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Overall survival among patients with activated phosphoinositide 3-kinase delta syndrome (APDS)

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Abstract

Background This study aimed to describe overall survival (OS) of patients with APDS relative to the global population as well as among subsets of patients with concurrent lymphoma or hematopoietic stem cell transplant (HSCT) relative to the overall APDS population.

Methods Patient-level data were extracted from a recent systematic literature review of 351 unique patients with APDS. OS was evaluated using the Kaplan-Meier method up to age 65 years. OS rate and corresponding 95% CI were reported at each decade of age. Global mortality estimates were obtained from World Health Organization life tables for 2019.

Results Of the 351 patients with APDS (APDS1, 267 [76.1%]; APDS2, 83 [23.6%]; unspecified, 1 [0.3%]), 41 (11.7%) died. The OS rate was 25.0% (95% CI, 1.6–62.7%) by the last death event at 64 years of age. Starting at 12 years of age, the OS rate was numerically lower in patients with APDS relative to the global population (median OS, 64 vs. 75 years, respectively). Relative to the overall APDS population, OS rates were numerically similar in those who underwent HSCT (median OS, 64 years for both; $p=0.569$), whereas OS rates were numerically lower in patients with concurrent lymphoma (median OS, 41 vs. 64 years, respectively; $p=0.109$). Publication bias in source data was a possible limitation.

Conclusion Reduced survival in patients with APDS suggests a high disease burden, particularly in those with concurrent lymphoma. These results highlight the unmet need for disease-modifying treatments for APDS.

Keywords Activated phosphoinositide 3-kinase delta syndrome (APDS), Hematopoietic stem cell transplant (HSCT), Inborn error of immunity (IEI), Lymphoma, Overall survival, Primary immunodeficiency (PID)

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Introduction

Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)—also known as p110 delta–activating variant causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI)—is an underrecognized, rare primary immunodeficiency (PID) that was first characterized in 2013 [1–3]. As an inborn error of immunity, APDS is caused by variants in one of two genes that encode subunits of PI3Kδ [3–5]. Gain-of-function mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*PIK3CD*) gene encoding the p110δ catalytic subunit of PI3Kδ lead to APDS1, and loss-of-function mutations in the phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) gene encoding the p85α regulatory subunit of PI3Kδ lead to APDS2 [1, 2, 4–9]. These genetic mutations result in overactivation of the PI3K/AKT/mTOR/S6K signaling pathway, which alters B-cell and T-cell growth, survival, proliferation, and differentiation, ultimately leading to immune deficiency and dysregulation [4–6, 9, 10].

Patients diagnosed with APDS exhibit a diverse range of symptoms that typically present in infancy or early childhood, with APDS1 and APDS2 often displaying similar clinical features [4, 11, 12]. Recurrent respiratory tract infections are nearly ubiquitous among patients with APDS and may be accompanied by other manifestations such as bronchiectasis, persistent herpesvirus infections, various viral and bacterial infections, non-neoplastic lymphoproliferation involving lymphadenopathy, splenomegaly and hepatomegaly, autoimmune and autoinflammatory conditions, neurodevelopmental issues, and growth deficiencies [4, 11, 12]. Additionally, concurrent lymphoma has been reported in up to 25% of patients with APDS [11–13]. Although some adults with APDS may be asymptomatic, many patients experience considerable morbidity, and infection-related fatalities have been documented in children and young adults with APDS [11].

Manifestations associated with APDS are variable and may be progressive and detrimental over time [4]. There are currently no treatment guidelines defining standard of care. Therapies for APDS can vary according to clinical manifestations and may include antimicrobial prophylaxis, mTOR inhibitors, immunomodulatory therapies, immunoglobulin replacement therapy, and splenectomy [4]. Notably, none of these treatment strategies target the underlying pathogenesis of APDS. Hematopoietic stem cell transplant (HSCT) has been used to treat APDS when severe immune deficiency is present. However, the risks of adverse events and mortality limit the clinical application of HSCT [4, 14–16]. In 2023, leniolisib, an oral selective PI3Kδ inhibitor, became the first and only treatment approved in the US for APDS after meeting both coprimary outcomes of reduction in index lymph node size and increase in the percentage of naïve to total B cells in the peripheral blood ($p < 0.001$ for both).

As APDS was only characterized within the last decade, there is a paucity of published literature on the clinical course of the disease, including the survival pattern of patients with APDS [5, 6]. Small cohort studies of APDS1 and APDS2 have reported 30-year overall survival rates of 86% and <75%, respectively [12, 16], while a larger systematic literature review of 256 patients with APDS reported a 30-year overall survival rate of 74% [17]. However, these analyses did not contextualize the overall survival of patients with APDS relative to the general population or account for the impact of therapies.

To shed light on these gaps in the literature, this study estimated the overall survival of patients with APDS relative to the global population using patient-level data from a systematic literature review. Additional objectives were to describe overall survival by APDS subtype, in patients with concurrent lymphoma, and censoring for patients who were treated with HSCT.

Methods

Patient-level data were extracted via a systematic literature review that has been previously detailed [18]. Briefly, the systematic literature review followed the PICO (population, intervention, comparator, and outcome) principle (Table 1) [19]. A comprehensive literature search in PubMed and Embase databases was conducted from the time of each database's inception to March 13, 2023, to identify relevant publications that included data on patients with APDS and their survival status [19, 20]. To be included in the study population, patients were required to have a reported APDS diagnosis *or* a first-degree relative with genetically confirmed APDS and at least 1 reported clinical sign consistent with APDS. When available, data on age at last observation, death, age at death, sex, APDS subtype (APDS1 or APDS2), concurrent lymphoma, HSCT, age at HSCT, and age at leniolisib initiation were extracted from the literature within the systematic literature review [1, 2, 7, 8, 11, 12, 15, 16, 21–120].

