CLINICAL TRIALS AND OBSERVATIONS

Morbidity and mortality in common variable immune deficiency over 4 decades

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The demographics, immunologic parameters, medical complications, and mortality statistics from 473 subjects with common variable immune deficiency followed over 4 decades in New York were analyzed. Median immunoglobulin levels were IgG, 246 mg/dL; IgA, 8 mg/dL; and IgM, 21 mg/dL; 22.6% had an IgG less than 100 mg/dL. Males were diagnosed earlier (median age, 30 years) than females (median age, 33.5 years; $P = .004$). Ninety-four percent of patients had a history of infections; 68% also had noninfectious complications: hematologic or organ-specific autoimmunity, 28.6%; chronic lung disease, 28.5%; bronchiectasis, 11.2%; gastrointestinal inflammatory disease, 15.4%; malabsorption, 5.9%; granulomatous disease, 9.7%; liver diseases and hepatitis, 9.1%; lymphoma, 8.2%; or other cancers, 7.0%. Females had higher baseline serum IgM ($P = .009$) and were more likely to develop lymphoma ($P = .04$); 19.6% of patients died, a significantly shorter survival than age- and sex-matched population controls ($P < .0001$). Reduced survival was associated with age at diagnosis, lower baseline IgG, higher IgM, and fewer peripheral B cells. The risk of death was 11 times higher for patients with noninfectious complications (hazard ratio = 10.95; $P < .0001$). Mortality was associated with lymphoma, any form of hepatitis, functional or structural lung impairment, and gastrointestinal disease with or without malabsorption, but not with bronchiectasis, autoimmunity, other cancers, granulomatous disease, or previous splenectomy. (*Blood*. 2012;119(7):1650-1657)

Introduction

Common variable immune deficiency (CVID) is a primary immune deficiency characterized by reduced serum levels of immunoglobulin (Ig)G, IgA, and/or IgM with reduced or absent specific antibody production.[1-4] The diagnosis is typically made between the ages of 20 and 40 years, but ∼ 20% are less than 20 years of age.[5] Potentially because of the symptom onset in young adult life and the heterogenous nature of the disease, a delay in diagnosis of 6 to 7 years is common.[5-7] Because of the relative prevalence, 1:25 000 to 1:50 000, and numbers of medical encounters, CVID is a clinically important immune defect.[4,5,7] The majority of subjects have normal numbers of peripheral blood B cells, but there are depleted numbers of circulating isotype switched memory B cells (IgD−IgM−CD27+), defective somatic hypermutation, and impaired formation of plasma cells in bone marrow and other tissues.[8-10]

Although there have been many investigations into the nature of this immune defect since it was first recognized in 1953,[11] the fundamental genetic or other causes of CVID remain unclear for the majority of patients. In a few rare cases, CVID has been linked to autosomal recessive genetic mutations, including inducible costimulatory,[12] CD19,[13,14] B cell–activating factor receptor,[15] CD20,[16] and CD81.[17] Both heterozygous and homozygous mutations in the gene for the B-cell receptor transmembrane activator and calcium-modulating cyclophilin ligand interactor (*TACI*) are found in 8% to 10% of subjects.[18-20] Although these are significantly associated with both immune deficiency and autoimmunity in CVID,[21,22] some of the same mutations also may be found in healthy controls and clinically "normal" relatives, suggesting that these are important disease-associated polymorphisms.[23] Recent genome-wide studies have demonstrated the unique genetic characteristics of this immune defect, showing both novel chromosomal associations and highly significant copy number loss and gain.[24]

The standard of care in CVID is replacement Ig given at frequent intervals for life,[25] and this replacement reduces the number of bacterial infections[26] and probably enhances survival.[7] However, immune globulin does not seem to protect against or treat the largely noninfectious complications such as functional and structural lung disease, autoimmunity, granulomatous disease, liver diseases and hepatitis, gastrointestinal inflammatory disease, or the development of cancer or lymphoma that are found in varying percentages of patients in different series.[6,7,27-32] These conditions are important, because in aggregate, the autoimmune and inflammatory conditions over time, lead to increased morbidity and mortality.[6,7,27] However, it is not clear whether all complications are equally deleterious or whether some of these are relatively benign with no increased risk to survival over long periods. We also lack biomarkers, preferably available at the time of diagnosis, to distinguish those subjects who are more likely to have selected clinical complications and poorer outcomes. Here, we examine the outcomes of a cohort of 473 CVID subjects followed by 1 group over 4 decades, and we present the demographic and immunologic markers associated with these complications and poorer survival.

