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Phenotyping Common Variable Immunodeficiency by Immune Dysregulation at Diagnosis: A Descriptive Comparison of Baseline Clinical and Laboratory Findings

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Abstract

Background

Common variable immunodeficiency (CVID) is a heterogeneous antibody deficiency associated with infectious and noninfectious complications. Infection history guides clinical assessment, but its relationship with routine immunological markers and immune dysregulation at diagnosis remains unclear. The study aims to compare the clinical and immunological profiles at diagnosis between CVID patients with immune dysregulation and those without. Immunological markers independently associated with immune dysregulation were further evaluated.

Results

At diagnosis, 34 patients (40%) were identified as CVID-ID (Immune Dysregulation) (+). Based on infection related components of the adult ESID warning signs, the annual frequency of clinically significant treatment requiring infectious episodes was significantly lower in the CVID-ID(+) group than in the CVID-ID(-) group (median 0 vs. 5 episodes; $p < 0.001$). Minor symptomatic mucosal/ upper respiratory tract infections events were more frequent in the CVID-ID(+) group than in the CVID-ID(-) group (23/34 [67.6%] vs. 22/51 [43.1%], $p = 0.027$). In multivariable analysis, reduced percentages of switched memory B-cells (SMBC) (OR: 0.56, 95% CI: 0.35–0.88; $p = 0.012$), lower $CD4^+$ T-cell percentages (OR: 0.92, 95% CI: 0.88–0.96; $p = 0.001$), and lower serum IgA levels (OR: 0.27, 95% CI: 0.09–0.81; $p = 0.020$) were independently associated with the immune dysregulation phenotype.

Conclusion

Lower SMBC percentages, $CD4^+$ T-cell proportions, and serum IgA levels were associated with the CVID-ID(+) phenotype at diagnosis. Although these patients had fewer clinically significant treatment requiring infections within the infection related components of the adult ESID warning signs, infection centered measures alone may not fully capture the diagnostic profile of patients presenting with immune dysregulation. These findings remain hypothesis generating.

1. INTRODUCTION

Common Variable Immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in adults, with an estimated prevalence ranging from 1:10,000 to 1:50,000, although reported prevalence may vary between countries and populations.(1–3)

It is defined by markedly reduced serum immunoglobulin (Ig) levels, particularly IgG and IgA, and impaired vaccine responses, reflecting underlying defects in B cell differentiation. In addition to B cell abnormalities, increasing evidence implicates T cell dysfunction in disease pathogenesis.(4, 5) Defects

in germinal center (GC) architecture and function at the tissue level impair class switch recombination and the generation of switched memory B cells (SMBC) and plasma cells, which contribute to hypogammaglobulinemia and dysregulated immune responses. (6–8)

Clinically, CVID encompasses a broad and heterogeneous spectrum. While recurrent sinopulmonary infections represent the classical presentation, a substantial proportion of patients also experience non-infectious complications, such as autoimmunity, lymphoproliferation, granulomatous disease, gastrointestinal inflammation, and malignancies. (9–11) Although immunoglobulin replacement therapy effectively reduces infection related morbidity and mortality, it has limited impact on the progression of non-infectious manifestations, highlighting that infection control alone may not fully reflect the broader clinical burden of CVID. (10, 12–14) This highlights the potential clinical relevance of recognizing non-infectious phenotypes and monitoring relevant immunological indicators.

Furthermore, several phenotypic classification systems have been proposed to stratify CVID based on infectious and non-infectious features. Notably, Chapel et al. described distinct clinical phenotypes in CVID, whereas Resnick et al. emphasized that noninfectious complications represent a substantial part of the disease spectrum. (10, 15, 16)

However, the extent to which infection burden differs between CVID patients with and without immune dysregulation at diagnosis remains insufficiently characterized. Phenotypic stratification at diagnosis may help clarify whether routine immunological parameters differ between patients with and without immune dysregulation, although these observations should be interpreted cautiously and confirmed in larger prospective cohorts. In recent years, increasing attention has been paid to the role of functional impairments in B and T cells in the pathogenesis of immune dysregulation. Accordingly, integrating immunological profiles with clinical manifestations may facilitate a more comprehensive assessment of CVID.

Although immune dysregulation is increasingly recognized as a major determinant of clinical heterogeneity in CVID, few studies have simultaneously evaluated infection burden and routine immunological parameters at the time of diagnosis in relation to immune dysregulation phenotype.

Accordingly, this study is designed to compare infection frequency and baseline immunological parameters between CVID phenotypes at diagnosis, and to assess their association with immune dysregulation.

