ORIGINAL ARTICLE

30-Year Review of Pediatric- and Adult-Onset CVID: Clinical Correlates and Prognostic Indicators

Carolyn Baloh[1,2] · Anupama Reddy[2,3] · Michele Henson[1,2] · Katherine Prince[2,4] · Rebecca Buckley[1,2,5] · Patricia Lugar[1,2,4,6] 🆔

Abstract

Purpose To evaluate mortality risk factors in pediatric-onset common variable immunodeficiency disorders (CVID), we evaluated the largest single-institution cohort of pediatric-onset CVID patients. Previous publications on CVID have provided valuable descriptive data, but lack risk stratification to guide physicians in management of these patients.

Methods Retrospective chart review of 198 subjects with CVID at a single institution, of whom 91 had disease onset at a pediatric age. Clinical and laboratory data were collected at diagnosis and in follow-up. Odds ratios and Fisher tests were utilized to examine trends. This study was approved by an institutional review board.

Results Clinical features and laboratory results for subjects diagnosed with CVID at a pediatric age are similar to those who had adult-onset CVID. However, majority of the deceased subjects (13/18) were at a pediatric age at CVID symptom onset. These subjects had a lower age at mortality, multiple comorbidities, and often depression. The most common cause of death was infection. Lung disease (OR 5, $p < 0.05$) and infection with severe/opportunistic organisms (OR 9, $p < 0.05$) are directly related to increased mortality. Delay in diagnosis of CVID is also correlated with mortality. Intermediary markers correlating with mortality include anemia, GERD, and depression.

Conclusions There are many similarities between patients with pediatric- and adult-onset CVID; however, the mortality of pediatric CVID in our cohort is striking. This is the first study to identify specific factors correlated with mortality in pediatric-onset CVID to guide pediatricians and subspecialists in managing these immunodeficient patients.

Keywords Common variable immunodeficiency disorders (CVID) · immunodeficiency · pediatric · depression · mortality · granulomatous lymphocytic interstitial lung disease (GLILD)

✉ Patricia Lugar
  Patricia.lugar@duke.edu

1   Department of Pediatrics, Duke University Medical Center, Durham, NC, USA

2   Duke University Medical Center, Durham, NC, USA

3   Center for Genomic and Computational Biology, Duke University Medical Center, Durham, NC, USA

4   Department of Internal Medicine, Duke University Medical Center, Durham, NC, USA

5   Department of Immunology, Duke University Medical Center, Durham, NC, USA

6   Departments of Internal Medicine and Pediatrics, Division of Pulmonary, Allergy and Critical Care, Duke University Medical Center, 1821 Hillandale Road, Suite 25A, Durham, NC 27705, USA

Abbreviations

CVID	Common variable immunodeficiency disorders
ESID	European Society for Immunodeficiencies
GLILD	Granulomatous lymphocytic interstitial lung disease
GERD	Gastroesophageal reflux disease
LOCID	Late-onset combined immune deficiency
MRSA	Methicillin-resistant *Staphylococcus aureus*
USIDNET	United States Immunodeficiency Network
VRE	Vancomycin-resistant *Enterococcus*
IRB	Institutional review board

Introduction

Common variable immunodeficiency disorder (CVID) is a primary immunodeficiency syndrome characterized by

recurrent infections due to poor antibody production and an increased incidence of cancer, granulomatous lung disease, autoimmune disease, and enteropathy. It is the most common treated primary immunodeficiency in children and adults with a reported prevalence in Caucasians of 1:25,000 to 1:50,000 [1, 2]. It has a significant impact on society with decreased quality of life and increased risk of mortality at younger ages than respective age- and sex-matched controls [3]. CVID patients report lower physical and social functioning than healthy controls and have lower mental health scores than age- and sex-matched diabetic and congestive heart failure patients [4]. They also have increased health care utilization related to primary management with more than one subspecialist [2].

The few available studies of pediatric CVID have yielded limited and conflicting data. Early studies of pediatric CVID identified an increased risk of autoimmunity and mortality compared with adult CVID [5, 6]. However, recent reports demonstrate few differences between pediatric and adult diseases, suggesting the disease process represents a continuum [7]. No studies have identified methods to risk-stratify pediatric CVID patients for poor outcomes. The current study attempted to better define CVID in patients with disease onset at a pediatric age of less than or equal to 18 years of age. Additionally, we sought to define subgroups of disease to determine which patients need closer monitoring for serious complications such as lung disease and mortality. This report represents to our knowledge the largest single-institution cohort of pediatric CVID to be reported upon.

Methods

A retrospective electronic chart review of all patients seen at a large academic institution with a diagnosis code of CVID, ICD-9 279.06 and/or ICD-10 D83.9, from January 2005 to 2016 was performed. Patients seen prior to 2005 were identified in an immunodeficiency database maintained at our institution. Diagnosis was confirmed by two reviewers using the 2014 ESID registry criteria for CVID (CB, PL) [8]. Clinical and laboratory criteria (ESID criteria) were met to ascertain a CVID diagnosis. Clinical features required at least 1 of the following: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or an affected family member with antibody deficiency. Diagnosis must not have been established before the 4th year of life, although symptoms may have been present much earlier. Laboratory criteria included a markedly low IgG with low IgA and/or IgM (at least 2 standard deviations below age normal level) and poor antibody responses to vaccines (below laboratory normal to tetanus or diphtheria and at least 50% of specific pneumococcal titers below 1.3) or low switched memory B cells (below 70%