Global mortality estimates were obtained from the World Health Organization (WHO) life tables for 2019 and were used to estimate overall survival for the global population [121].

Statistical analysis

Overall survival was evaluated using the Kaplan-Meier method and defined as the time from birth to the age of death due to any cause. The overall survival rate and corresponding 95% CIs were estimated up to 65 years of age, as the maximum age of death reported in the individual patient data was 64 years. Median overall survival was defined as the age when the overall survival rate of

Table 1 PICO criteria

Category	Inclusion criteria	Exclusion criteria
Population	• Patients with APDS *OR* patients with ≥ 1 clinical sign consistent with the clinical spectrum of APDS[a] *AND* a first-degree relative who has a genetically confirmed diagnosis of APDS	• Studies not reporting individual patient data for outcome of interest
Interventions or comparators	• Any	• Not applicable
Outcomes	• Age at last observation • Alive status • Age at death	• No reported outcome of interest
Publication type	• Articles, letters, clinical communications, and case series	• Any other publications
Language	• English language • Study publication date: 2013[b] to March 2023	• Studies published in languages other than English or prior to 2013[b]

[a]Clinical signs included documented severe recurrent sinopulmonary infections (> 2 events within 3 years of each other); bronchiectasis; lymphadenopathy for greater than 1 month; any nodular lymphoid hyperplasia; chronic hepatomegaly or chronic splenomegaly; severe, persistent, or recurrent Herpesviridae infections (e.g., Epstein-Barr virus, cytomegalovirus); autoimmune cytopenia; enteropathy; lymphoma; hypogammaglobulinemia; elevated levels of immunoglobulin M; reduced number of $CD3^+CD4^+$ T cells; increased number of follicular helper T cells; reduced number of naïve T cells; clinical diagnosis of CVID or a primary immunodeficiency; evidence of PI3K pathway activation; and additional clinical features within the clinical spectrum of APDS, with a consensus. [b]Studies included were published in 2013 or later, as APDS was characterized in 2013. APDS, activated phosphoinositide 3-kinase delta syndrome; CVID, common variable immunodeficiency; PI3K, phosphoinositide 3-kinase; PICO, population, intervention, comparison, and outcome

patients with APDS was 50%. To ensure that the overall survival rate in patients with APDS accounted for therapies used as supportive care, patients treated with leniolisib were censored at the age of leniolisib initiation. In the analysis that censored for HSCT, patients who underwent HSCT were censored at the age of transplant.

The overall survival rate of the global population was derived using the probability of dying (q_x) at specific age intervals. Overall survival rates of the global population were calculated using the following formula:

$$S_t = \left(1 - q_{x(t)}\right) \times S_{t-1}$$

Where S_t represents the overall survival rate at age interval t, $q_{x(t)}$ represents the probability of dying at time t, and S_{t-1} represents the overall survival rate at the prior age interval. The overall survival rate at 0 years of age was imputed as 1.

Overall survival rates between groups of patients were compared using a log-rank test to determine whether differences in survival were statistically significant. Comparisons were made between the following groups: (1) patients with APDS1 versus APDS2 (2) patients with APDS with concurrent lymphoma versus without concurrent lymphoma, and (3) patients with APDS who received HSCT versus those who did not receive HSCT.

All analyses were conducted using SAS Enterprise Guide software Version 7.15 (SAS Institute, Cary, NC).

Results

Patient characteristics

Among 108 eligible publications from the systematic literature review (Fig. 1), 351 unique patients with APDS were identified: 267 patients (76.1%) with APDS1 and 83 patients (23.6%) with APDS2 (Table 2) [18]. One patient (0.3%) did not have a specified APDS subtype and was excluded from the stratified analyses. Overall, 171 patients (49%) were male, 135 (38%) were female, and 45 (13%) did not have sex reported. Lymphoma was reported in 43 patients (12.3%) with APDS. A total of 46 patients (13.1%) were reported to have undergone HSCT, of whom 6 patients were excluded from the censoring analysis, as the age at the time of the procedure was not reported. Leniolisib use was reported for 13 patients (3.7%), none of whom were treated with HSCT.

Overall survival

Of the 351 patients with APDS, 41 (11.7%) died, and the median overall survival was 64 years (Fig. 2). The estimated overall survival rate reached 25.0% (95% CI, 1.6–62.7%) by the last death event at 64 years of age. Starting from 12 years of age, the estimated overall survival of patients with APDS was numerically lower relative to the global population, with the estimated overall survival rate being 17.0% and 21.2% lower at 30 and 40 years of age, respectively. The median overall survival in the global population was 75 years.

Among the 267 patients with APDS1, 31 (11.6%) died, and median overall survival was 64 years (Fig. 3A). The estimated overall survival rate among patients with APDS1 reached 27.1% (95% CI, 1.6–66.2%) by the last death event at 64 years of age. Starting from 11 years of age, the estimated overall survival of patients with APDS1 was numerically lower relative to the global population. At 30 and 40 years of age, the estimated overall survival rate was 15.0% and 18.9% lower, respectively, relative to the global population.

