Original Article

DOI: 10.5582/irdr.2025.01074

Understanding the disease burden and unmet needs of patients with primary immunodeficiency in China: A quantitative study

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SUMMARY: To quantitatively describe the disease burden and living status of patients with primary immunodeficiency (PID) in China, a descriptive, nationwide cross-sectional survey was conducted in September 2024 *via* a patient organization, yielding 435 valid responses. Among respondents, 82% were male and 77% were pediatric; antibody deficiencies were the most common category (63%), with X-linked agammaglobulinemia (49%) being the most frequent self-reported subtype. The mean diagnostic delay was 3 years, with 45.2% waiting over 1 year and 78.6% experiencing prior misdiagnosis or missed diagnosis. Although 82% received immunoglobulin therapy, only 7% reported being relatively healthy without complications. Health-related quality of life (HRQoL) utility values, measured *via* EQ-5D instruments, were 0.87 for children and 0.84 for adults, appearing lower than reference population norms. Educational disruption affected 25.1% of pediatric patients, while 27% of adult patients were unemployed and 47.1% required frequent sick leave. Caregiving demands were extensive, with 53.4% of pediatric patients requiring dedicated care, resulting in 51.5% of their primary caregivers resigning from their jobs. In conclusion, PID imposes substantial medical, psychological, and socioeconomic burdens in China. These descriptive findings highlight an urgent need for earlier diagnosis, improved therapeutic access, and integrated societal support systems for education, employment, and caregiving.

Keywords: rare diseases, primary immunodeficiency, quality of life, care burden

1. Introduction

Primary immunodeficiency (PID) is a group of disorders caused by genetic mutations that disrupt the development or function of immune organs, immune-active cells, and immune molecules such as immunoglobulins, cytokines, complement, and cell surface proteins (*1*). These defects result in impaired immune function, though the severity of disease can vary considerably among patients. With a compromised immune system, individuals with PID are unable to mount effective defenses against bacterial, viral, or fungal infections. Consequently, they are prone to recurrent infections and may also develop complications involving multiple systems, including the respiratory, hematological, gastrointestinal, integumentary (skin and mucosa), and endocrine systems.

Due to classifications of disease groups being updated frequently, there is still no unified international standard for estimating the prevalence of PID or its newly reclassified counterpart, inborn errors of immunity (IEI). According to several registry-based prevalence reports published in Europe, the prevalence of PID in Europe was approximately 5 cases per 100,000 population (*2-4*). More recent studies, however, suggest that the prevalence of IEI may be around 1 in 1,000, likely due to the inclusion of additional disease entities in updated classifications (*5*). In China, no epidemiological studies on PID have yet been conducted, and therefore no specific data on its incidence or prevalence are available. Nonetheless, among patients currently diagnosed, the more common subtypes include severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), X-linked hyper-IgM syndrome (XHIM), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS), common variable immunodeficiency (CVID), and activated PI3K delta syndrome (APDS).

Currently, PID has been included in the second Chinese national list of rare diseases (No. 66), but the lack of systematic data presents a major obstacle to effective healthcare planning and policy formulation.

In addition, research on PID in China has primarily focused on clinical aspects, while studies addressing patients' quality of life remain relatively limited. As a result, there is a significant knowledge gap regarding the social and psychological impacts of PID on patients'

living status in China.

To address this gap, the current study was designed as a descriptive, cross-sectional, questionnaire-based survey. It aims to describe the demographic characteristics of the patient population, clinical subtypes, healthcare/diagnosis and treatment experiences, quality of life, social participation, as well as caregiving burdens. The expected objectives are as follows: *i*) to describe the demographic characteristics of the surveyed PID patients in China, including age and gender distribution; and *ii*) to report the current status of these PID patients and their families in terms of diagnosis and treatment, medication, disease burden, and quality of life.

2. Methods

The project employed a quantitative research design by incorporating quantitative patient surveys to comprehensively gather data and capture the current circumstances and needs of patients with PID.

2.1. Study design and participants

The current study employed a descriptive, cross-sectional, questionnaire-based survey design using convenience sampling to assess the healthcare/diagnosis experience, quality of life, social participation, and caregiving burden among PID patients and their caregivers in China.

The current study was conducted in strict accordance with ethical standards. As this was an anonymous, non-interventional online survey, formal ethical approval from a medical institutional review board was not applicable/obtained. However, the study was conducted in strict adherence to the ethical principles of the Declaration of Helsinki regarding the protection of human subjects. Prior to completing the questionnaire, all participants were informed of the study sponsor, the objectives of the survey, the intended use of the data, and the measures implemented to ensure data confidentiality and security. Submission of the completed questionnaire was regarded as provision of informed consent to participate and acknowledgment that the data would be used solely for the purposes of this research.

The inclusion criteria for this study were: *i*) patients formally diagnosed with PID or their primary caregivers; and *ii*) residing in China. The exclusion criteria were: *i*) refusal to provide informed consent; *ii*) duplicate submissions from the same IP address or user; and *iii*) questionnaires with largely incomplete or logically implausible responses.

