Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

The relationship between neutropenia and disease prognosis in patients with Common Variable Immunodeficiency (CVID)

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Received 22 July 2025; Accepted 16 October 2025
Available online 1 January 2026

KEYWORDS
common variable immunodeficiency;
neutropenia;
autoimmune cytopenia;
primary immunodeficiency;
survival analysis

Abstract
Objective: This study aimed to determine the frequency of neutropenia in patients with common variable immunodeficiency (CVID) and investigate its relationship with disease prognosis.
Methods: Data from 84 patients diagnosed with CVID and followed between 2019 and 2024 at the Department of Adult Clinical Immunology and Allergy, Necmettin Erbakan University, were retrospectively reviewed. Patients were divided into two groups based on the presence or absence of neutropenia. Demographic data, clinical findings, laboratory parameters, and survival rates were compared. Statistical analyses included the Mann-Whitney U test, the Chi-square test, and the Kaplan-Meier survival analysis.
Results: A total of 84 patients diagnosed with CVID were included in the study, with a median age of 38 years (range, 20-79 years). Of the participants, 48.8% were females (n = 41). Neutropenia was observed in 28.5% of patients (n = 24). The most common presenting complaints included autoimmune cytopenias, such as anemia and thrombocytopenia. Compared to non-neutropenic patients (n = 60), those with neutropenic CVID had a significantly higher mortality rate (33.3% vs 6.7%, P = 0.004). According to Kaplan-Meier survival analysis, the 8-year survival rates were 57.5 and 92.5% for neutropenic and for non-neutropenic CVID patients (p < 0.001), respectively.
Conclusion: This study suggests that neutropenia in CVID patients may be more than just a hematological issue; it could also serve as an important clinical marker associated with increased mortality. Recognizing and closely monitoring neutropenia is essential for effective CVID management.

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https://doi.org/10.15586/aei.v54i1.1489

Introduction

Common Variable Immunodeficiency (CVID) is a diverse primary immunodeficiency characterized by hypogammaglobulinemia. With an estimated incidence of 1 in 20,000 to 1 in 50,000, CVID is the most common symptomatic primary immunodeficiency disorder.[1] In addition to recurrent infections, it is associated with immune-mediated thrombocytopenia, hemolytic anemia, lymphoproliferation, splenomegaly, lymphoma or leukemia, enteropathy, nodular regenerative hyperplasia of the liver, bronchiectasis, granulomatous lymphocytic interstitial lung disease (GLILD), autoimmune disorders, and various gastrointestinal complications.[2,3]

Following recurrent infections, autoimmune manifestations are the second most common findings in CVID. Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) occur in more than 20% of CVID patients.[4,5]

Neutropenia is defined as an absolute neutrophil count (ANC) below 1.5 × 10¤/L. The clinical effects of neutropenia can vary widely, from a benign condition such as ethnicity-related neutropenia to life-threatening infections caused by drug-induced agranulocytosis. Neutropenia is uncommon in CVID patients and has been reported in some studies with a prevalence ranging from less than 1–3.4%.[6,7] However, the exact prevalence, underlying mechanisms (including autoimmune, congenital, drug-induced, or viral causes), clinical course, and prognosis of neutropenia in CVID remain unclear. Although intravenous immunoglobulin (IVIg) replacement therapy is a common and effective treatment for CVID, affected individuals may still experience acute neutropenic episodes during IVIg replacement therapy.[8,9]

Therefore, understanding the prevalence, clinical implications, and impact of neutropenia on survival in patients with CVID is very important. In the literature, neutropenia is often described as a rare finding in CVID and is generally considered a secondary blood disorder. However, its link to autoimmune complications and infections indicates that neutropenia should be viewed within a broader clinical context. This study aimed to find out how common neutropenia is in patients diagnosed with CVID, explore its relationship with clinical and laboratory parameters, and assess its effects on mortality. By comparing patients with and without neutropenia, the potential prognostic significance of this finding was evaluated.