Among the 83 patients with APDS2, 10 (12.0%) died, and median overall survival was not reached (Fig. 3B). The estimated overall survival rate among patients with APDS2 reached 55.6% (95% CI, 28.6–75.9%) by the last death event at 41 years of age. Starting at nearly 15 years of age, the estimated overall survival of patients with APDS2 was numerically lower relative to the global population. At 30 and 40 years of age, the estimated overall survival rate was 21.4% and 26.3% lower, respectively, relative to the global population. There was no significant

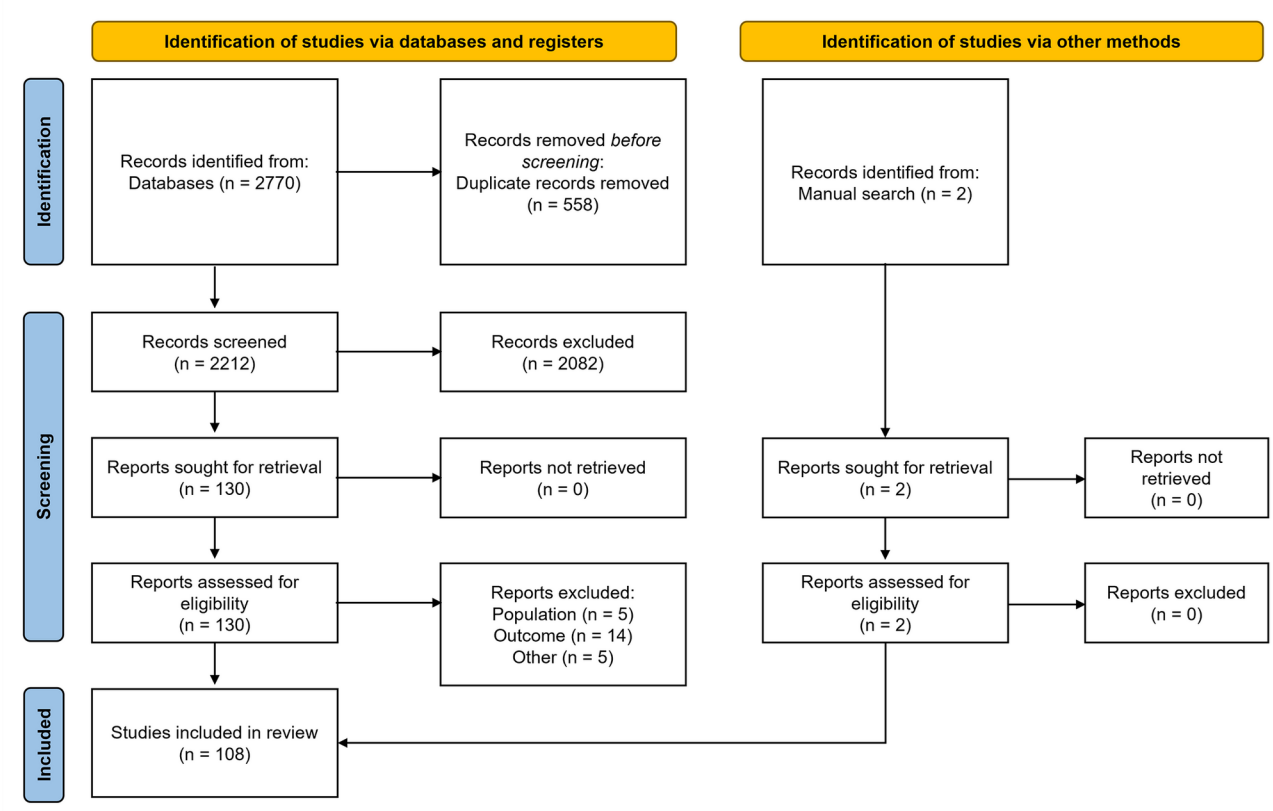


Fig. 1 PRISMA flow diagram providing the review process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 2 Patient characteristics[a]

Characteristic	Patients (*N* = 351)
Sex, No. (%)	
Male	171 (49)
Female	135 (38)
Not reported	45 (13)
APDS type, No. (%)	
APDS1 (*PIK3CD*)	267 (76.1)
APDS2 (*PIK3R1*)	83 (23.6)
Not reported	1 (0.3)
Age at last follow-up	
Alive	
No. of patients with available data	310
Mean (range), y	17.1 (0.5–67)
Deceased	
No. of patients with available data	41
Mean (range), y	19.6 (1–64)

[a]Because of rounding, percentages may not total 100%. APDS, activated phosphoinositide 3-kinase delta syndrome; *PIK3CD*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; *PIK3R1*, phosphoinositide-3-kinase regulatory subunit 1

difference in overall survival between patients with APDS1 and patients with APDS2 ($p = 0.899$) (Fig. 3C).

In the 43 patients with APDS and reported concurrent lymphoma, 13 (30.2%) died and the median overall survival was 41 years (Fig. 4A). Relative to the overall population of patients with APDS, the estimated overall survival of patients with APDS and concurrent lymphoma was numerically lower across nearly all ages. The estimated overall survival rate among patients with APDS and concurrent lymphoma reached 42.7% (95% CI, 17.9–65.7%) by the last death event at 41 years of age, relative to the estimated overall survival rate of 66.8% (95% CI, 53.7–76.9%) in the overall population of patients with APDS at the same age. Overall survival was further compared between the 43 patients with concurrent lymphoma and the 308 patients without concurrent lymphoma (Fig. 4B). Although the overall survival rate was observed to be up to 23.5% lower in patients with APDS and concurrent lymphoma compared with those without lymphoma, the difference between these two groups was not significant ($p = 0.109$).

