# Retrospective Analysis of a Longitudinal Single Institution 219 Common Variable Immunodeficiency Patient Cohort

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# Abstract

Common variable immunodeficiency is a heterogenous disorder of the immune system associated with immunodeficiency, lymphoproliferation, autoimmunity, and malignancy. Certain laboratory characteristics of common variable immunodeficiency patients can be associated with an increase of related clinical sequelae, though there is limited data on predictive characteristics for clinical sequelae in CVID patients. The purpose of this study was to analyze a unique large CVID patient cohort for predictive laboratory characteristics of clinical sequelae. A retrospective chart review was performed of a longitudinal cohort of CVID patients treated at a single institution, largely by a single provider with higher dose replacement immunoglobulin, that has not been previously described. 219 CVID patients were followed for 1,990 patient-years. 86% of the patients were on immunoglobulin with an average IgG trough of 1260 mg/dL. Low IgG at time of diagnosis, low CD19 absolute cell count, and poor mitogen induced lymphocyte proliferation were associated with increase of CVID clinical sequelae. In particular, this cohort demonstrates the novel finding that low IgG at time of diagnosis prior to immunoglobulin replacement is associated with a higher incidence of lymphoma, bronchiectasis, granulomatous disease, lymphoid hyperplasia, splenomegaly, and hepatic disease.


# Introduction

The clinical course of common variable immunodeficiency (CVID) patients is varied and can include infection, autoimmunity, gastrointestinal disease, neurologic disease, lung disease, lymphoproliferation, granulomas, and malignancy.[1–3] Patients with CVID are known to have a range of cellular and humoral immune defects.[4] There is limited data on predictive characteristics for clinical sequelae in CVID patients. This particular cohort of CVID patients treated at a single institution for many years largely by the same provider has not been previously described. This study's aim was to describe this unique cohort of CVID patients and analyze their underlying clinical, laboratory, and phenotypic characteristics.

# Methods

We used our institution's Clinical Looking Glass software to access the computerized medical record and find all patients within a single hospital system with an International Classification of Diseases (ICD) code of CVID or hypogammaglobulinemia. 539 patients were recognized by the software and a manual chart review was performed to identify 219 patients with CVID (Table 1). CVID diagnosis was confirmed by 2015 International Consensus Document criteria.[5] Patients were required to have low IgG and low IgA or IgM at least 2 standard deviations below mean age-adjusted reference ranges, be older than 4 years of age, poor response to T-dependent and T-independent antigens, have evidence of recurrent infections, autoimmunity, or lymphoproliferation, and exclusion of other causes of hypogammaglobulinemia. Approximately 20% of the 219 patients did not have pre-immunoglobulin (IG) laboratory data available but were immunologist confirmed long-standing CVID patients. These 20% patients were also evaluated for a low post-IG IgA and/or IgM and a low IgG if there was a break in IG treatment to confirm diagnosis. Patients were included if their pre-immunoglobulin treatment IgG (pre-IG-IgG) was below 400 mg/dL and

other criteria were met, though some patients were included with slightly higher values if suspicion was high and all other criteria were clear. 320 patients were excluded from the initial 539 patients as 48 patients had no records available, 112 had no signs of immunodeficiency on chart review, 49 patients had a secondary immunodeficiency (i.e. chronic steroids, rituximab, protein-loosing enteropathy, malignancy), and 111 patients had another diagnosed primary immunodeficiency (i.e. specific antibody deficiency, isolated IgG deficiency). Some patients with protein-loosing enteropathy were included if they had other clinical and laboratory characteristics strongly suggestive of CVID as opposed to having a primary enteropathy causing hypogammaglobulinemia. Patients believed to have hypogammaglobulinemia secondary to lymphopenia from immunosuppressive or immunomodulatory therapies were excluded but there were some patients included who were on such therapies at time of diagnosis since their clinical and laboratory characteristics were strongly suggestive of CVID. Additionally, patients with a known genetic defect such as LRBA deficiency, hyper IgM syndrome, and Bruton's agammaglobulinemia were excluded. However, few cohort patients underwent comprehensive genetic testing. 32% of the 219 CVID patient cohort underwent TNFRSF13B evaluation but only approximately 20% underwent more comprehensive genetic testing. This study was approved by the medical center's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act.