of age-related normal value). Cases of transient hypogammaglobulinemia of infancy or with secondary causes for hypogammaglobulinemia were excluded from review and analysis. No subjects had profound T cell deficiency defined as 2 of the following: low CD4 (< 300 for 2–6 years, < 250 for 6–12 years, and < 200 for > 12 years), low % naïve CD4 (< 25% for 2–6 years, < 20% for 6–16 years, and < 10% for > 16 years), or absent T cell proliferation. Data recorded included disease characteristics, laboratory evaluation, comorbidities, and outcomes. Patients were divided into those with disease onset at a pediatric age, defined as less than or equal to 18 years of age, and disease onset at an adult age, defined as over 18 years of age. Symptomology used for this classification included recurrent infections, severe infections, and disease comorbidities. These groups were further divided by sex to allow for more detailed analysis assessing any differences attributable or skewed by gender. Numbers of comorbidities were recorded as 0–4 using cancer, lymphoproliferative/ granulomatous disease, autoimmune disease, and enteropathy as major comorbid diagnoses. Granulomatous lymphocytic interstitial lung disease (GLILD) is a feared comorbidity of CVID, but often patients do not undergo lung biopsy to confirm this diagnosis; therefore, the true prevalence is unknown. We examined both biopsy-confirmed GLILD and all lung findings recorded in the patient record that could represent CVID-associated lung disease and not necessarily GLILD, including bronchiectasis, persistence of radiographic lung nodules, lymphocytic interstitial pneumonia, and interstitial lung disease. This broader category was generally labeled "lung disease." Depression was defined by a diagnosis of depression being present in the patient's chart, which assumes a physician diagnosis of depression. Odds ratios and Fisher tests were utilized to examine trends. This study was approved by the Duke University Institutional Review Board, and as this was a retrospective chart review involving existing data and posing no more than minimal risks to subjects, the need for individual consent was waived.

Results

Overall Demographics

Using the strict criteria outlined in our methods, our total cohort comprised 198 patients with CVID. The age at CVID symptom onset was divided between pediatric-onset (less than or equal to 18 years of age, $N = 91$) and adult-onset (greater than 18 years of age, $N = 107$) groups (Table 1). Sixty percent of those with pediatric age at symptom onset were diagnosed within 5 years (OR 2.6, $p < 0.05$), which was significantly different from the diagnosis delay seen in those with symptom onset at an adult age. Both females and males had a bimodal distribution of

Table 1 Demographic and clinical characteristics of pediatric- and adult-onset CVID cohorts

	Pediatric-onset cohort (n = 91) Number (%)	Adult-onset cohort (n = 107) Number (%)
Sex		
Male	54 (59)	36 (34)
Female	37 (41)	71 (66)
Race		
Caucasian	83 (91)	103 (96)
Non-Caucasian*	8 (9)	4 (4)
Age at diagnosis		
Pediatric (≤ 18 years of age)	75 (82)	0 (0)
Adult (> 18 years of age)	16 (18)	107 (100)
Mean age at diagnosis in years (range)	12	45
Time from symptom onset to diagnosis		
< 5 years	55 (60)**	33 (31)
5–10 years	16 (18)	13 (12)
> 10 years	13 (14)	33 (31)**
Mean length of follow-up in years (range)	8.6	5.7
Still following	30 (33)	66 (62)
Deceased	13 (14)**	4 (4)
Family history of disease-associated condition	42 (46)	70 (65)**
Family history of immune deficiency	10 (11)	17 (16)
Family history of autoimmunity	24 (26)	32 (30)
Family history of cancer	17 (19)	45 (42)**
5 most common infections		
Sinusitis	67 (74)	88 (70)
Pneumonia	57 (63)	67 (43)
Bronchitis	41 (45)	54 (15)
Acute otitis media	65 (71)**	19 (54)
Chickenpox/shingles	18 (20)	16 (13)
Disease-associated conditions		
Cancer	10 (11)	24 (22)**
Solid cancers	4 (4)	15 (14)**
Leukemia/lymphoma	7 (8)	11 (10)
Autoimmune disease	44 (48)	44 (41)
Autoimmune hematologic disease	30 (33)**	15 (14)
Lymphoproliferative/granulomatous disease	40 (44)	37 (35)
Enteropathy	29 (32)	30 (28)

*Non-Caucasian subjects were comprised of African American (8), Hispanic (2), Middle Eastern (1), and Native American (1)

**$p < 0.05$ from Fisher's test between pediatric and adult cohorts indicating enrichment in that cohort

Demographic and clinical data for the overall cohort and by age group at onset of symptoms are displayed in this table. Data that significantly differ ($p < 0.05$) between pediatric- and adult-onset cohorts are indicated by double asterisks (**) and are limited to prompt diagnosis within less than 5 years from symptom onset, deceased status, family history, acute otitis media, cancer, and hematologic autoimmune disease

disease onset; however, early life onset was particularly pronounced in males and later life onset was particularly pronounced in females (Figure 1S). Patients were followed for a mean of 7 years, with a range of 4–32 years. Eighteen patients (9%) were deceased by 2016, with a majority (N = 13) of these patients having had pediatric CVID onset. This was a significant correlation (OR 4.3, $p < 0.05$).

Overall Clinical Features

Regardless of age at onset, the most frequent types of infections were sinusitis, pneumonia, bronchitis, acute otitis media, and shingles./shingles. Nearly seven percent of subjects, regardless of age at CVID onset, experienced sepsis at least once in their lifetime; majority of these episodes were related to

indwelling central lines. Infections with more severe pathogens including methicillin-resistant *Staphylococcus aureus* (N = 12), vancomycin-resistant *Enterococcus* (N = 3), *Pseudomonas* (N = 4), *Clostridium difficile* (N = 5), and *Aspergillus* (N = 7) were uncommon.