Materials and Methods

Study design and participants

This retrospective study included 84 patients diagnosed with common variable immunodeficiency (CVID) who were followed at the Department of Adult Immunology and Allergy Diseases at Necmettin Erbakan University between 2019 and 2024. These patients were selected from a total of 108 individuals with CVID based on predefined exclusion criteria (Figure 1). Diagnoses were confirmed according to the European Society for Immunodeficiencies (ESID) diagnostic criteria for CVID.[5] Data were collected from both electronic health records and physical medical files.

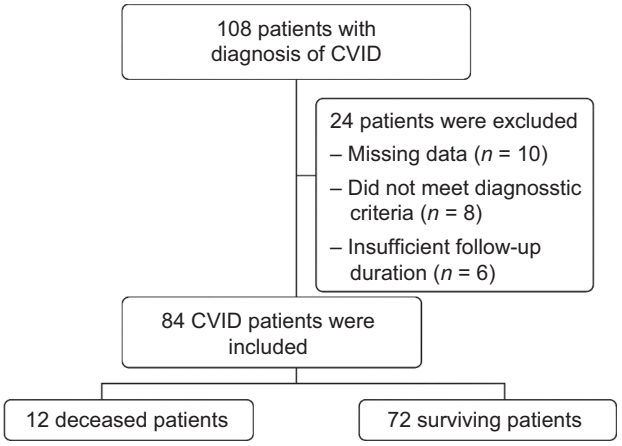

Figure 1 Flowchart of patient screening. Inclusion and exclusion criteria were strictly applied throughout the screening process.

Evaluation of demographic and laboratory data

The demographic characteristics and laboratory findings of the included patients were evaluated, including age, sex, mortality status, complete blood count (CBC), immunoglobulin levels, and peripheral lymphocyte subset analysis. Patients were divided into two groups based on the presence of neutropenia. Those with an absolute neutrophil count (ANC) below 1500/mm^3 (1.5 × 10^9/L) in the CBC were classified as neutropenic. The diagnosis was based on persistent or recurrent low counts observed during the follow-up period, rather than a single abnormal test result, consistent with the chronic nature of the condition in our cohort. For statistical comparison, the lowest recorded ANC (nadir) for each patient during their follow-up period was used.

Mortality data

Demographic characteristics, laboratory findings, immunological parameters, and mortality rates were compared between the two groups. In addition, the association between neutropenia and overall survival and mortality was analyzed.

Statistical analysis

Continuous variables were presented as medians with interquartile ranges (IQR), while categorical variables were shown as counts and percentages. To compare CVID patients with and without neutropenia regarding mortality and survival, the Mann–Whitney U test was used for continuous variables, and the χ^2 test was applied for categorical variables. Differences in survival between groups based on neutropenia were evaluated using Kaplan–Meier survival analysis, with the log-rank test used for comparisons. All analyses were performed with the SPSS statistical package (v22.0) and GraphPad Prism software (v8.0; GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

Ethics statement

This study protocol was approved by the Ethics Committee of Necmettin Erbakan University Faculty of Medicine, with approval number 2025/5600. Because the study is retrospective, written informed consent from participants was not required, in accordance with local regulations.

Results

Evaluation of demographic and clinical data

This study included 84 patients diagnosed with CVID, with a median age of 38 years (range: 20–79) and a male-to-female ratio of 43:41. Neutropenia, defined as an absolute neutrophil count <1500 × 10^6/L, was observed in 28.5% of the patients (n = 24). Among neutropenic patients, the male-to-female ratio was 13:11, with a median age of 31 years (range, 27–52), compared to 41 years (range, 34–49) in the non-neutropenic group. This age difference was not statistically significant (P = 0.058).

In neutropenic patients, the most common presenting symptoms were autoimmune cytopenias, such as thrombocytopenia or anemia, independent of infection (n = 9). Analysis of the complaints in the 24 neutropenic CVID patients revealed that anemia (41.7%) and recurrent infections (33.3%) were the most frequently reported symptoms. Other complaints included thrombocytopenia (12.5%), liver failure (4.2%), recurrent warts (4.2%), and diarrhea (4.2%).

In contrast, among the 60 non-neutropenic CVID patients, the most common symptom was recurrent infection (73.3%), followed by anemia (13.3%), thrombocytopenia (8.3%), and diarrhea (5.0%) (Figure 2).