2. METHODS

Study Design

This retrospective cohort study was conducted at a single tertiary immunology center. Eighty-five adult patients diagnosed with CVID and followed at the Immunology and Allergy Clinic of Necmettin Erbakan University Medical Faculty between 2018 and 2024 were included. The date of CVID diagnosis was

considered the diagnostic index date for all analyses. Analyses were restricted to clinical and immunological data obtained at the time of the initial diagnostic evaluation; no interventions, treatment assignments, or follow up outcomes were used for phenotype definition.

Inclusion Criteria

Patients were eligible if they fulfilled the 2019 European Society for Immunodeficiencies (ESID) diagnostic criteria for CVID, including (2):

- Marked hypogammaglobulinemia, defined by reduced serum IgG and IgA levels, with or without low IgM, confirmed on at least two occasions and below two standard deviations of age adjusted reference values;
- Evidence of impaired antibody production, documented by inadequate responses to protein and/or polysaccharide vaccines and/or reduced SMBC proportions;
- Exclusion of secondary causes of hypogammaglobulinemia;
- Diagnosis established after the age of four years;
- Absence of profound T-cell deficiency, as defined by ESID criteria.

None of the patients had received systemic immunosuppressive therapy prior to diagnosis, ensuring that baseline immunological assessments were not influenced by treatment.

Exclusion Criteria

Patients were excluded from the study if they met any of the following:

- History of lymphoproliferative malignancy within two years prior to diagnosis;
- $CD4^+$ T cell count <200/mm^3, to exclude individuals with features compatible with late-onset combined immunodeficiency (LOCID) rather than CVID. **A summary of the patient selection process and phenotypic classification is presented in Figure 1.(17)**

Phenotype Definition

Patients were referred from various specialties, including pulmonology, gastroenterology, and internal medicine, due to recurrent infections, cytopenias, lymphoproliferation, or abnormal immunoglobulin levels. Participants were classified at diagnosis according to the presence of immune dysregulation into two phenotypes: (i) CVID-ID(+), defined by the presence of at least one immune dysregulation related non-infectious complication at diagnosis; and (ii) CVID-ID(−), defined by the absence of such complications.

CVID-ID(+) was defined a priori as the presence of at least one of the following at diagnosis: autoimmune cytopenia or other clinically confirmed autoimmunity (e.g., rheumatologic diseases not fully explained by primary rheumatologic disorders alone), granulomatous disease/GLILD, unexplained

polyclonal lymphoproliferation (e.g., persistent lymphadenopathy, hepatomegaly, and/or splenomegaly), and/or CVID associated enteropathy. Infection history and infection burden were not used for phenotype definition and were analyzed separately.

Phenotype assignment was based exclusively on data recorded at the diagnostic index date. Immunological parameters, including SMBC, were evaluated independently and were not used to define phenotype; for regression analyses, these variables were handled as continuous measures.

Infection Assessment

Infection burden was assessed using the infection related components of the adult ESID warning signs for primary immunodeficiency. (18) These included:

- ≥4 infections requiring antibiotics within 1 year (e.g., otitis, bronchitis, sinusitis, pneumonia),
- recurrent infections or infections requiring prolonged antibiotic therapy,
- ≥2 severe bacterial infections (e.g., osteomyelitis, meningitis, septicemia, cellulitis),
- ≥2 radiologically confirmed pneumonias within 3 years,
- infections with unusual localization or unusual pathogens.

Minor upper respiratory tract infections (URTI) or limited mucosal symptoms managed without systemic antimicrobial therapy were recorded separately and were not included in the primary annual infection frequency count**.**

Minor symptomatic events were also recorded as a secondary category to capture less severe presentations. These were defined as symptomatic upper respiratory tract or mucosal episodes that did not fulfill the predefined severity thresholds but still required clinical attention. This distinction was used to explore whether patterns of infection presentation differed between the CVID-ID(+) and CVID-ID(-) phenotypes.

Infection histories were defined as clinically documented episodes requiring physician evaluation and/or systemic antimicrobial therapy. For each patient, annual infection frequency was estimated on the basis of clinically significant episodes occurring during the year preceding the diagnostic index date. Infection histories were assessed by at least three physicians through detailed clinical interviews and cross-checked against hospital records and the national electronic health record system to confirm specific episodes, hospitalizations, and antimicrobial use, with the aim of improving data accuracy and reducing recall bias. Accordingly, the primary infection frequency measure used in this study reflects clinically significant infections rather than total symptomatic events.