Of 40 patients reported to have undergone HSCT and for whom an age at transplant was available, 5 (12.5%) died. The mean follow-up time between transplant and last reported age was 3.7 years (SD, 4.5; range, 0–16), with 16 (40%) and 9 (22.5%) patients having at least 3 and 5 years of follow-up after transplant, respectively. The overall survival of patients with APDS was largely consistent across ages after censoring for HSCT (Fig. 5A). The median overall survival of patients with APDS censored for HSCT was 64 years, consistent with the overall

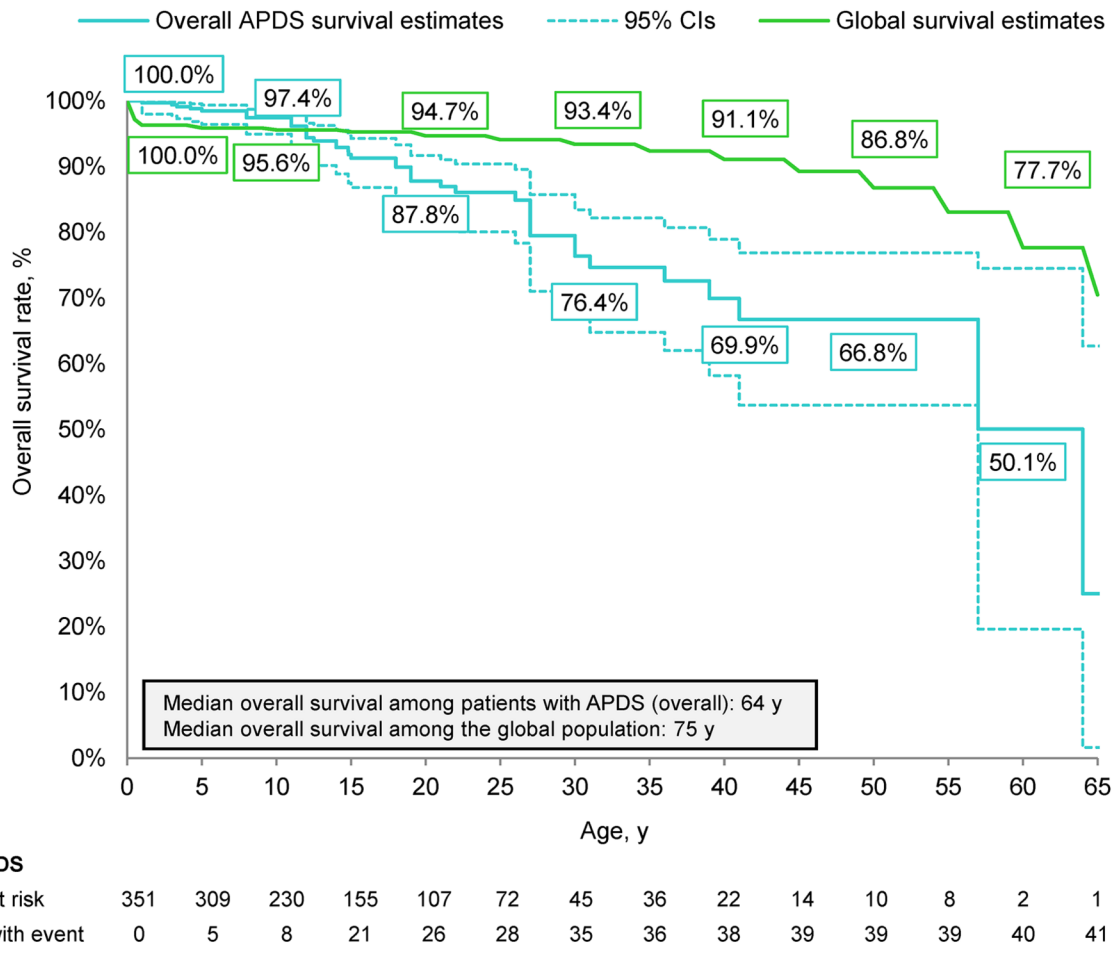


Fig. 2 Kaplan-Meier curve of overall survival in patients with APDS and the global population. APDS, activated phosphoinositide 3-kinase delta syndrome

APDS population. Beginning at approximately 4 years of age, estimated overall survival when censoring for HSCT was numerically higher than the overall survival when not censoring for HSCT, with the largest difference in the estimated overall survival rate observed at 15 years of age (censored for HSCT, 92.3% [95% CI, 88.0–95.2%]; not censored for HSCT, 91.3% [95% CI, 86.8–94.3%]). Overall survival was also evaluated between the 46 patients with APDS who had undergone HSCT and those who had not ($n = 305$) (Fig. 5B). Although median overall survival among patients with APDS who had not undergone HSCT was 57 years and was not reached in those who had undergone HSCT, no significant difference was observed between these two groups ($p = 0.569$).

Discussion

Using individual data from 351 patients with APDS obtained via a systematic literature review, this study estimated a lower overall survival rate among the overall APDS population relative to the global population and across APDS subtype. Early mortality in patients with APDS was evidenced by a median overall survival of 64 years, an 11-year difference compared with 75 years in the global population. In addition, overall survival rates for patients with APDS were up to 28% lower than that of the global population, underscoring the significant morbidity of APDS that can lead to shorter lifespans. The estimated 30-year overall survival rate observed in this study (76.4%) aligns with a previous report of the 30-year overall survival rate in 256 patients with APDS (74%), among whom no significant difference in overall survival between APDS1 and APDS2 was also observed [17]. To our knowledge, our study provides the most current and comprehensive estimate of overall survival among patients with APDS [12, 16, 17].