2.2. Data collection and questionnaire development

An online questionnaire survey was conducted in September 2024, with patient recruitment facilitated through the patient organization PID Care China. Given this recruitment strategy, a convenience sample of patients heavily engaged with advocacy networks was obtained. A total of 448 questionnaires were collected, of which 435 were valid. No valid responses were obtained from Tianjin Municipality, Hainan Province, Qinghai Province, Tibet Autonomous Region, Ningxia Hui Autonomous Region, or the Hong Kong, Macao, and Taiwan regions.

The survey instrument consisted of two parts: a standardized, internationally validated tool for measuring quality of life (EQ-5D), and a self-developed questionnaire designed by the research team to capture specific socio-clinical parameters. The development of the self-designed items was formulated based on a comprehensive literature review and tailored specifically to the context of PID in China. To ensure content validity and clinical relevance, the initial draft of the questionnaire underwent expert review by clinical immunologists and leaders from the patient advocacy group (PID Care China). Revisions were made based on their feedback to ensure the terminology was patient-friendly and clinically accurate before national distribution. The collected data were automatically recorded *via* the Jinshuju platform and analyzed using statistical software.

The survey was organized into five major domains:

i) Demographics and clinical profile

This domain collected information on age, gender, geographic distribution and clinical profile.

ii) Diagnosis/healthcare and treatment experience

Items in this section collected detailed information on multiple aspects of patients' medical journeys. Specifically, it captured the initial reasons for seeking medical consultation, the interval between symptom onset and confirmed diagnosis, and experiences of misdiagnosis or missed diagnosis. It also examined the geographic distribution of diagnosis, including whether patients were diagnosed locally or needed to travel to other cities or provinces, as well as the medical departments where diagnoses were ultimately confirmed. In addition, this section assessed current treatment modalities, together with patients' prognosis under existing treatment regimens.

iii) Health-related quality of life (HRQoL)

HRQoL was measured using the EuroQol five-dimension instrument (EQ-5D), a widely applied, standardized, self-reported measure of health status suitable for diverse patient populations and diseases. The EQ-5D evaluates quality of life across five dimensions: mobility, usual activities, self-care, pain/discomfort, and

anxiety/depression, with each dimension represented by a single item.

For pediatric patients, the EQ-5D-Y-3L (youth version) was employed, in which each dimension is rated on three levels: no problems, moderate problems, or extreme problems.

For adult patients, the EQ-5D-5L was employed, with each dimension rated on five levels: no problems, some problems, moderate problems, severe problems, or extreme problems.

Respondents indicated the statement that best described the patient's health status. In addition, the EQ-5D includes the EQ Visual Analogue Scale (EQ-VAS), which captures the respondent's perception of the patient's overall health on the day of survey completion.

For adult respondents, HRQoL scores (EQ-5D-5L utility values) were calculated and compared with Chinese population norms. For pediatric patients, due to the complete absence of Chinese EQ-5D-Y normative data, Japanese adolescent EQ-5D-Y health utility norms were used as a reference. Japan and China share geographic and broad cultural proximities, making the Japanese value set a reasonable proxy for East Asian populations. However, this comparison was undertaken with caution, emphasizing overall descriptive trends rather than direct numerical equivalence.

iv) Social participation

For minors, participation was evaluated based on school attendance status (regular attendance, temporary suspension, or permanent discontinuation) and the number of school days missed. For adults, employment status was categorized as unemployed, part-time or flexible employment, full-time employment, agricultural work, or retired. Additional indicators included limitations in physical health affecting employability, restrictions in social participation due to health conditions, and the frequency of health-related absences in work.

v) Caregiving burdens

This domain examined the need for caregiving among patients of different age groups, the frequency of care required, the identity of the primary caregiver, and the caregiver's employment status. It further assessed the degree to which caregiving responsibilities disrupted employment, the reasons for such disruption, and the number of workdays missed due to caregiving duties.

2.3. Statistical analysis

Data were analyzed using R studio. In alignment with the descriptive nature of the study design, all statistical analyses were strictly descriptive. Continuous variables were presented as means, and categorical variables were summarized using frequencies and percentages. No inferential statistical tests (*e.g.*, hypothesis testing or *p*-value calculations) were performed, as the study aimed solely to describe the current landscape of disease burden rather than to test comparative or causal relationships between variables.

3. Results

3.1. Participant demographics

The majority of PID patients participating in this survey were male (82%), with females accounting for 18%. Pediatric patients constituted 77% of the respondents, while adult patients (≥ 18 years) comprised 23%. Approximately 47% were under 10 years of age, 35% were between 10–19 years, 11% were between 20–29 years, 6% were between 30–39 years, and only 1% were aged 40 years or above. Patients originated from 28 provinces, autonomous regions, and municipalities across China, with the largest proportions from Guangdong, Henan, and Shandong Provinces.

3.2. Clinical profile

In this study, patients' PID conditions were classified into the following major groups: antibody deficiencies (63%), combined immunodeficiencies (14%), combined immunodeficiencies with syndromic features (6%), defects of innate immunity (6%), autoinflammatory disorders (3%), diseases of immune dysregulation (2%), phagocytic defects (2%), bone marrow failure syndromes of monogenic origin (0.5%), phenocopies of PID (0.5%), and cases with uncertain diagnosis (3%). Patients or their caregivers self-reported the disease category according to the patients' diagnosis.