Evaluation of laboratory findings

Immunoglobulin levels (IgG, IgA, and IgM) were found to be lower in the neutropenic group; however, these differences did not reach statistical significance (P > 0.05). Additional clinical characteristics of all CVID patients are presented in Table 1. Regardless of neutropenia status, all patients received regular intravenous immunoglobulin (IVIg) replacement therapy at a dose of 400–600 mg/kg per month from the time of diagnosis.

Furthermore, patients who were unresponsive to treatment—defined as having more than three infectious episodes or experiencing severe infections despite IVIg therapy, as well as those with bronchiectasis, chronic sinusitis, or recurrent acute otitis media—were administered prophylactic antibiotics tailored to the specific type of infection. Among the neutropenic patients, granulocyte colony-stimulating factor (G-CSF) therapy was given in three cases. Corticosteroid treatment was administered to patients with immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA).

Mortality data

At the end of the study period, 12 patients had died, and 72 were alive. Of those who died, eight belonged to the neutropenic group and four to the non-neutropenic group.

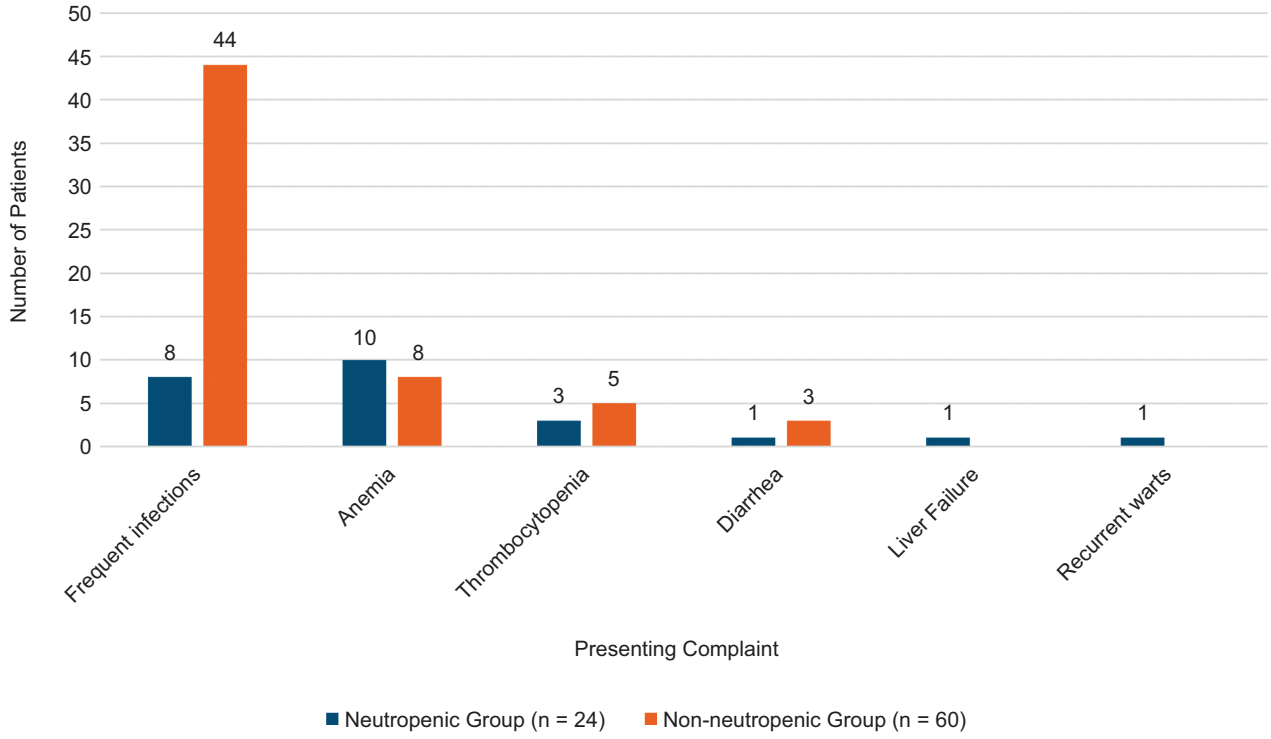

Figure 2 Comparison of presenting complaints in CVID patients.