Table 1
Exclusion and inclusion criteria for final CVID cohort used for analysis.

| **539 Patients (total initial cohort)** | **ICD code of CVID or hypogammaglobulinemia who underwent manual chart review** |
|---|---|
| 48 Patients (excluded) | No records available |
| 112 Patients (excluded) | No evidence of immunodeficiency on chart review |
| 49 Patients (excluded) | Secondary immunodeficiency<br>20 steroid induced hypogammaglobulinemia<br>8 rituximab induced hypogammaglobulinemia<br>6 protein loosing enteropathy (3 congestive heart failure, 1 end stage renal disease, 1 plastic bronchitis, 1 sepsis)<br>5 chronic lymphocytic leukemia<br>5 multiple myeloma<br>3 monoclonal gammopathy of undetermined significance<br>1 lymphoma<br>1 dysgammaglobulinemia |

| 539 Patients (total initial cohort) | ICD code of CVID or hypogammaglobulinemia who underwent manual chart review |
|---|---|
| 111 Patients (excluded) | Another diagnosed primary immunodeficiency |
| | 45 IgG deficiency |
| | 22 specific antibody deficiency |
| | 7 IgG subclass deficiency |
| | 4 transient hypogammaglobulinemia of infancy |
| | 4 T cell lymphopenia |
| | 4 IgA deficiency |
| | 4 IgM deficiency |
| | 4 severe combined immunodeficiency |
| | 3 undiagnosed syndrome |
| | 2 Good's syndrome |
| | 2 hyper IgM syndrome |
| | 1 X-linked lymphoproliferative disease |
| | 1 Bruton's agammaglobulinemia |
| | 1 LRBA deficiency |
| | 1 IPEx syndrome |
| | 1 IKBKB deficiency |
| | 1 IgG4 related disease |
| | 1 CHARGE syndrome |
| | 1 ataxia telangiectasia |
| | 1 APECED |
| | 1 ALPS |
| 219 Patients (final cohort for analysis) | Confirmed met diagnostic criteria for CVID and underwent further statistical analysis |

# Results

Baseline demographic, clinical, and laboratory characteristics (Table 2) in addition to phenotypic characteristics (Table 3) of the 219 CVID patients were collected retrospectively. Table 3 lists phenotypic characteristics either before or after starting IG. Of note, after starting IG treatment, 7 CVID patients were

diagnosed with autoimmune cytopenia, 5 granulomatous–lymphocytic interstitial lung disease (GLILD), and 1 lymphoma – the remaining diagnoses for these diseases were made prior to starting IG treatment.

Table 2
Baseline demographic, clinical, and laboratory characteristics of CVID patient cohort.

| Characteristic | Result | Number of patients value available |
|---|---|---|
| Sex | 58% female | 219 |
| | 42% male | |
| Race | 75% White | 131 |
| | 8% African American | |
| | 17% other race | |
| Ethnicity | 14% Hispanic | 96 |
| | 86% not Hispanic | |
| Home | 30% New York City | 219 |
| | 49% other New York state | |
| | 21% out of state | |
| Average age | 54 years (current age) | 219 |
| | 42 years (at diagnosis) | |
| | 52 years (at last follow-up) | |
| IG replacement | 86% on IG (at some point) | 219 |
| | 14% not on IG (due to refusal or lost to follow-up) | |
| Average IgG trough | 1260 ± 419 mg/dL | 166 |
| Average IgG trough difference (trough subtracted from pre-IG-IgG level) | 809 ± 463 mg/dL | 139 |
| Years patients were followed | 10 years (on average) | 219 |
| | 1,990 patient-years (total) | |
| | 1,725 patient-years (on IG) | |
| B cell immunity | 46% low total B cells | 183 |
| | 56% low switch memory B cells | 41 |
| Average pre-diagnosis IgG | 410 ± 172 mg/dL | 178 |

| Characteristic | Result | Number of patients value available |
|---|---|---|
| T cell immunity | 52% low total T cells | 188 |
| | 37% phytohemagglutinin and/or concanavalin A induced lymphocyte proliferation below laboratory standard | 103 |
| Family history | 28% family history concerning for immunodeficiency | 199 |
| Genetic testing | 36% TACI variant (heterozygous or homozygous) | 70 |