Data Collection

Demographic and clinical data were retrospectively retrieved from medical records, including age, sex, age at symptom onset, age at diagnosis, and diagnostic delay (defined as the interval between symptom

onset and confirmed diagnosis).

Immunological Assessment

Baseline immunological parameters collected at diagnosis included percentages of $CD3^+$ T cells, $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, $CD19^+$ B cells, SMBC, and natural killer cells. Serum immunoglobulin levels (IgG, IgA, IgM, and IgE) were recorded. Specific antibody responses to protein and polysaccharide antigens were assessed using tetanus toxoid and the 23-valent pneumococcal polysaccharide vaccine, in accordance with ESID criteria.

Serum Immunoglobulin Measurements

Serum immunoglobulin levels were quantified by nephelometry (BNII System, Siemens Healthcare Diagnostics, Erlangen, Germany), following the manufacturer's protocols.

Flow Cytometric Evaluation

Cell acquisition and analysis were performed using a BD FACS Canto II Flow Cytometer (BD Biosciences), following the manufacturer's instructions. SMBC were defined as $CD19^+CD27^+IgD^-$.

Statistical Analysis

Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and visual inspection of Q–Q plots. Between-group comparisons were performed using the independent-samples t-test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Variables showing between-group differences ($p < 0.05$) were further evaluated in univariate logistic regression analyses; variables with $p < 0.10$ were entered into the multivariable logistic regression model. Two-sided p-values < 0.05 were considered statistically significant.

2.4. Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Necmettin Erbakan University Ethics Committee (approval no. 2023/4361). The requirement for informed consent to participate was waived by the Ethics Committee due to the retrospective nature of the study. All data were fully anonymized before analysis, and no personally identifiable information was recorded.

3. RESULTS

Clinical and laboratory features of patients

A total of 85 patients with CVID were included, of whom 34 (40%) were CVID-ID(+) and 51 (60%) were classified as CVID-ID(-). The two phenotypic groups were comparable in terms of sex distribution, current age, age at symptom onset, and age at diagnosis (all $p > 0.05$). In contrast, diagnostic delay was significantly longer in the CVID-ID(+) group, whereas annual infection frequency was markedly higher

among CVID-ID(-) patients (p = 0.029 and p < 0.001, respectively; Table 1). The CVID-ID(+) group exhibited a lower annual frequency of clinically significant treatment-requiring infectious episodes based on infection related components of the adult ESID warning signs compared to the CVID-ID(-) group [median 0 (0–4) vs. 5 (4–7), p < 0.001]. However, a more detailed analysis of the infection profile showed that fewer patients in the CVID-ID(+) group met the infection-related components of the adult ESID warning signs than in the CVID-ID(-) group (16/34 [47.1%] vs 47/51 [92.2%], p < 0.001). Conversely, minor symptomatic mucosal/URTI events were recorded more frequently in the CVID-ID(+) group (23/34 [67.6%] vs. 22/51 [43.1%], p = 0.027).

Immunological characteristics

Distinct differences in baseline immunological profiles were observed between phenotypes (Table 2). The CVID-ID(+) group exhibited significantly lower $CD19^+$ B-cell proportions and more reduced SMBC percentages compared with the CVID-ID(-) group (p = 0.005 and p = 0.001, respectively). In parallel, median $CD4^+$ T-cell percentages and the $CD4^+/CD8^+$ T-cell ratio were also lower in CVID-ID(+) patients (p < 0.001 and p = 0.024). By contrast, total $CD3^+$ T cells, $CD8^+$ T cells, and NK-cell proportions did not differ significantly between groups (all p > 0.05).

Regarding humoral parameters, serum IgA levels were significantly lower in the CVID-ID(+) group, whereas IgG, IgM, and IgE levels were comparable between phenotypes (Table 2).

The multivariable logistic regression model demonstrated adequate calibration according to the Hosmer–Lemeshow test (p = 0.866), with an overall classification accuracy of 77.6%. In multivariable analyses, In multivariable analyses, lower SMBC percentages, lower $CD4^+$ T-cell percentages, and lower serum IgA levels were independently associated with the immune dysregulation phenotype. (OR: 0.56, 95% CI: 0.35–0.88; p = 0.012, OR: 0.92, 95% CI: 0.88–0.96; p = 0.001, OR: 0.27, 95% CI: 0.09–0.81; p = 0.020, respectively).