There were few significant correlations with age at disease onset and disease comorbidities. Pediatric age onset was inversely correlated with development of any malignancy (OR 0.4, $p < 0.05$), whereas lymphoma was not associated with age at onset either way. There was no association with autoimmune disease as a broad diagnosis and age at onset; however, autoimmune hematologic disease was significantly associated with pediatric CVID onset (OR 3.3, $p < 0.05$). There were no significant correlations between age at CVID symptom onset and enteropathy or lymphoproliferative disease.
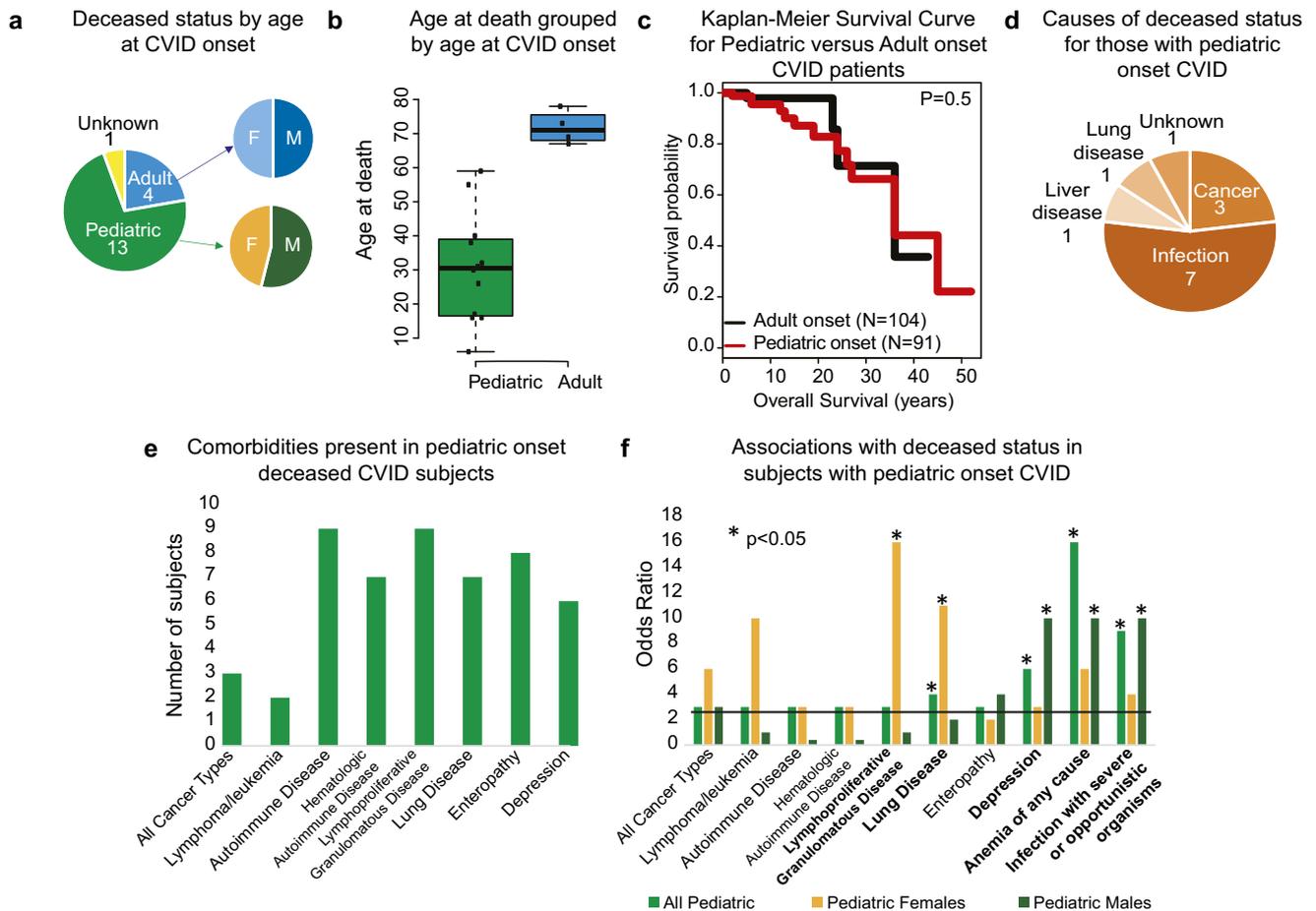
Fig. 1 Mortality is enriched in pediatric-onset CVID subjects. **a** Number of subjects in deceased cohort. Green-shaded, pediatric-onset CVID; blue-shaded, adult-onset CVID; and yellow, unknown age of onset. Age onset shown in (M) males versus (F) females. **b** Age at death grouped by age group at CVID onset. **c** Kaplan-Meier survival curve for pediatric- versus adult-onset CVID patients. **d** Causes of mortality for those with pediatric-onset CVID. **e** Comorbidities known in the deceased pediatric-onset subjects. **f** Significant associations with mortality in subjects with pediatric-onset CVID. $*p < 0.05$

Overall Laboratory Parameters

Switched memory B cells have been used as a prognostic tool to define more complicated disease. Switched memory B cells express antigen-specific IgG which is secreted when antigen is present. Sufficient numbers of B cell subsets are important for maintaining protective IgG, and the lack of adequate numbers of switched memory B cells correlates with hypogammaglobulinemia and comorbidities in CVID. There were a total of 52 patients in the overall cohort that had switched memory B cell data to interpret. A few of those with switched memory B cell data had repeated testing and in none of those cases did the absolute number or percentage of switched memory B cells change enough to change the designation of low or normal. Of those with switched memory B cell data, 4 had pediatric-onset CVID; the remaining had adult-onset disease. Forty-one of the 52 patients had low switched memory B cells. There were no significant findings associated with having low switched memory B cells. There were too few pediatric-onset CVID patients with switched

memory B cell data to perform statistical analysis, and there did not appear to be any trends within this subgroup. However, in the entire cohort analyzed, an elevated CD21-/lo and/or low switched memory B cells were associated with lymphoproliferative disease and GLILD, consistent with previous publications (data not shown) [9–12]. There were no striking differences in other B cell subsets, nor in T cell or NK cell subsets between the cohorts. The data are summarized in Tables 2 and S1.