Methods

CVID subjects

Subjects with CVID were seen in the Immune Deficiency Clinic at Mount Sinai Medical Center from 1986 through the present. Part of the cohort was

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previously seen at Memorial Sloan-Kettering Cancer Center (1974-1986). The diagnosis of CVID was made by standard criteria, including reduced serum IgG, IgA and/or IgM, by at least 2 SDs below the mean for age, with poor or absent antibody production to both protein and carbohydrate vaccines and exclusion of other causes of hypogammaglobulinemia.[1,2,4,5,7] Subjects under age 4 years without continued follow-up and subjects with lymphoid cancer diagnosed within 2 years after the diagnosis of CVID were excluded. Immunologic parameters included enumeration of T and B cells, CD4, and CD8 T cells and $IgM^-IgD^-CD27^+$ isotype switched memory B cells as a proportion of total B cells. Lymphocyte proliferative responses to mitogens, including phytohemagglutinin, concanavalin A, and pokeweed, were performed by standard methods. All subjects received Ig replacement therapy after diagnosis. Clinical information was obtained during patient visits; for subjects no longer receiving care at Mount Sinai, follow-up information was obtained from patients, their physicians, chart and medical records review, or a combination. All studies were undertaken with the consent of the Mount Sinai Medical Center Institutional Review Board.

Infectious and inflammatory complications

Both infectious and noninfectious illnesses were assessed from the clinical history and examination of medical records. Confirmation of malignancy, lymphoma, and granulomatous disease were based on pathology reports of tissues examined either at Mount Sinai or an outside facility. The diagnosis of chronic lung disease was based on radiologically evident or biopsy-proven structural lung disease, impaired lung function, or both. Structural lung disease included pulmonary infiltrates, nodules, fibrocystic parenchymal changes, granulomatous or lymphocytic infiltrates (confirmed on lung biopsy), bronchiectasis, or a combination. Impaired lung function was defined as a loss of vital capacity, restrictive or obstructive lung disease, reduced diffusion capacity of the lungs for carbon monoxide, reduced oxygen saturation with or without need for chronic oxygen therapy, or a combination. Infectious and noninfectious gastrointestinal disease was diagnosed by clinical history, stool and blood studies, and endoscopy with mucosal biopsy as required. Chronic diarrhea was defined as frequent loose or liquid stools for 3 or more months with no infectious cause identified. Malabsorption was defined as intestinal dysfunction causing substantial and chronic weight loss, documented vitamin or nutritional deficiencies, or a comnbination. Liver diseases and hepatitis were diagnosed by liver function tests above the upper limit of normal, sonographic studies, computerized tomography scans, specific PCR studies, and liver biopsy as needed.

Statistical methods

Baseline laboratory results before initiating immune globulin replacement are used for serum immune globulins; other test results were those done on the first clinic visit when possible. The percentage of patients meeting a specific immunologic criterion (eg, switched memory B cells, < 0.55%)[33] represents a percentage of the total number of observed values for that immunologic parameter. Immunologic differences between males and females were assessed using Mann-Whitney Wilcoxon tests. Complication rates in males versus females were assessed using Fisher exact tests. Statistical significance was defined as $P < .05$. Associations between age at diagnosis, age at death, and other immunologic factors were assessed with Spearman correlation coefficients using Prism 4 software (GraphPad). For mortality analysis, the time since diagnosis was determined using the age at diagnosis of CVID if known; otherwise, the age at initial evaluation was used for this diagnosis. The endpoint used was the time of last known follow-up or the date of death. Probabilities of survival after diagnosis of CVID were estimated from Kaplan-Meier life tables and compared with the expected survival of males and females in the general population based on US mortality rates. The median year of diagnosis in our cohort was 1994; thus, our population was compared with the 1994 US population life tables for each sex.[34] Patients for whom the date of death or the date of last follow-up could not be accurately determined were excluded from the mortality analysis. The Cox proportional hazards model was used for the analysis of factors that might be associated with increased risk of death. For this analysis, the time between the age at diagnosis and the age at either death, or at last known follow-up, was used as the "time" variable. These analyses were performed using SAS/STAT Version 9.2 of the SAS system for Windows software.[35]

Results

Demographics and immunologic parameters

The cohort included 473 patients (208 males and 265 females) confirmed as having CVID at Memorial Sloan-Kettering Cancer Center (1974-1986) or Mount Sinai Medical Center (1986-2010). The median age at characteristic symptom onset (major infection or other characteristic condition) was 24 years for males and 27 years for females (not significantly different), but males were diagnosed with CVID earlier, at a median age of 30 years, than females at a median age of 33.5 years ($P = .004$). Twenty-eight percent were under age 21 years at diagnosis. Median immunoglobulin levels were IgG, 246 mg/dL; IgA, 8 mg/dL; and IgM, 21 mg/dL; 22.6% had an IgG less than 100 mg/dL. For the group as a whole, baseline serum IgG levels were closely correlated with both baseline serum IgA (r = 0.37, $P < .0001$) and serum IgM (r = 0.41, $P < .0001$). Serum IgA was less than 7 mg/dL in 31.7%, and serum IgM was less than 25 mg/dL in 53.7%. Ten percent of subjects had 1% or fewer peripheral B cells, and 35% had 0.55% or fewer isotype switched memory B cells, compatible with the class 1 grouping described previously.[9,33] As reported previously,[33] females with CVID had both significantly higher serum IgM levels ($P = .009$) and greater numbers of isotype-switched memory B cells ($P = .03$) compared with CVID males. Peripheral $CD4^+$ T cells were less than normal controls (480 cu/mm) in 29% and less than 200 cu/mm in 3.6%. Lymphocyte proliferative defects (defined as below the lower limit of normal) to 1 or more of the mitogens were found in 50%, and 6% of patients had lymphocyte proliferation less than 10% of normal (Table 1).