Table 3
Phenotypic characteristics of CVID patient cohort. Most cohort patients displayed several different phenotypic characteristics related to CVID.

| Characteristic | Result (%) | Select Details (n) |
|---|---|---|
| Infections | 96%<br>*16% infections only phenotype | 154 sinusitis<br>117 bronchitis<br>110 pneumonia<br>40 otitis<br>35 pharyngitis<br>28 H. pylori<br>27 Epstein–Barr virus<br>26 fungal infection (thrush, onychomycosis)<br>25 urinary tract infections<br>19 encephalitis/meningitis<br>18 varicella-zoster virus (usually not disseminated)<br>18 sepsis<br>8 herpes simplex virus (usually not disseminated)<br>8 Human papillomavirus<br>6 Giardia<br>1 human immunodeficiency viruses |
| Autoimmune disease | 61% | 17 idiopathic thrombocytopenic purpura<br>11 inflammatory bowel disease<br>9 vasculitis<br>8 hemolytic anemia<br>7 neutropenia |
| Allergic disease | 51% | 67 allergic rhinitis<br>55 asthma |

| Characteristic | Result (%) | Select Details (n) |
|---|---|---|
| Endocrine disease | 48% | 35 hypothyroidism<br>58 Hashimoto's<br>7 type I diabetes |
| Gastrointestinal disease | 42% | 69 reflux disease<br>11 inflammatory bowel disease<br>5 nodular hyperplasia of bowel |
| Neurologic disease | 40% | 43 neuropathy<br>12 seizure disorder<br>7 chronic inflammatory demyelinating polyneuropathy<br>5 stiff person syndrome |
| Lung disease | 28% | 22 bronchiectasis<br>21 GLILD |
| Granulomatous disease | 12% | 21 GLILD |
| Lymphoid hyperplasia | 26% | 45 adenopathy<br>5 nodular hyperplasia of bowel |
| Splenomegaly | 15% | 8 splenectomy |
| Malignancy | 21% | 15 lymphoma<br>9 breast cancer<br>7 leukemia<br>5 skin cancer<br>2 lung cancer<br>2 gastric cancer |
| Arthritis | 21% | N/A |
| Chronic fatigue | 15% | N/A |
| Hepatic disease | 12% | N/A |
| Renal disease | 12% | N/A |

| Characteristic | Result (%) | Select Details (n) |
|---|---|---|
| Monoclonal gammopathy | 6% | N/A |
| Known deaths | 1.5% | 2 infections<br>1 heart failure |
| Bone marrow transplant | 1% | 1 acute lymphoblastic leukemia<br>1 non-Hodgkin's lymphoma<br>*both survived |

CVID patients with lower pre-IG-IgG were more likely to have a diagnosis of lymphoma, bronchiectasis, granulomatous disease, lymphoid hyperplasia, splenomegaly, or hepatic disease than CVID patients with a higher pre-IG IgG (*p* 0.02, < 0.01, < 0.01, < 0.01, < 0.01, 0.02; comparison of means; Table 4). Of note, this cohort did have a higher pre-IG-IgG than other described cohorts (average 410 mg/dL).[1–3] This is likely due to many patients included in the cohort having lower IgG but incomplete medical records documenting the exact pre-IG-IgG number and therefore not included in the calculation of the average in addition to the exclusion of patients with primary immunodeficiencies with profound hypogammaglobulinemia (Table 1) who might be included in other CVID cohorts.