Subjects all had an IgG at diagnosis of less than 2 standard deviations below normal for their age range at the time of diagnosis. Most recent IgG was collected for all patients and was increased compared with baseline due to immunoglobulin replacement. Pediatric subjects tended to have a very low IgA at diagnosis with 86% having an IgA level less than 29 mg/dL, with 29 mg/dL being the lower limit of normal for a 4-year-old. This trend was not as pronounced for adult-onset subjects. Pediatric patients were more likely than adult patients to have a low diphtheria and/or tetanus titer at diagnosis, and over 90% of pediatric or adult patients had low pneumococcal

antibody titers at diagnosis. This is not surprising, as poor antibody titers to *Streptococcus pneumoniae* serotypes are often used to demonstrate poor specific antibody production upon challenge in CVID. IgM has been postulated to be an indicator for prognosis and development of complications in CVID. On average, IgM levels trended upward over time for the overall cohort as well as the cohorts broken down by age at disease onset (Tables 2 and S2).

Mortality in Pediatric-Onset CVID Subjects

A total of 18 patients out of the 198 reviewed in our cohort were deceased by 2016, and a majority [13] had disease onset at a pediatric age (Fig. 1a). Age at death within this pediatric group was 31 years of age. This was a dramatic difference from the average age at death, 72 years, seen for those with adult symptom onset (Fig. 1b). The time from diagnosis to death was not significantly different between those with pediatric- versus adult-onset CVID symptoms (Fig. 1c). The most common cause of death regardless of age of onset was infection, followed by cancer, lung disease, and liver disease (Fig. 1d). More patients had a diagnosis of cancer than attributed as a cause of death. Autoimmune disease, enteropathy, lung disease, and depression were common in deceased patients (Fig. 1e).

The presence of lung disease was significantly associated with mortality (OR 5, $p < 0.05$), an association which is even more marked for pediatric females. Pediatric females also showed a significant odds ratio for overall lymphoproliferative/granulomatous disease and mortality

(OR 16, $p < 0.05$) (Fig. 1f). Additional findings that were significantly associated with mortality for those with pediatric-onset CVID included presence of anemia (OR 16, $p < 0.05$), GERD (OR 6, $p < 0.01$), infection with severe organisms (OR 9, $p < 0.05$), and depression (OR 6, $p < 0.05$) (Fig. 1e). Given a majority of the deceased subjects having CVID onset at a pediatric age, the lower age at mortality for this group, and numerous comorbidities experienced, we sought to better characterize those subjects with pediatric-onset CVID and understand characteristics that portend increased mortality risk.

The Association of Lung Disease with Mortality

The only disease comorbidity significantly associated with mortality was lymphoproliferative granulomatous disease in the females with CVID onset at a pediatric age (OR 16, $p < 0.005$). Lymphoproliferative granulomatous disease encompasses granulomatous lymphocytic interstitial lung disease (GLILD), splenomegaly, generalized lymphadenopathy, and hepatomegaly. GLILD itself was not associated with mortality, although there were too few patients who had a lung biopsy to evaluate for the diagnosis of GLILD. GLILD has been established as a poor prognostic factor in CVID patients in prior publications [11, 13]. We posited that nodules, bronchiectasis, lymphocytic interstitial pneumonia, and interstitial lung disease could all represent lung disease secondary to CVID, but could not be classified as GLILD. Bronchiectasis which may represent a number of etiologies was the most prevalent of these categories (Figure 2Sa). Therefore, "lung disease" represents any persistent change in lung imaging or

Table 2 Laboratory parameters at diagnosis for pediatric- and adult-onset CVID cohorts

Laboratory test	Pediatric-onset cohort ($n = 91$)	Adult-onset cohort ($n = 107$)
Mean immunoglobulin levels, mg/dL (range)		
IgG (normal adult range 588–1573)	221 (0–583)	287 (0–732)
IgA (normal adult range 46–287)	9 (0–100)	23 (0–182)
IgM (normal adult range 57–237)	25 (0–167)	39 (0–256)
Percentage of patients with abnormal titer		
Diphtheria	93	58
Tetanus	83	38
Pneumococcus	92	96
Flow cytometry results: mean absolute values, cells/mcL		
Mean absolute CD19+ (B cells) (normal adult range 91–409)	254 ($N = 39$)	210 ($N = 66$)
Mean absolute CD21− (B cell subset) (normal adult range 0.3–22)	27 ($N = 5$)	18 ($N = 49$)
Mean absolute switched memory B cells CD27+IgM−IgD− (B cell subset) (normal adult range 7–61)	3 ($N = 4$)	9 ($N = 46$)

Due to incomplete data sets for all laboratory parameters, the number of patients with data is represented in parenthesis as above

This table outlines the overall immunoglobulin levels, percentage of patients with abnormal vaccine titers, and most important flow cytometry results at diagnosis. Pediatric-onset patients appear to have abnormal diphtheria and tetanus titers more commonly than adult-onset patients. Immunoglobulin levels and flow cytometry values are similar regardless of age at onset. Additional flow cytometry values are available in Table S1

function. Lung disease was significantly associated with mortality (OR 4, $p < 0.05$). Lymphocytic interstitial pneumonia and bronchiectasis were each independently associated with mortality. Lymphocytic interstitial pneumonia and lung nodules were significantly associated with mortality for pediatric-onset females, while bronchiectasis was significantly associated with mortality for pediatric-onset males (Figure 2Sb).