With regard to specific PID subtypes (Table 1), the most participants were diagnosed with X-linked agammaglobulinemia (XLA), representing approximately 49% of the total sample. Other relatively common subtypes included combined immunodeficiency (CID, 7%), severe combined immunodeficiency (SCID, 6%), and common variable immunodeficiency (CVID, 5%).

3.3. Diagnosis/healthcare experience

3.3.1. Symptoms at first medical consultation

Patients presented with a diverse range of initial symptoms (Figure 1A). The most frequently reported reasons for the first medical consultation were recurrent upper respiratory tract infections (48.5%), persistent fever (42.6%), and severe respiratory problems (31.1%). These leading reasons were similarly distributed across both pediatric and adult groups (Figure 1B).

3.3.2. Time to diagnosis and misdiagnosis

Table 1. Distribution of specific PID subtypes

Disease Types	Number of Patients Participated	Number of Participating Patients	Proportion
X-Linked Agammaglobulinemia/XLA	212		49%
Combined Immunodeficiency/CID	31		7%
Severe Combined Immunodeficiency/SCID	26		6%
Common Variable Immunodeficiency/CVID	23		5%
PIK3CD Mutation (GOF)/APDS	15		3%
Hiper-IgE Syndrome/HIES	14		3%
Mendelian Susceptibility To Mycobacterial Diseases/MSMD	9		2%
Chronic Granulomatous Disease	8		2%
Other	8		2%
Inflammasome-Associated Autoinflammatory Diseases	7		2%
Inherited thrombocytopenia With Immunodeficiency	7		2%
NFKB2 Deficiency	6		1%
Invasive Fungal Infections	6		1%
EBV-Susceptible lymphoproliferative Disease	4		1%
Other Combined Immunodeficiency Syndromes	4		1%
PIK3R1 Deficiency	3		1%
Familial Hemophagocytic Lymphohistiocytosis	3		1%
Severe Viral Susceptibility Disorders	3		1%

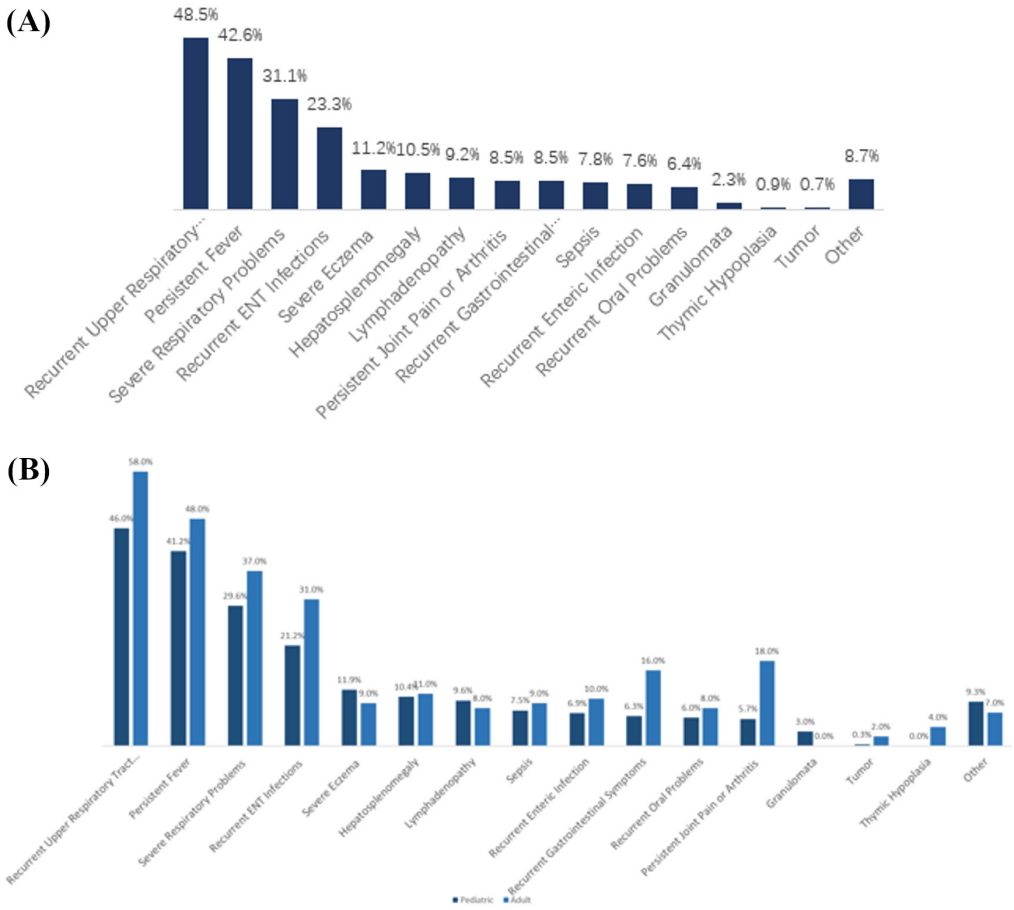

Figure 1. (A) Distributions of initial symptoms and (B) Symptoms grouped by age.

