics of 48 included studies in this systematic review are presented in **Table S1**. Sample sizes of CVID patients varied from 10 up to 1285 in a study from European society for Immunodeficiency (ESID). The studies have been conducted in 19 unique countries [most of the studies originated in USA (n=7), Iran (n=6) and France (n=7)]; the oldest study was carried out in 1985 and the latest in 2019. The results of meta-regression analyses, showed publication year of study marginally significantly contributed to heterogeneity of malignancy prevalence in the world (**Figure S1**). The trend of prevalence in the world was increasing, so for each 10-year, prevalence increases 2% [Coef. =1.9% (95% CI: -0.15, 4.0), *P*=0.069].

### *3.2. Meta-analysis*

As seen in **Figure 2**, the highest and lowest prevalence of malignancy was reported by Aydogan, et al. (21) in Turkey (40.0%, 95% CI: 12.2-73.8) and Bateman, et al. (22) in Germany (1.7%, 95% CI: 0.4-9.2), respectively. Only 1 studies reported the prevalence of malignancy more than 20% (21). Based on the results of the random effects method, the pooled prevalence of malignancy in 8123 CVID patients was 8.6% (95% CI: 7.1-10.0; $I^2$=79.2%) (**Figure 2**). Also 3 of 48 included articles reported the Standardized Prevalence Ratio (SPR), the observed numbers of cancer cases compared with the expected numbers,

### *3.3. The frequency of malignancy*

Our findings showed that 48 studies assessed malignancy and reported 790 cases of malignancies among 8123 CVID studied patients among which five of them had 2 types of malignancy (23, 24). Of these 48 studies, 38 studies reported lymphoma with 320 cases (40.50%) and 12 studies reported gastric cancer with 59 cases (7.46%). Other reported cancers included breast cancer with 42 cases (5.31%), skin cancer with 28 cases (3.54%), lung cancer with 13 cases (1.64%), thymic cancer with 12 cases (1.51%), leukemia with 14 cases (1.77%) and melanoma with 7 cases (0.88%), respectively. In addition, other types of cancers and unspecified cancers reported in 26 studies, with 108 and 187 cases (13.67% and 23.67%), respectively (**Figure 3**).

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Lymphoma have been reported in 38 studies with 320 affected case of a total of 7420 CVID patients with an estimated prevalence between 0.93% and 30.0%. Based on the results obtained from the random effects method performed in this study, the pooled prevalence of lymphoma among total CVID patients was 4.1% (95% CI: 3.3- 4.9; $I^2$=62.6%). There was only one study that reported no lymphoma in pediatric patients. Of 320 patients with lymphoma, 109 (34.06%) patients were diagnosed as NHL (including B-cell NHL (49.5%, n = 54), T-cell NHL (2.7%, N=3) and unknown-type NHL (47.8%, N=52) and 23 (7.18%) patients were diagnosed as Hodgkin lymphoma (HL). In the remaining 188 (58.75%) patients, the type of lymphoma was not described. The prevalence of gastric cancer was reported to be between 0.48% and 5.5%. Based on the results obtained from the random effect method, the pooled prevalence of gastric cancer in 3772 CVID patients was estimated as 1.5% (95% CI: 0.78-2.2; $I^2$=68.9%). Systematic review of original reports revealed that breast cancer prevalence ranged between 0.45% to 3.0% and the pooled prevalence in 3174 CVID patients was 1.3% (95% CI: 0.64-1.9; $I^2$=54.9%). Pooled prevalence of thymic cancer in 2799, leukemia in 2404, melanoma and skin cancer in 1713 and lung cancer in 2483 evaluated CVID patients were 0.18%, 0.45%, 0.31% and 0.40%, respectively.

### *3.4. Comparison of CVID patients with and without malignancy*

To gain more insight into the characteristics of patients of CVID with malignancy, we compared demographic, immunological and clinical data of CVID patients with and without malignancy in 9 completely defined studies. These studies comprised 187 CVID patients, of which 26 patients with malignancy were diagnosed during childhood or adolescence. The median (IQR) age at diagnosis of CVID (in years) in patients with malignancy was significantly higher than in patients without malignancy [26.5(21.5) vs. 18(27.5), $p$=0.03], while the age of onset of CVID was not statistically different in two groups (p=0.07). Moreover, patients of CVID with malignancy had significantly higher IgG, IgM and IgA serum levels ($p$=0.01, $p$=0.01 and $p$=0.001, respectively) as well as, CD8+ T cells percentages [median (IQR): 37.5(6.4) vs. 32.0(20.0), $p$=0.052] compared to those without malignancy. In contrast, higher percentages of CD19+ lymphocytes [4(5.1) vs. 7(7.7), $p$=0.051] was found in CVID patients without malignancy. The detailed compared parameters are shown in **Table 1**.

The most frequent clinical manifestation in these selected 187 CVID patients were sinusitis (75.5%), splenomegaly (45.7%), bronchiectasis (40%), pneumonia (39.2%), AD (39%),



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granulomatous lesion (19.1 %), failure to thrive (FTT) (15.2%) and malabsorption (10.1%) (**Table 2**). Among these clinical features, the frequency of autoimmunity and malabsorption was significantly higher in CVID patients with malignancy compared to those without this phenotype (57.6% vs. 36%, $p$=0.036 and 30.8% vs. 6.1%, $p$=0.022), respectively. As shown in **Table 3** there were at least 9 types of ADs in CVID patients with malignancy of which autoimmune cytopenias [AIHA (31%, n=8) and ITP (27%, n=7)] and ulcerative colitis (11%, n=3) were the most observed. Moreover, polyautoimmunity was reported in 53.3% (n=8) of CVID patients with malignancy. Surprisingly, lymphoproliferative manifestations failed to show a significant difference between two groups.