4. DISCUSSION

In the present study, CVID-ID(+) patients showed a distinct diagnostic profile, characterized by decreased SMBC proportions, lower $CD4^+$ T-cell percentages, and reduced serum IgA levels. They also had a lower burden of clinically significant, treatment requiring pyogenic infections, as captured by the infection related components of the adult ESID warning signs, than CVID-ID(-) patients. The median annual frequency of these episodes was 0 (IQR 0–4) in the CVID-ID(+) group versus 5 (IQR 4–7) in the CVID-ID(-) group (p < 0.001). One possible explanation is that warning sign based frameworks primarily capture severe, treatment requiring pyogenic infections and may therefore be less sensitive in patients presenting predominantly with immune dysregulation at diagnosis. Because infection frequency in this study was restricted to clinically significant episodes, the apparently low infectious burden in the CVID-ID(+) group may be more appropriately viewed as a potential limitation of infection-centered assessment frameworks, rather than evidence of a less clinically apparent infectious phenotype. As infection-related variables were not used for phenotype assignment, these observed infection patterns should be

interpreted as accompanying clinical features rather than defining elements of the classification. Accordingly, reliance on severe infection history alone may be insufficient for timely recognition of patients presenting with immune dysregulation at diagnosis.

In this cohort, manifestations of immune dysregulation were common at diagnosis, even though infection frequency appeared relatively low within the conventional warning framework. This observation is in line with previous reports showing that non-infectious complications constitute a substantial component of the CVID phenotype. Chapel et al. demonstrated that CVID segregates into distinct clinical phenotypes, and a substantial proportion of patients in that cohort belonged to phenotypes characterized by non-infectious complications, while Resnick et al. reported noninfectious complications in 68% of patients. In addition, Cabañero-Navalón et al. found that non-infectious complications were the initial presentation in approximately one-third of patients. (10, 15, 19, 20)' In the present cohort, the baseline prevalence of the CVID-ID(+) phenotype was 40%. Together, these findings are consistent with the view that clinically significant immune dysregulation may already be present at diagnosis, even when infection burden appears limited within conventional warning frameworks.

The independent association of lower SMBC percentages with the CVID-ID(+) phenotype is consistent with the EUROclass framework and with previous studies linking impaired memory B-cell maturation to non-infectious complications in CVID. (21-24) Although reduced SMBC is a well recognized feature of CVID, it was demonstrated by the current data that this reduction is significantly more marked in the presence of immune dysregulation. SMBC are central to durable humoral immunity, and their reduction may reflect defective B-cell maturation beyond susceptibility to recurrent infections. In this cohort, the persistence of this association in multivariable analysis suggests that lower SMBC percentages may represent an associated laboratory feature of immune dysregulation at diagnosis in this cohort.

Regarding the T-cell compartment, $CD4^+$ T-cell reductions in this cohort were not as profound as those reported in LOCID; however, the significantly lower $CD4^+$ T-cell percentages observed in the CVID-ID(+) group suggest that even modest relative reductions may be associated with the immune dysregulation phenotype. (24, 25) Along with lower SMBC percentages and serum IgA levels, reduced $CD4^+$ T-cell percentages were among the laboratory variables most consistently associated with the CVID-ID(+) phenotype in this cohort. (26, 27) The agreement between the group comparisons (Table 2) and the multivariable analysis (Table 3) further supports the robustness of these associations.

Lower serum IgA levels could be consistent with underlying impairment in mucosal homeostasis; (28) however, as direct markers were not evaluated, this interpretation should be considered strictly hypothesis generating.

Lower SMBC percentages, $CD4^+$ T-cell proportions, and serum IgA levels were independently associated with immune dysregulation at diagnosis. Taken together, these findings may be compatible with a distinct baseline immunological profile in CVID-ID(+). However, because the study was retrospective and based on data obtained at diagnosis, the contributions of diagnostic timing, referral patterns, and unmeasured functional immune defects cannot be excluded. (16, 23, 29)

A significantly longer diagnostic delay was observed in the CVID-ID(+) group than in the CVID-ID(-) group (median, 10 vs 7 years), which may reflect the more heterogeneous clinical presentation of these patients. In the present cohort, although the CVID-ID(+) group showed a more altered baseline immunological profile, they had a lower burden of pyogenic infections at diagnosis, as captured by the infection related components of the adult ESID warning signs. This pattern differs from reports describing higher infection rates in more clinically complicated CVID subgroups (30) and may reflect differences in clinical presentation at diagnosis rather than a truly lower susceptibility to infection. The lower infection frequency may reflect the clinical status at diagnosis, when immune dysregulation related complications may already have been established despite a limited history of severe pyogenic infections. Taken together, these findings suggest that reliance on an infection centered screening perspective alone may contribute to delayed recognition, particularly in patients presenting with immune dysregulation related complications at diagnosis.