Table 4
Correlations between clinical phenotype and laboratory values using comparison of means.

| Clinical Phenotype | Low Pre-IG-IgG | Statistics |
|---|---|---|
| CVID with Lymphoma | IgG 306±148 mg/dL (n = 14) vs. | $p = 0.02$ |
| CVID without Lymphoma | IgG 418±171 mg/dL (n = 164) | |
| CVID with Bronchiectasis | IgG 274±249 mg/dL (n = 18) vs. | $p < 0.01$ |
| CVID without Bronchiectasis | IgG 425±154 mg/dL (n = 160) | |
| CVID with Granulomatous Disease | IgG 237±224 mg/dL (n = 18) vs. | $p < 0.01$ |
| CVID without Granulomatous Disease | IgG 429±154 mg/dL (n = 160) | |
| CVID with Lymphoid Hyperplasia | IgG 332±211 mg/dL (n = 45) vs. | $p < 0.01$ |
| CVID without Lymphoid Hyperplasia | IgG 436±148 mg/dL (n = 133) | |
| CVID with Splenomegaly | IgG 311±185 mg/dL (n = 27) vs. | $p < 0.01$ |
| CVID without Splenomegaly | IgG 427±164 mg/dL (n = 151) | |
| CVID with Hepatic Disease | IgG 327±206 mg/dL (n = 20) vs. | $p = 0.02$ |
| CVID without Hepatic Disease | IgG 420±165 mg/dL (n = 158) | |

CVID with CD19 lymphopenia (absolute cell count below 78 cells/μL) were more likely to have an autoimmune diagnosis than CVID patients with normal CD19 counts ($p < 0.01$; chi square; Table 5). Other studies showed that low switch memory B cells are associated with CVID autoimmunity.[6] These CD19 counts were performed prior to immunosuppressive or B cell depletive therapy as those values for those on these therapies were excluded from analysis.

Table 5
Correlations between clinical phenotype and laboratory values using chi square.

| Clinical Phenotype | Clinical Phenotype | Statistics |
|---|---|---|
| CVID with CD19 Lymphopenia and Autoimmune Disease / All CVID with CD19 Lymphopenia<br><br>(74/99) | CVID with Normal CD19 Counts and Autoimmune Disease / All CVID with Normal CD19 Counts<br><br>(44/84) | $p < 0.01$<br><br>Δ 23%<br><br>CI 9%-36%<br><br>$\chi^2$ 10.4 |
| CVID with Poor Mitogen Induced Lymphocyte Proliferation and Granulomatous Disease / All CVID with Poor Mitogen Induced Lymphocyte Proliferation<br><br>(9/38) | CVID with Normal Mitogen Induced Lymphocyte Proliferation and Granulomatous Disease / All CVID with Normal Mitogen Induced Lymphocyte Proliferation<br><br>(3/65) | $p < 0.01$<br><br>Δ 19%<br><br>CI 6%-35%<br><br>$\chi^2$ 8.6 |
| CVID with Poor Mitogen Induced Lymphocyte Proliferation and Lymphoid Hyperplasia / All CVID with Poor Mitogen Induced Lymphocyte Proliferation<br><br>(15/38) | CVID with Normal Mitogen Induced Lymphocyte Proliferation and Lymphoid Hyperplasia / All CVID with Normal Mitogen Induced Lymphocyte Proliferation<br><br>(13/65) | $p = 0.03$<br><br>Δ 19%<br><br>CI 2%-37%<br><br>$\chi^2$ 4.6 |
| CVID with Poor Mitogen Induced Lymphocyte Proliferation and Splenomegaly / All CVID with Poor Mitogen Induced Lymphocyte Proliferation<br><br>(10/38) | CVID with Normal Mitogen Induced Lymphocyte Proliferation and Splenomegaly / All CVID with Normal Mitogen Induced Lymphocyte Proliferation<br><br>(6/65) | $p = 0.02$<br><br>Δ 17%<br><br>CI 2%-34%<br><br>$\chi^2$ 5.3 |