The mean interval from symptom onset to confirmed diagnosis was three years. Overall, 45.2% of patients required more than one year, and 11.6% experienced diagnostic delays exceeding five years (Figure 2A). Descriptive comparisons indicated that pediatric patients were diagnosed within one year more frequently than adults (58.0% *vs*. 41.9%) (Figure 2B). A high proportion of patients (78.6%) reported experiencing misdiagnosis or missed diagnosis (Figure 2C), with 66.0% reporting that physicians provided only symptomatic treatment without establishing a clear diagnosis. These patterns were largely consistent across age groups (Figure 2D).

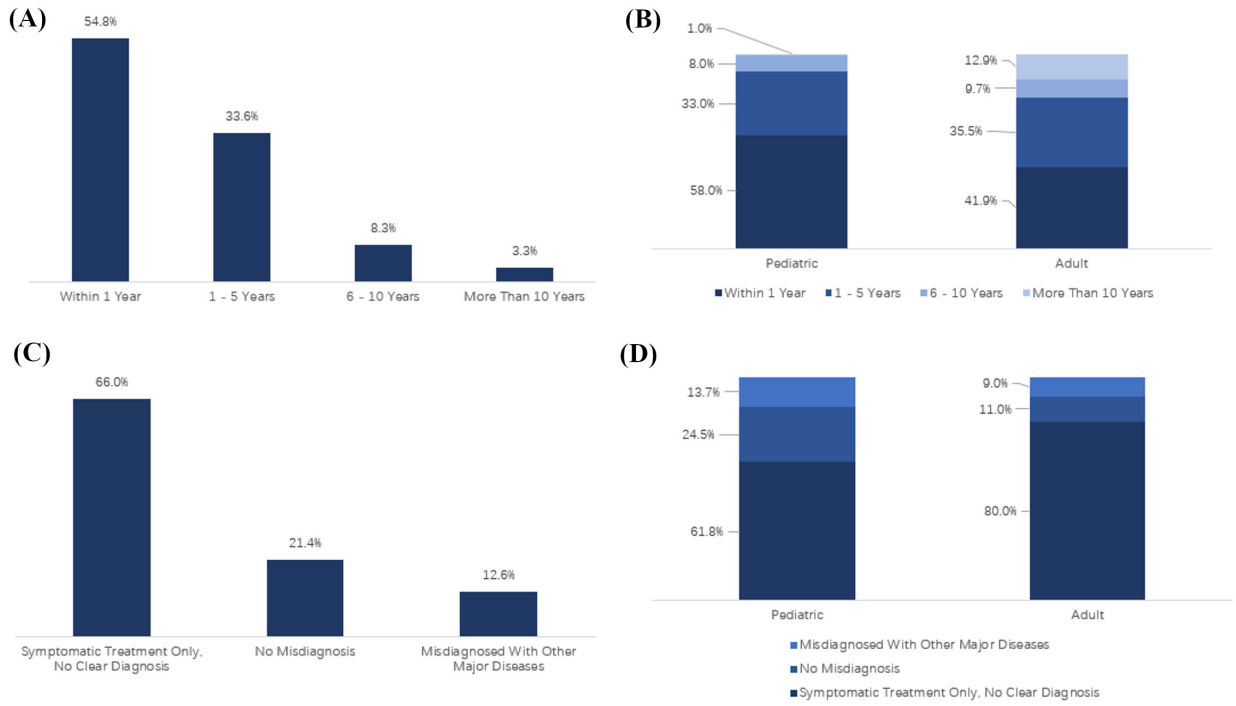

Figure 2. (A) Overall distribution of time-to-diagnosis; (B) Time-to-diagnosis grouped by age; (C) overall misdiagnosis of patients; and (D) Misdiagnosis grouped by age.

3.3.3. Geographic distribution of diagnosis

The survey showed a high proportion of patients required travelling for their diagnosis, with 64.8% unable to obtain a confirmed diagnosis locally. Around 46.0% of the participants were diagnosed outside their home province. The leading locations for confirmed diagnosis were Shanghai (21.6%), Beijing (15.6%), Guangdong (12.0%), and Chongqing (11.3%).

3.3.4. Departments of diagnosis

Due to the heterogeneity of initial symptoms, patients received their diagnoses across various clinical specialties. Overall, 56.1% of patients were diagnosed in immunology departments, whereas 12.4% were diagnosed in respiratory department, 11.5% in pediatrics, 7.6% in hematology departments, 2.8% in infectious diseases departments and 2.8% in critical care departments.

3.3.5. Treatment modalities and prognosis

Most patients received immunoglobulin replacement therapy (82%) and other pharmacological therapies (83%) as their primary treatment, while 17% underwent hematopoietic stem cell transplantation. Despite ongoing treatment, only 7% of survey participants reported being relatively healthy with no complications (Figure 3). Approximately 56% experienced persistent symptoms such as recurrent colds or chronic rhinitis, and 48% experienced bronchitis or pneumonia.