Since the infection related components of the adult ESID warning signs predominantly emphasize clinically significant, severe infectious episodes, the clinical profile of the 67.6% of CVID-ID(+) patients who presented with non severe mucosal infectious manifestations may remain outside conventional warning thresholds. (1, 3) At the same time, the coexistence of lower SMBC percentages, reduced $CD4^+$ T-cell proportions, and lower serum IgA levels may be compatible with a form of immune dysfunction in which abnormalities of B-cell maturation, T-cell proportions, and mucosal immune regulation are already present at diagnosis. In this setting, infectious manifestations may be less likely to present as recurrent severe pyogenic episodes, while the overall immune response pattern may be skewed toward immune dysregulation rather than effective pathogen-directed responses. This limited representation of a classical severe infection history may contribute to delayed recognition of CVID, particularly in patients presenting with autoimmunity or lymphoproliferation. Because functional immune responses and markers of mucosal or systemic immune activation were not directly assessed, this interpretation should be considered hypothesis generating.

This study has several limitations. Its retrospective, single center design and relatively modest sample size may limit the generalizability of the findings. The combination of lower SMBC percentages, lower $CD4^+$ T-cell percentages, and lower serum IgA levels should be considered hypothesis generating until validated in larger, prospective multicenter cohorts. In addition, the lower pyogenic infection burden observed in the CVID-ID(+) group may have been influenced by referral patterns and the timing of assessment at diagnosis. Because the data were collected retrospectively, non-severe or self-limited mucosal infections may also have been underrepresented. Finally, genetic data and detailed mechanistic analyses were not available; therefore, further molecular and sequencing-based studies are needed to clarify the biological basis of these phenotypes.

These findings have two main clinical implications. First, an infection-centered diagnostic approach alone may be insufficient, as the CVID-ID(+) phenotype can present at diagnosis with a relatively low pyogenic infection burden despite underlying immunological abnormalities. Accordingly, reliance on a history of severe infections alone may delay timely recognition in a subset of patients. Second, the

integration of routinely available immunological parameters such as SMBC percentages, $CD4^+$ T-cell proportions, and serum IgA levels into early clinical assessment may assist in identifying patients with immune dysregulation, even in the absence of a classical infectious history. Collectively, these findings support a broader diagnostic perspective at the time of CVID diagnosis, in which non-infectious manifestations and routine immunological parameters are considered alongside infection history.

5. CONCLUSION

In this study, immune dysregulation in CVID was associated with a distinct immunological profile at diagnosis, characterized by lower switched memory B-cell percentages, reduced $CD4^+$ T-cell proportions, and lower serum IgA levels. Although the CVID-ID(+) phenotype was associated with fewer clinically significant pyogenic infections at diagnosis, this finding should not be interpreted as suggesting a less impaired immune state. Rather, immune dysregulation may already be clinically evident even when severe infection history is not a dominant feature.

These findings support the consideration of routine immunological parameters alongside clinical features during the early assessment of CVID. These associations highlight a potentially distinct immunological profile at diagnosis that merits validation in larger prospective multicenter cohorts. While they are not yet suitable for definitive risk stratification, they may inform early clinical recognition when considered alongside infection history.

Abbreviations

CVID
Common Variable Immunodeficiency
CVID-ID(-)
Common Variable Immunodeficiency without immune dysregulation
CVID-ID(+)
Common Variable Immunodeficiency with immune dysregulation
ESID
European Society for Immunodeficiencies
GC
Germinal Center
Ig
Immunoglobulin
LOCID
Late Onset Combined Immunodeficiency.
SMBC
Switched Memory B Cells
URTIs
Upper Respiratory Tract Infections

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine (Approval No: 2023/4361). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was waived due to the retrospective design of the study. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ÜYE conceptualized and designed the study, performed data acquisition, analysis, and interpretation, and drafted the manuscript. FÇ and SA confirmed CVID diagnoses and providing relevant data. FÇ and ŞA contributed significantly to the study design, data interpretation and revised the manuscript for intellectual content. FSA, RE, MK, FAA, TÖ, and SK assisted in data acquisition. ŞA provided overall supervision for the study. All authors read and approved the final version of the manuscript.

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Authors' information

Not applicable.

