Immunologic biomarkers of noninfectious complications and overall survival in common variable immunodeficiency

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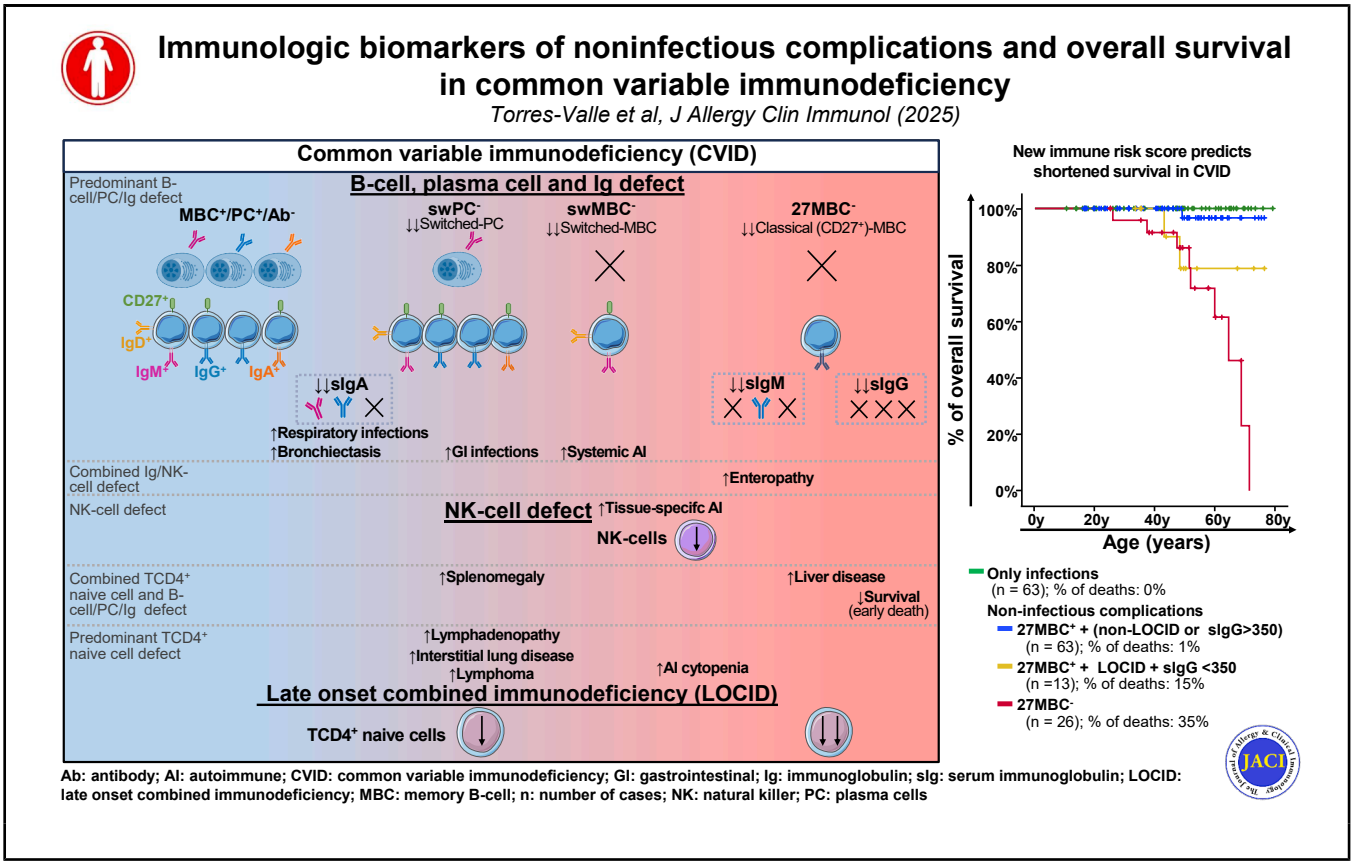
GRAPHICAL ABSTRACT



Ab: antibody; AI: autoimmune; CVID: common variable immunodeficiency; GI: gastrointestinal; Ig: immunoglobulin; sIg: serum immunoglobulin; LOCID: late onset combined immunodeficiency; MBC: memory B-cell; n: number of cases; NK: natural killer; PC: plasma cells

Capsule summary: Age-matched analysis of serum antibody levels, TCD4$^+$ naive, natural killer cell, and memory B-cell/plasma cell subset counts revealed strong associations with infectious and noninfectious clinical complications of common variable immunodeficiency and also demonstrated predictive value for overall patient survival.

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Immunologic biomarkers of noninfectious complications and overall survival in common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) includes a heterogeneous group of disorders of predominantly antibody deficiencies featuring infectious and noninfectious complications that might lead to severe organ damage and shortened survival. Appropriate clinical management of CVID has been hampered by the lack of robust biomarkers to predict the development of clinical complications and patient outcome.

Objective: We investigated the association of individual serologic, cellular, and molecular biomarkers with disease behavior and outcome in CVID.

Methods: A multicenter cohort of 209 CVID patients was studied using age-matched reference values from 334 healthy donors to better define TCD4$^+$-naive cell defects (late-onset combined immunodeficiency [LOCID]) and classify CVID-associated B-cell/plasma cell (PC) and natural killer (NK) cell defects.

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Results: Globally, susceptibility to respiratory infections was strongly associated with low serum immunoglobulin (sIg), particularly sIgA, whereas noninfectious complications and disease severity mostly depended on TCD4$^+$-naive cell, NK cell, and B-cell/PC defects. LOCID was independently associated with splenomegaly, lymphadenopathy, interstitial lung disease, cytopenia, and lymphoma. Milder B-cell/PC defects (MBC$^+$/PC$^+$/Ab$^-$) protected from noninfectious complications, whereas a marked defect of classical CD27$^+$ memory B cells (27MBC$^-$) (with decreased NK cell and sIgM) was associated with enteropathy and (with LOCID and sIgA) liver disease. Together, lower sIgG, LOCID, and particularly 27MBC$^-$, were strongly associated with shorter survival and early death in CVID. Conversely, CVID-associated pathogenic/risk alleles did not emerge as independent factors associated with disease behavior and outcome.

Conclusion: Our results provide a new set of biomarkers closely associated with infectious and noninfectious complications of CVID, which together predict survival and might contribute to guide patient monitoring and clinical management. (J Allergy Clin Immunol 2026;157:454-69.)

Key words: *Common variable immunodeficiency, CVID, late-onset combined immunodeficiency, TCD4$^+$-naïve cells, NK cells, memory B cells, plasma cells, immunoglobulins, disease complications, survival*

Abbreviations used

27MBC$^-$: Subjects who lack sw-PC and classical CD27$^+$ MBC
Ab: Antibody
AI: Autoimmune
CI: Confidence interval
CVID: Common variable immunodeficiency
GI: Gastrointestinal
HD: Healthy donor
HR: Hazard ratio
IgRT: Immunoglobulin replacement therapy
ILD: Interstitial lung disease
LLN: Lower limit of normality
LOCID: Late-onset combined immunodeficiency
LRTI: Lower respiratory tract infection
MBC: Memory B cells
MBC$^+$/PC$^+$/Ab$^-$: Patients with preserved IgH-switched MBC and PC
NK: Natural killer
OS: Overall survival
PB: Peripheral blood
PC: Plasma cells
sIg: Serum immunoglobulin
sw: Switched
swMBC$^-$: Subjects who lack both sw-PC and sw-MBC but show preserved CD27$^+$ MBC
swPC$^-$: Subjects who lack sw-PC but show preserved sw-MBC
URTI: Upper respiratory tract infection

More than half of all symptomatic primary immunodeficiency patients receive a diagnosis of common variable immunodeficiency (CVID), with a prevalence in the general population of 1:25,000 to 1:50,000 individuals.[1-3] CVID comprises a heterogeneous group of patients with unexplained decreased serum immunoglobulin (sIg) G and low sIgA and/or sIgM.[4] Recurrent/severe respiratory infections are the hallmark of CVID and historically the major cause of disease morbidity; however, other nonrespiratory infections, together with autoimmune (AI) and lymphoproliferative complications, are also frequently observed.[5,6] Since the introduction of immunoglobulin replacement therapy (IgRT) for CVID, the management of noninfectious complications has progressively emerged as a major clinical challenge.[5,6] Thus, irreversible organ damage, including liver disease, respiratory failure, and/or severe enteropathy, and malignant (lymphoid) neoplasia, associated with systemic lymphoid hyperplasia,[5,7-10] are today reported as the main causes of disease morbidity and mortality.