## 4. Discussion

Although over the past years the early diagnosis and medical treatment of CVID have improved, there is accumulating evidence from epidemiological studies proving a high frequency of malignancy in these patients leading to high incidence of death (9, 11). Several studies have reported various prevalence rates of malignancy, of which one large study on 473 CVID patients in 2012 (13) showed a prevalence of 15.2% while another large study on 416 cases in 2010, reported a lower prevalence rate of 9.1% (16), that can be caused by using different ESID/PAGID diagnosis criteria for CVID according to the year of publication of the articles. To the best of our knowledge, this is the first systematic review and meta-analysis of malignancy prevalence in CVID and the pooled prevalence of malignancy in 8123 CVID patients was 8.6%.

Lymphoma was the most frequently reported type of malignancy in CVID (>4% of reported patients and 40.5% of cancers) which reflects the results of the cohort study by de Resnick. et al. (13) who showed that 39 out of 73 CVID patients with malignancy were diagnosed with lymphoma (53.4%). Recently, a large cohort study by Mayor et al. (20) evaluated 119 CVID patients with a malignancy and among them, 37(31%) cases had lymphoma.

The incidence of malignant lymphoma around the world has been increasing at a rate of 3-4% over the last 4 decades (25). It was reported that malignant lymphoma comprises 3.37% of all malignancy worldwide (25, 26). According to the report by Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015), the prevalence of HL in general population is



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574,400 (95% uncertainty interval [UI]: 519,000 to 672,900) and NHL is 4,292,300 (95% UI: 3,741,000 to 4,593,600) in the world over the period of 1990 to 2015 (27). It was reported that, cellular and humoral immunodeficiency in CVID patients (28) and a high incidence of chronic viral infections (mainly herpes virus family viruses) predispose them to a higher prevalence of lymphoma (29, 30). In conferment to this point, several studies showed that NHL in immunodeficient patients is frequently caused by infection with the Epstein-Barr virus (EBV) infection (8, 31-33).

Cancers of the stomach are more frequently diagnosed in developed nations. The average incidence rate among high-middle Human Development Index (HDI) nations is 20 per 100,000 for males, while the average rate among low-middle HDI nations is 6.6 per 100,000 (26). According to the GBD 2015, the prevalence of stomach cancer and breast cancer in general population is 3,539,400 (3,339,900 to 3,776,200) and 21,361,800 (20,249,500 to 22,266,300), respectively in the world over the period of 1990 to 2015 (27). However, in the current study, the prevalence of the various type of gastrointestinal cancer was between 0.48% and 14.6% in which the majority was gastric cancer (72 %) and colorectal cancer (22%). It should be noted that the lack of a detailed description of gastrointestinal cancer types in the 42% of cases may have led to the incorrect classification of gastrointestinal cancers and incorrect comparison. However, in a prospective study of 220 CVID patients who followed for 11 years showed a 47-fold increased risk of gastric cancer (n=7, 3.18%) (34). The probable risk factors for the increased prevalence of gastric cancer in CVID patients are *Helicobacter pylori* infection and pernicious anemia (19). In an Italian study by Zullo et al., upper gastrointestinal endoscopy revealed that 2 of 14 CVID patients with *H.pylori* infection had gastric cancer (one high-grade dysplasia and one adenocarcinoma) (35). The available data suggest an increased risk of gastric cancer in CVID patients, maybe the result in greater use of antibiotics in these patients to eliminate *H.pylori* (19).

It has been confirmed that AD is an integral part of immune dysregulation in a quarter of CVID patients (36). Our comparative systematic review showed that the incidence of AD in CVID with malignancy was higher than those other CVID patients. Approximately two-thirds of CVID patients (73%) with malignancy had a concomitant diagnosis of AD, especially autoimmune cytopenia, emphasizing the role of uncontrolled inflammation in tumorigenesis of this subgroup of CVID patients. In other studies in patients with no immunodeficiency, the



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association between AD and malignancy is well established (37, 38). Based on the results obtained from 24 patients diagnosed with marginal zone lymphoma, 50% of them had an AD, with significantly increased rates for autoimmune cytopenia (39). It has been hypothesized also that neo-antigens expressed by tumors initiate autoimmune response due to abnormal exposure or presentation of these antigens (40, 41). Then again clonal B-cell proliferation might develop in response to auto-antigens exposed during tissue damage due to autoimmune stimulation in CVID patients (10).

Patients of CVID with malignancy had significantly higher $CD8^+$ T-cells which have been seen in other cases with malignancy as well (42-44). In one study of non CVID patients with different types of cancer, the results showed that majority of analyzed patients (91%) had increased $CD8^+$ T lymphocytes specific for telomerase which is a universal tumor-associated antigen (TAA) (42). $CD8^+$ T lymphocytes play a central role in tumor progression control through their capacity for identification of TAA and selective killing of malignant cells (45, 46). The observation of increased CD8+ T-cell in patients of CVID with malignancy is compatible with the simultaneous incidence of malignancy and AD. On the one hand, increased tumor antigen-specific $CD8^+$ T cells, can contribute to tissue damage, which leads to the development of AD (47, 48).

We also observed the remarkably lower percentage of $CD19^+$ lymphocytes among those patients of CVID with malignancy. Yang et al. confirmed that CD19 expression decreased in peripheral blood specimen of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (49). In another study on patients with splenic lymphoma and mantle-cell lymphoma, the number of CD19 molecules was significantly lower compared to normal B-cells (50). Moreover, the decrease of $CD19^+$ cells was reported in patients who had stage III gastric cancer (51). Whether the reduced CD19+ lymphocyte was because of a reduced expression of CD19 on B cells or a true reduction in B cell production needs to be investigated.