Infectious conditions

Although 6% of the group reported no infections, 94% of patients had a history of at least 1 significant infection, in most cases, of the sinopulmonary tract. Of these, 187 patients (40%) had had at least 1 episode of pneumonia. When known, the predominant organisms included *Streptococcus* species and *Hemophilus influenza*. Other unusual infections were noted in 15.4%, including shingles because of herpes zoster (in 12), giardia (in 11), *Pneumocystis jiroveci* (in 6), mycoplasma and salmonella (in 4 each), candidiasis, mycobacterial disease, and papilloma viral infections (in 3 each), *Molluscum contagiosum*, measles, progressive multifocal leukoencephalopathy, cytomegalovirus, and *Clostridium difficile* (in 2 each), and unknown anaerobic organism (probably *Clostridium perfringins*), campylobacter, cryptococcus, histoplasmosis, listeriosis, nocardia, varicella, and HIV (in 1 each). Of the 6 patients with *P jiroveci*, 3 were being treated with steroids, 1 was being treated with steroids and 6-mercaptopurine for gastrointestinal inflammatory disease, and 2 were not receiving any immunosuppressive therapy. Of note, 1 of the patients being treated with steroids had T-cell lymphopenia and died of *Pneumocystis* infection.

Inflammatory and autoimmune complications

Although 32% of the group had infections as their only manifestation of immune deficiency, 68% of the group had 1 or more inflammatory or autoimmune manifestation (Table 2). Chronic lung disease leading to radiographic changes, with or without

Table 1. Immunologic parameters by sex

	Normal range*	Males (n = 208), median (range)	Females, (n = 265) median (range)	Mann-Whitney test
Immunoglobulins, mg/dL				
IgG	700-1 600	244 (6-630)	246 (0-594)	0.66
IgA	70-400	8 (0-221)	8 (0-495)	0.38
IgM	40-230	19 (0-247)	24 (0-400)	0.009†
Lymphocytes (%)				
T cells (n = 338)	55-89	74 (0-94)	75 (0-97)	0.40
B cells (n = 396)	5-15	9 (0-38)	10 (0-53)	0.16
Isotype switched memory B cells (n = 208)	6.5-29.2	0.88 (0-21)	1.3 (0-23)	0.03†
Absolute CD4 count (n = 140)	480-1 700 CU/MM	582 (96-1 661)	698 (130-2 383)	0.13
CD4/CD8 ratio (n = 262)	1-3	1.5 (0-8)	1.6 (0-9)	0.31
Lymphocyte proliferative response (cpm)				
Phytohemagglutinin (n = 160)	16 000-29 000	16 848 (183-40 165)	16 383 (370-39 870)	0.49
Concanavalin A (n = 191)	10 000-24 000	10 077 (66-34 600)	9 540 (56-34 300)	0.53
Pokeweed mitogen (n = 196)	5 000-13 000	2 665 (32-19 800)	4 284 (28-18 734)	0.36

*Normal range listed is for adult patients.
†Statistically significant ($P < .05$).

functional impairment, developed in 28.5%, equally in males and females. Bronchiectasis, included in the total number of subjects with chronic lung disease but also assessed separately, was documented in 11.2%. Progressive lung disease led to the need for chronic oxygen therapy in 29 patients (6.1%) and lung transplantation in 3 of these. Hematologic or organ-specific autoimmune disease was diagnosed in 28.6% of subjects, equally in males and females. As in previous studies, immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) were the most common of these diseases. Seven patients were found to have anti-IgA

antibodies. Other autoimmune conditions included anticardiolipin antibody, antiphospholipid syndrome, diabetes mellitus, inflammatory bowel disease, pernicious anemia, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, multiple sclerosis, neutropenia, primary biliary cirrhosis, systemic lupus erythematosis, autoimmune thyroid disease, vasculitis, psoriasis, and vitiligo.