We also assessed for laboratory values that were associated with lymphoproliferative disease, GLILD, or lung disease. A lower absolute number of CD27+IgM−IgD− switched memory B cells was significantly associated with lymphoproliferative disease for the overall cohort (OR 2.1, $p < 0.05$). There were an inadequate number of pediatric-onset CVID subjects with switched memory B cell data to perform statistical analysis. The mean absolute number of switched memory B cell in the subjects with lymphoproliferative granulomatous disease was extraordinarily low at 0.74 as compared with 8.96 for those without lymphoproliferative granulomatous disease.

Depression as an Important Intermediary Diagnosis Between Comorbidities and Mortality

Depression was common among our study population, being present in 18% of those with pediatric-onset CVID and 26% of those with adult-onset CVID. In addition to being common, it was significantly associated with mortality (OR 6, $p < 0.05$). There was no record of any patients attempting or committing suicide. Depression was also significantly associated with a number of CVID comorbidities including lymphoma/leukemia, hematologic autoimmune disease, lymphoproliferative granulomatous disease, and enteropathy (Fig. 2a). As depression itself would not have caused mortality, we postulated that it may be a marker of those with more poorly controlled comorbidities leading to death. Additional studies are needed to confirm this hypothesis. Additionally, we found that for any subject with pediatric onset of CVID, he or she had a 5 times increased odds of depression if the CVID diagnosis was not made within 10 years of their symptom onset ($p < 0.05$) (Fig. 2b). Those diagnosed with CVID within 5 years of symptom onset had a significantly lower incidence of depression.

The Additional Importance of a Delay in Diagnosis of CVID

Regardless of age at CVID onset, the majority of patients who went on to develop lymphoma had a delay in diagnosis of at least 5 years ($n = 12$). Specifically, within the pediatric CVID onset group, leukemia/lymphoma was 10-fold more likely with diagnosis delay of at least 5 years ($p < 0.05$) correlating with the 8-fold increase in family history of cancer with diagnosis delay of at least 5 years ($p < 0.05$). Delay in diagnosis of at least 5 years also significantly correlates with increased

likelihood of requiring surgery (OR 5, $p < 0.05$), and having a total of 4 CVID comorbidities (OR 7, $p < 0.05$). Types of surgery included head and neck surgery (i.e., tonsillectomy, adenoidectomy, tympanostomy tubes, sinus surgery) ($n = 40$), splenectomy ($n = 11$), lymph node biopsy ($n = 10$), and appendectomy ($n = 3$). A delay in CVID diagnosis of 5–10 years specifically correlated a 3-fold increased likelihood of having an infection with a more concerning organism such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *Pseudomonas* ($p = 0.05$), as well as 4-fold increased likelihood of mortality regardless of the presence or absence of depression ($p < 0.05$).

Additional Factors Associated with Mortality

There was an increased odds of mortality when subjects with pediatric-onset CVID experienced infections with highly pathogenic organisms including MRSA, VRE, *Pseudomonas*, and *Clostridium difficile* (OR 9, $p < 0.05$). There were three deceased subjects who experienced these types of infections. Two deceased patients had isolated *Clostridium difficile* infections. One deceased subject had an isolated *Pseudomonas* infection, and one had *Pseudomonas* and VRE. These patients were also significantly more likely to have an abnormal T cell proliferative response to antigens (OR 4, $p = 0.01$), despite having normal T cell absolute number and percentages on flow cytometry.

Another finding significantly associated with mortality was anemia of any cause (OR 16, $p < 0.05$). Of the 45 pediatric-onset subjects, 45 had anemia with 19 of them having autoimmune hemolytic anemia and 15 of the 45 having Evan's syndrome. Twelve of the deceased pediatric-onset patients had anemia with 5 of the 12 having had autoimmune hemolytic anemia and 4 of the 12 having had Evan's syndrome. Kaplan Meier curves suggest cytopenias are associated with mortality, but that the relationship is not due to autoimmune cytopenias (Fig. 3).

Discussion

We report the largest single-institution cohort of pediatric-onset CVID, the most common treated primary immunodeficiency. Despite CVID patients having poor protective antibody quantity and function, immune function is disordered and gives way to disease-associated comorbidities such as lymphoma, lymphoproliferation, granulomatous disease, enteropathy, and chronic progressive lung disease. These comorbidities lead to poor quality of life and mortality. In this work, we attempt to provide risk stratification data in pediatric-onset CVID to date.
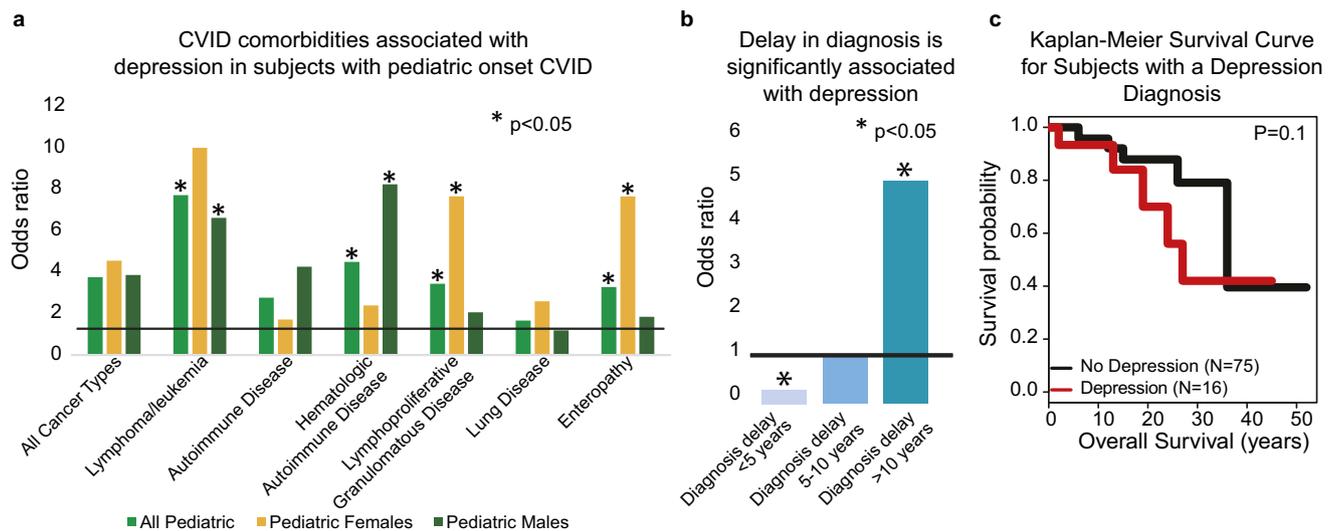
Fig. 2 Development of depression from CVID comorbidities or delayed CVID diagnosis is significantly associated with mortality. **a** CVID comorbidities associated with depression development in subjects with pediatric-onset CVID. **b** Delay in diagnosis is significantly associated with depression development. **c** Kaplan-Meier survival curve for depression showing a trend of decreased survival from time of diagnosis for those with depression that did not reach statistical significance. *$p < 0.05$