Appropriate clinical management of CVID has long been hampered by the lack of robust biomarkers to predict the development of clinical complications and patient outcome. Although deeply reduced sIgG, sIgA, and sIgM have been associated in CVID with more severe infectious and noninfectious complications, their independent predictive value has not been confirmed.[5] Moreover, despite CVID-associated mutations are detected in 25% to 30% of patients,[11] the pathogenic nature of many variants has not been confirmed,[12] and their link with specific clinical phenotypes remains controversial.[11,13,14] Conversely, more robust associations have been observed between the alterations of specific subsets of blood lymphocytes and disease behavior and outcome.[15-24] Thus, severe switched (sw) memory B-cell (MBC) defects have been recurrently associated with splenomegaly, liver disease, and granuloma in large CVID cohorts of both children and adults.[15,16] More recently, detailed dissection of MBC and plasma cells (PC) into their immunoglobulin isotype and immunoglobulin subclass subsets by high-sensitive flow cytometry identified 6 CVID subgroups lacking (1) sw-PC, either alone (CVID-1) or together with (2) IgA$^+$ MBC (CVID-2); (3) IgG$_2^+$ MBC (CVID-3); (4) all sw-MBC subsets (CVID-4); (5) classical CD27$^+$ MBC (CVID-5); and (6) total MBC (CVID-6).[17] Other B-cell alterations, including decreased total B cells and increased percentages of nonclassical (CD21^{lo}) B cells, have been also associated with specific noninfectious complications in CVID.[18] Additionally, an impaired T-cell response associated with decreased TCD4$^+$-naive cell counts in blood has been recurrently observed in CVID,[21,22,25] highlighting the existence of a late-onset combined immunodeficiency (LOCID) (as defined by the Freiburg2019[22] and the DEFI2015[21] criteria), which has been associated with an increased risk of lymphoproliferative disorders, AI cytopenia (mostly anemia and/or thrombocytopenia), and higher mortality among CVID patients with abnormally low numbers of TCD4$^+$-naïve cells in blood.[20-22,25,26] However, the TCD4$^+$-naïve cell cutoff values used in both classifications do not consider the major age-related differences observed in healthy individuals.[27] Although the above serum,[5] cellular,[15-23] and molecular[11,13,14] biomarkers have been associated with disease outcome in multiple CVID cohorts, none of those studies has simultaneously compared their predictive value.

We investigated the association of a broad spectrum of serum, cellular, and molecular biomarkers with disease

behavior and outcome in a large multicenter cohort of CVID patients by using highly sensitive age-matched analyses. Our goal was to identify those immunologic variables associated with severe infectious and noninfectious complications of CVID that might be used to predict disease outcome and patient survival.

METHODS

Patient and samples

Overall, 209 CVID patients (median [range] age, 42 [5-89] years; 102 men and 107 women) from 16 different European centers whose disease was diagnosed according to the International Union of Immunologic Societies criteria[4] were studied in parallel to 334 healthy donors (HDs) (age, 40 [4-99] years; 165 men and 169 women). More details are provided in this article's Methods section in the Online Repository available at www.jacionline.org.

Ethics statement

Each participant and/or parents/guardians provided informed consent to participate in accordance with the Declaration of Helsinki. The study was approved by the local ethics committees (central approval nos. PI19032018 and PI202002437).

Immunophenotypic studies

$TCD4^+$-naive cell/natural killer (NK) cell and B-cell/PC counts were determined in blood of 209 of 209 and 144 of 209 CVID patients in parallel with 272 of 334 and 334 of 334 age-matched HDs using the EuroFlow2025 primary immunodeficiency orientation tube recommended for the screening of primary immunodeficiency/inborn errors of immunity[27,28] and the EuroFlow2025 immunoglobulin heavy chain isotype B-cell immune monitoring tube (www.EuroFlow.org) (see Table E1 and Fig E1 in the Online Repository available at www.jacionline.org), respectively.[17,29] A minimum of 5×10^6 leukocytes per sample were measured, and ≥20 clustered cells defined a cell population (limit of detection of <0.03 cells/μL), as previously described.[17,30] CVID patients with significantly reduced $TCD4^+$ naive cell numbers in blood compared to age-matched healthy controls were classified as having LOCID.

Assessment of serum immunoglobulin

sIgG, sIgA, and sIgM levels at both diagnosis and at enrollment were quantified in 199 of 209 CVID patients, as described in the Methods section in the Online Repository.

Whole-exome sequencing of blood-derived genomic DNA

Total genomic DNA was purified from peripheral blood (PB) of 134 of 209 CVID patients to generate whole-exome sequencing libraries with an exome coverage of 60 Mb (SureSelect Human All Exon V6 kit, Agilent Technologies, Santa Clara, Calif), including coding regions from the RefSeq, CCDS, GENCODe, HGMDcds, OMINcds, and COSMIC databases, as detailed in the Methods section in the Online Repository.

Statistical methods

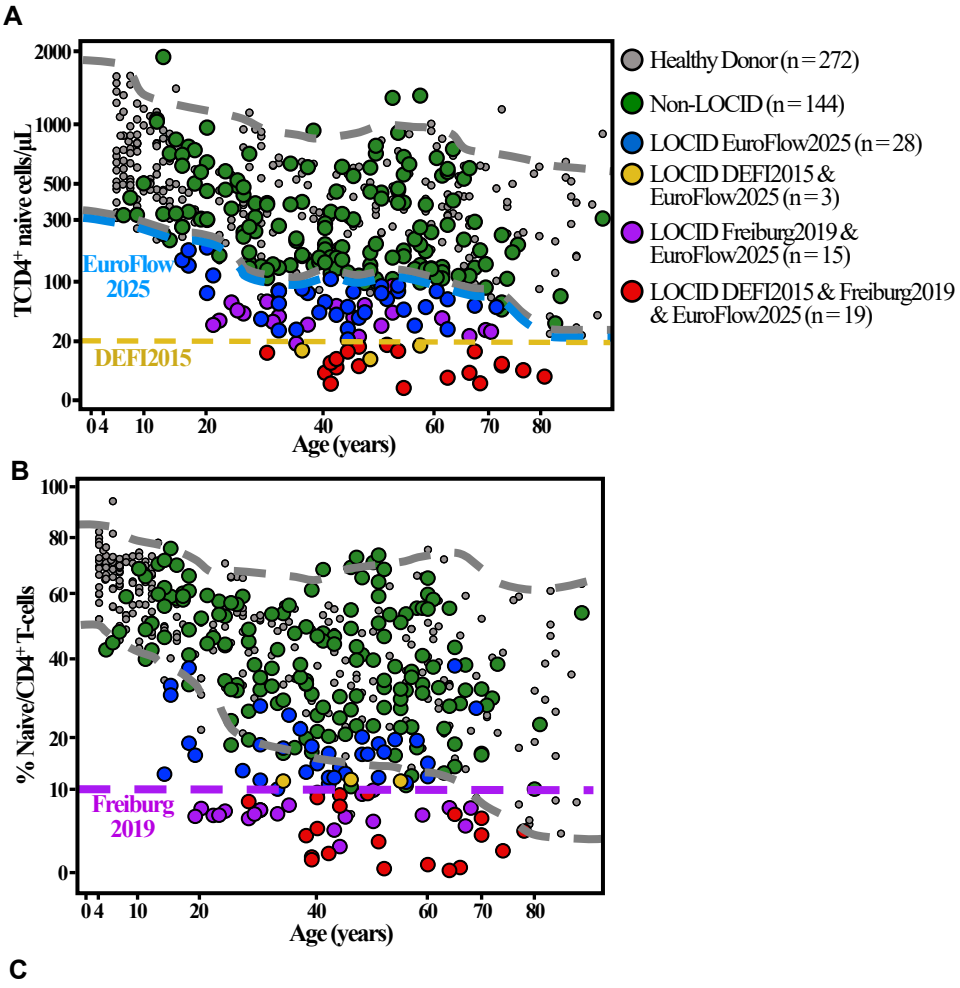
Statistical analyses were performed by SPSS v28.0 (IBM, Armonk, NY), GraphPad Prism v8 (GraphPad Software, La Jolla, Calif), and the MultiExperiment Viewer (MeV v4.9.0) software packages,[31] as described in the Methods section in the Online Repository.

RESULTS

Classification of CVID based on blood $TCD4^+$-naive cell counts

Absolute counts and percentages (from $TCD4^+$ cells) of $TCD4^+$-naive cells were decreased compared to age-matched HDs in 75 (36%) of 209 and 63 (30%) of 209 CVID patients (Fig 1, *A* and *B*). These frequencies almost tripled and doubled those found with the DEFI2015 (10%; $P < .001$) and the Freiburg2019 (16%; $P < .001$) criteria, respectively (Fig 1, *C*). Receiver operating characteristic curve analysis of the most discriminating cutoff of normalized $TCD4^+$-naive cell counts (see the Methods section and Fig E2, *A,* in the Online Repository available at www.jacionline.org) revealed that a ratio between the absolute $TCD4^+$-naive cell count and the lower limit of normality (LLN) for the corresponding age group of <0.9 (referred to hereafter as the EuroFlow2025 criteria for LOCID) was the most sensitive criterion to identify CVID patients with combined immunodeficiency–like disease complications (Fig 1, *A,* and see Table E2, *A,* in the Online Repository).

Although LOCID patients identified with the new EuroFlow2025 criteria did not show different age at diagnosis and at enrollment than the other CVID patients (see Table E3 in the Online Repository available at www.jacionline.org), they displayed higher frequencies of lower respiratory tract infections (LRTI) ($P = .04$), gastrointestinal (GI) infections ($P = .004$), skin infections ($P < .001$), sepsis ($P = .003$), splenomegaly ($P < .001$), lymphadenopathy ($P < .001$), interstitial lung disease (ILD) ($P < .001$), liver disease ($P < .001$), lymphoma ($P = .004$), enteropathy ($P = .002$), and cytopenia (anemia and/or thrombocytopenia) ($P < .001$), together with lower sIgG at diagnosis ($P = .008$) and lower sIgA and sIgM at enrollment ($P \leq .002$), and an increased death rate ($P < .001$). Conversely, no differences were observed regarding the frequency of upper respiratory tract infections (URTI), bronchiectasis, systemic/tissue-specific AI, and nonhematopoietic tumors (Fig 2, *A,* and Table E3). The larger number of LOCID patients identified with the new (age-corrected) EuroFlow2025 criteria versus the DEFI2015 and Freiburg2019 criteria was due to an enrichment in patients with noninfectious complications ($P < .001$ vs non-LOCID CVID) (see Table E4 in the Online Repository), whereas no differences ($P > .05$) were observed regarding the sensitivity to identify patients with infections only. Briefly, the EuroFlow2025 criteria showed a sensitivity 2 to 3 times higher for splenomegaly, lymphadenopathy, ILD, liver disease, enteropathy, and cytopenia compared to the DEFI2015 ($P < .001$) and Freiburg2019 criteria ($P \leq .04$) (Fig E2, *B*). Moreover, the sensitivity for lymphoma was also higher with the EuroFlow2025 criteria, at 86% versus 71% for the DEFI2015 and 57% for the Freiburg2019 criteria ($P > .05$ because of the small number of lymphoma cases [n = 7]) (Table E4).