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Tables

Table 1 to 3 are available in the Supplementary Files section.

Figures

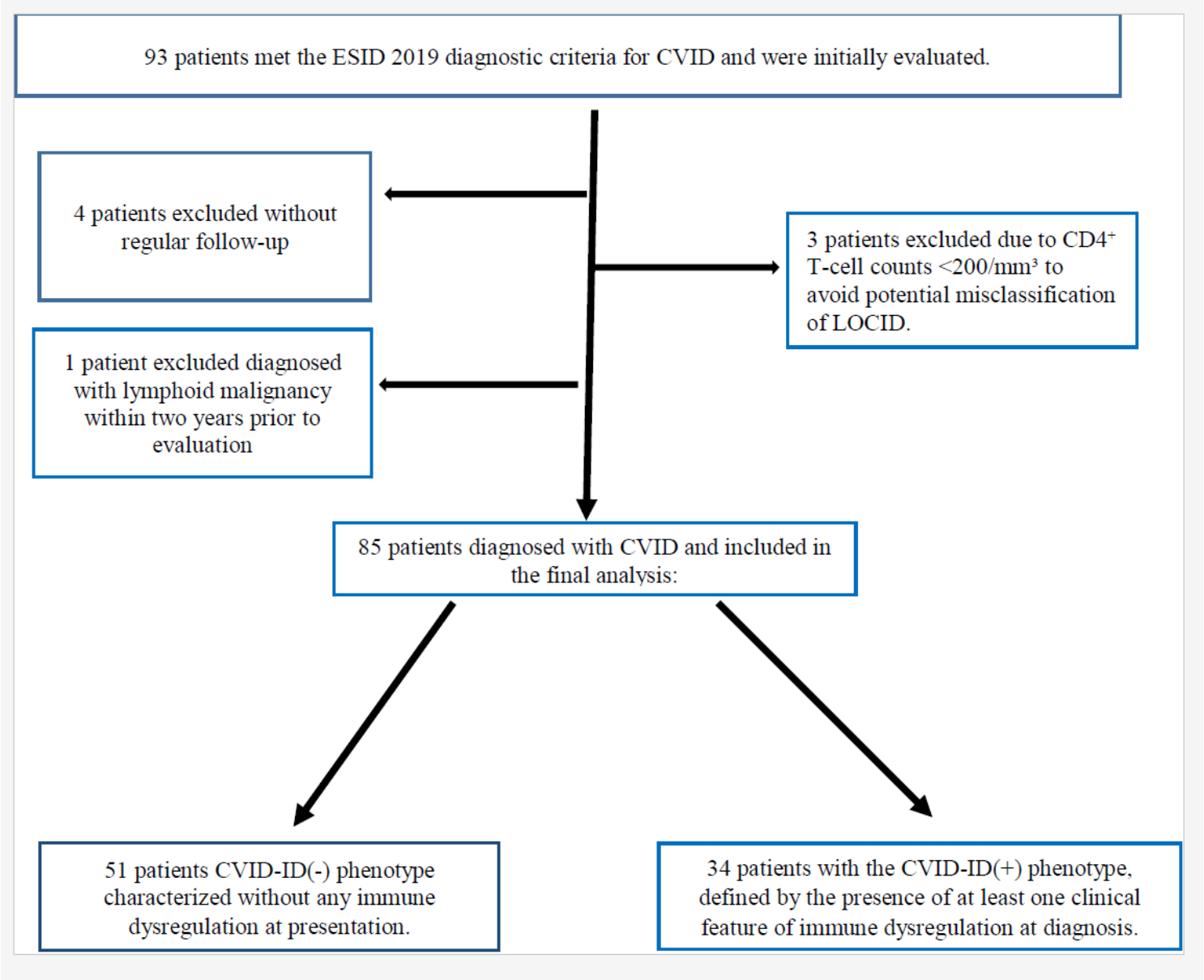


Figure 1

Patient selection process and phenotypic classification of the CVID cohort.

The flowchart depicts the inclusion and exclusion criteria based on ESID 2019 standards. Out of 93 initially evaluated patients, 85 were included in the final analysis and stratified into CVID-ID(-) (n=51) and CVID-ID(+) (n=34) phenotypes.

Abbreviations: ESID, European Society for Immunodeficiencies; CVID, Common Variable Immunodeficiency; CVID-ID(-), CVID without immune dysregulation; CVID-ID(+), CVID with immune dysregulation, LOCID, Late-onset combined immunodeficiency.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx
- Table3.docx