Noninfectious gastrointestinal disease was documented in 15.4% of patients, including inflammatory bowel disease (Crohn disease, ulcerative colitis, ulcerative proctitis), chronic diarrhea of unknown etiology, gastrointestinal bleeding (1 case because of ITP),

Table 2. Selected complications

Associated condition	No.	% of cohort (n = 473)
Infections only (no complications)	151	31.9
Chronic lung disease (functional/structural)	135	28.5
Bronchiectasis	53	11.2
Autoimmunity	134	28.6
ITP	67	14.2
AIHA	33	7
Evans syndrome	20	4.2
Rheumatoid arthritis	15	3.2
Anti-IgA antibody	7	1.5
Alopecia	5	1.1
Neutropenia, pernicious anemia, anticardiolipin antibody, antiphospholipid syndrome, diabetes mellitus, juvenile rheumatoid arthritis, uveitis, multiple sclerosis, systemic lupus erythematosis, autoimmune thyroid disease, lichen planus, vasculitis, vitiligo, psoriasis	< 5	< 1
Gastrointestinal disease	73	15.4
Malabsorption	28	5.9
Inflammatory bowel disease (Crohn disease, ulcerative colitis, ulcerative proctitis)	20	4.2
Chronic diarrhea	9	1.9
Idiopathic mucosal inflammation	6	1.3
Nodular lymphoid hyperplasia	5	1.1
Gastrointestinal bleeding, irritable bowel syndrome, partial gastrectomy, diverticulitis, esophagitis	1	< 1
Liver disease/hepatitis	43	9.1
Hepatitis C	9	1.9
Liver granuloma	8	1.7
Idiopathic liver disease	8	1.7
Non-A, non-B hepatitis*	6	1.3
Chronic hepatitis of unknown origin	5	1.1
Primary biliary cirrhosis	3	< 1
Nodular regenerative hyperplasia	2	< 1
Hepatitis B, cirrhosis of unknown etiology	1	< 1

*Diagnosed before availability of the hepatitis C PCR.

Table 3. Granulomatous disease by location

Tissue location	No. (n = 46)
Lung	20
Multiple locations (ie, liver, lung, and spleen)	7
Lymph node	6
Liver	4
Skin	3
Spleen	2
Bone marrow	1
Brain	1
Neck tissue	1
Operative site	1

diverticulitis, irritable bowel syndrome, and esophagitis. Malabsorption developed in 28 subjects (6%). Nodular lymphoid hyperplasia was known in 5 patients, but this is likely to be an underestimate. A history of hepatic disease was found in 9.1% of the CVID group; 16 of these had infectious hepatitis, and the rest had noninfectious causes, including granulomatous disease, known in 8 patients, or otherwise poorly understood cryptogenic cirrhosis or hepatitis.

Granulomatous disease

Granulomatous disease diagnosed by tissue biopsy was found in 46 subjects (9.7%). Depending on the tissues biopsied, 20 had granulomas in the lung, 6 in lymph nodes, 4 in liver, 3 in skin, and 2 in the spleen. One patient in each of the following categories had granuloma found in the bone marrow, brain, neck, and at a surgical site postoperatively. Seven of these patients had granuloma found in biopsy specimens from multiple locations (eg, liver, lungs, and spleen; Table 3).

Lymphoma and other malignancies

Thirty-nine patients (8.2%) had a lymphoid malignancy, all B cell in type (Table 4). As noted in previous reports,[6,36] lymphoma was more common in females (28) than males (11; *P* = .04). Of these, non-Hodgkin B-cell lymphomas were the most common, with some of these being further classified into specific B-cell phenotypes, including mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, and T cell–rich B cell EBV-associated lymphoma. One patient was initially diagnosed with MALT lymphoma; however the pathology was reviewed at the National Cancer Institute and the diagnosis was reclassified as monoclonal B lymphocytosis.[37] Cancers of other sorts developed in 33 patients (7%), 22 females and 11 males (*P* = .28; Table 5). Two patients developed 2 distinct primary malignancies; 1 with colon and prostate cancer and 1 with prostate and skin cancer.

Table 4. Lymphoma and selected outcomes

Lymphoma type	No. (n = 39)	Outcome
Non-Hodgkin lymphoma, B-cell type, not further classified	23	11 died of lymphoma, 12 alive
Diffuse large B-cell lymphoma	3	2 died of lymphoma, 1 also had severe lung disease, 1 alive
Hodgkin disease	4	3 developed B-cell lymphoma years after treatment for Hodgkin disease, 2 of these died of lymphoma, 2 alive
MALT	5	3 no treatment, 2 chemotherapy, 5 alive
Marginal zone lymphoma/monoclonal B lymphocytosis	1	No treatment given, 1 alive
Monoclonal B lymphocytosis	1	No treatment given, 1 alive
Diffuse poorly differentiated lymphoma with IgM-κ macroglobulinemia	1	1 died of lymphoma
T cell–rich B cell EBV + lymphoma	1	1 died of lymphoma