Our findings reveal elevated levels of IgG, IgM and IgA in a subgroup of CVID patients with malignancy which agrees with some studies that showed the immunoglobulin subclass levels increase in patients with malignancy, especially HL and in association with more advanced stages of the disease (52, 53) and gastric cancer (54). In ESID study included seven centers and 334 CVID patients has been found that a higher serum IgM is associated with lymphoid



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hyperplasias and lymphoid malignancy (5). The reason of high level of serum immunoglobulin in patients of CVID with malignancy is not clear; the possible reasons could be related to the mechanisms of pathophysiology for malignancy such as lymphocytic infiltration. Long-term cohort studies may be fundamental to fully evaluate these associations.

As mentioned previously, one limitation of this study is that the report of cancerous cases in CVID patients was the only inclusion criteria to study, so many of these articles may only focus on cancer and do not provided complete and accurate information about other clinical and immunological findings, so this is a weak point of our study. Moreover, our findings showed that the prevalence of cancer in cohorts of CVID patients was varied with high heterogeneity. As the studies were conducted in different countries with different goals, the prevalence of heterogeneity in the studies were correlated with other sources of variation, in addition to sampling error. Therefore, we used meta-analysis with the Random Model to integrate and obtain a pooled prevalence. Although the results showed high heterogeneity and this was a potential limitation in this study, it was the best way to estimate an overall effect size to show an overall picture of the magnitude of the problem and use these numbers in health policy. Another limitation of the present study is the lack of articles reporting the standardized incidence ratio (SIR) in the CVID cohorts. Of the total included studies, only three studies reported standardized prevalence ratio (SPR), which, due to the low number of studies, we could not integrate into the conducted meta-analysis.

**5. Expert opinion**

Our study confirmed the high prevalence of malignancy in patients with CVID and provides information about the clinical and immunologic characteristics of these patients which is potentially valuable in the early diagnosis and management. Individuals with malignancy may underlie the elevated DNA repair deficiency prevalence and it could be a hint for the presence of genes involved in DNA repair in CVID patients helping towards finding a cause of immunodeficiency. In the recent years some clinical immunologist believed that malignancy should be excluded from the main clinical phenotypes of CVID due to independency from underlying etiologies, however, our results were not consistent with this opinion as patients with malignancy present a specific phenotype not compatible with other CVID phenotype. Up to now the exact pathological mechanisms for this high prevalence of malignancy development are



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not fully determined; however, several mechanisms including immune dysregulation, impaired clearance of oncogenic viruses, genetic predisposition, impaired genetic stability and iatrogenic causes have been proposed to contribute to the development of malignancies in CVID patients.

## 6. Five-year view

Over the past few years, with the increasing number of disease genes identified in CVID (by using new emerging techniques such as whole exome sequencing, whole genome sequencing, and single-cell RNA sequencing), it has become clear that CVID is an umbrella diagnosis and that many of these genetic defects cause distinct disease entities. There is accumulating evidence that at least a subgroup of CVID patients with monogenic inheritance (e.g. PIK3CD**,** PIK3R1, CD27, CD70, and NF-κB) (55-58) and EBV susceptibility predispose to malignancy. It is hoped that with the help of recent advances in genetic diagnosis and its usage in multicenter or population-based collaborations, the panel of mutated genes responsible for genetic predisposition to malignancy in CVID patients has to be determined and classified in the next years. This clarification may allow for the design of novel therapeutic approaches for the treatment and management of these new monogenic entities.

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***Declaration of interest***

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*



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**References**


1. Tam JS, Routes JM. Common variable immunodeficiency. American journal of rhinology & allergy. 2013;27(4):260-5.
2. Saikia B, Gupta S. Common Variable Immunodeficiency. Indian journal of pediatrics. 2016;83(4):338-44.
3. Azizi G, Rezaei N, Kiaee F, Tavakolinia N, Yazdani R, Mirshafiey A, et al. T-Cell Abnormalities in Common Variable Immunodeficiency. Journal of investigational allergology & clinical immunology. 2016;26(4):233-43.
4. Azizi G, Bagheri Y, Tavakol M, Askarimoghaddam F, Porrostami K, Rafiemanesh H, et al. The Clinical and Immunological Features of Patients with Primary Antibody Deficiencies. Endocrine, metabolic & immune disorders drug targets. 2018;18(5):537-45.
5. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112(2):277-86.
6. Aghamohammadi A, Abolhassani H, Moazzami K, Parvaneh N, Rezaei N. Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. Journal of investigational allergology & clinical immunology. 2010;20(5):372-9.
7. Aghamohammadi A, Rezaei N, Gharagozlou M, Ramyar A, Mahjoub F, Rezaei-Kalantari K, et al. Hodgkin lymphoma in two siblings with common variable immunodeficiency. Pediatr Hematol Oncol. 2007;24(5):337-42.
8. Gompels MM, Hodges E, Lock RJ, Angus B, White H, Larkin A, et al. Lymphoproliferative disease in antibody deficiency: a multi-centre study. Clin Exp Immunol. 2003;134(2):314-20.
9. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. Journal of clinical immunology. 2007;27(3):308-16.
10. Cunningham-Rundles C, Cooper DL, Duffy TP, Strauchen J. Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. American journal of hematology. 2002;69(3):171-8.
11. Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, et al. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol. 2002;130(3):495-500.
12. Mohammadinejad P, Aghamohammadi A, Abolhassani H, Sadaghiani MS, Abdollahzade S, Sadeghi B, et al. Pediatric patients with common variable immunodeficiency: long-term follow-up. Journal of investigational allergology & clinical immunology. 2012;22(3):208-14.
13. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650-7.
14. Abolhassani H, Aghamohammadi A, Imanzadeh A, Mohammadinejad P, Sadeghi B, Rezaei N. Malignancy phenotype in common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2012;22(2):133-4.