Table 1 Demographic and laboratory characteristics of CVID patients.

Parameter	Reference range	Neutropenic (n = 24)	Non-neutropenic (n = 60)	P
Gender				0.730
Female, n (%)		11 (45.8)	30 (50.0)	
Male, n (%)		13 (54.2)	30 (50.0)	
Age, years		31 (27-52)	41 (34-49)	0.058
WBC (10^9/L)	4-10	1.6 (0.82-2.4)	5.0 (2.0-19.0)	<0.001
Neutrophil (10^9/L)	1.5-7.0	0.65 (0.4-1.14)	5.0 (4.3-6.12)	<0.001
Lymphocyte (10^9/L)	0.9-2.9	0.51 (0.26-0.9)	3.04 (2.2-3.7)	<0.001
Hb (g/dL)	12-16	8.8 (8.0-11.3)	12.3 (10.7-13.7)	<0.001
Platelet (10^9/L)	150-450	76 (50-158)	213 (150-263)	<0.001
IgG (mg/dL)	700-1600	334 (24-610)	360 (220-570)	0.699
IgM (mg/dL)	46-304	21 (17-330)	22 (23-350)	0.223
IgA (mg/dL)	70-400	26 (25-390)	26 (18-40)	0.536
CD3+ T Cells (%)	57-85	78 (70-86)	76 (68-86)	0.436
CD3+CD4+ T Cells (%)	30-61	52 (24-40)	32 (26-40)	0.098
CD3+CD8+ T Cells (%)	12-42	36 (28-52)	38 (30-49)	0.825
CD19+ B Cells (%)	6-29	6 (2-11)	7 (2-13)	0.625
CD16+/56+ NK Cells (%)	4-25	11 (6-15)	8 (3-16)	0.186
CD19+/CD27+IgD- SMBC (%)	9.2-18.9	3 (1-7)	4 (1-14)	0.427

Data are presented as n (%) for categorical variables or median (interquartile range) for continuous variables. P-values were calculated using the Chi-square test or Mann–Whitney U test, as appropriate. SMBC: Switched memory B cells.

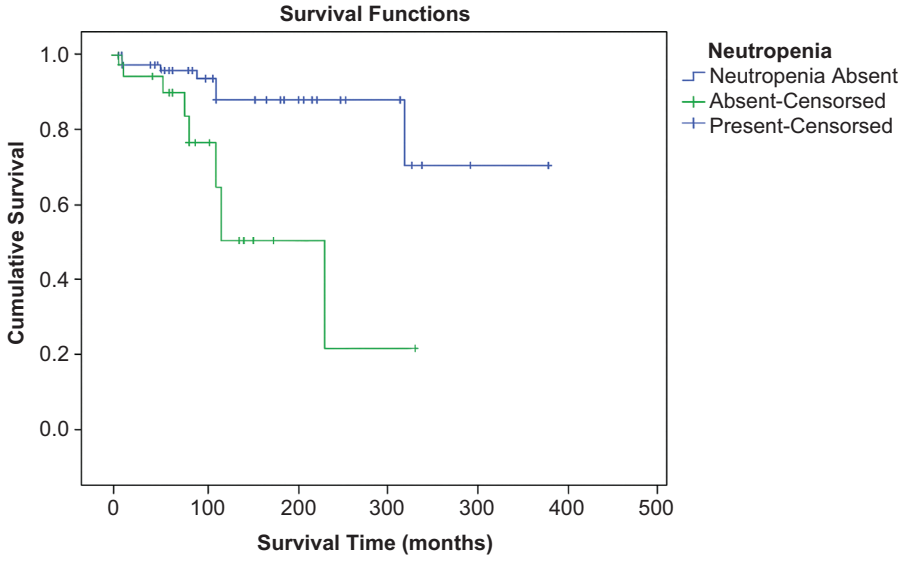

Figure 3 Survival analysis of patients.