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Age	All CVID	LOCID DEFI2015	LOCID Freiburg2019	LOCID EuroFlow2025	p-value
4-9y	3	0 (0%)	0 (0%)	0 (0%)	N.S.
10-19y	24	0 (0%)	1 (4%)	4 (17%)	N.S.
20-39y	65	5 (8%)	11 (17%)	**21 (32%)***	**≤0.002**
40-59y	77	9 (12%)	11 (14%)	**25 (32%)***	**<0.001**
60-69y	27	4 (15%)	7 (26%)	**11 (41%)#**	**0.02**
>70y	13	4 (31%)	4 (31%)	4 (31%)	N.S.
TOTAL	**209**	**22 (10%)**	**34 (16%)**	**65 (31%)***	**<0.001**

FIG 1. Distribution of TCD4$^+$-naive cells in blood of both non-LOCID and LOCID CVID patients compared to age-matched HDs. Absolute counts **(A)** and percentages **(B)** of TCD4$^+$-naive cells in blood of both non-LOCID (n = 144) and LOCID (n = 65) CVID patients compared to HDs (n = 272) grouped by age. Individual cases are represented as *green dots* (non-LOCID), *blue dots* (LOCID patients defined only by EuroFlow2025 criteria), *yellow dots* (LOCID patients identified by DEFI2015 and EuroFlow2025 criteria), *purple dots* (LOCID patients classified as such by Freiburg2019 and EuroFlow2025 criteria), *red dots* (LOCID patients classified as such by 3 different criteria), and *gray dots* (HDs). *Dotted blue line* represents EuroFlow2025 cutoff, or <0.9 of TCD4$^+$-naive cells/μL normalized by respective age-matched specific fifth percentile value (ie, LLN); *dotted yellow line* represents DEFI2015 cutoff (<20 TCD4$^+$-naive cells/μL) and *dotted purple line* depicts Freiburg2019 cutoff (<10% TCD4$^+$-naive cells) to define LOCID patients; and *dotted gray lines* represent age-associated reference fifth and 95th percentile values. **(C)** Number and frequency of patients identified as LOCID by DEFI2015 (22/209, 10%), Freiburg2019 (34/209, 16%), and EuroFlow2025 (65/209, 31%) criteria in each age group. *P < .05 vs LOCID by DEFI2015 and Freiburg2019 criteria; #P < .05 vs LOCID by DEFI2015 criteria. McNemar test for paired variables was used. *NS* indicates no statistically significant differences.

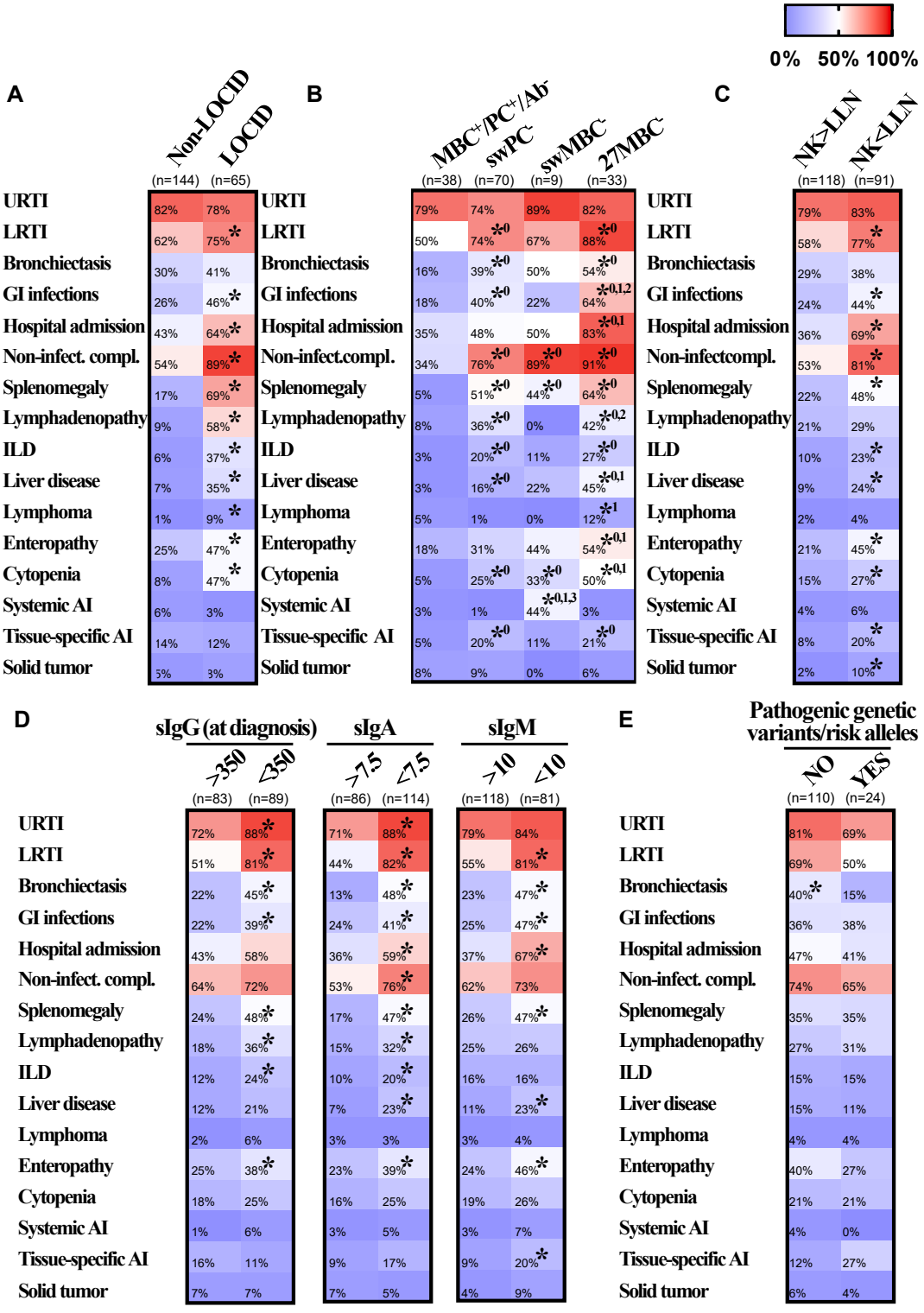

FIG 2. Clinical features of CVID patients distributed into different subgroups by $TCD4^+$-naive cells and both MBC and PC counts in blood as defined by EuroFlow2025 classification criteria, NK cell counts, serum immunoglobulin (sIgG at diagnosis, sIgA, and sIgM) levels, and presence vs absence of pathogenic genetic variants/risk alleles (n = 209). Each heat map represents frequency of patients presenting with individual clinical features (rows) vs different patient groups (columns) defined by number of $TCD4^+$-naive cells (LOCID by EuroFlow2025: <0.9 of $TCD4^+$-naive cells/μL normalized by respective age-matched specific fifth percentile value [ie, LLN]) **(A)**, both MBC and PC counts in blood as per EuroFlow2025 criteria **(B)**, NK cell counts **(C)**, serum immunoglobulin levels **(D)**, and presence vs absence of pathogenic genetic variants/risk alleles **(E)**. Noninfectious complications include splenomegaly, lymphadenopathy, ILD, liver disease, lymphoma, enteropathy, cytopenia, systemic AI, and tissue-specific AI. $*P < .05$; $*^0P < .05$ vs $MBC^+/PC^+/Ab^-$; $*^1P < .05$ vs $swPC^-$; $*^2P < .05$ vs $swMBC^-$; $*^3P < .05$ vs $27MBC^-$. Chi-square and Fisher exact tests were used. *Cytopenia* refers to anemia and/or thrombocytopenia.

Updated EuroFlow2025 classification of CVID according to B-cell/PC immune profile in blood

Unsupervised clustering analysis identified 7 CVID patient clusters with differentially altered B-cell/PC subset profiles (Fig 3; see the Methods section, Fig E3 and Table E5 in the Online Repository). Six corresponded to the CVID1-6 groups defined by Blanco et al[17] (Fig 3; see Fig E3, *A,* Fig E4, and Fig E5 in the Online Repository). The additional CVID-0 group corresponded to patients with a milder B-cell/PC defect (Fig 3, Fig E3, *A,* and Fig E4), with detectable (normal or decreased) sw-PC. Notably, a close association was observed between the CVID0-6 and the EUROclass groups (Fig 3 and Fig E3, *B*).[17,18] However, CVID1-3 patients included a similar frequency of all EUROclass groups except B^-, and SmB^- cases were found across all EuroFlow2025 CVID0-6 groups (Fig E3, *B*).