In this study, a divergence in survival between patients with APDS and the global population was observed beginning in adolescence and sustained through adulthood. Nearly all patients with APDS (98%) experience their first symptoms of APDS in infancy or childhood at a median age of 2.0 years (range, birth to 22 years). In contrast, the median age of diagnosis is 13.4 years (range, 0–56 years) [18]. Delays in APDS diagnosis of a median 7.0 years (IQR, 3.4–14.0 years) and mean 10.6 years

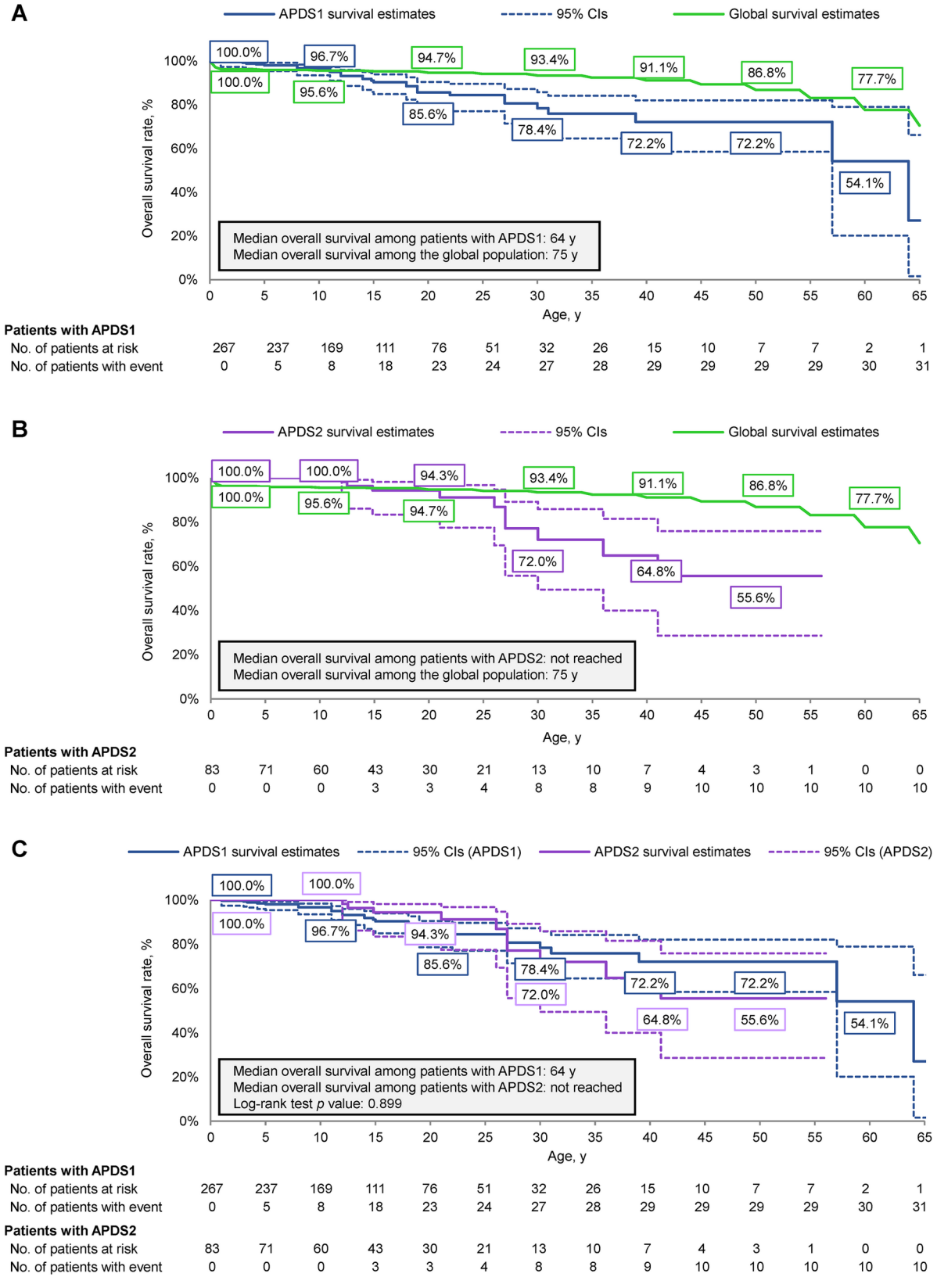
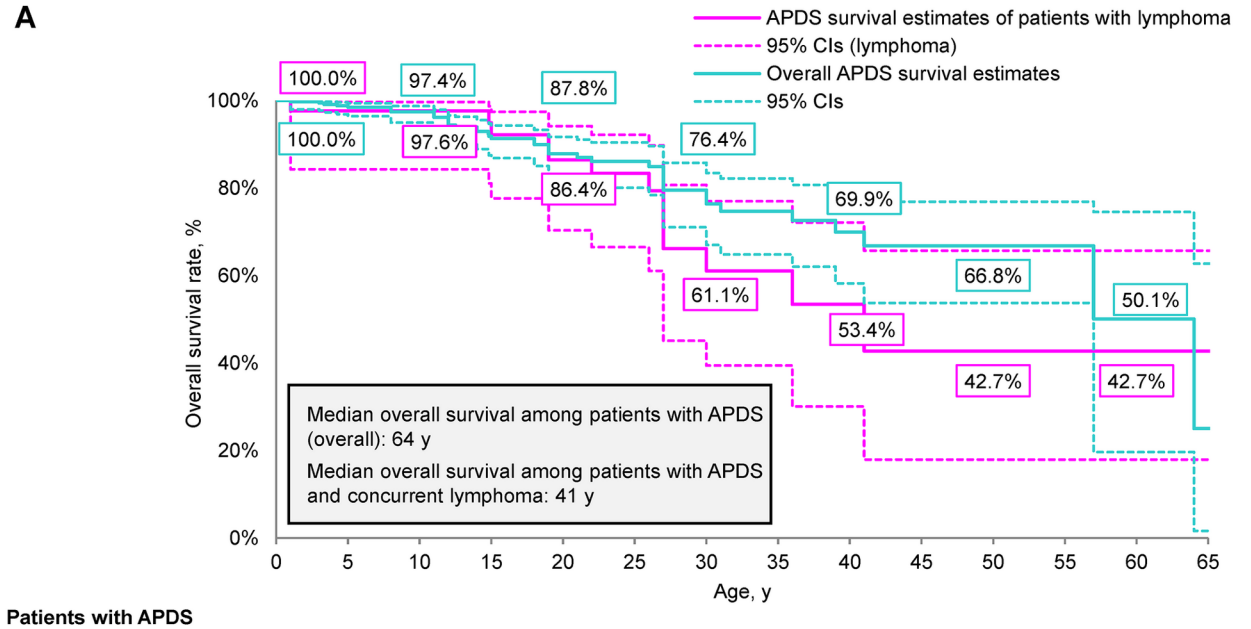
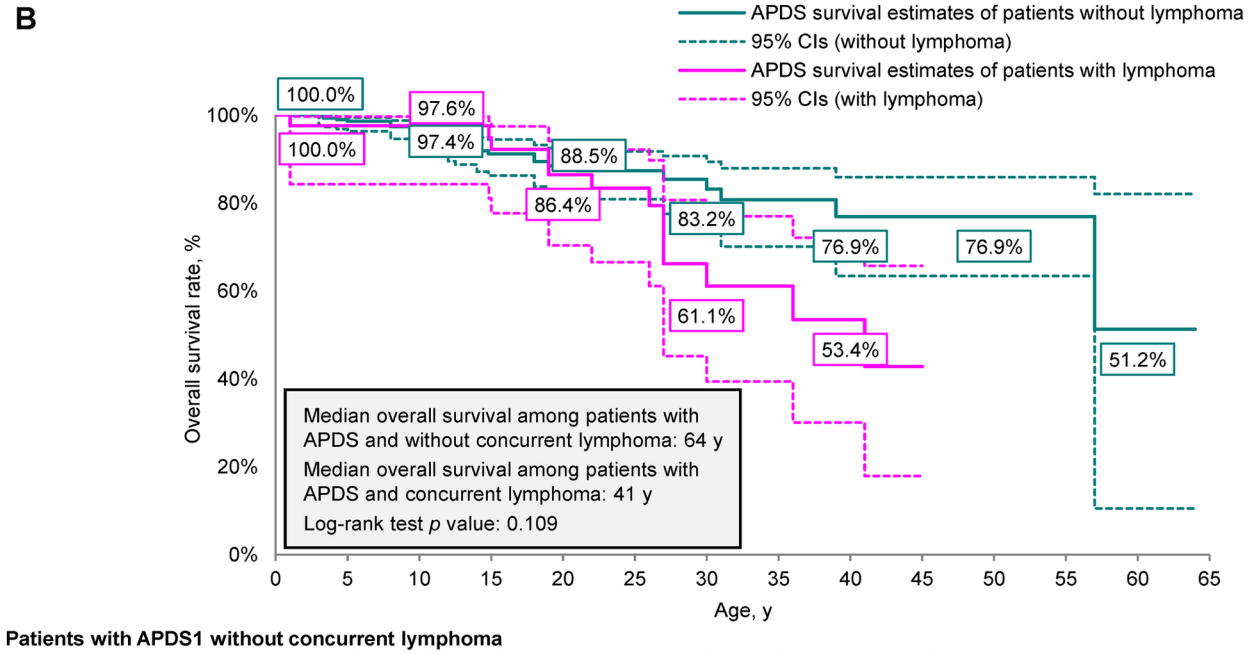