CVID patients with poor mitogen induced lymphocyte proliferation were more likely to have a diagnosis of granulomatous disease, lymphoid hyperplasia, or splenomegaly than CVID patients with normal mitogen induced lymphocyte proliferation ($p < 0.01$, 0.03, 0.02; chi square; Table 5). Mitogen studies were performed with phytohemagglutinin, concanavalin A, pokeweed as stimulants and $^3$H-thymidine incorporation was measured by scintillation counter. Mitogen studies were typically repeated to confirm actuality. Low values were considered if lower than reference ranges. Other studies have shown T cell abnormalities in CVID lymphoproliferation.[4]

Additional correlations between laboratory characteristics and clinical phenotypes were not significant in this cohort. In particular, this study did not reveal an association between GLILD and autoimmunity or splenomegaly as seen in other cohorts, likely due to a low number of total GLILD cases.[7] Additionally, while prior research showed high IgM as a risk factor for lymphoma, that was not seen in our cohort.[1]

Other correlations compared to clinical phenotype that were found to not be clinically significant included but not limited to sex, T cell lymphopenia, TACI variant, positive family history, pre-IG-IgM, recurrent sinopulmonary infections, and age at CVID diagnosis.

# Discussion

Phenotypic characteristics of this CVID cohort are largely similar to other large published CVID cohorts, though this cohort has an overall higher incidence of autoimmunity and malignancy.[1–3] This cohort provides some novel prognostic criteria in CVID patients. The CVID associated complications (lymphoma, bronchiectasis, granulomatous disease, lymphoid hyperplasia, splenomegaly, and hepatic disease) were associated with lower pre-IG-IgG and this has not been previously described. Gathmann et al[3] reported only the association of splenomegaly with low pre-IG-IgG. If these specific correlations can be demonstrated in other CVID cohorts, this can help in risk assessment and management of CVID patients with a profoundly low IgG at time of diagnosis. It is also possible that these inflammatory or lymphoproliferative complications could affect measured immune parameters and cause these findings.

This patient cohort is unique in that the majority of the patients were treated longitudinally by a single provider (for a total of 1,990 patient-years) and were typically treated with higher dose replacement IG (goal IgG trough 1200–1400 mg/dL, average IgG trough 1260 mg/dL). Many patients in the cohort were followed for 30 + years. Prior reports showed that higher IgG troughs can prevent infections and pulmonary complications.[8, 9] Lee et al.[8] suggested that titrating the IgG trough level up to 960 mg/dL progressively reduces the rate of infections and that there is less additional benefit beyond that. Interestingly, our cohort with higher IgG troughs has an overall low incidence of autoimmune cytopenia, GLILD, and lymphoma. However, there have been no randomized prospective studies to date looking to see if higher IgG troughs could prevent such CVID sequelae. There is stronger evidence in this cohort that pre-IG-IgG is the most predictive of serious CVID sequelae. Additionally, patients were preferentially on subcutaneous IG over intravenous (IV) for ease of administration and decrease likelihood of adverse events – with provider preferential use of hyaluronidase-facilitated subcutaneous for increased dosing interval.

For the cohort characteristics described in Table 3, there were several findings of interest. Firstly, the numbers for infections were likely under reported as these were not always consistently reported in the medical record. The cases of meningitis/encephalitis are high and this is likely because we included aseptic meningitis which could have been a complication of replacement IG. Some of these patients were followed for 30 + years and had complications from IVIG many years ago. The incidence of splenomegaly and bronchiectasis is low, possibly due to this cohort being an overall mild phenotype or, arguably, due to the high IgG trough of this cohort. Defining inflammatory bowel disease (IBD) in this cohort was difficult as CVID patients can suffer various forms of gut inflammation. We deferred to a gastroenterologist's diagnosis, which has limitations since not all gastroenterologists are familiar with various forms of CVID related gut disease. We included IBD as an autoimmune disease since we believed this labeled diagnosis of IBD likely largely included autoimmune gut disease. The total number of Hashimoto's diagnoses in this