According to disease severity, these 7 CVID0-6 groups were reclassified into 4 larger clinically relevant groups: (1) patients with preserved IgH-switched MBC and PC (MBC^+/PC^+/antibody [Ab] negative; CVID-0), (2) subjects who lacked sw-PC but had preserved sw-MBC ($swPC^-$; CVID1-3), (3) patients who lacked both sw-PC and sw-MBC, but showed preserved $CD27^+$ MBC ($swMBC^-$; CVID-4); and (4) individuals who lacked sw-PC and classical $CD27^+$ MBC ($27MBC^-$; CVID5-6) (Fig 3; Table E2, *B*). Although no significant age differences were found at diagnosis and at enrollment between $MBC^+/PC^+/Ab^-$ and the other 3 CVID groups, preservation of sw-PC in $MBC^+/PC^+/Ab^-$ patients translated into higher sIgA ($P \leq .002$ vs $swPC^-$, $swMBC^-$, and $27MBC^-$) and sIgM ($P \leq .003$ vs $swPC^-$ and $27MBC^-$) at enrollment, and greater sIgG ($P < .001$ vs $swPC^-$ and $27MBC^-$) at diagnosis (see Table E6 in the Online Repository available at www.jacionline.org). Moreover, $MBC^+/PC^+/Ab^-$ patients rarely (<10%) showed splenomegaly ($P \leq .009$ vs $swPC^-$, $swMBC^-$, and $27MBC^-$), lymphadenopathy ($P \leq .001$ vs $swPC^-$ and $27MBC^-$), ILD ($P \leq .009$ vs $swPC^-$ and $27MBC^-$), liver disease ($P \leq .03$ vs $swPC^-$ and $27MBC^-$), cytopenia ($P \leq .04$ vs $swPC^-$, $swMBC^-$, and $27MBC^-$), systemic AI ($P = .003$ vs $swMBC^-$), or tissue-specific AI ($P = .03$ vs $swPC^-$) (Fig 2, *B,* and Table E6). Among $swPC^-$, $swMBC^-$, and $27MBC^-$ patients, specific clinical profiles were observed. Briefly, half of $swMBC^-$ patients had systemic AI versus <5% of the other patients ($P \leq .005$), whereas cytopenia was observed in half of $27MBC^-$ patients versus <25% of $MBC^+/PC^+/Ab^-$ and $swPC^-$ patients ($P \leq .01$). In turn, $swPC^-$ and $27MBC^-$ patients more frequently had ILD (20% and 27%, respectively) and lymphadenopathy (36% and 42%) compared to $MBC^+/PC^+/Ab^-$ (3% and 8%, respectively; $P \leq .009$) and $swMBC^-$ patients (0 with lymphadenopathy; $P \leq .03$). Enteropathy was observed in 54% of $27MBC^-$ patients versus 18% and 31% of $MBC^+/PC^+/Ab^-$ and $swPC^-$ patients, respectively ($P \leq .02$), while liver disease was particularly frequent among $27MBC^-$ patients (45% vs 3% and 16% of $MBC^+/PC^+/Ab^-$ and $swPC^-$ patients; $P \leq .002$). The more severe phenotype of $27MBC^-$ patients had higher hospital admission rates (83% vs 35% and 48% of $MBC^+/PC^+/Ab^-$ and $swPC^-$ patients; $P \leq .004$) (Fig 2, *B,* and Table E6).

Classification of CVID based on blood NK cell counts

Ninety-one CVID patients (43%) had abnormally decreased (vs age-matched HDs) PB NK cell counts (Table E2, *C*), associated with lower sIgG at diagnosis ($P < .04$), lower sIgA/sIgM at enrollment ($P \leq .002$), and more severe clinical phenotypes: higher frequency of LRTI ($P = .003$), GI infections ($P = .002$), splenomegaly ($P < .001$), ILD ($P = .01$), liver disease ($P = .003$), enteropathy ($P < .001$), cytopenia ($P = .03$), tissue-specific AI ($P = .01$), nonhematopoietic tumors ($P = .02$), and increased death rate ($P = .04$). Conversely, similar frequencies of URTI, bronchiectasis, lymphadenopathy, lymphoma, and systemic AI were observed between patients with defective versus normal NK cell counts in blood (Fig 2, *C,* and see Table E7 in the Online Repository available at www.jacionline.org).

Classification of CVID according to serum immunoglobulin isotype levels

No differences in age at diagnosis were observed according to sIgG, sIgA, and sIgM. Patients with sIgG <350 mg/dL and sIgA <7.5 mg/dL at diagnosis had higher frequencies of URTI ($P \leq .01$), LRTI ($P < .001$), bronchiectasis ($P \leq .001$), GI infections ($P \leq .009$), splenomegaly ($P = .001$), lymphadenopathy ($P \leq .007$), ILD ($P \leq .04$), and enteropathy ($P \leq .04$) (Fig 2, *D,* and see Table E8 in the Online Repository available at www.jacionline.org). Conversely, lower sIgM (<10 mg/dL) at diagnosis was only associated with a greater frequency of LRTI ($P = .004$) and bronchiectasis ($P = .008$). Interestingly, deterioration of sIgA and sIgM levels along the disease course was observed in 25% and 22% of CVID patients, respectively (see Table E9 in the Online Repository). Deterioration of sIgA or sIgM levels was associated with increased frequencies of splenomegaly ($P \leq .001$), lymphadenopathy ($P \leq .03$), liver disease ($P \leq .03$), enteropathy ($P \leq .02$), and cytopenia ($P \leq .04$) (Table E9). Accordingly, the association of sIgA and sIgM increased when evaluated at enrollment (vs diagnosis) (Fig 2, *D,* and Table E8).

Frequency and clinical features of CVID patients harboring pathogenic genetic variants/risk alleles

Pathogenic genetic variants were identified in 13 (10%) of 134 CVID patients: 3 subjects with variants of the *NFKB1* gene, 2 with *CTLA4* and *RAG1* gene variants, and 1 variant of the *CD19*, *NFKB2, IRF2BP2, LRBA, TNFAIP3,* and *SP110* genes, each occurring in a single patient (see Table E10 in the Online Repository available at www.jacionline.org). Moreover, 11% of patients harbored *TNFRSF13B* genetic variants, classified as risk alleles for CVID.[11] Together, the pathogenic genetic variants/risk alleles identified accounted for 26 (19%) of 134 patients. Those genetic variants/risk alleles were associated with a lower percentage of bronchiectasis ($P = .01$) but not with age, serum immunoglobulin levels, or other disease features (Fig 2, *E,* and see Table E11 in the Online Repository).

Sequential monitoring of $TCD4^+$-naive cell and B-cell/PC immune profiles in blood of CVID patients

In 58 CVID patients, 112 sequential flow cytometry studies were performed over a median (range) follow-up of 4 (1-12) years. After this period, most patients displayed the same immune profile defined by their (normalized) PB $TCD4^+$-naive cell counts (100%) and PB B-cell/PC numbers (95%), except for 3 patients (5%). Of these 3, 1 patient progressed from $MBC^+/PC^+/Ab^-$ to $swPC^-$ after 4 years, and 2 patients