The demographic factors of our cohort, including average age at diagnosis, distribution of disease onset, and age at diagnosis, are comparable to other large cohorts including the European Society for Immunodeficiencies (ESID) and the USIDNET, and American cohort [7, 14, 15]. In this report, our subjects were followed for a long duration—up to 32 years. Our mortality rate of 9% was lower than in other studies, with another large academic institution reporting 19.6% mortality [11]; however, this may be related to a better understanding of treatment for disease-associated complications over the last 10 years.

There were few differences between those with pediatric-onset CVID compared with adult-onset CVID cohorts. Subjects in both groups experienced similar types of infections, with the same infections comprising the top five infections in each group. Similar to the EuroClass trial and USIDNET study, we found a significant enrichment in AOM in pediatric CVID. In unusual cases, severe or opportunistic infections have been known to occur in CVID [16, 17]. In our cohort, there was a significantly increased mortality rate when subjects with pediatric-onset CVID experienced infections with more severe or opportunistic organisms. Additionally, 6–7% of patients in both the pediatric and the adult cohorts experienced sepsis at one point in their life. Central line placement is a known risk factor for sepsis even in non-CVID patients and must be weighed especially carefully in immunodeficient patients. The DEFI group proposed an updated subgrouping of CVID called late-onset combined immune deficiency (LOCID) with criteria of primary hypogammaglobulinemia with either a profound T cell defect or opportunistic infections [18]. The patients in our cohort with opportunistic infections meet criteria for this classification; however, they did not have the increased incidence of splenomegaly, granuloma, gastrointestinal disease, or lymphoma seen in the DEFI LOCID cohort [18]. Further characterization of CVID patients with opportunistic infections, likely with genetic diagnoses, will help us to better understand these patients differed in their phenotypes.

With regard to CVID comorbidities, we found a significant enrichment in hematologic autoimmune disease in the pediatric-onset CVID patients consistent with prior publication [7]. It is essential that general pediatricians and pediatric hematologists screen for CVID in patients with hematologic autoimmune disease. Many patients present with autoimmune thrombocytopenia or hemolytic anemia before they develop recurrent infections [19]. Additionally, management of autoimmune disease with immunosuppression further increases risk of severe infections in an undiagnosed CVID patient, which remains the most significant cause for mortality overall in our cohort. Death due to bacterial infections and/or opportunistic infections has been reported in patients with CVID and autoimmune thrombocytopenia [19]. There was also a larger percentage of the pediatric-onset cohort that had multiple CVID comorbidities, therefore not fitting into Dr. Chapel's CVID phenotypes [15]. Few other significant differences were found, which can likely be attributed to the overall heterogeneity of the disease.