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15. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. The Journal of allergy and clinical immunology. 2011;127(6):1329-41 e2; quiz 42-3.
16. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood. 2010;116(8):1228-34.
17. Tak Manesh A, Azizi G, Heydari A, Kiaee F, Shaghaghi M, Hossein-Khannazer N, et al. Epidemiology and pathophysiology of malignancy in common variable immunodeficiency? Allergologia et immunopathologia. 2017;45(6):602-15.
18. Leone P. Common Variable Immunodeficiency and Gastric Malignancies. Pediatric blood & cancer. 2018;19(2).
19. Dhalla F, da Silva SP, Lucas M, Travis S, Chapel H. Review of gastric cancer risk factors in patients with common variable immunodeficiency disorders, resulting in a proposal for a surveillance programme. Clin Exp Immunol. 2011;165(1):1-7.
20. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry. The Journal of allergy and clinical immunology. 2018;141(3):1028-35.
21. Aydogan M, Eifan AO, Gocmen I, Ozdemir C, Bahceciler NN, Barlan IB. Clinical and immunologic features of pediatric patients with common variable immunodeficiency and respiratory complications. Journal of investigational allergology & clinical immunology. 2008;18(4):260-5.
22. Bateman EA, Ayers L, Sadler R, Lucas M, Roberts C, Woods A, et al. T cell phenotypes in patients with common variable immunodeficiency disorders: associations with clinical phenotypes in comparison with other groups with recurrent infections. Clin Exp Immunol. 2012;170(2):202-11.
23. Piquer Gibert M, Alsina L, Giner Munoz MT, Cruz Martinez O, Ruiz Echevarria K, Dominguez O, et al. Non-Hodgkin lymphoma in pediatric patients with common variable immunodeficiency. European journal of pediatrics. 2015;174(8):1069-76.
24. Kralickova P, Milota T, Litzman J, Malkusova I, Jilek D, Petanova J, et al. CVID-Associated Tumors: Czech Nationwide Study Focused on Epidemiology, Immunology, and Genetic Background in a Cohort of Patients With CVID. Frontiers in immunology. 2018;9:3135.
25. Huh J. Epidemiologic overview of malignant lymphoma. The Korean journal of hematology. 2012;47(2):92-104.
26. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
27. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.
28. Abbott JK, Gelfand EW. Common Variable Immunodeficiency: Diagnosis, Management, and Treatment. Immunology and allergy clinics of North America. 2015;35(4):637-58.
29. Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. The Journal of experimental medicine. 2005;202(4):479-84.
30. Gangemi S, Allegra A, Musolino C. Lymphoproliferative disease and cancer among patients with common variable immunodeficiency. Leukemia research. 2015;39(4):389-96.



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31. Grulich AE, Vajdic CM, Cozen W. Altered immunity as a risk factor for non-Hodgkin lymphoma. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007;16(3):405-8.
32. Sherkat R, Sabri MR, Dehghan B, Bigdelian H, Reisi N, Afsharmoghadam N, et al. EBV lymphoproliferative-associated disease and primary cardiac T-cell lymphoma in a STK4 deficient patient: A case report. Medicine. 2017;96(48):e8852.
33. Sander CA, Medeiros LJ, Weiss LM, Yano T, Sneller MC, Jaffe ES. Lymphoproliferative lesions in patients with common variable immunodeficiency syndrome. The American journal of surgical pathology. 1992;16(12):1170-82.
34. Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, et al. Prospective study of cancer in patients with hypogammaglobulinaemia. Lancet. 1985;1(8423):263-6.
35. Zullo A, Romiti A, Rinaldi V, Vecchione A, Tomao S, Aiuti F, et al. Gastric pathology in patients with common variable immunodeficiency. Gut. 1999;45(1):77-81.
36. Azizi G, Abolhassani H, Asgardoon MH, Alinia T, Yazdani R, Mohammadi J, et al. Autoimmunity in common variable immunodeficiency: epidemiology, pathophysiology and management. Expert review of clinical immunology. 2017;13(2):101-15.
37. Turesson C, Matteson EL. Malignancy as a comorbidity in rheumatic diseases. Rheumatology (Oxford, England). 2013;52(1):5-14.
38. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmunity reviews. 2017;16(10):1049-57.
39. Dasanu CA, Bockorny B, Grabska J, Codreanu I. Prevalence and Pattern of Autoimmune Conditions in Patients with Marginal Zone Lymphoma: A Single Institution Experience. Connecticut medicine. 2015;79(4):197-200.
40. Zaenker P, Gray ES, Ziman MR. Autoantibody Production in Cancer--The Humoral Immune Response toward Autologous Antigens in Cancer Patients. Autoimmunity reviews. 2016;15(5):477-83.
41. Pardoll D. Does the immune system see tumors as foreign or self? Annual review of immunology. 2003;21:807-39.
42. Filaci G, Fravega M, Setti M, Traverso P, Millo E, Fenoglio D, et al. Frequency of telomerase-specific CD8+ T lymphocytes in patients with cancer. Blood. 2006;107(4):1505-12.
43. Forsberg O, Carlsson B, Malmstrom PU, Ullenhag G, Totterman TH, Essand M. High frequency of prostate antigen-directed T cells in cancer patients compared to healthy age-matched individuals. The Prostate. 2009;69(1):70-81.
44. Weynants P, Thonnard J, Marchand M, Delos M, Boon T, Coulie PG. Derivation of tumor-specific cytolytic T-cell clones from two lung cancer patients with long survival. American journal of respiratory and critical care medicine. 1999;159(1):55-62.
45. Bossi G, Trambas C, Booth S, Clark R, Stinchcombe J, Griffiths GM. The secretory synapse: the secrets of a serial killer. Immunological reviews. 2002;189:152-60.
46. Durgeau A, Virk Y, Corgnac S, Mami-Chouaib F. Recent Advances in Targeting CD8 T-Cell Immunity for More Effective Cancer Immunotherapy. Frontiers in immunology. 2018;9:14.
47. Walter U, Santamaria P. CD8+ T cells in autoimmunity. Current opinion in immunology. 2005;17(6):624-31.
48. Liblau RS, Wong FS, Mars LT, Santamaria P. Autoreactive CD8 T cells in organ-specific autoimmunity: emerging targets for therapeutic intervention. Immunity. 2002;17(1):1-6.
49. Yang W, Agrawal N, Patel J, Edinger A, Osei E, Thut D, et al. Diminished expression of CD19 in B-cell lymphomas. Cytometry Part B, Clinical cytometry. 2005;63(1):28-35.