3.4. HRQoL

3.4.1. Pediatric patients

Among pediatric patients, the most frequently reported problems on the EQ-5D-Y-3L were pain/discomfort and depression/anxiety (Figure 4A). The mean EQ-VAS score was 66.5. According to the Chinese EQ-5D-Y-3L value set, the mean health utility value was 0.87 (*6*). Based on a comprehensive literature search of PubMed, CNKI, and Wanfang databases (up to September 2024) using the terms "EQ-5D-Y" and "China" or "Chinese adolescents", no published studies were identified that summarize EQ-5D-Y population norms for healthy Chinese adolescents. Therefore, Japanese adolescent health utility norms (ranging from 0.911 to 0.942) were utilized as a descriptive proxy (*7*).

3.4.2. Adult patients

Among adult patients, the most frequently reported problems on the EQ-5D-5L were anxiety/depression and pain/discomfort (Figure 4B). The mean VAS score was 65.9, appearing lower than the Chinese population norm of 87.1 (*6*). Based on the Chinese EQ-5D-5L value set (*8*), the mean health utility value of adult PID patients was 0.84, appearing lower than the reported Chinese population norm of approximately 0.95 (*9*).

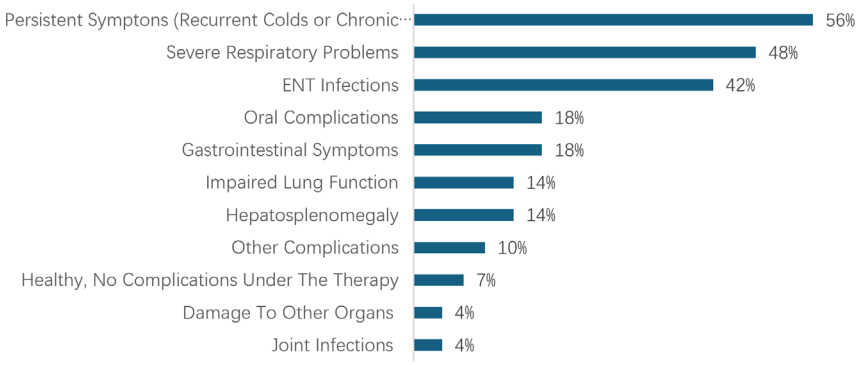

Figure 3. Patient prognosis under current treatment, symptoms and complications.

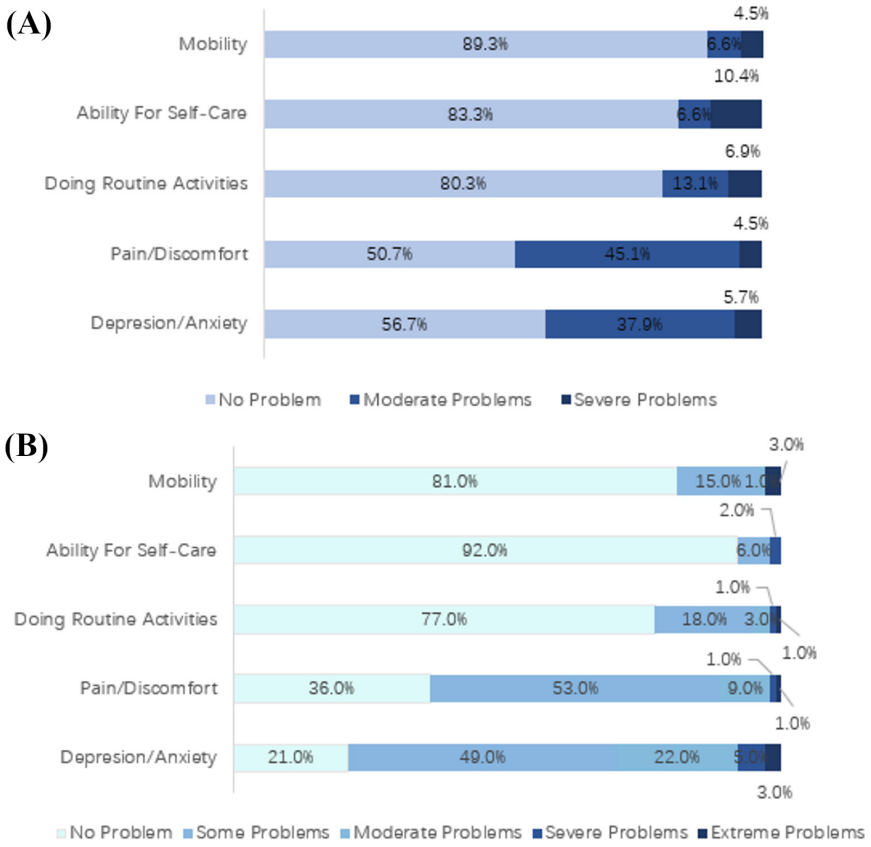

Figure 4. (A) HRQoL of pediatric patients and (B) HRQoL of adult patients. *Abbreviation*: HRQoL, health-related quality of life.

3.5. Impact of PID on education in pediatric patients

Among pediatric patients, 74.9% were able to continue their education without major disruption, while 25.1% experienced varying degrees of impact. Specifically, 11.9% discontinued their education, 11.6% were temporarily suspended, and 1.5% transferred to special schools.