Table 5. Other cancers and selected outcomes

Malignancy type	No. (n = 33)	Outcome
Breast cancer	9	1 died of breast cancer, 2 died of other causes, 6 alive
Gastric cancer	3	2 died of gastric cancer, 1 alive
Melanoma	3	1 died of other causes, 2 alive
Malignancy of unknown primary	3	3 alive
Colon cancer	2	1 died of colon cancer, 1 died of other causes
Lung cancer	2	2 died of lung cancer
Oral cancer	2	1 died of oral cancer, 1 alive
Skin cancer	2	2 alive
Hepatic carcinoid tumor	1	1 died of carcinoid tumor
Colon, prostate cancer	1	1 alive
Prostate, skin cancer	1	1 alive
Thyroid cancer	1	1 alive
Vaginal cancer	1	1 alive
Ovarian cancer	1	1 died of ovarian cancer
Esophageal cancer	1	1 died of esophageal cancer

Splenectomy

Thirty-nine patients (19 males and 20 females), 8.2% of the cohort, are known to have undergone a splenectomy. The majority of these were for either uncontrolled cytopenias (ITP or AIHA) or hypersplenism. In only 1 case was splenectomy performed after the introduction of rituximab, which has greatly reduced the need for splenectomy for either ITP or AIHA in subsequent subjects. However, 2 patients required rituximab after splenectomy, which also successfully led to remission of cytopenias. Only 1 subject, not yet on immunoglobulin replacement, had severe postoperative bacterial sepsis, but other complications developed in a few cases on Ig replacement, including fistulas to other organs or the exterior skin in 2, and unexplained portal hypertension and secondary liver failure in 2 (Table 6).

Survival

Of the 411 subjects with known follow-up (87% of the cohort), 93 patients (19.6%) had died. The median age at death was 44 years for females (range, 10-90 years) and 42 years for males (range, 9-79 years), not significantly different. The predominant causes of death included respiratory failure from chronic lung disease, lymphoid or other malignancy, or overwhelming infections (Table 7). To further examine the mortality of this cohort, we compared those with known long-term follow-up, 226 females (48%) and 185 males (39%), to age-matched population controls. The survival of both male (*P* = .0001) and female (*P* < .0001) CVID subjects was significantly reduced compared with 1994 US reference information[34] (Figure 1). The risk of death in this interval was nearly 11 times higher for CVID patients with 1 or more of the noninfectious complications than for subjects who had infections only (hazard ratio [HR] = 10.96; *P* < .0001; Table 8). Kaplan-Meier analysis confirmed this observation, with a long-term survival of 95% for patients without versus 42% for those with noninfectious
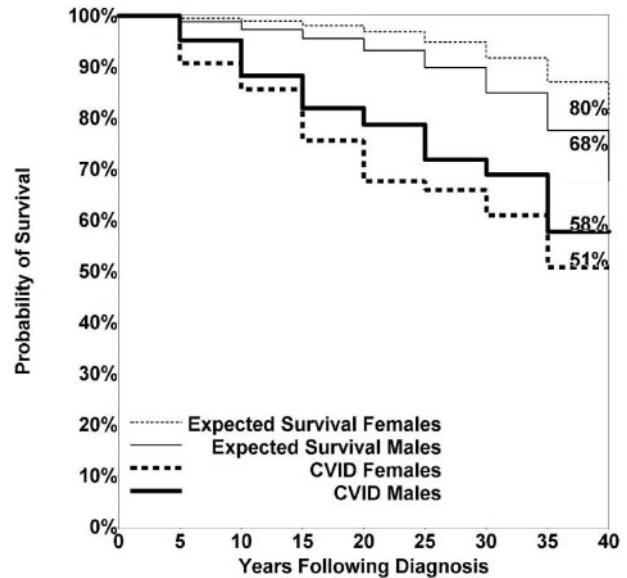
Table 6. Splenectomy reasons and selected outcomes

Reason	No. (n = 39)	Outcome
ITP	12	11 cases resolved ITP, 1 case complicated by postoperative sepsis but this patient was not yet on immunoglobulin therapy
Hypersplenism	9	6 cases resolved with no sequelae, 2 cases resolved hypersplenism but later developed liver failure with portal hypertension of unclear etiology, 1 case later developed bone marrow failure
AIHA	6	4 cases resolved AIHA, 2 cases complicated by fistulae, 1 from the pancreas to the back, 1 to the stomach and abdominal wall
Hodgkin disease staging	2	2 patients received chemotherapy for Hodgkin disease, both later died of lymphoma
Enlarged spleen and hypersplenism	2	1 case resolved, 1 case improved
Unknown reason	2	1 patient eventually developed lymphoma
Lymphoma	1	Patient found to have lymphoma
ITP/AIHA	1	Patient needed rituximab for recurrence
Enlarged spleen	1	Splenomegaly with no other pathology
Abscess of spleen	1	Patient with splenic abscess with extension to psoas muscle
Enlarged spleen, presumed lymphoma	1	Patient with granulomata on pathology after splenectomy, no lymphoma found
Presumed lymphoma (medical error)	1	Spleen lost; pathology unknown, but patient given chemotherapy