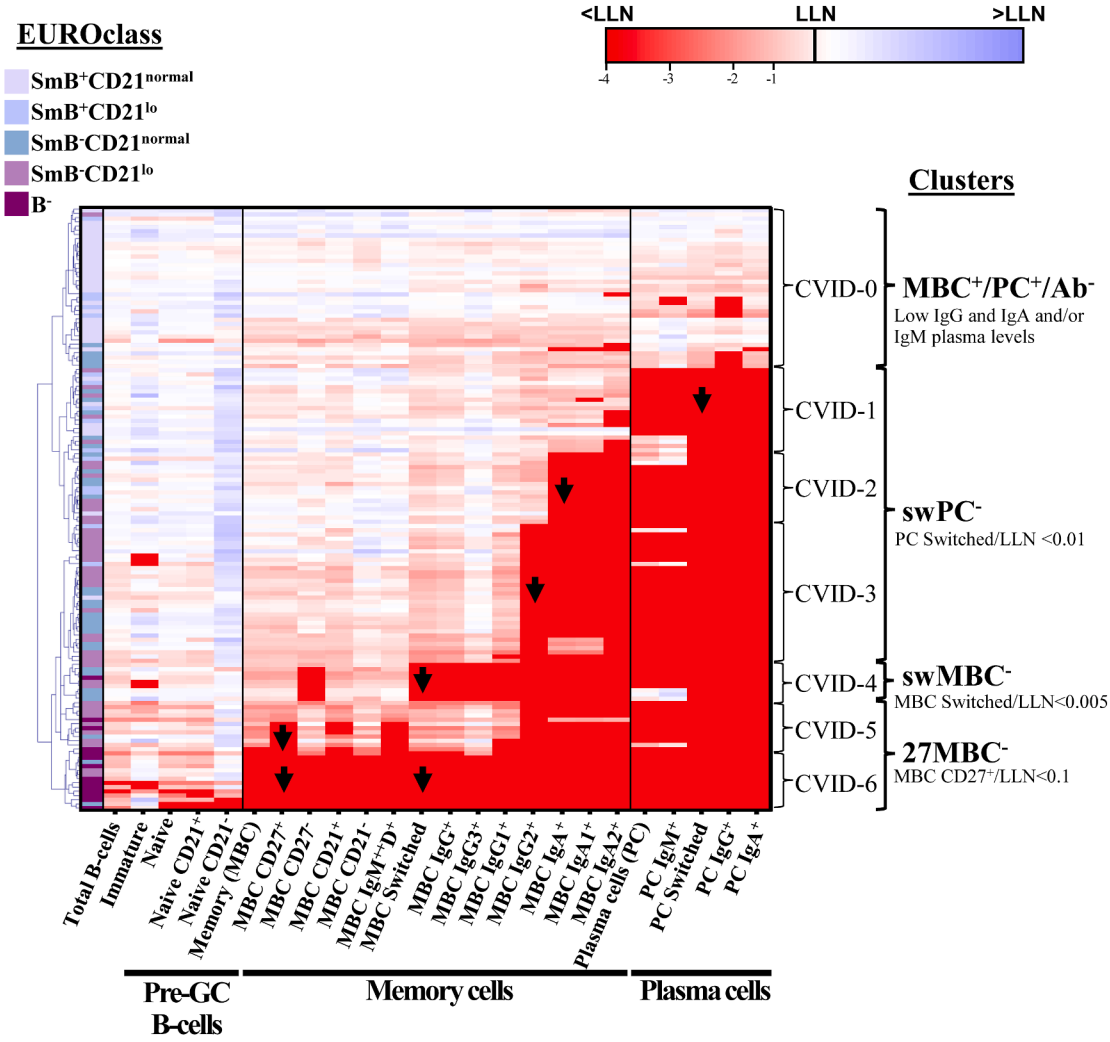

FIG 3. Distribution of CVID patients according to their MBC and PC subset immune profiles in blood (n = 144). Heat map represents hierarchical clustering analysis results according to absolute count of different B-cell and PC subsets identified (columns) in blood normalized by LLN (ie, fifth percentile value) found among age-matched HDs vs individual CVID patients (rows). *Intense red colors* represent deeper degree of deficiency on $\log_{10}$ scale compared to LLN of corresponding age-matched group of each individual CVID patient; *intense blue colors* represent normal values above LLN. CVID-0 to CVID-6 patient clusters were defined by hierarchical clustering analysis using Euclidean distances and complete linkage clustering method, with main B-cell/PC subset counts distributed differently among individual patients included in each group. These 7 groups (CVID-0 to CVID-6) were further grouped into 4 clinically relevant groups ($MBC^+/PC^+/Ab^-$, CVID-0; $swPC^-$, CVID1-3; $swMBC^-$, CVID-4; and $27MBC^-$, CVID5-6), as depicted at *right*. CVID EUROclass classification subgroup (SmB^+CD21^{normal}, SmB^+CD21^{lo}, SmB^-CD21^{normal}, SmB^-CD21^{lo}, and B^-) of each individual CVID patient is color coded from *lighter to darker violet* in *left column. Black arrows* indicate MBC and PC subsets that contributed most to discriminate individual patient clusters from all other CVID patient groups, as summarized in EuroFlow2025 updated CVID classification in Fig E3, *A. GC,* Germinal center.

progressed from $swPC^-$ to $swMBC^-$ at 4 and 7 years after the first analysis (Fig 4, *A* and *B*). NK cell counts also remained stable in all but 3 patients (5%) in whom NK cell defects emerged during follow-up (Fig 4, *C*).

Cellular, serologic, and gene mutational profiles independently associated with clinical manifestations of CVID

Multivariate analysis identified sIgA at enrollment to be the only independent biomarker associated with URTI ($P = .001$), LRTI ($P < .001$), and bronchiectasis ($P < .001$). In turn, GI infections were independently associated with the $MBC^+/PC^+/Ab^-$ ($P = .04$) and $27MBC^-$ ($P = .003$) B-cell/PC profiles. Similarly, the need for hospital admission for treatment of severe infections was independently associated with $27MBC^-$ ($P = .03$) and NK cell defect ($P = .003$) (Fig 5, *A*).

In contrast to sIgG, sIgA, and sIgM levels, immune cell profiles showed a strong independent association with noninfectious complications of CVID. Thus, $TCD4^+$-naive cell counts were independent factors associated with most noninfectious complications of CVID ($P = .03$): splenomegaly ($P < .001$),

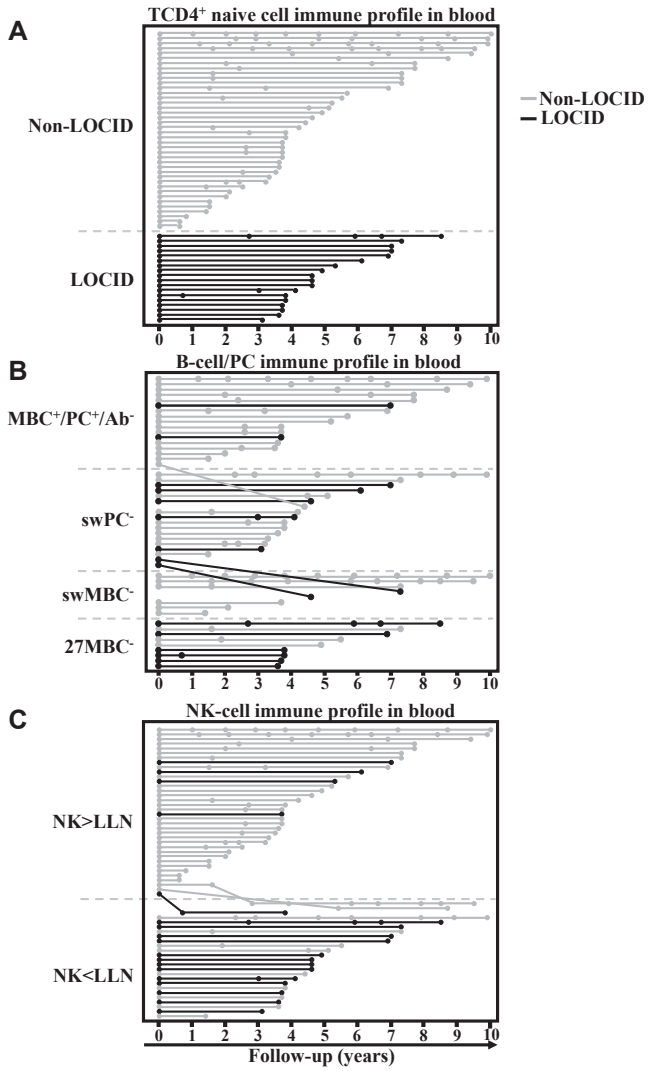

FIG 4. Kinetics of altered TCD4$^+$-naive cell **(A)**, B-cell/PC **(B)**, and NK cell **(C)** immune profiles in blood of CVID patients (n = 58) with 2 or more follow-up (median [range], 4 [1-12] years) studies. *Horizontal lines* indicate stable B-cell/PC or NK cell immune profile for LOCID *(black lines)* and non-LOCID *(gray lines)* patients.

lymphadenopathy ($P < .001$), ILD ($P < .001$), liver disease ($P = .01$), lymphoma ($P = .02$), and anemia/thrombocytopenia ($P < .001$). Likewise, the PB B-cell/PC profile emerged as an independent (negative) biomarker associated with noninfectious complications (MBC$^+$/PC$^+$/Ab$^-$, $P < .001$), particularly splenomegaly (MBC$^+$/PC$^+$/Ab$^-$, $P = .002$), and showed a (positive) association with liver disease (27MBC$^-$, $P = .01$) together with decreased sIgA ($P = .03$), of enteropathy (27MBC$^-$, $P = .02$) together with decreased sIgM ($P = .04$), and of systemic AI (swMBC$^-$, $P < .001$). NK cell defects were independently associated with some noninfectious complications, such as enteropathy ($P = .02$) and tissue-specific AI ($P = .02$) (Fig 5, *B*).

The strong independent association between TCD4$^+$-naive cell counts and noninfectious complications was further supported by an inverse correlation ($r^2 = -0.6$, $P < .001$) observed between the number of lymphoproliferation-associated manifestations (splenomegaly, lymphadenopathy, ILD, liver disease, or lymphoma) and TCD4$^+$-naive cell counts (Fig E6, *A*). Interestingly, a direct correlation was also found between the severity of B-cell/PC defects and LOCID ($r^2 = 0.40$, $P < .001$), with 67% versus 26% LOCID cases among 27MBC$^-$ and 27MBC$^+$ patients, respectively (Fig E6, *A* and *B*).

Predictors of CVID patient survival

After a median follow-up of 5 years, only patients who had experienced noninfectious complications had died (13/209, 1%) (see Table E12 and Fig E7 in the Online Repository available at www.jacionline.org). This led to a significantly shortened overall survival (OS) ($P = .007$) and lower age at death ($P = .01$) among CVID patients who had noninfectious complications versus those with infections only (5-year OS [95% confidence interval (CI)] rates of 88% [78-93] vs 100%, respectively) (Fig E7). Among patients with noninfectious complications, a lower ($P \leq .001$) median age at death and 5-year OS rates (hazard ratio [HR] and 95% CI) were also observed for LOCID patients (10 [3-34], $P < .001$; and 9 [2-30], $P < .001$, respectively), 27MBC$^-$ (19 [5-72], $P < .001$ and 16 [4-61], $P < .001$, respectively) and lower baseline sIgG (8 [2-31], $P = .002$ and 9 [2-33], $P = .001$, respectively), compared to the other patient groups (Fig 6, *A*). In contrast, neither sIgA nor sIgM (at baseline or at enrollment) nor the presence of pathogenic/risk alleles predicted CVID patient survival (see Table E13 in the Online Repository). On the basis of these results and biomarkers, 3 risk groups of CVID patients were defined among those displaying noninfectious complications, with significantly different outcomes (Fig 6, *B* and *C*), as follows: (1) low-risk 27MBC$^+$ patients with either normal TCD4$^+$-naive cell counts (>0.9 LLN) or baseline sIgG >350 mg/dL, with a similarly good outcome to those with infections only (HR = 3 and 2 for age at death and 5-year OS rates, respectively; $P > .05$); (2) intermediate-risk 27MBC$^+$ patients who simultaneously had LOCID (by EuroFlow2025 criteria) and strongly reduced baseline sIgG (<350 mg/dL), with intermediate OS rates (HR = 7 and 10, $P \leq .003$ vs patients with infections only); and (3) high-risk 27MBC$^-$patients (independent of TCD4$^+$-naive cell counts and sIgG), who had the poorest outcome (HR = 21 and 15, $P < .001$ vs patients with infections only), with 5-year OS rates of 98%, 81%, and 70%, respectively. The new risk score showed the highest predictive value for shortened OS and age at death, as reflected by a higher *C*-index value (95% CI) of 0.86 (0.75-0.93) and 0.85 (0.74-0.93) compared to LOCID (0.54 [0.45-0.64] and 0.53 [0.45-0.64]), the B-cell/PC profile (0.54 [0.41-0.67] and 0.55 [0.43-0.69]), NK cell counts (0.64 [0.54-0.75] and 0.67 [0.53-0.79]), and sIgG (0.59 [0.49-0.70] and 0.66 [0.53-0.79]) (see Fig E8 in the Online Repository) alone or in different combinations (LOCID and sIgG: 0.82 [0.70-0.91] and 0.82 [0.70-0.92]; LOCID, B-cell/PC, and NK cell counts: 0.85 [0.73-0.93] and 0.84 [0.72-0.93]) (Fig E8), as well as the previous Freiburg[15] (0.66 [0.55-0.78] and 0.71 [0.58-0.82]) and EUROclass[18] (0.70 [0.55-0.82] and 0.77 [0.61-0.88]) classifications, which were based on sw-MBC and CD21 expression, respectively (Fig E8).