Beyond attendance status, the disease exerted substantial impacts through frequent school absences and discrimination (Figure 5A), with 37.3% of pediatric participants missing 6 or more days of school per month (Figure 5B).

Among adult patients, 38% were enrolled as students, while 27% were unemployed or between jobs. Only 35% were engaged in full-time (26%) or part-time employment (9%).

Employed adults reported substantial work-related challenges, including frequent sick leave (47.1%), reduced job competitiveness (41.4%), and restricted occupational choices (38.6%) (Figure 6A). Among employed adults, 100% reported missing at least 1–5 days of work per month due to PID (Figure 6B).

3.6. Caregiving burdens

Caregiving support was required for 53.4% of pediatric patients and 21.0% of adult patients. Parents served as

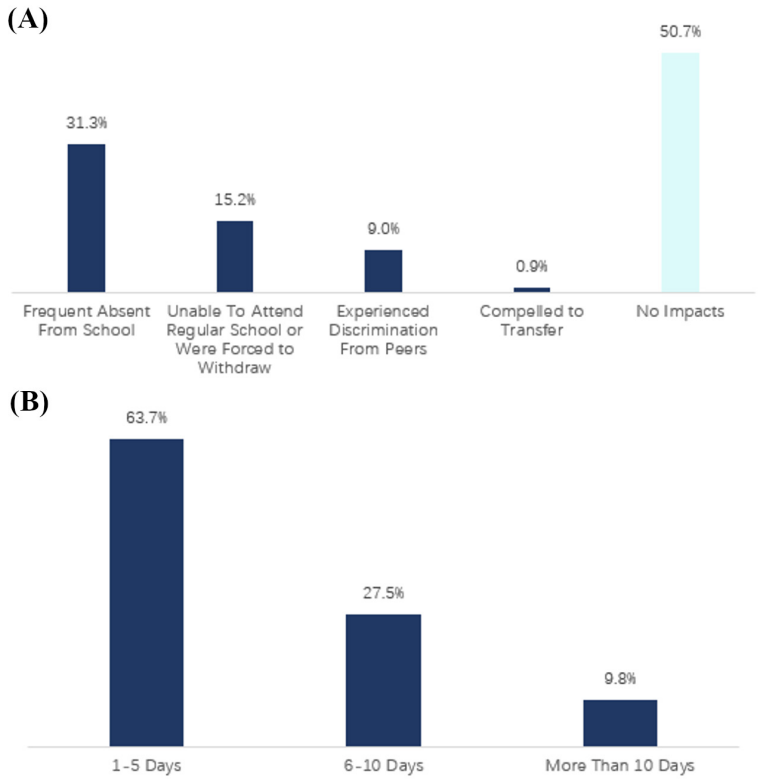

Figure 5. (A) Impact of PID on education of pediatric patients and (B) Absence per month of pediatric patients due to PID. *Abbreviation*: PID, primary immunodeficiency.

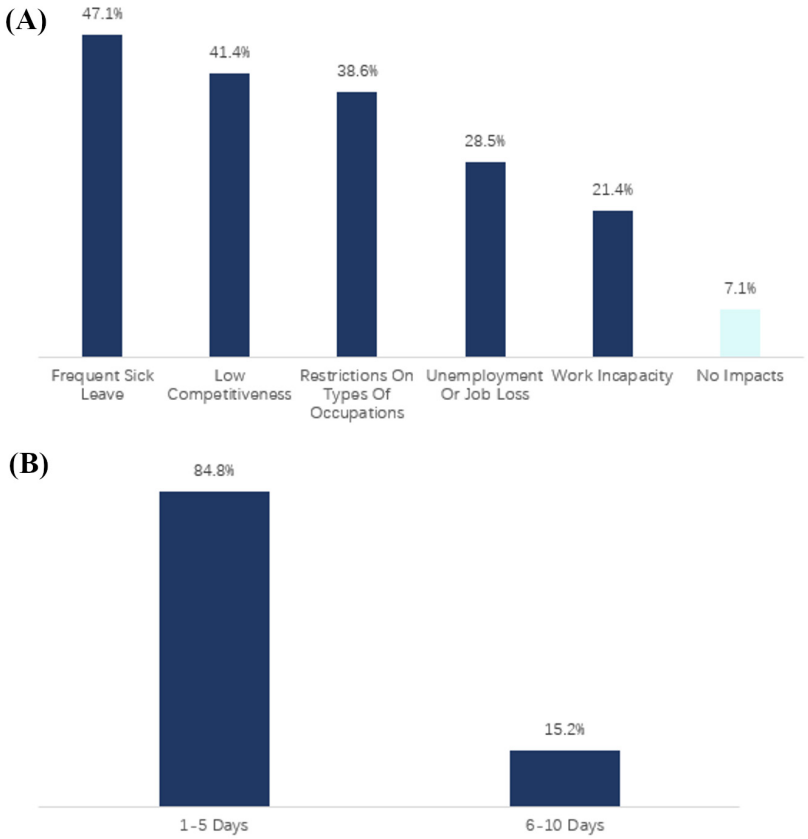

Figure 6. (A) Impact of PID on employment of adult patients and (B) Days of absence of adult patients per month due to PID. *Abbreviation*: PID, primary immunodeficiency.