cohort is very high. We believe this is likely an overdiagnosis and that anti-thyroid antibodies detected in the patients were likely from the replacement immunoglobulin. Therefore, we decided not to include these numbers in our autoimmune calculations. Allergic rhinitis and asthma were diagnosed per patient report, though this is likely an overestimation. Patients with CVID can have recurrent infectious sinusitis that is misdiagnosed as allergic rhinitis. Patients with CVID can also have infectious pulmonary disease or other pulmonary sequelae that can be misdiagnosed as asthma. Neuropathy is also high in this cohort. Neuropathy was diagnosed by patient report, though many of the patients had confirmed electromyography and nerve conduction studies. This high percentage is likely due to a referral bias from local neurologists who work closely with our immunology department. TACI variants were also higher than expected but that is because any variant was included that wasn't clearly classified as benign, including heterozygous/homozygous variants.

A major limitation of this study is that due to it being a retrospective chart review, there were many incomplete medical records. Additionally, many patients have not been followed for many years and a diagnosis other than CVID might be elucidated by genetic testing and/or re-evaluation. Since CVID patients are commonly treated with immunosuppressive or immunomodulatory therapies for autoimmune or lymphoproliferative disease, attempts were made to eliminate this as a confounder both in identifying CVID patients for the cohort and analyzing laboratory values, though there still could have been a confounding effect due to the limitations of information available in a chart review.

# Conclusions

Despite the improved outcome with IG replacement treatment strategies, there remains significant morbidity, mortality, and poor quality of life in CVID patients beyond infectious and pulmonary complications. This study supports that certain baseline laboratory characteristics, particularly the novel finding of pre-IG-IgG's association with a higher incidence of lymphoma, bronchiectasis, granulomatous disease, lymphoid hyperplasia, splenomegaly, and hepatic disease, can be used to predict clinical sequelae and phenotypes of CVID.

# Declarations

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Authorship Contributions

Melissa Gans conceptualized the study, performed the chart review and statistical analysis, and contributed to writing of the manuscript. Brian Goodman contributed to the chart review and the writing of the manuscript. Larry Bernstein, Rachel Eisenberg, and Arye Rubinstein contributed to conceptualizing the study and the writing of the manuscript.

Disclosures of Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Availability of Data and Material

Data and material are available upon request.

Code Availability

Not applicable.

Ethics Approval

This study was approved by the medical center's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act.

Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

# References

1. Chapel, H., et al., *Common variable immunodeficiency disorders: division into distinct clinical phenotypes.* Blood, 2008. **112**(2): p. 277-86.

2. Ho, H.E. and C. Cunningham-Rundles, *Non-infectious Complications of Common Variable Immunodeficiency: Updated Clinical Spectrum, Sequelae, and Insights to Pathogenesis.* Front Immunol, 2020. **11**: p. 149.

3. Gathmann, B., et al., *Clinical picture and treatment of 2212 patients with common variable immunodeficiency.* J Allergy Clin Immunol, 2014. **134**(1): p. 116-26.

4. Mouillot, G., et al., *B-cell and T-cell phenotypes in CVID patients correlate with the clinical phenotype of the disease.* J Clin Immunol, 2010. **30**(5): p. 746-55.

5. Bonilla, F.A., et al., *International Consensus Document (ICON): Common Variable Immunodeficiency Disorders.* J Allergy Clin Immunol Pract, 2016. **4**(1): p. 38-59.

6. Sanchez-Ramon, S., et al., *Memory B cells in common variable immunodeficiency: clinical associations and sex differences.* Clin Immunol, 2008. **128**(3): p. 314-21.

7. Hartono, S., et al., *Predictors of granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency.* Ann Allergy Asthma Immunol, 2017. **118**(5): p. 614-620.

8. Lee, J.L., et al., *A Systematic Review and Meta-regression Analysis on the Impact of Increasing IgG Trough Level on Infection Rates in Primary Immunodeficiency Patients on Intravenous IgG Therapy.* J Clin Immunol, 2020.

9. Orange, J.S., et al., *Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies.* Clin Immunol, 2010. **137**(1): p. 21-30.