DISCUSSION

Despite the numerous studies run since CVID was first described,[32] the potential association between the altered CVID

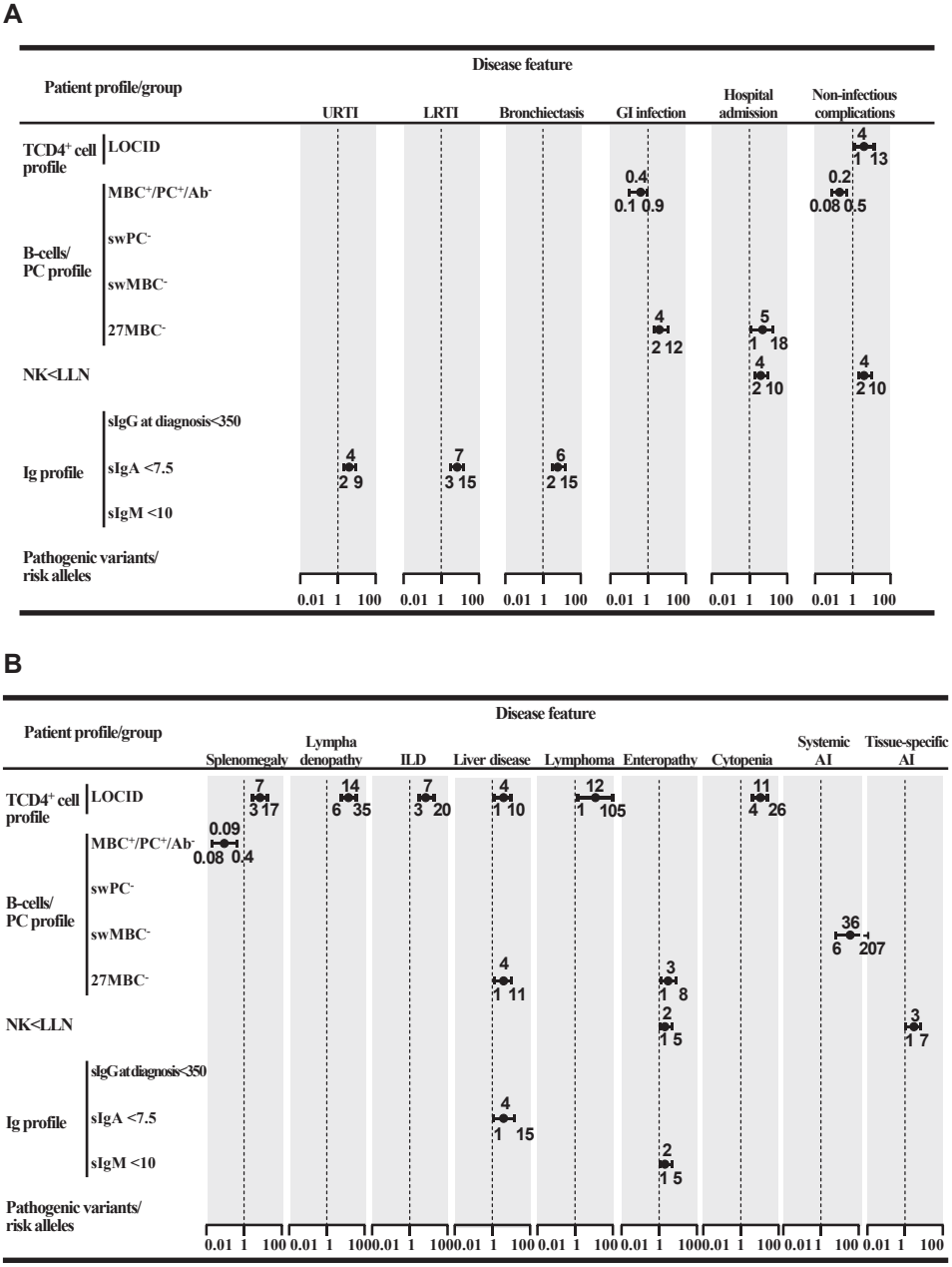

FIG 5. Altered immune cell and specific immunoglobulin profiles independently associated with different clinical features of CVID patients identified by multivariate logistic regression analysis (n = 144 patients). Forest plots display odds ratios (ORs) and 95% CIs as measure of association between CVID patient groups defined by specific immunoglobulin levels (sIgG, sIgA, and sIgM), $TCD4^+$-naive cell counts, and both B-cell and PC subset defects and NK cell defects identified in blood of CVID patients compared to age-matched HDs. **(A)** Multivariate analysis results for CVID patients with infectious disease complications. **(B)** Results of multivariate analysis for CVID patients with noninfectious complications of disease. Cutoff values used for specific immunoglobulin levels at diagnosis were as follows: sIgG < 350 mg/dL, sIgA < 7.5 mg/dL, and sIgM < 10 mg/dL. OR < 1 indicates that corresponding CVID group is associated with lower risk of experiencing that specific clinical complication (protective factor); OR > 1 indicates association with greater risk for that specific clinical complication to occur (risk factor). LOCID EuroFlow2025 cutoff was <0.9 of $TCD4^+$-naive cells/μL normalized by respective age-matched specific fifth percentile value (ie, LLN). Noninfectious complications include splenomegaly, lymphadenopathy, ILD, liver disease, lymphoma, enteropathy, cytopenia, systemic AI, and tissue-specific AI. ORs were calculated in multivariate analyses by a logistic regression model. *Cytopenia* refers to anemia and/or thrombocytopenia. *OR,* Odds ratio.