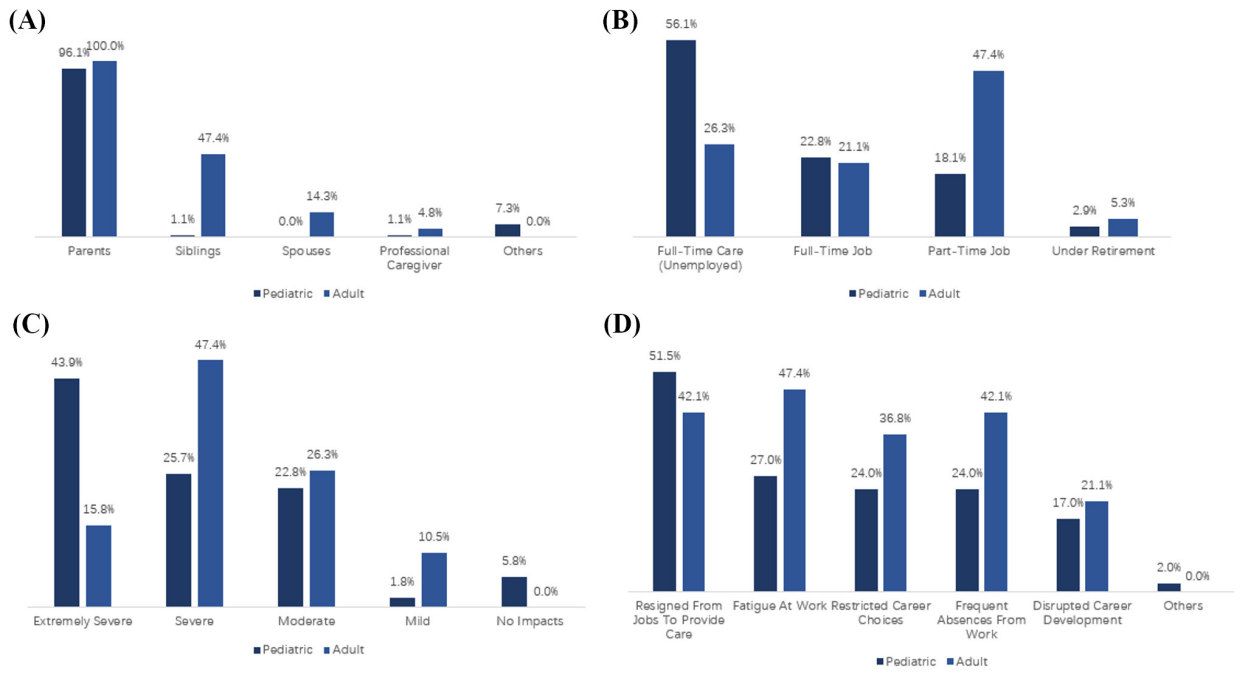

Figure 7. (A) Caregiver identity of different age groups; (B) Employment status of caregivers of different age groups; (C) The severity of impact of PID on employment of caregivers grouped by age; and (D) The impact of PID on employment of caregivers grouped by age.

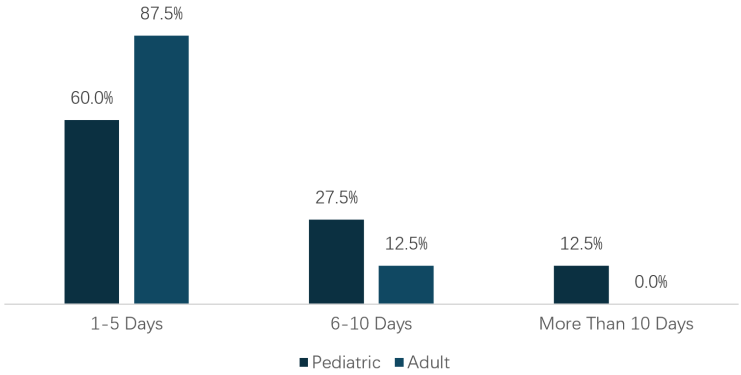

Figure 8. Days of absence of caregivers grouped by age.

the primary caregivers for nearly all pediatric (96.1%) and adult (100%) patients requiring care (Figure 7A).

Among those needing care, 36.9% of pediatric patients and 4.8% of adult patients needed full-time caregiving; 42.5% of pediatric patients and 28.5% of adult patients needed care for most of the day and 20.5% of pediatric patients and 66.7% of adult patients occasionally needed care.

Caregiving burden has shown to impact the employment status of primary caregivers, where 56.1% of pediatric patient caregivers and 26.3% adult patient caregivers were unemployed and providing full-time care (Figure 7B). Specifically, 51.5% of pediatric patient caregivers and 42.1% of adult patient caregivers had resigned from their jobs entirely to provide care (Figure 7D). Only 5.8% of pediatric patient caregivers reported no impact on their employment due to caregiving needs (Figure 7C).