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50. Cabezudo E, Carrara P, Morilla R, Matutes E. Quantitative analysis of CD79b, CD5 and CD19 in mature B-cell lymphoproliferative disorders. Haematologica. 1999;84(5):413-8.
51. Hong WS, Hong SI, Kim CM, Kang YK, Song JK, Lee MS, et al. Differential depression of lymphocyte subsets according to stage in stomach cancer. Japanese journal of clinical oncology. 1991;21(2):87-93.
52. Amlot PL, Green L. Serum immunoglobulins G, A, M, D and E concentrations in lymphomas. British journal of cancer. 1979;40(3):371-9.
53. Lichtenstein A, Taylor CR. Serum immunoglobulin levels in patients with non-Hodgkin's lymphoma. American journal of clinical pathology. 1980;74(1):12-7.
54. Saito T, Kuwahara A, Kinoshita T, Shigemitsu Y, Shimoda K, Miyahara M, et al. Increases in immunoglobulin and complement in patients with esophageal or gastric cancer. Surgery today. 1992;22(6):537-42.
55. Alkhairy OK, Perez-Becker R, Driessen GJ, Abolhassani H, van Montfrans J, Borte S, et al. Novel mutations in TNFRSF7/CD27: Clinical, immunologic, and genetic characterization of human CD27 deficiency. The Journal of allergy and clinical immunology. 2015;136(3):703-12 e10.
56. Abolhassani H, Edwards ES, Ikinciogullari A, Jing H, Borte S, Buggert M, et al. Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency. The Journal of experimental medicine. 2017;214(1):91-106.
57. Maccari ME, Abolhassani H, Aghamohammadi A, Aiuti A, Aleinikova O, Bangs C, et al. Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase delta Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase delta Syndrome Registry. Frontiers in immunology. 2018;9:543.
58. Fliegauf M, Bryant VL, Frede N, Slade C, Woon ST, Lehnert K, et al. Haploinsufficiency of the NF-kappaB1 Subunit p50 in Common Variable Immunodeficiency. American journal of human genetics. 2015;97(3):389-403.
59. Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, et al. Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. Journal of clinical immunology. 2003;23(5):385-400.
60. Ardeniz O, Basoglu OK, Gunsar F, Unsel M, Bayraktaroglu S, Mete N, et al. Clinical and immunological analysis of 23 adult patients with common variable immunodeficiency. Journal of investigational allergology & clinical immunology. 2010;20(3):222-36.
61. Herbst EW, Armbruster M, Rump JA, Buscher HP, Peter HH. Intestinal B cell defects in common variable immunodeficiency. Clin Exp Immunol. 1994;95(2):215-21.
62. Seve P, Bourdillon L, Sarrot-Reynauld F, Ruivard M, Jaussaud R, Bouhour D, et al. Autoimmune hemolytic anemia and common variable immunodeficiency: a case-control study of 18 patients. Medicine. 2008;87(3):177-84.
63. Ramyar A, Aghamohammadi A, Moazzami K, Rezaei N, Yeganeh M, Cheraghi T, et al. Presence of Idiopathic Thrombocytopenic Purpura and autoimmune hemolytic anemia in the patients with common variable immunodeficiency. Iranian journal of allergy, asthma, and immunology. 2008;7(3):169-75.
64. Furudoi A, Gros A, Stanislas S, Hamidou M, Furudoi E, Oksenhendler E, et al. Spleen Histologic Appearance in Common Variable Immunodeficiency: Analysis of 17 Cases. The American journal of surgical pathology. 2016;40(7):958-67.
65. Vlkova M, Ticha O, Nechvatalova J, Kalina T, Litzman J, Mauri C, et al. Regulatory B cells in CVID patients fail to suppress multifunctional IFN-gamma+ TNF-alpha+ CD4+ T cells differentiation. Clinical immunology (Orlando, Fla). 2015;160(2):292-300.