Fig. 3 Kaplan-Meier curve of overall survival in patients with (**A**) APDS1 or (**B**) APDS2 and the global population, or (**C**) APDS1 versus APDS2. APDS, activated phosphoinositide 3-kinase delta syndrome

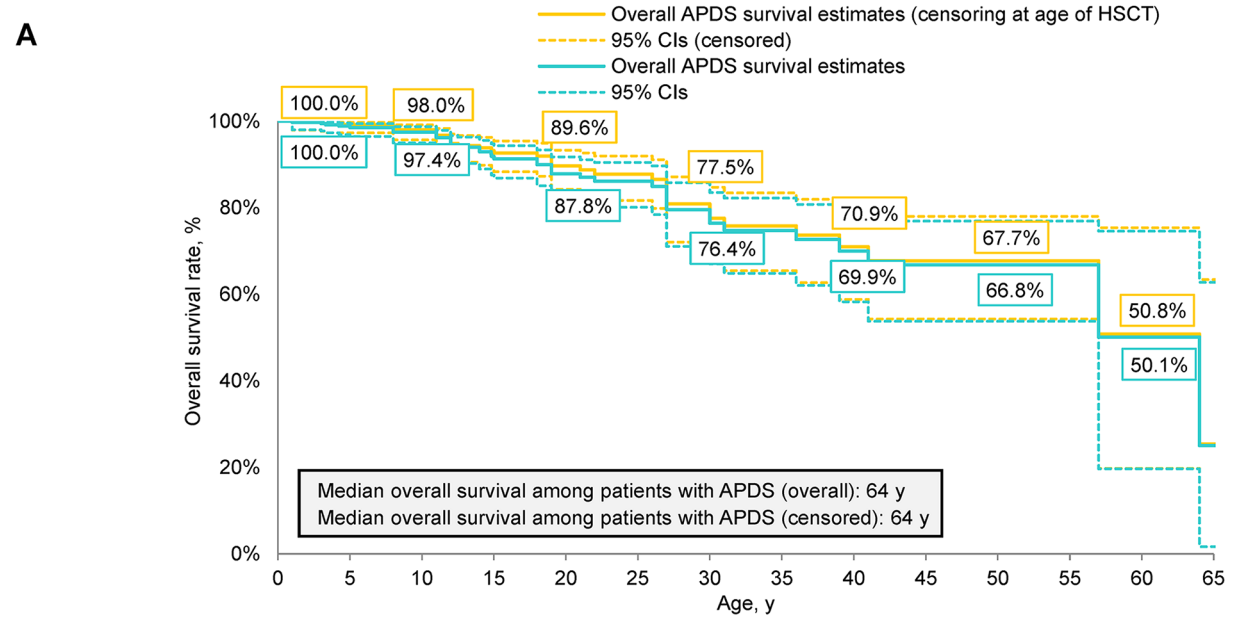


Patients with APDS														
No. of patients at risk	351	309	230	155	107	72	45	36	22	14	10	8	2	1
No. of patients with event	0	5	8	21	26	28	35	36	38	39	39	39	40	41
Patients with APDS with concurrent lymphoma														
No. of patients at risk	43	41	38	34	29	21	11	8	5	2	2	1	1	1
No. of patients with event	0	1	1	3	5	6	11	11	12	13	13	13	13	13

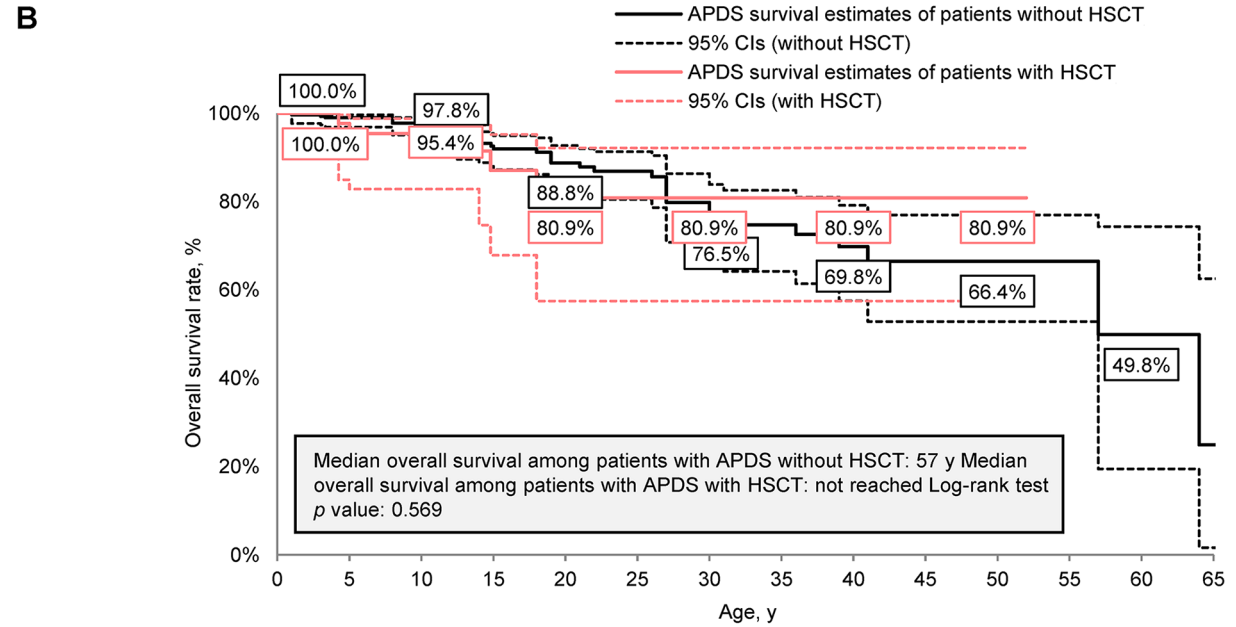


Patients with APDS1 without concurrent lymphoma														
No. of patients at risk	308	268	192	121	78	51	34	28	17	12	8	7	1	0
No. of patients with event	0	4	7	18	21	22	24	25	26	26	26	26	27	28
Patients with APDS with concurrent lymphoma														
No. of patients at risk	43	41	38	34	29	21	11	8	5	2	2	1	1	1
No. of patients with event	0	1	1	3	5	6	11	11	12	13	13	13	13	13

Fig. 4 Kaplan-Meier curve of overall survival in (**A**) patients with APDS and APDS with concurrent lymphoma or (**B**) patients with APDS with concurrent lymphoma versus without concurrent lymphoma. APDS, activated phosphoinositide 3-kinase delta syndrome



Patients with APDS														
No. of patients at risk	351	309	230	155	107	72	45	36	22	14	10	8	2	1
No. of patients with event	0	5	8	21	26	28	35	36	38	39	39	39	40	41
Patients with APDS (censoring at age of HSCT)														
No. of patients at risk	345	305	219	146	100	70	44	36	22	14	9	8	2	1
No. of patients with event	0	3	6	17	21	23	30	31	33	34	34	34	35	36



Patients with APDS without HSCT														
No. of patients at risk	305	268	201	136	97	68	43	35	21	13	9	8	2	1
No. of patients with event	0	3	6	17	21	23	30	31	33	34	34	34	35	36
Patients with APDS with HSCT														
No. of patients at risk	46	41	29	19	10	4	2	1	1	1	1	0	0	0
No. of patients with event	0	2	2	4	5	5	5	5	5	5	5	5	5	5

Fig. 5 Kaplan-Meier curve of overall survival in (**A**) patients with APDS and censoring at age of HSCT or (**B**) patients with APDS with HSCT versus without HSCT. APDS, activated phosphoinositide 3-kinase delta syndrome; HSCT, hematopoietic stem cell transplant

(range, 0–44 years) have been previously reported [18, 122]. The mortality implications of early onset of APDS manifestations coupled with delays in diagnosis and lack of effective early interventions are not fully understood. However, findings from our study suggest that timely diagnosis and effective management of APDS at first presentation of symptoms may improve survival in these patients but should be confirmed in future analyses of OS relative to the diagnostic timing.