High rates of absenteeism were also reported among employed caregivers, particularly those caring for pediatric patients (Figure 8).

4. Discussion

Based on a comprehensive literature search of PubMed, CNKI, and Wanfang databases (up to September 2024) using terms such as "primary immunodeficiency," "disease burden", and "China", the current study provides one of the first comprehensive descriptive quantitative assessments of the disease burden and unmet needs of patients with PID in China. The findings highlight profound challenges across diagnosis, treatment, quality of life, education, employment, and caregiving, underscoring the urgent need for integrated medical and

social support systems.

A major finding is the delay in diagnosis. On average, patients required three years from symptom onset to confirmed diagnosis, with nearly half (45.2%) waiting more than one year and 11.6% experiencing delays of over five years. Furthermore, 78.6% of patients reported misdiagnosis or missed diagnosis, with many initially receiving only symptomatic treatment. These data reveal critical gaps in early detection and clinical awareness. Expanding physician training in immunology, improving access to specialized diagnostic tests, and promoting the establishment of regional referral networks are crucial steps to reduce diagnostic delays and improve patient outcomes.

HRQoL results further underscores the heavy disease burden. Both pediatric and adult patients reported considerable emotional and physical distress. Average EQ-VAS scores for both pediatric (66.5) and adult patients (65.9) appeared numerically lower than population norms. Similarly, utility values (0.87 in children; 0.84 in adults) were lower than those of the general Chinese population and appeared lower than reported values for certain other chronic diseases in previous literature. These results indicate that the heavy burden of the disease and the restrictions it imposes, underscoring the need for interventions that address not only the physical health of patients with PID but also their psychological well-being and social integration. Establishing patient support networks, providing targeted mental health resources, and advancing policies that improve the socio-economic conditions of patients and their families should be regarded as integral components of a comprehensive care strategy.

The societal impact of PID is equally pronounced. Among pediatric patients, one in four reported disruptions of education, including school suspension, dropout, or transfer to special schools. Even those who remained in mainstream education frequently missed classes. Among adults, frequent sick leave, reduced job competitiveness, and occupational limitations were widespread. These findings reflect the significant constraints PID imposes on educational attainment and employment stability, ultimately restricting social participation and future opportunities. Policies that facilitate school and workplace support (*e.g.*, flexible attendance, remote working), could substantially improve the social integration of PID patients.

The burden extends beyond patients to their families. For caregivers, particularly of pediatric patients, the impact of caregiving burden on their career was severe. Frequent absences, reduced career development, and loss of income were widespread. These findings indicate the need for targeted caregiver support programs, including financial assistance, respite care services, and flexible workplace policies that accommodate caregiving responsibilities.

The current study has several important limitations. First, as a cross-sectional survey, the study is fundamentally descriptive and cannot establish causal relationships between PID and the reported socio-economic or quality-of-life outcomes. Second, the study lacks a healthy control or comparator group, limiting the ability to make definitive inferential comparisons. Third, participant recruitment was facilitated through a patient organization (PID Care China), resulting in a convenience sample. This approach introduces selection bias, as it may preferentially include patients and families with higher disease awareness, stronger social support, or greater engagement with advocacy groups, thereby limiting the nationwide generalizability of the findings. Fourth, all data, including PID diagnosis and specific subtype classifications, were collected *via* self-reported questionnaires. Without verification through medical records, this raises concerns about potential misclassification (particularly at the subtype level), recall bias, and reporting inaccuracies, which may not be able to fully capture the nuanced experiences of PID patients and their families. Finally, the lack of Chinese normative data for EQ-5D-Y required reliance on Japanese reference values, which may limit direct comparability due to cross-country methodological and cultural differences. Future research should integrate qualitative methods, such as patient and caregiver interviews, to better capture lived experiences, and utilize clinical registry data to verify medical parameters.

In conclusion, this study highlights the multifaceted disease burden of PID in China, spanning medical, psychological, educational, occupational, and caregiving dimensions. Addressing these challenges requires a holistic approach that goes beyond clinical management to include social support systems and policy-driven initiatives. Efforts to shorten diagnostic delays, expand access to advanced therapies, strengthen mental health and educational support, and protect caregiver employment rights are urgently needed. Such measures will not only improve clinical outcomes but also promote the long-term well-being and social inclusion of PID patients and their families.

Acknowledgements

We would like to express our sincere gratitude to the clinical experts who participated in the current study and generously shared their extensive professional knowledge and practical experience regarding the current status of diagnosis and treatment in the field of PID. Our heartfelt thanks go to Dr. An Yunfei, Dr. Duan Xiaojun, Professor Li Changqing, Professor Pamela Lee, Professor Mao Huawei, Professor Yang Linhua, and Professor Yang Yue for their invaluable contributions to this study. Experts are listed in alphabetical order by family name. We would also like to extend our special thanks to Ms. Jessie Qu, Chairperson of PID Care China, who served as the Scientific and Patient Advocacy Consultant for

this study and provided critical insights from the patient community perspective.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 12, 2025; Revised March 31, 2026; Accepted April 19, 2026.

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Released online in J-STAGE as advance publication April 23, 2026.