The ultimate concern with CVID is the associated mortality, and the average age of death of the 18 deceased patients in our overall cohort was only 41 years of age, consistent with the young ages of death published elsewhere [20]. The average age at death dropped to 31 years of age if CVID symptom onset occurred before 19 years of age. Factors correlating with mortality in pediatric CVID have not been well explored
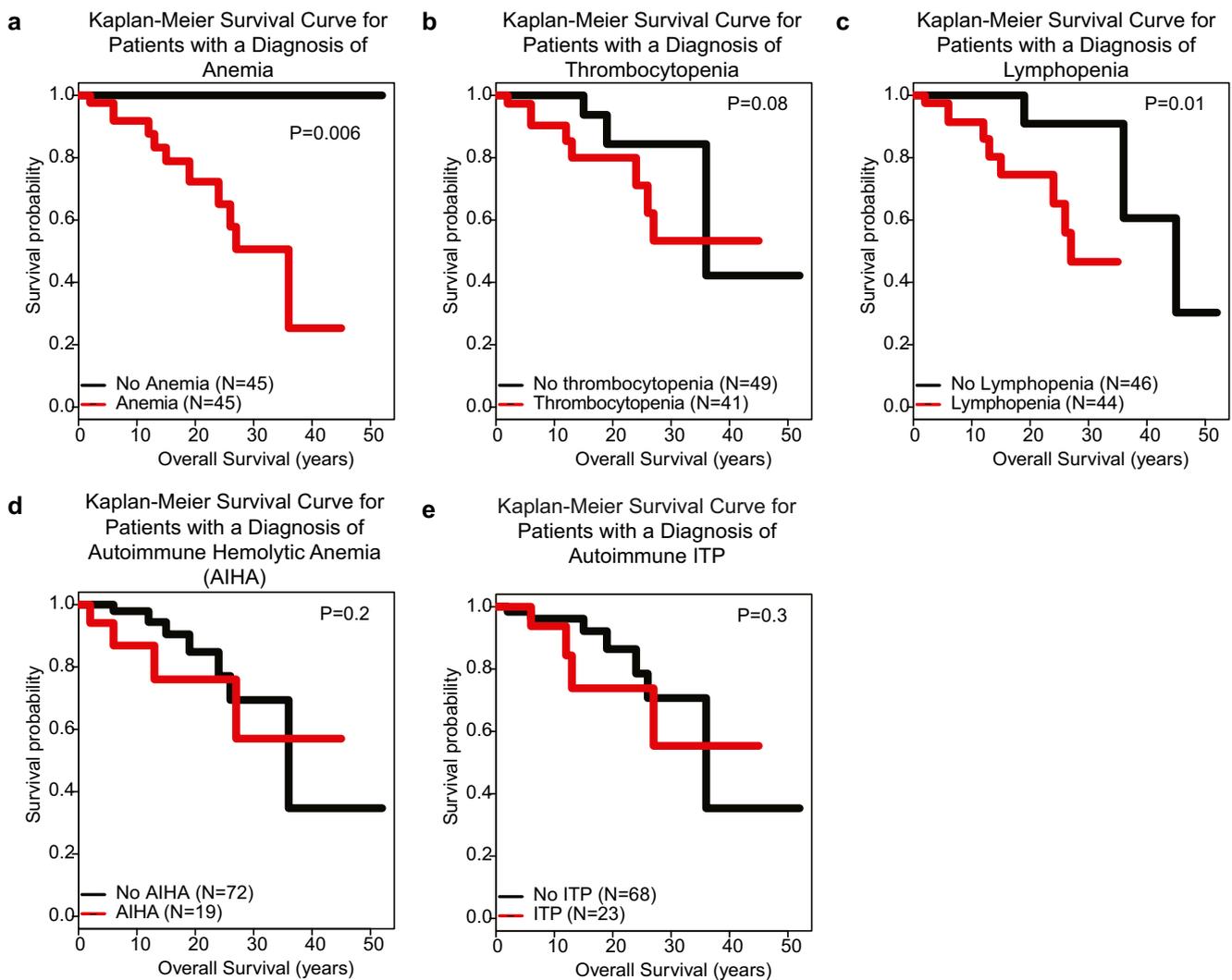
Fig. 3 Cytopenias are associated with mortality independent of autoimmune component. Kaplan-Meier survival curves for pediatric-onset subjects with anemia (a), thrombocytopenia (b), lymphopenia (c), autoimmune hemolytic anemia (AIHA) (d), and autoimmune thrombocytopenia (ITP) (e). p values for curves provided on graphs

previously. The most common cause of death for our pediatric CVID onset subjects was infection, although most subjects had evidence of relatively severe disease with multiple disease comorbidities, severe infections, anemia, and depression. Of the disease comorbidities, lymphocytic granulomatous disease and lung disease are significantly associated with mortality. An explanation for mortality in these patients was likely the use of immunosuppressive agents to manage disease comorbidities, although chronic inflammation may have also played a role.

GLILD is one of the most feared comorbidities of CVID as it has been shown to be associated with decreased survival in adults [13, 21]. In this cohort, the number of biopsy-confirmed GLILD was small and therefore not significantly associated with survival. Significant lung disease, however, was associated with increased mortality. Specific features of lung disease that are the most important include lymphocytic interstitial

pneumonia, lung nodules, and bronchiectasis. This emphasizes that patients seen in a pulmonology clinic or by their pediatrician who have lung findings (i.e., fibrosis, nodules, bronchiectasis) should be evaluated for immunodeficiency with immunoglobulin levels and vaccine titers. Additionally, a lung biopsy may not be required to ascertain whether a pediatric patient with CVID is at higher risk, but they should be monitored closely.

The mental health of patients with CVID has been addressed in the literature, but remains under-recognized clinically [3, 4]. Our study revealed that 18% of those with pediatric-onset CVID experienced depression, roughly double than what was found in the USIDNET study [7]. This emphasizes the importance of monitoring CVID patients of all ages for depression. Reasons why patients with CVID develop psychological distress and depression are manifold and include decreased physical functioning from recurrent

infections or comorbidities, fatigue secondary to CVID, and/
or fatigue secondary to immunoglobulin wear-off effects [22,
23]. The significant relationship between depression and death
and between depression and specific comorbidities is novel in
our study. Additionally, our study is the first to show the in-
creased risk of depression if the CVID diagnosis is delayed
beyond 5 years from symptom onset. Depression screening
may be useful to risk-stratify those with more severe comor-
bidities and/or infections and who are at greater risk of mor-
tality. Limitations we present in reporting depression include
the diagnosis was physician- or patient-reported without fur-
ther description such as the presence of major depressive dis-
order or treatment.

There is a striking relationship between anemia and mor-
tality. Autoimmune hemolytic anemia and autoimmune
thrombocytopenia are not significantly related to mortality
suggesting anemia's relationship with mortality is due to
chronic inflammation. There is little data regarding anemia
(regardless of whether it is autoimmune) in the literature; how-
ever, one group did address anemia of any cause and found it
was significantly correlated with autoimmunity, lymphopro-
liferation, and mortality [24]. This study did not address the
cause for anemia in CVID patients, and a literature search
revealed no discussions of causes for anemia in CVID patients
aside from autoimmune causes. Additional study would be
useful to better understand whether the anemia in CVID pa-
tients is due to chronic disease, nutrient disease from enterop-
athy, bone marrow suppression, or secondary to thyroid dis-
ease. Further analysis of why anemia is correlated so strongly
with mortality is also necessary as this finding has now been
replicated in two studies. At this time, we know it is a "risk
stratifier" for mortality and that further investigation is
needed.