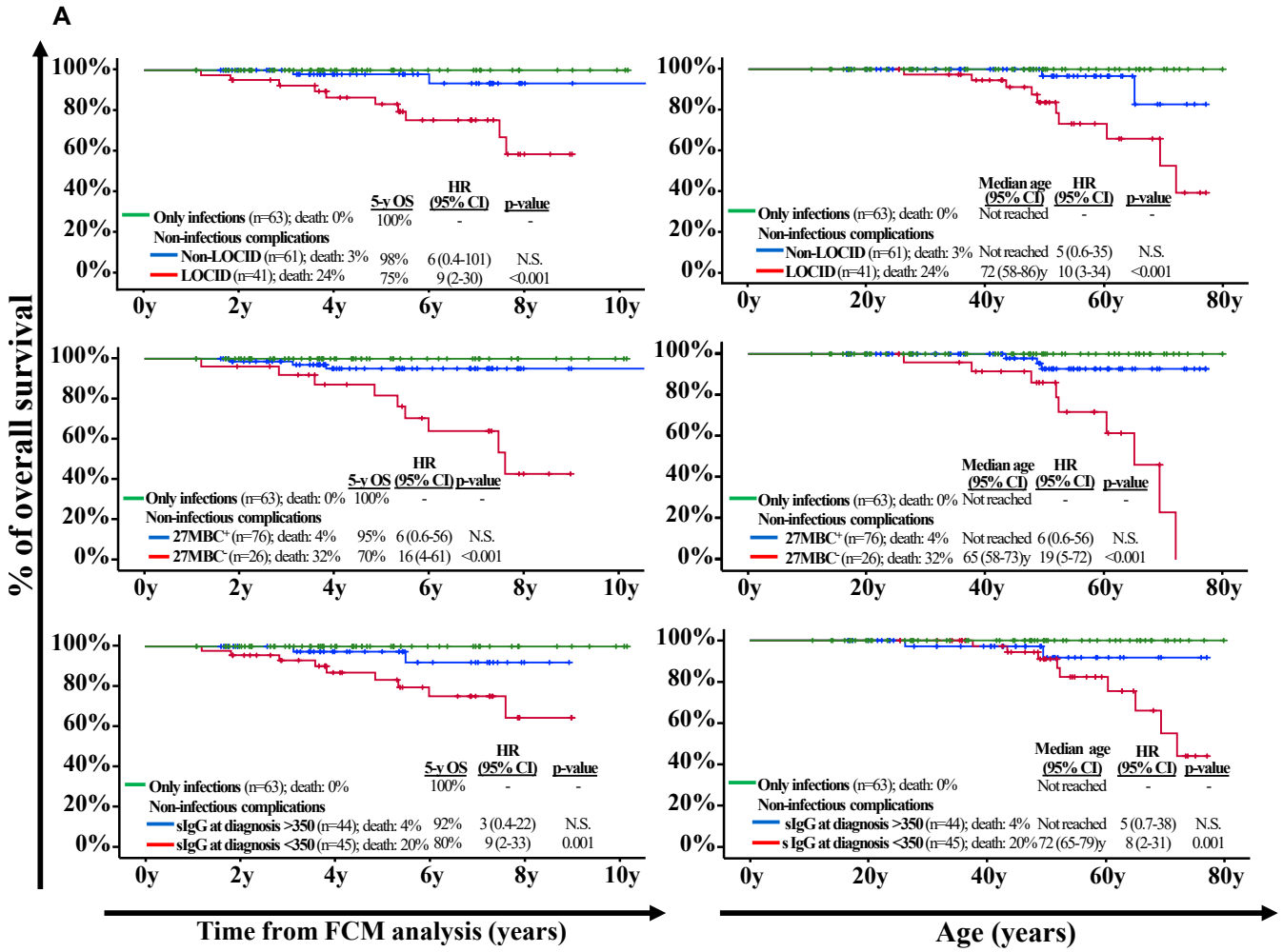

FIG 6. OS of CVID patients classified as patients presenting only with infections vs patients with noninfectious complications of disease distributed into different subgroups according to TCD4$^+$-naive cell and both MBC and PC counts in blood as defined by EuroFlow2025 classification criteria, and sIgG levels at diagnosis and combined serologic and cellular data (n = 167). **(A)** OS curves from first FCM study *(left)* and according to patient age *(right)* to death or last follow-up time point. *Lines* represent OS curve for distinct CVID patient groups. **(B** and **C)** OS of CVID patients grouped according to presence or absence of noninfectious complications of disease and altered TCD4$^+$-naive cell plus B-cell/PC subset immune profiles in blood plus sIgG levels at diagnosis. Kaplan-Meier OS curves are shown according to time from FCM analysis *(B)* and birth *(C)* to death or last follow-up visit. *Colored lines* represent OS curves for distinct CVID patient groups, where plus sign represents individual censored cases. OS and age at death curves were plotted by Kaplan-Meier test and compared by 1-sided log-rank test, and HRs with 95% CIs were estimated by Mantel-Haenszel test; *NS* indicates no statistically significant differences. *FCM,* Flow cytometry.

alleles found in 25% to 30% of cases, and the disease clinical phenotype has been confirmed for few CVID-like variants,[33-35] as also found here in 19% of patients, suggesting that most CVID patients might exhibit multiple deleterious polymorphisms together with additional predisposing epigenetic factors.[36] In fact, even when specific pathways are affected, the patients' clinical presentation and phenotypes may differ significantly,[11,35] as also supported by the absence of an independent association between the CVID-associated risk alleles/genotypes found here and the potential multifactorial nature of the disease.[13,14,36] Conversely, increased evidence suggests that CVID heterogeneity might be better dissected on the basis of serologic and cellular biomarkers that have been more consistently associated with the distinct clinical manifestations of the disease.[5,15-24] Here, we validated these findings using age-matched analyses of all candidate biomarkers using a large multicenter CVID cohort.

Recurrent and severe infections remain a hallmark of CVID; however, after the introduction of IgRT, noninfectious manifestations have become the main clinical complication of CVID.[7] The nature of these noninfectious complications is complex and might be a product of an interplay between, for example, leaky mucosal barrier and dysregulated immunity. Previous studies have suggested that these might be due to a low-grade chronic inflammatory process[37,38] induced by recurrent/opportunistic infections[38,39] and/or mucosal translocation of the microbiota,[40-42] leading to hyperplasia of secondary lymphoid tissues (eg, splenomegaly and lymphadenopathies) that might be followed by lymphoid infiltration of other antigen-exposed organs such as

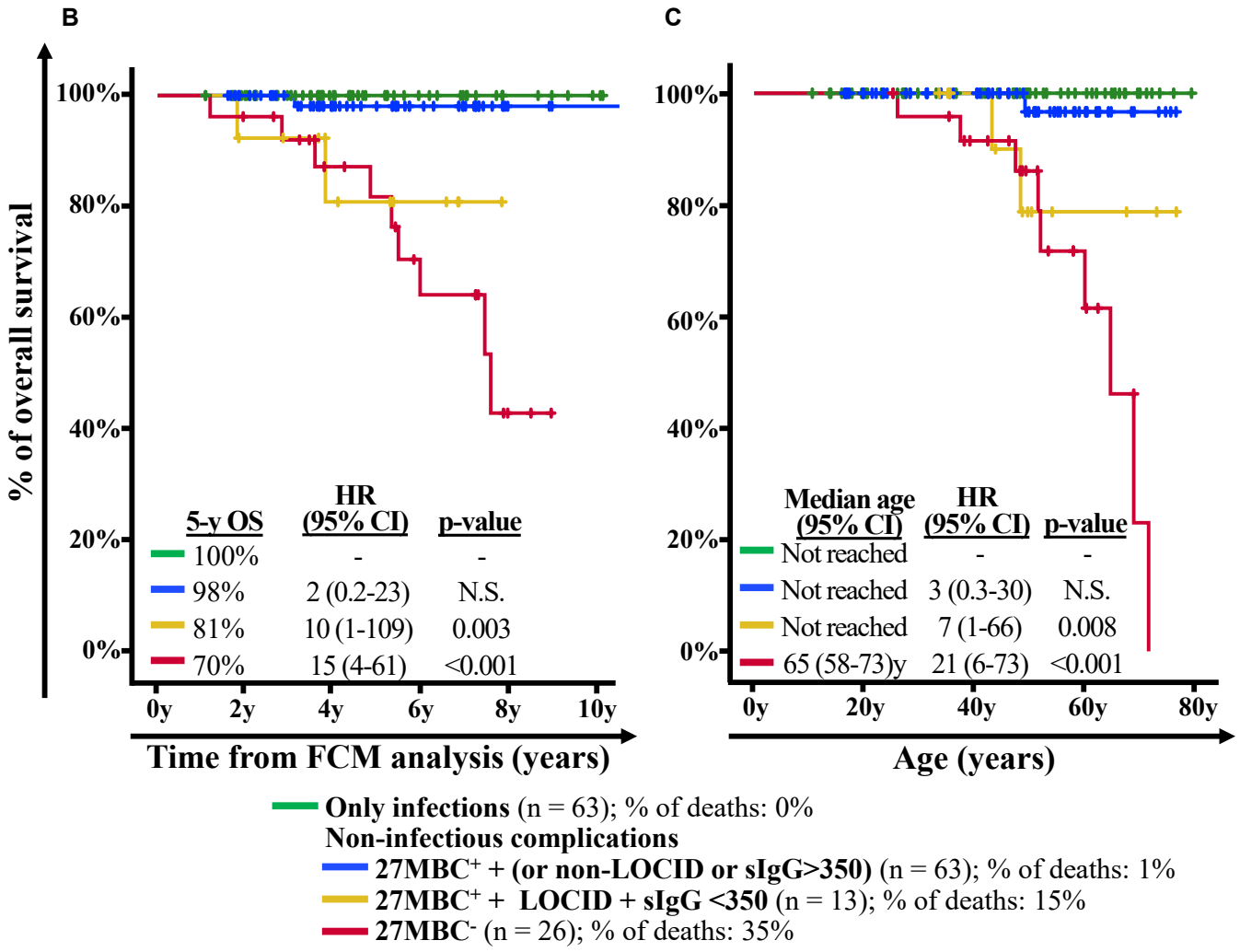

FIG 6. *(Continued).*

lung or liver,[5,8-10,23] frequently linked to cytopenia (anemia and/or thrombocytopenia) (see Fig E9 in the Online Repository available at www.jacionline.org).[43-45] In the worst cases, uncontrolled lymphoproliferation leads to severe tissue damage (eg, ILD, liver disease) and malignant lymphoma.[1,5,10] Although these processes might partially reflect an attempt to form tertiary lymphoid tissues like ILD, they are not observed in all involved tissues (eg, liver), and immunosuppressive therapy did not consistently improve the inflammatory lesions.[9,10] Importantly, histopathologic analyses revealed that hyperplastic lesions are mostly formed by functionally impaired T (and B) cells unable to form productive follicles,[42,46-48] indicating that at least a subset of patients might have a more complex immune defect involving T and B cells. Thus, unproductive recruitment of T cells to peripheral tissues, associated with decreased numbers of blood circulating $TCD4^+$ cells, particularly $TCD4^+$-naive cells, have been consistently reported in CVID patients with noninfectious lymphoproliferative complications.[21,22] Our results support and extend these observations in a large CVID cohort and provide a more accurate cutoff for the definition of LOCID. Thus, the new age-matched $TCD4^+$-naive cell cutoff more accurately identified CVID cases of a lymphoproliferative phenotype compared to the well-established (age-independent) DEFI2015 and Freiburg2019 criteria.[21,22] Despite serum immunoglobulin levels and B-cell/PC profiles associated in the univariate analysis with noninfectious complications,[5,15,16,18] the age-matched $TCD4^+$-naive cell defect emerged in our series as an independent biomarker associated with lymphoproliferative complications linked to a 5 to 15 times higher risk of splenomegaly, lymphadenopathy, ILD, liver disease, lymphoma, and anemia/thrombocytopenia. These findings support a common immunopathogenic mechanism related to the dysregulated T-cell production and (potentially also) response in these patients. In line with this hypothesis, we found an inverse correlation between the number of affected tissues and age-normalized $TCD4^+$-naive cell counts in blood, where patients with less $TCD4^+$-naive cells displayed more complex lymphoproliferative phenotypes. Together, these results underscore the need for more careful and frequent evaluation of splenomegaly, ILD, and liver disease in LOCID cases. Despite the above findings, OS of LOCID patients was only significantly reduced

when associated with a more pronounced B-cell/PC defect, reflected by lower sIgG and/or a more markedly decreased pool of classical $CD27^+$ MBC ($27MBC^-$).