Our findings also highlight the exacerbated mortality of patients with APDS and concurrent lymphoma, with a median overall survival of 41 years. The cumulative risk of lymphoid malignancy has been previously estimated to be as high as 78% at 40 years of age, and up to 62% of APDS fatalities may be attributable to lymphoma [12, 123]. In this study, the overall survival rate in patients with APDS and concurrent lymphoma was 42.7% at 41 years of age, compared with 66.8% in the overall APDS population at the same age. Although we did not observe a significant difference in overall survival between patients with APDS with and without concurrent lymphoma, an empirical assessment of the data suggests an accelerated decline in survival among patients with APDS and concurrent lymphoma relative to those without concurrent lymphoma and to the overall APDS population. Thus, our findings underscore the considerable influence of concurrent lymphoma on overall survival and emphasize the importance of focusing mitigation efforts on decreasing the incidence of lymphoma in patients with APDS.

Previous literature suggests that HSCT can reverse some phenotypes of APDS or achieve a cure; the reported overall survival rates after HSCT were 81% over follow-up periods ranging from 8 months to 16 years and 86% at 2 years [14, 15]. However, prior studies have also reported high rates of complications following HSCT, including graft instability or failure and severe infection [14–16]. In this study, we observed that the estimated overall survival of patients with APDS remained largely unchanged when censoring for HSCT. Moreover, no significant difference was noted when overall survival in patients with APDS who were reported to have undergone HSCT was compared with overall survival in those who had not. With the data available at the time of this analysis, our results suggest that HSCT may not provide a meaningful clinical benefit in survival in patients with APDS and ongoing evaluation is warranted. Further investigations are warranted to assess whether the benefits observed with HSCT outweigh the risk of adverse complications including graft failure or instability, poor graft function, graft vs. host disease, and mortality [14–17, 122].

The results of this study should be considered within the context of its limitations. First, this study relied on published data, potentially introducing publication bias. However, this study includes a large collection of publications describing patients with APDS across multiple countries to help mitigate bias. Secondly, age-related information in the literature predominantly focuses on early decades of life, resulting in fewer data available for the construction of Kaplan-Meier curves for later decades. Given the recent characterization of APDS in 2013 and a median age of diagnosis of 12 years, the distribution of age among patients with APDS observed in our study may be reflective of real-world trends [1, 2, 122]. Additionally, the follow-up time after HSCT was based on follow-up times noted in the literature. Therefore, the time between age at HSCT and last age observed may not have been sufficient to capture the long-term survival benefit associated with transplant. Likewise, literature references reported that only 13 patients received leniolisib, which precluded the assessment of the impact of leniolisib on overall survival. With the approval of leniolisib for treatment of APDS in 2023 by the US Food and Drug Administration, future studies may extend the present findings by evaluating its impact on mortality. Additionally, the creation of an *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification* (*ICD-10-CM*) code for APDS (D81.82) in 2023 may also help identify patients for future analyses. Finally, due to lack of individual data for the global population, CIs for survival estimates could not be calculated in this population, and a statistical comparison of overall survival between the overall APDS population and global population was not feasible. Despite these limitations, our assessment of APDS mortality relative to the global population sheds light on the considerable burden of this disease. Moreover, our study assesses the largest number of patients with APDS for whom survival has been evaluated, increasing the generalizability of our findings to the broader APDS population, and it is the first study to evaluate the impact of concurrent lymphoma and HSCT on survival.

Conclusions

This study provides the most current and comprehensive estimate of overall survival in patients with APDS. Relative to the global population, the overall survival rate was lower among the overall APDS population and across APDS subtype, with no difference in mortality between APDS1 and APDS2. The observed lack of improvement in survival after HSCT warrants further investigation of the impact of this therapy in patients with APDS. Findings from this study indicate a high disease burden associated with APDS, particularly in patients with concurrent lymphoma, highlighting the unmet need for disease-modifying treatments to improve survival in this patient population.

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Author contributions
AH, MM, RR, GG, and FL contributed to the study concept and design. AH, MM, RR, HLM, GG, FL, and KB contributed to data acquisition and analysis. JEMU contributed to data analysis. All authors contributed to data interpretation, provided critical feedback during manuscript development, and approved the final manuscript for publication.

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Data availability
Data used within this manuscript are available in PubMed and Embase.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
AH and HLM are employees of Pharming Healthcare, Inc. JEMU reports consulting for and steering committee membership with Pharming Healthcare, Inc, both outside of the current work, advising fees from Pfizer and Bausch Health, speaker fees from AstraZeneca, clinical trial funding (to institution) from Regeneron and Sanofi, and drug donation for clinical trial use from Novartis. KB is an employee of KJM Büsch Consulting GmbH. MM, RR, GG, and FL are employees of Groupe d'analyse, Ltée, a consulting company that received research funding from Pharming Healthcare, Inc, to conduct this study.

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