The mortality rate was significantly higher in neutropenic CVID patients (33.3%) compared to non-neutropenic patients (6.7%) (P = 0.004). The median ANC at the time of death was 865/mm³ (IQR, 395–935) for the neutropenic group and 4570/mm³ (IQR, 3468–5960) for the non-neutropenic group. Among the eight neutropenic patients who died, the average time from the onset of neutropenia to death was 15.5 months. Of those with a known cause of death, three patients died of septic shock, and one likely died from cardiac failure during lymphoma treatment. According to Kaplan–Meier survival analysis, the 8-year survival rate was 57.5% for neutropenic CVID patients and 92.5% for non-neutropenic CVID patients, indicating a statistically significant difference (P < 0.001) (Figure 3).

Discussion

In this study, we aimed to investigate the prevalence of neutropenia and its association with mortality in CVID patients monitored at our clinic. Although factors such as malignancy, interstitial lung disease, and autoimmune complications are commonly associated with increased mortality in CVID, neutropenia is generally considered a

secondary finding. To date, only a limited number of studies have directly examined this issue. Therefore, we believe that this study provides one of the few insights emphasizing the potential prognostic significance of neutropenia in patients with CVID.

This study's retrospective analysis of 84 patients diagnosed with CVID found a neutropenia prevalence of 28.5%. This neutropenia was classified as peripheral and followed a chronic course. Although some patients experienced temporary improvements with various treatments, most remained neutropenic throughout their follow-up. Recurrent infections were common among these patients, but a definitive association between infections and neutropenia was not established. Survival rates were significantly lower in CVID patients with neutropenia. Additionally, patients who initially had anemia and thrombocytopenia were more likely to develop neutropenia later on. The clinical profile of neutropenic patients, rich in hematological and systemic features, suggests that neutropenia in CVID is often a component of a wider spectrum of immune dysregulation, not merely an isolated finding leading to infections.

Autoimmune cytopenias, especially ITP and AIHA, are among the most common autoimmune manifestations in CVID.[10] They are reported to occur up to 700 times more often in CVID patients than in the general population.[11] In our study, ITP and/or AIHA were observed in 22 out of 84 patients (26%). Conversely, neutropenia is considered a rare finding in CVID and has been identified as a marker of poor prognosis in large patient series cohorts.[12,13] The reported frequency of neutropenia in CVID varies across studies; while some series report relatively high rates ranging from 5 to 10%, larger cohorts have found the prevalence to be between 1 and 2%. Indeed, in the cohort study by Cunningham-Rundles et al., which included individualized data from 55 out of 248 CVID patients, neutropenia was identified in only 2 patients, corresponding to a prevalence of 0.8%.[14] Similarly, Resnick et al. confirmed a prevalence of less than 1% in a larger group of 473 patients from the same center, although these patients were not further analyzed individually.[12] The EUROclass study, which enrolled 303 European CVID patients, did not differentiate neutropenia from other autoimmune conditions cytopenias.[3] In a US-based case series from Mount Sinai involving 473 patients, the prevalence was 14% for ITP, 7% for AIHA, 4% for Evans syndrome, and less than a certain percentage (1%) for autoimmune neutropenia.[12] In the multicenter DEFI study, 473 CVID patients were evaluated, and neutropenia was reported in 16 patients, with a frequency of 3.4%.[15] However, in large cohort studies, data on mortality and immunological abnormalities linked to neutropenia in CVID remain limited. Therefore, case series with fewer patients may also offer valuable insights. In a study by Lemos et al., neutropenic episodes occurred in 10 of 42 patients (23.8%) receiving IVIg replacement therapy over an average follow-up of 6.4 years. Neutropenia was not clearly associated with antibiotic prophylaxis or immunoglobulin levels.[8] While the prevalence of neutropenia in CVID patients is generally reported to range between 1 and 10% in the literature, the frequency observed in our study was 28.5%. Several factors could explain this discrepancy. First, our center is a tertiary referral hospital, which typically treats more complex patients with significant signs of immune dysregulation. Additionally, in our study, neutropenia was defined not only based on isolated laboratory findings but also on chronic neutropenia with clinical impact. The combination of electronic health record review and manual file screening may have also increased diagnostic sensitivity. The high prevalence of autoimmune cytopenias in our patient population may have further contributed to the higher occurrence of neutropenia.