complications (Figure 2). These data agree with a previous study on CVID subjects from the European Society for Immunodeficiencies (ESID) registry.[7] However, we found here that not all complications were associated with reduced survival. Patients with gastrointestinal disease (HR = 2.78; P = .0004); liver diseases and hepati-

Table 7. Causes of death

| Cause of death	No. (n = 93)	Comments
Lung failure	34	14 of these from respiratory failure, 3 after lung transplant
Lymphoma	17	2 cases with coexistent lung disease and 1 with coexistent liver disease contributing to death
Cancers	10	2 lung, 2 stomach, 1 ovarian, 1 esophageal, 1 carcinoid, 1 oral, 1 breast, 1 colon
Liver disease	8	1 after liver transplant, 4 infectious hepatitis
Other infections	5	Pneumocystis pneumonia, measles, nocardia brain abscess, multiple anaerobes, meningitis
Heart disease	4	1 with coexisting lung disease
Aplastic anemia	4	1 with coexisting neurodegenerative disease
Unknown cause of death	4	
Progressive multifocal leukoencephalopathy	2	
Vasculitis	1	
Neurodegenerative disease	1	
Autonomic amyloidosis	1	
Accidental death	1	
Suicide	1	

Figure 1. Kaplan-Meier overall survival curves. CVID females and CVID males versus expected survival of females and males from the 1994 US population life tables. Both CVID females (P < .0001) and CVID males (P = .0001) had significantly shorter survival than population controls.

tis (HR = 2.48; P = .0003); lymphoma (HR = 2.44; P = .001); chronic lung disease, including radiologic or functional lung disease, or both as described here (HR = 2.06; P = .001); or malabsorption (HR = 2.06; P = .022) had reduced survival in this interval, compared with CVID patients without these particular complications. In contrast, patients with any of the autoimmune conditions, cancers other than lymphoma, history of splenectomy, presence of granulomatous disease, or the development of bronchiectasis alone did not have significantly reduced survival over the 4 decades of study. Kaplan-Meier survival curves also affirmed these observations, showing significantly reduced survival for patients with gastrointestinal disease (P = .005), malabsorption (P = .0196), chronic lung disease (P = .0002), liver diseases and hepatitis (P < .0001), and lymphoma (P < .0001) but not for subjects with a history of autoimmunity (P = .1), cancer other than lymphomas (P = .21), previous splenectomy (P = .08), granuloma (P = .78), or the radiologic observation of bronchiectasis with lack of other findings (P = .54).

Table 8. Cox proportional hazards modeling of complications

	HR	95% CI	P
Any complication	10.96	(3.46, 34.69)	< .0001*
Gastrointestinal disease	2.78	(1.44, 3.59)	.0004*
Liver disease/hepatitis	2.48	(1.51, 4.09)	.0003*
Lymphoma	2.44	(1.43, 4.16)	.0010*
Chronic lung disease (structural and functional)	2.06	(1.34, 3.16)	.0010*
Malabsorption	2.06	(1.11, 3.81)	.0218*
Splenectomy	1.69	(0.91, 3.12)	.0957
Cancer	1.51	(0.795, 2.87)	.2084
Autoimmunity	1.36	(0.87, 2.12)	.1735
Granuloma	1.27	(0.65, 2.48)	.4939
Bronchiectasis	0.76	(0.39, 1.48)	.4235

Adjusted for age at diagnosis.
*P value significant at the .05 level.
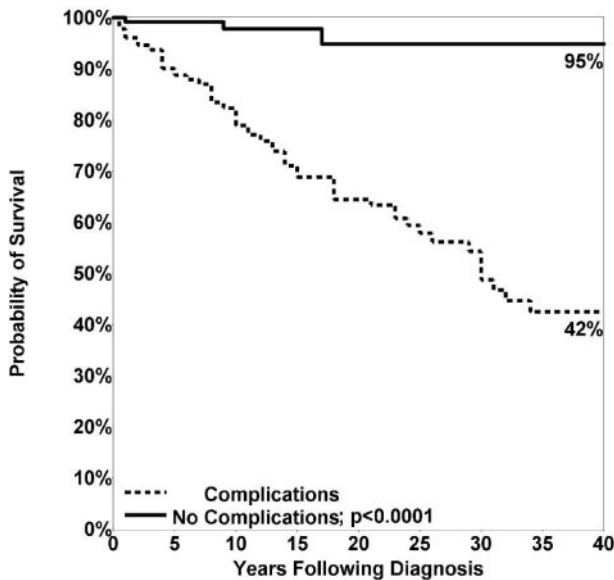
Figure 2. Kaplan-Meier curve for patients with and without noninfectious complications. Patients with noninfectious complications were significantly more likely to die than those with infections only ($P < .0001$).