Our study is the most comprehensive study of pediatric-
onset CVID patients to date and the only study to elucidate
mortality for this population. As more pediatric symptom on-
set CVID patients are studied, it is hoped that there will be a
better understanding of the importance of our significant find-
ings such as anemia and depression in risk-stratifying patients.
Additional patient numbers would also allow for a better un-
derstanding of lung disease in those with pediatric-onset
CVID, particularly if they were followed over time for find-
ings such as lung nodules and had biopsies to elucidate
pathology.

Compliance with Ethical Standards

This study was approved by the Duke University Institutional Review
Board, and as this was a retrospective chart review involving existing data
and posing no more than minimal risks to subjects, the need for individual
consent was waived.

Conflict of Interest The authors declare that they have no conflict of
interest.

References

1. Boyle JM, Buckley RH. Population prevalence of diagnosed pri-
mary immunodeficiency diseases in the United States. J Clin
Immunol. 2007;27(5):497–502.
2. Sullivan KE, Boyle M, Nauman E, Carton T. Health care utilization
by patients with common variable immune deficiency defined by
International Classification of Diseases, Ninth Revision code
279.06. Ann Allergy Asthma Immunol. 2015 Sep;115(3):248–50.
3. Quinti I, Pulvirenti F, Giannantoni P, Hajjar J, Canter DL, Milito C,
et al. Development and initial validation of a questionnaire to mea-
sure health-related quality of life of adults with common variable
immune deficiency: the CVID_QoL questionnaire. J Allergy Clin
Immunol Pract. 2016;4(6):1169–79 e4.
4. Tcheurekdjian H, Palermo T, Hostoffer R. Quality of life in com-
mon variable immunodeficiency requiring intravenous immuno-
globulin therapy. Ann Allergy Asthma Immunol. 2004 Aug;93(2):
160–5.
5. Conley ME, Park CL, Douglas SD. Childhood common variable
immunodeficiency with autoimmune disease. J Pediatr. 1986
Jun;108(6):915–22.
6. Hausser C, Virelizier JL, Buriot D, Griscelli C. Common variable
hypogammaglobulinemia in children. Clinical and immunologic
observations in 30 patients. Am J Dis Child. 1983;137(9):833–7.
7. Sanchez LA, Maggadottir SM, Pantell MS, Lugar P, Rundles CC,
Sullivan KE, et al. Two sides of the same coin: pediatric-onset and
adult-onset common variable immune deficiency. J Clin Immunol.
2017;37(6):592–602.
8. Grimbacher B, Party ERW. The European Society for
Immunodeficiencies (ESID) registry 2014. Clin Exp Immunol.
2014;178(Suppl 1):18–20.
9. Hartono S, Motosue MS, Khan S, Rodriguez V, Iyer VN, Divekar
R, et al. Predictors of granulomatous lymphocytic interstitial lung
disease in common variable immunodeficiency. Ann Allergy
Asthma Immunol. 2017 May;118(5):614–20.
10. Mouillot G, Carmagnat M, Gerard L, Garnier JL, Fieschi C, Vince
N, et al. B-cell and T-cell phenotypes in CVID patients correlate
with the clinical phenotype of the disease. J Clin Immunol.
2010;30(5):746–55.
11. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C.
Morbidity and mortality in common variable immune deficiency
over 4 decades. Blood. 2012;119(7):1650–7.
12. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M,
Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H,
Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-
van der Cruyssen F, le Garff M, Debre P, Jacobs R, Jones J,
Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE,
Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M,
Oksenhendler E, Peter HH, Warnatz K The EUROclass trial: defin-
ing subgroups in common variable immunodeficiency. Blood. 2008
1;111(1):77–85.
13. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes
JM. Granulomatous-lymphocytic lung disease shortens survival in
common variable immunodeficiency. J Allergy Clin Immunol.
2004 Aug;114(2):415–21.
14. Gathmann B, Mahlaoui N, Ceredih GL, Oksenhendler E, Warnatz
K, et al. Clinical picture and treatment of 2212 patients with com-
mon variable immunodeficiency. J Allergy Clin Immunol.
2014;134(1):116–26.

15. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112(2):277–86.

16. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr. 2009 Jun;154(6):888–94.

17. Esolen LM, Fasano MB, Flynn J, Burton A, Lederman HM. Pneumocystis carinii osteomyelitis in a patient with common variable immunodeficiency. N Engl J Med. 1992 Apr 9;326(15):999–1001.

18. Malphettes M, Gerard L, Carmagnat M, Mouillot G, Vince N, Boutboul D, et al. Late-onset combined immune deficiency: a subset of common variable immunodeficiency with severe T cell defect. Clin Infect Dis. 2009;49(9):1329–38.

19. Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore). 2004;83(4):254–63.

20. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34–48.

21. Cadranel J, Bouvry D, Wislez M. Respiratory manifestations of common variable immunodeficiency in adults. Rev Mal Respir. 2003;20(1 Pt 1):126–33 Manifestations respiratoires au cours du deficit immunitaire commun variable de l'adulte.

22. Tabolli S, Giannantoni P, Pulvirenti F, La Marra F, Granata G, Milito C, et al. Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies. Front Immunol. 2014;5:–605.

23. Hajjar J, Kutac C, Rider NL, Seeborg FO, Scalchunes C, Orange J. Fatigue and the wear-off effect in adult patients with common variable immunodeficiency. Clin Exp Immunol. 2018;194(3):327–38.

24. Farmer JR, Ong MS, Barmettler S, Yonker LM, Fuleihan R, Sullivan KE, et al. Common variable immunodeficiency non-infectious disease endotypes redefined using unbiased network clustering in large electronic datasets. Front Immunol. 2017;8:–1740.