Bone marrow (BM) biopsy was performed in six of the eight deceased patients, and all showed normal marrow findings. A normal BM evaluation, combined with the exclusion of other causes of peripheral neutropenia (such as splenic sequestration, toxins, or drug-related suppression), and its frequent coexistence with ITP or AIHA, supports the hypothesis that neutropenia in CVID is an autoimmune manifestation. Among the 24 neutropenic patients, 22 received intermittent corticosteroid therapy after developing neutropenia, and 3 were treated with G-CSF. In two of the eight neutropenic patients who died, a lymphoproliferative disorder (LPD) developed during follow-up.

The treatment of autoimmune neutropenia in CVID is not well defined. Management should be based on the severity and duration of neutropenia, as well as any related septic complications. Therapeutic options may include corticosteroids, high-dose immunoglobulin (1–2 g/kg), and granulocyte colony-stimulating factor (G-CSF). Some studies have noted paradoxical neutropenia after immunoglobulin replacement, especially in cases of ITP; however, this effect is usually transient.[8,16] Splenectomy and rituximab therapies are generally ineffective and may only cause temporary increases in neutrophil levels.[17] Recently, abatacept and mTOR inhibitors (such as sirolimus) have shown promise, especially in patients with lymphoproliferative disorders.[18] In our cohort, patients were not specifically treated for neutropenia itself but rather for complications that resulted from neutropenia.

Although several studies have examined the prevalence of neutropenia in patients with CVID, data directly assessing its long-term impact on survival remain limited. The literature often discusses the connection between neutropenia and increased risks of infections or autoimmune cytopenias; however, there is a notable lack of comparative studies demonstrating higher mortality rates among CVID patients with neutropenia. Similar to our findings, Ghorbani et al. evaluated 220 CVID patients and reported that 18 (8.1%) developed neutropenia, with 12 of them subsequently dying. The study highlighted that neutropenia was linked to a mortality rate as high as 61.1% in CVID patients.[19] Consistent with these findings, our study also emphasizes the negative prognostic effect of neutropenia on overall survival.

The notably lower survival rate observed in neutropenic patients suggests that neutropenia may be more than just a hematological finding; it could also indicate a poor prognosis in CVID. This underscores the need for larger, prospective studies to further verify and support these findings. Additionally, although malignancy, interstitial lung disease, and autoimmune complications are often highlighted as major factors linked to mortality in CVID, neutropenia is frequently viewed as a secondary concern. This study is among the few that emphasizes the potential prognostic importance of neutropenia in this patient group.

This study has several limitations. First, its retrospective design limited data collection to existing medical records. Additionally, the single-center nature of the study resulted in a relatively small sample size, contributing to some missing data points. Moreover, certain autoimmune findings were assessed based on clinical follow-up notes, which may have introduced heterogeneity due to the use of nonstandardized definitions. Finally, the single-center design limits the generalizability of the findings to larger populations.

Conclusion

This study shows that neutropenia in patients with CVID is not just a hematologic abnormality but may also serve as an important clinical marker linked to higher mortality. The higher prevalence of noninfectious symptoms and autoimmune manifestations among neutropenic patients suggests that underlying immune dysregulation may play a key role. These findings highlight the importance of vigilant monitoring for neutropenia during the follow-up of CVID patients. Further prospective studies are warranted to facilitate earlier interventions and to develop personalized therapeutic strategies for this high-risk population.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Further information is available from the corresponding author upon request.

Author's Contribution

E.H. and F.Ç. designed the study; E.H., M.E.G., F.S., S.K., and S.A.S. conducted the research; E.H., F.Ç., M.E.G., and Ş.A. analyzed the data; E.H. and F.Ç. wrote the manuscript; and E.H. was primarily responsible for the final content. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

Funding

The authors received no financial support for this article.