Although hypogammaglobulinemia is a hallmark of CVID,[4,49] a lack of PC in PB,[17] lymph nodes,[50] and mucosa[51] has been reported in only small CVID cohorts. By taking advantage of high-sensitive flow cytometry methods, we here describe for the first time in a multicenter study a subset of ~20% CVID patients with a preserved ability to produce immunoglobulin-switched PC ($MBC^+/PC^+/Ab^-$). Interestingly, $MBC^+/PC^+/Ab^-$ patients did not seem to represent an early phase of disease because they did not show a younger age than other CVID patients, and their disease did not appear to evolve into a more severely affected B-cell profile in the short to medium term. It is notable that although transient increases in circulating PC may occur in other immune conditions during ongoing infections, such increases have not been observed in CVID.[52] In contrast, the presence of sw-PC in patients with milder disease was associated with less severe hypogammaglobulinemia and respiratory infections only in many cases. Indeed, detection of sw-PC was an independent biomarker associated with protection against nonrespiratory (eg, GI) infections and noninfectious complications. Further detailed analysis of the MBC IgH isotype/subclass profiles also confirmed the presence of a hyper-IgM–like subgroup of CVID patients[17] (but without hyper-IgM–like gene mutations), which lacked sw-MBC but had nearly normal $IgMD^+$ MBC counts and higher frequencies of lupus-like disease complications, splenomegaly, and anemia/thrombocytopenia. At the other extreme, the lack of a preserved minimum pool of classical $CD27^+$ MBC emerged as the most lethal immune defect, as also suggested by others.[53] Thus, CVID patients with undetected $CD27^+$ (and $CD21^+$)[30] MBC systematically experienced noninfectious complications, particularly those involving the gut–spleen–liver axis and the lung. In addition to greater morbidity, lack of classical $CD27^+$ MBC was also associated with a poorer survival, with a third of $27MBC^-$ patients dying within 5 years, mostly of ILD, chronic liver disease, and/or severe enteropathy.

As previously reported,[54] half of our CVID patients had abnormally decreased NK cell counts in blood. Those patients showed a more severe clinical phenotype with a higher frequency of noninfectious complications as well as more pronounced immune defects, such as deeper (sIgG/sIgA/sIgM) hypogammaglobulinemia, higher frequency of LOCID, and more severe B-cell phenotypes, leading to reduced OS.[53] Multivariate analysis showed that most of these associations are due to the overlap of the NK cell defect with LOCID and/or MBC/PC defects, with decreased NK cell counts retaining an independent association only with enteropathy and liver disease, as previously suggested.[23,54] These findings suggest that in CVID, circulating NK cells might be recruited to gut and liver, either as part of the underlying immunopathogenic mechanisms[23] or as an attempt to locally control inflammation.[55]

Our results might further contribute to the refinement of the immunopathogenic classification of CVID by defining 4 CVID groups with unique B-cell/PC defects associated with different clinical phenotypes. Those included first a group of CVID-like patients with hypogammaglobulinemia but (almost) normal unswitched and switched MBC and PC ($MBC^+/PC^+/Ab^-$), in whom potentially defective antibody secretion[15,18] might be associated with polymorphisms with incomplete penetrance,[11,13] and/or defects in the ability of PC to secrete antibodies against specific types of bacteria,[15,52] leading to a predominance of infections with similar profiles (except for bronchiectasis) in patients with preserved IgG^+ or IgA^+ PC and with very few noninfectious complications. A second, larger group of patients with a deeper germinal center defect consisting of undetected circulating sw-PC and a heterogeneous composition of sw-MBC ($swPC^-$) comprises patients with higher loads of damaging polymorphisms, although the frequency of pathogenic variants/risk alleles was similar to the $MBC^+/PC^+/Ab^-$ group, suggesting that either non-identified genes or epigenetic factors are responsible of the deeper B-cell defect. The third group of patients, $swMBC^-$, showed compromised switching ability, but preserved compartment (normal or reduced) of unswitched MBC. No CVID-like pathogenic variants were detected in these patients, who more frequently showed AI deficiency–like clinical features (eg, systemic AI). The fourth group, $27MBC^-$, included patients unable to produce an effective germinal center reaction, who might only have residual numbers of $CD27^-$ ($CD21^-$) MBC, associated in most of cases of LOCID (also observed among $swPC^-$ patients) and lymphoid hyperplasia across several tissues. Interestingly, although a lower incidence of CVID-like mutations was observed in $27MBC^-$ patients (vs $MBC^+/PC^+/Ab^-$ and $swPC^-$ patients), those mutations were potentially more deleterious (eg, stop-codon vs nonsynonymous variants) (see Table E14 in the Online Repository available at www.jacionline.org).

In most cases analyzed, the $TCD4^+$, B-cell/PC, and NK cell defects remained stable for (several) years,[26] suggesting that they might be intrinsically linked to the genetic and/or epigenetic causes of the immune defect (eg, hypogammaglobulinemia). Nevertheless, in a minority of patients, the immune defect progressively became more pronounced, pointing to the need for further longitudinal studies with long-term patient monitoring. In contrast to sIgG production, which cannot be monitored in patients receiving IgRT, immune cells might be more robust biomarkers of disease progression.

Despite IgRT, a subset of CVID patients still experience recurrent/chronic infections, particularly respiratory and GI infections, often requiring hospital admission.[56] The susceptibility to infection of CVID patients undergoing IgRT has been associated with lower (baseline) sIgG,[56,57] (baseline and long-term) sIgA[37,56] and/or sIgM,[37,58] and deeper B-cell[59,60] and $TCD4^+$ cell[58,61] defects. However, the precise underlying mechanism remains elusive, and specific recommendations to mitigate this persistent susceptibility to infection are needed.[62] In line with retrospective analyses of international registries (eg, the European Society for Immunodeficiencies and the United States Immunodeficiency Network),[1,63] we show here that recurrent respiratory infections and enteropathy occurring under IgRT, are closely related to lower sIgA and sIgM, respectively. Thus, CVID patients with sIgA < 7.5 mg/dL displayed a 4- to 6-fold higher risk of URTI, LRTI, bronchiectasis, and liver disease, while those with sIgM < 10 mg/dL had a 2-fold increased risk of enteropathy. Although this association was observed with both baseline and longer-term sIgA and sIgM levels, in 20% to 30% of patients, these serum immunoglobulin isotypes strongly decreased during follow-up in parallel with increased disease severity, supporting the utility of long-term sIgA/sIgM monitoring in CVID and suggesting that although IgRT doses should continue to be adjusted according to sIgG levels, the use of sIgA/sIgM-enriched IgRT formulations might provide additional benefit for this subset of patients with progressively decreasing

sIgA/sIgM levels[62] that are due to the inability of IgG antibodies to cross mucosal barriers.[64]

On the basis of all above findings, potential preventive and diagnostic steps might be taken. Thus, while CVID patients producing detectable sw-PC and sw-MBC ($MBC^+/PC^+/Ab^-$) might not require intense clinical care, and while in some cases IgRT could be adapted to sIgA levels and clinical evolution, LOCID patients may benefit from closer evaluation and regular monitoring, potentially including (eg, annual) chest computed tomography and liver function tests, clotting profile, and abdominal imaging, particularly in LOCID patients with lower NK cells/sIgM, because the management of noninfectious complications benefits from early diagnosis and/or immediate (immunosuppressive) treatment; however the optimal frequency and extent of these investigations remains to be prospectively defined. Likewise, larger prospective multicenter clinical studies are also needed to elucidate whether LOCID patients with lower sIgG—particularly those unable to produce a germinal center reaction ($27MBC^-$)—should be considered for allogeneic hematopoietic stem cell transplantation in addition to being more closely monitored.

In summary, using commercially available *in vitro* diagnostic device–cleared reagent kits and software tools for automated flow cytometric analysis of informative populations of blood circulating B, T, and NK cells that were based on age reference values,[65,66] we confirmed and extended previous observations showing that the clinical behavior and outcome of CVID are closely associated with the underlying immune defects. We suggest that detailed serologic and immune $TCD4^+$ plus NK cell and B-cell/PC analyses that are based on highly sensitive and standardized methods, combined with robust age-matched reference ranges, might contribute to better prediction of the clinical behavior of the disease and improve patient management.

Our results confirm that many CVID patients have a T-cell defect, which emerged as a warning sign of the development of lymphocyte hyperplasia, tissue infiltration, and organ damage that, when combined with a severe humoral and cellular B-cell defect (low baseline sIgG and undetected $CD27^+$ MBC), led to a shortened OS with a need for treatment measures capable of restoring B-cell immunity (eg, allogeneic hematopoietic stem cell transplantation).[67,68] Importantly, the defective B-cell phenotype also had a moderate prognostic impact independent of $TCD4^+$-naive cell counts, because it was associated with milder disease in patients who had a preserved ability to generate PC, in contrast to the severe clinical phenotype and greatly shortened survival of patients with undetected classical $CD27^+$ MBC ($27MBC^-$). Although our study provides novel insights useful to both physicians and academic practitioners, our conclusions are potentially limited by the split of the whole cohort into smaller groups defined by a set of variables selected from a higher number of parameters in a retrospective analysis of patients who had experienced variable disease courses and who had received distinct preventive and therapeutic treatment. Because of this, further prospective longitudinal studies in large multicenter CVID cohorts that included more pediatric cases and longer follow-up are needed to validate our findings and derive new recommendations for improved patient management.

DISCLOSURE STATEMENT

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Key messages

- **Detailed age-matched immunoglobulin levels and blood immune cell counts contribute to a better understanding of the clinical behavior of CVID.**
- **Low sIgG, LOCID, decreased NK cell counts, and lack of $CD27^+$ MBC identify CVID patients at higher risk of organ damage and shorter survival.**

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