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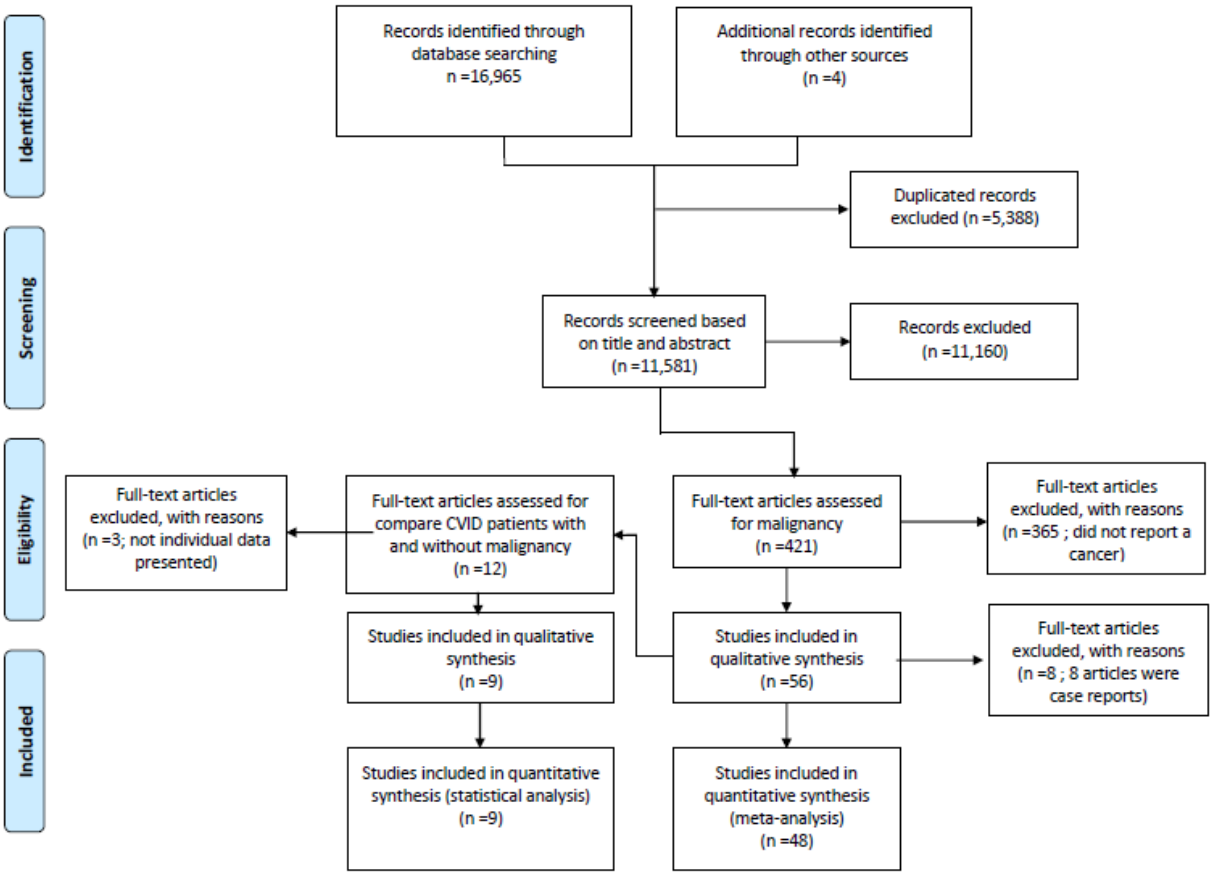



**Figure 1:** Flow diagram of the systematic review and meta-analysis for malignancy in CVID

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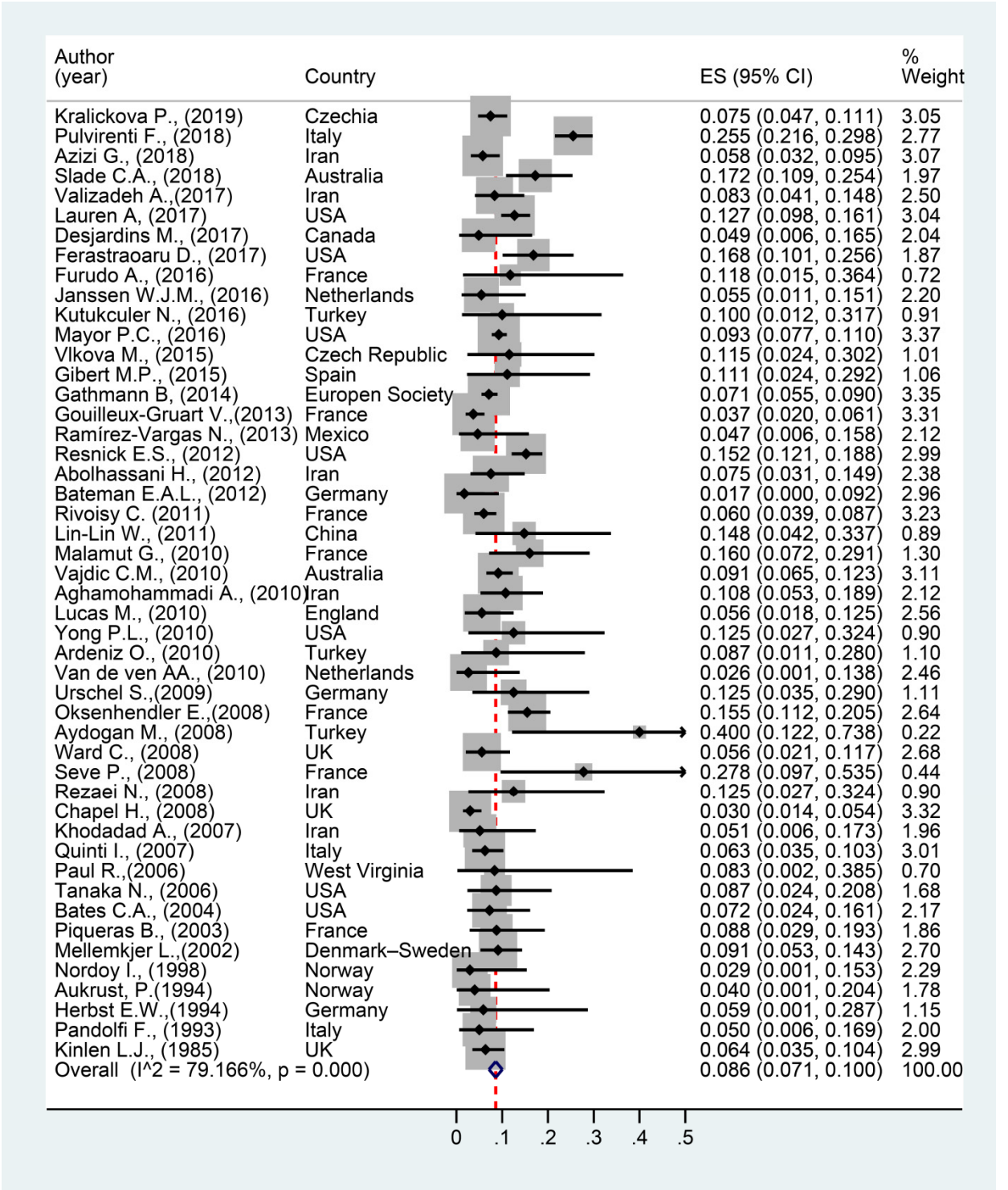