References

1. Remiker A, Bolling K, Verbsky J. Common Variable Immunodeficiency. Med Clin North Am. 2024;108(1):107–21. https://doi.org/10.1016/j.mcna.2023.06.012
2. Ameratunga R, Jordan A, Cavadino A, Ameratunga S, Hills T, Steele R, et al. Bronchiectasis is associated with delayed diagnosis and adverse outcomes in the New Zealand Common Variable Immunodeficiency Disorders cohort study. Clin Exp Immunol. 2021;204(3):352–60. https://doi.org/10.1111/cei.13595
3. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, et al. The EUROclass trial: Defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77–85. https://doi.org/10.1182/blood-2007-06-091744
4. Boileau J, Mouillot G, Gérard L, Carmagnat M, Rabian C, Oksenhendler E, et al. Autoimmunity in common variable immunodeficiency: Correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun. 2011;36(1):25–32. https://doi.org/10.1016/j.jaut.2010.10.002
5. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763–70. https://doi.org/10.1016/j.jaip.2019.02.004
6. Cham B, Bonilla MA, Winkelstein J. Neutropenia associated with primary immunodeficiency syndromes. Seminars Hematol. 2002;39(2):107–12. https://doi.org/10.1053/shem.2002.31916
7. Feuille EJ, Anooshiravani N, Sullivan KE, Fuleihan RL, Cunningham-Rundles C. Autoimmune cytopenias and associated conditions in CVID: A report from the USIDNET Registry. J Clin Immunol. 2018;38(1):28–34. https://doi.org/10.1007/s10875-017-0456-9
8. Lemos S, Jacob CM, Pastorino AC, Castro APB, Fomin ÂB, Carneiro-Sampaio MM. Neutropenia in antibody-deficient patients under IVIG replacement therapy. Pediatr Allergy Immunol. 2009;20(1):97–101. https://doi.org/10.1111/j.1399-3038.2008.00741.x
9. Paquin-Proulx D, Sandberg JK. Persistent immune activation in CVID and the role of IVIg in its suppression. Front Immunol. 2014;5:637. https://doi.org/10.3389/fimmu.2014.00637
10. Lopes-da-Silva S, Rizzo LV. Autoimmunity in common variable immunodeficiency. J Clin Immunol. 2008;28:46–55.
11. Odnoletkova I, Kindle G, Quinti I, Grimbacher B, Knerr V, Gathmann B, et al. The burden of common variable immunodeficiency disorders: A retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. Orphanet J Rare Dis. 2018;13(1):201. https://doi.org/10.1186/s13023-018-0941-0
12. 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. https://doi.org/10.1182/blood-2011-09-377945
13. 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. J Clin Immunol. 2007;27(3):308–16. https://doi.org/10.1007/s10875-007-9075-1
14. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol (Orlando, Fla). 1999;92(1):34–48. https://doi.org/10.1006/clim.1999.4725
15. Guffroy A, Mourot-Cottet R, Gérard L, Gies V, Lagresle C, Pouliet A, et al. Neutropenia in patients with common variable immunodeficiency: A rare event associated with severe outcome. J Clin Immunol. 2017;37(7):715–6. https://doi.org/10.1007/s10875-017-0434-2
16. Berkovitch M, Dolinski G, Tauber T, Aladjem M, Kaplinsky C. Neutropenia as a complication of intravenous immunoglobulin (IVIG) therapy in children with immune thrombocytopenic purpura: Common and non-alarming. Int J Immunopharmacol. 1999;21(6):411–5. https://doi.org/10.1016/s0192-0561(99)00020-x

17. Niebanck AE, Kwiatkowski JL, Raffini LJ. Neutropenia following IVIG therapy in pediatric patients with immune-mediated thrombocytopenia. J Pediatr Hematol Oncol. 2005;27(3):145–7. https://doi.org/https://doi.org/10.1097/01.mph.0000155871.26380.84
18. Bride KL, Vincent T, Smith-Whitley K, Lambert MP, Bleesing JJ, Seif AE, et al. Sirolimus is effective in relapsed/refractory autoimmune cytopenias: Results of a prospective multi-institutional trial. Blood. 2016;127(1):17–28. https://doi.org/https://doi.org/10.1182/blood-2015-07-657981
19. Ghorbani M, Fekrvand S, Shahkarami S, Yazdani R, Sohani M, Shaghaghi M, et al. The evaluation of neutropenia in common variable immune deficiency patients. Expert Rev Clin Immunol. 2019;15(11):1225–33. https://doi.org/10.1080/1744666x.2020.1677154