Laboratory markers, complications, and survival

To identify demographic parameters associated with mortality, the Cox proportional hazards model, adjusted for age at diagnosis, was used. For each year of increase in age at diagnosis, the risk of death increased by 2.7% overall (HR = 1.027; $P < .0001$). The age at death was significantly correlated with both earlier age at symptom onset (r = 0.8, $P < .0001$) and age at diagnosis (r = 0.88, $P < .0001$). Examining immunologic parameters associated with mortality by Cox proportional hazards modeling, a lower baseline serum IgG level (HR = 0.998; $P = .0079$), fewer peripheral blood B cells (HR = 0.933; $P = .0004$), or an increased serum IgM level at diagnosis (HR = 1.005; $P = .0021$) were all associated with an increased mortality in this interval (Table 9).

Finally, we examined the relationship between initial immunologic parameters—serum IgG, IgA, IgM, and percentage of B cells and isotype-switched memory B cells—and the odds of developing any of the noninfectious inflammatory and autoimmune complications. Higher levels of baseline serum IgG or IgA and higher percentages of peripheral blood B cells or isotype-switched memory B cells at the time of diagnosis were found significantly protective against noninfectious complications in general. Lower levels of isotype-switched memory B cells increased the risk of autoimmunity, as noted previously.[33,38] Lower percentages of peripheral B cells increased the risk of nonlymphomatous cancers and higher serum IgM levels increased the risk of lymphoma. Higher levels of

Table 9. Cox proportional hazards modeling of immunologic variables

	HR	95% CI	P
Age at diagnosis alone	1.027	(1.01, 1.04)	< .0001*
IgG	0.998	(0.996, 0.999)	.0079*
IgA	0.995	(0.99, 1.01)	.1577
IgM	1.005	(1.00, 1.01)	.0021*
T cells	0.994	(0.98, 1.01)	.3437
B cells	0.933	(0.898, 0.969)	.0004*

Adjusted for age at diagnosis.
*P value significant at the .05 level.

Table 10. Odds ratios for specific complications given immunologic parameters

	Immunologic parameter	Odds ratio	95% CI	P
Any complication	IgG (lower)	0.998	0.997,1.000	.0146*
	B cells (lower)	0.965	0.941,0.989	.0049*
	IgA (lower)	0.993	0.987,0.998	.0097*
	Isotype switched memory B cells (lower)	0.914	0.860,0.971	.0037*
Autoimmunity	Isotype switched memory B cells (lower)	0.924	0.854,1.000	.0487*
Cancer	B cells (lower)	0.923	0.862,0.989	.0220*
Lymphoma	IgM (higher)	1.007	1.001,1.013	.0139*
Liver disease/hepatitis	IgM (higher)	1.006	1.001,1.012	.0219*
	B cells (lower)	0.939	0.890,0.991	.0228*
Chronic lung disease (structural and functional)	IgG (lower)	0.998	0.997,1.000	.0201*
	IgM (lower)	0.993	0.987,0.998	.0139*
	B cells (lower)	0.951	0.922,0.981	.0015*
	IgA (lower)	0.990	0.982,0.998	.0207*
	Isotype switched memory B cells (lower)	0.910	0.830,0.998	.0451*

*P value significant at the .05 level.

baseline serum IgM and lower levels of B cells increased the risk of liver diseases and hepatitis. Lower levels of serum IgG, IgA, and IgM at baseline; fewer B cells; or fewer isotype-switched memory B cells increased the risk for chronic lung disease (Table 10).

Discussion

We report the demographics, immunologic parameters, clinical characteristics, associated conditions, and mortality statistics for 473 patients diagnosed with CVID seen in New York over 4 decades. In contrast to previous large studies on CVID that are aggregates of subjects followed at a number of medical centers, the current report is based at 1 medical center with more uniform case management. It should be noted that the population seen at this referral center may represent more severe and complicated cases of CVID.