**Figure 2**: Pooled prevalence of malignancy assessed with a random effects method.

ES: effect size; CI: confidence interval.



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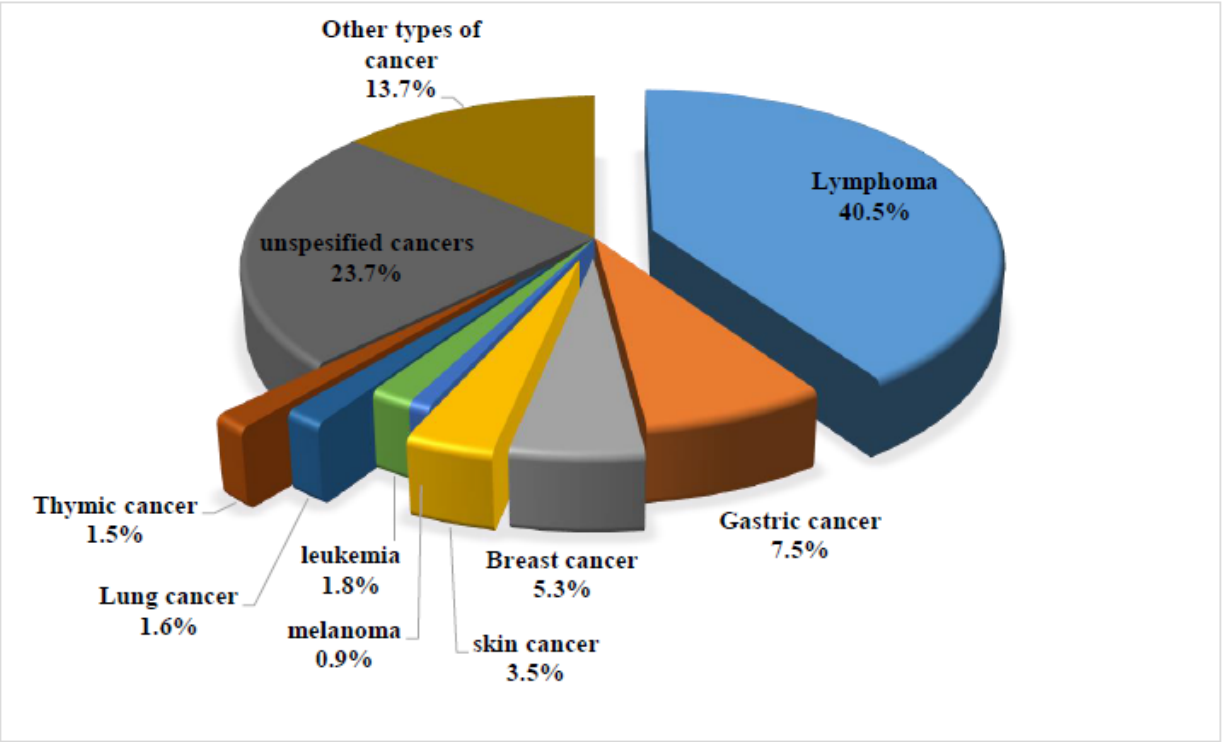



**Figure 3**: The pooled frequency of various types of malignancy among 8123 CVID patients included in the systematic review.