The overall mortality in this cohort over this period was 19.6%, reduced from the 24% noted in our previous study a decade ago, and significantly improved from the data collected by Healy et al[39] in 1971 before the introduction of intravenous immunoglobulin replacement (29% mortality). Both males and female subjects had significantly decreased survival at every time point, compared with sex- and age-matched controls. This is greater than that found for the ESID CVID cohort, with a 15% mortality over a similarly extended period,[7] and greater than Quinti et al at 6%,[31] for a significantly younger cohort followed for 11 years. The enhanced survival in CVID over time is probably because of the introduction of Ig replacement, and rising Ig trough levels over time that have greatly reduced the number of bacterial infections and improved the quality of life of subjects with immune defects in general.[6,7,25,26,30,31,40] We also can speculate that the introduction of better and longer acting antibiotics have improved treatment regimens and extended life expectancy in CVID patients. Although female CVID patients tended to be older at diagnosis, they did not demonstrate a significantly enhanced survival over males. The more striking observation was that the 68% of subjects who had

developed any of the noninfectious complications had markedly decreased survival compared with the 32% subjects with infections only (HR = 10.96; $P < .0001$). In fact, 89 of the 93 subjects who died had 1 or more of the noninfectious complications, and only the 4 others had infections only.

Because the noninfectious complications include an aggregate of inflammatory and autoimmune conditions, we then analyzed these separately to identify those more likely to cause mortality. Somewhat surprisingly, we found that only chronic lung disease, lymphoma, liver diseases and hepatitis, and gastrointestinal inflammatory disease with or without documented malabsorption were associated with worse survival. We did not find that the presence of bronchiectasis alone on chest tomography, history of autoimmunity, splenectomy, or cancers other than lymphoma significantly increased the risk of death in this 4-decade interval. As found in our previous study,[6] lung disease, found in 28.5% of the cohort overall, was the main cause of death. In contrast to a previous study,[30] we did not find that granuloma found in a variety of tissues, and in the lung in 26 cases, was associated with shorter survival. Bates et al had reported that patients with granulomatous lung disease along with lymphocytic interstitial pneumonia, follicular bronchiolitis, and pulmonary lymphoid hyperplasia, taken together, had shorter survival.[30] Potentially, granulomatous disease in the lungs (found in > 50% of our 46 subjects with granulomata), as opposed to other organs, could lead to greater tissue destruction and ultimately respiratory failure. It should be noted that granulomatous disease is likely to be underdiagnosed in our cohort, because many patients did not undergo tissue biopsy.

Lymphoma, found in 39 cases (8.2%), was the second most common cause of death in our cohort. For unclear reasons, this is a higher overall incidence than other studies, including the ESID cohort (3%),[7] a CVID group in Italy (1.8%),[31] the United Kingdom (3.8%),[27] and a combined Danish-Swedish cohort (2%).[41] Although a significant cause of mortality, 22 of these subjects are alive, 4 of whom (3 with MALT and 1 with marginal zone lymphoma) are stable and had not received treatment up to 8 years after diagnosis of lymphoma. Although the presence of nonlymphoid cancers was not significantly associated with mortality, these were the third most common cause of death in this group. In contrast to older published data that suggested a higher incidence,[27,42] we noted only 3 cases of gastric cancer, potentially related to the reduced incidence of this cancer overall, or greater use of antibiotics in these subjects that could eliminate colonizing *Helicobacter pylori*.[43]

By examining immunologic parameters using Cox regression analysis adjusted for age at diagnosis, we detected that lower baseline serum levels of IgG and higher levels of IgM were associated with poorer survival. Lower levels of IgG or IgA significantly increased the odds ratio for the development of any complication. In contrast, higher baseline serum IgM levels were associated with increased risk of lymphoma or any form of hepatitis. In this regard, as found previously,[6,33] females with CVID had higher levels of serum IgM, and greater numbers of isotype switched memory B cells, and possibly not coincidentally, a higher

incidence of B-cell lymphoma.[6,36,41,44] Fewer peripheral B cells continued to be associated with reduced survival in CVID.[6] Although the phenotype of circulating B cells was available for only about half of this patient population, we found that lower numbers of isotype switched memory B cells were associated with both autoimmunity and chronic lung disease, in accordance with previous studies.[9,33,45-49]

Although the genetic causes of CVID are likely to be multiple and most remain to be elucidated, these data show that the overall survival of patients has improved over time. More than 50% of the surviving subjects in this cohort are either students, working, retired but healthy, or otherwise pursuing normal activities of daily living, which suggests that the majority of patients carry out normal lives on replacement Ig therapy. However, selected, but not all, complications are still associated with increased morbidity and mortality. Baseline biomarkers as outlined here may provide clues to these clinical outcomes. Additional biomarkers are necessary to improve both prognostic and therapeutic information, including possibly the need for much higher doses of Ig, earlier use of biologic therapies, and if clear phenotypes emerge, recommendation for stem cell transplant in selected subjects. Further large cohort studies, particularly international efforts that include data from subjects with diverse genetic backgrounds, may provide improved biomarkers and a better understanding of the genetics of this syndrome.

Authorship

Contribution: E.S.R. and C.C.-R. contributed data collection and analysis and wrote the manuscript; and E.L.M. and J.H.G. contributed statistical analysis and figure preparation.

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