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**Table 1-** Demographic and corresponding immunologic data of CVID patients with and without malignancy.

| Parameters, number of evaluated patients | Total (n=187) | Patients with malignancy (n=26) | Patients without malignancy (n=161) | *P* value |
|---|---|---|---|---|
| **Sex ratio (M/F), n=187** | 87/100 | 14/12 | 73/88 | 0.526 |
| **Consanguinity (%), n=23** | 7 (30.4) | 5 (35.7) | 2 (22.2) | 0.657 |
| **Age (y), Median (IQR), n=132** | 45.0 (30.5) | 30.5 (25.5) | 46.0 (30.7) | 0.310 |
| **Age at onset (y), Median (IQR), n=49** | 12.0 (19.5) | 15.0 (25.0) | 10.0 (20.2) | 0.072* |
| **Age at diagnosis (y), Median (IQR), n=61** | 20.0 (26.0) | 26.5 (21.5) | 18.0 (27.5) | 0.034** |
| **Diagnostic delay (y), Median (IQR), n=46** | 11.0 (11.2) | 7.0 (14.0) | 11.0 (12.0) | 0.189 |
| **IgG (mg/dl), Median (IQR), n=151** | 113.0 (231.0) | 151.0 (112.0) | 63.0 (202.5) | 0.013** |
| **IgA (mg/dl), Median (IQR), n=148** | 4.0 (12.3) | 21.0 (18.0) | 2.0 (8.3) | 0.001** |
| **IgM (mg/dl), Median (IQR), n=151** | 10.0 (23.1) | 17.0 (18.5) | 7.3 (23.7) | 0.017** |
| **$CD3^+$ lymphocytes, %cell/mL, n=17** | 76.0 (8.8) | 76.0 (20.8) | 71.6 (30.0) | 0.646 |
| **$CD4^+$ T cells,% cell/mL(IQR), n=73** | 39.0 (16.5) | 39.0 (21.2) | 38.0 (17.0) | 0.665 |
| **$CD8^+$ T cells, %cell/mL(IQR), n=73** | 33.0 (9.0) | 37.5 (6.4) | 32.0 (20.0) | 0.052* |
| **$CD19^+$ lymphocytes(IQR), %cell/mL, n=74** | 7.0 (7.2) | 4.0 (5.1) | 7.0 (7.7) | 0.051* |

*M; Male, F; Female; N; Count, y; Year, Ig; Immunoglobulin, IQR; Interquartile range*
*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 <0.05*

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**Table 2-** Main clinical characteristics of CVID patients with and without malignancy

| **Clinical manifestation, (evaluated patients with/without malignancy)** | **Total patient with clinical presentation (%)** | **Patients with malignancy and clinical presentation (%)** | **Patients without malignancy and clinical presentation (%)** | ***P* value** |
|---|---|---|---|---|
| **Granuloma; n=136 (18/118)** | 26 (19.1) | 3 (16.7) | 23 (19.5) | 1.0 |
| **Splenomegaly; n=162 (21/141)** | 74 (45.7) | 10 (47.6) | 64 (45.4) | 0.848 |
| **Autoimmunity; n=187 (26/161)** | 73 (39.0) | 15 (57.6) | 58 (36.0) | 0.036** |
| **Pneumonia; n=74 (13/61)** | 29 (39.2) | 7 (53.8) | 22 (36.1) | 0.233 |
| **Sinusitis; n=53 (8/45)** | 40 (75.5) | 6 (75.0) | 34 (75.6) | 1.0 |
| **Rhinitis; n=44 (7/37)** | 1 (2.3) | 0 (0.0) | 1 (100) | 1.0 |
| **Malabsorption; n=79 (13/66)** | 8 (10.1) | 4 (30.8) | 4 (6.1) | 0.022* |
| **Failure to thrive; n=79 (13/66)** | 12 (15.2) | 4 (30.8) | 8 (12.1) | 0.103 |
| **Bronchiectasis; n=105 (16/89)** | 42 (40.0) | 9 (56.2) | 33 (37.1) | 0.150 |

*The value is presented as absolute frequency and the numbers in the parentheses are the corresponding percent values.*

** p-value is statistically significant <0.05*

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**Table 3-** The various types of autoimmune diseases among CVID patients with malignancy in various studies

| Case number | Type of malignancy | Type of autoimmune disorder | First author (Year) | Reference | Patient identification (refer to Table S1) |
|---|---|---|---|---|---|
| 1 | B cell lymphoma | AIHA | Piqueras, (2003) | (59) | P36 |
| 2 | Diffuse B-cell lymphoma, | AIHA | Ardeniz, (2010) | (60) | P12 |
| 3 | HL | AIHA + PA | Herbst, (1994) | (61) | P9 |
| 4 | T cell NHL | AIHA + ITP | Seve, (2008) | (62) | P5 |
| 5 | B cell NHL | AIHA + ITP | Seve, (2008) | (62) | P14 |
| 6 | MALToma | AIHA + ITP | Ramyar, (2008) | (63) | P5 |
| 7 | B cell -NHL | AIHA + ITP + AIN | Seve, (2008) | (62) | P9 |
| 8 | B cell -NHL | AIHA + ITP + AIN | Seve, (2008) | (62) | P15 |
| 9 | Squamous cell carcinoma | ITP | Furudoi, (2016) | (64) | P2 |
| 10 | B cell lymphoma | ITP | Piqueras, (2003) | (59) | P57 |
| 11 | Thymoma | UC + RA | Ardeniz, (2010) | (60) | P16 |
| 12 | Wilms tumour | UC | Aydogan, (2008) | (21) | P1 |
| 13 | NHL | UC | Aydogan, (2008) | (21) | P8 |
| 14 | Basal cell carcinoma | SLE + vitiligo + DM1 | Vlkova, (2015) | (65) | P9 |
| 15 | Gastric cancer | PA | Vlkova, (2015) | (65) | P24 |

*NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma; AIHA: Autoimmune Hemolytic Anemia; PA: Pernicious Anemia; ITP: Idiopathic Thrombocytopenic Purpura; AIN: Autoimmune Neutropenia; UC: Ulcerative Colitis; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematous; DM1: Diabetes Mellitus Type 1*

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**Figure S1**: Meta-analysis of the prevalence of malignancy in CVID patients during the years. Size of circles indicated the sample size of each study

**Table S1. Main characteristics of the included studies on the prevalence of malignancy in CVID patients**



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