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ORIGINAL ARTICLE

Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis

Hassan Abolhassani[1,2,3] · Fatemeh Kiaee[1,3] · Marzieh Tavakol[4] · Zahra Chavoshzadeh[5] · Seyed Alireza Mahdaviani[6] · Tooba Momen[7] · Reza Yazdani[1,3] · Gholamreza Azizi[8] · Sima Habibi[1,3] · Mohammad Gharagozlou[9] · Masoud Movahedi[9] · Amir Ali Hamidieh[10] · Nasrin Behniafard[11] · Mohammamd Nabavi[12] · Mohammad Hassan Bemanian[12] · Saba Arshi[12] · Rasol Molatefi[13] · Roya Sherkat[14] · Afshin Shirkani[15] · Reza Amin[16] · Soheila Aleyasin[16] · Reza Faridhosseini[17] · Farahzad Jabbari-Azad[17] · Iraj Mohammadzadeh[18] · Javad Ghaffari[19] · Alireza Shafiei[20] · Arash Kalantari[21] · Mahboubeh Mansouri[22] · Mehrnaz Mesdaghi[22] · Delara Babaie[5] · Hamid Ahanchian[17] · Maryam Khoshkhui[17] · Habib Soheili[23] · Mohammad Hossein Eslamian[24] · Taher Cheraghi[25] · Abbas Dabbaghzadeh[18,43] · Mahmoud Tavassoli[26] · Rasoul Nasiri Kalmarzi[27] · Seyed Hamidreza Mortazavi[28] · Sara Kashef[16] · Hossein Esmaeilzadeh[16] · Javad Tafaroji[29] · Abbas Khalili[30] · Fariborz Zandieh[20] · Mahnaz Sadeghi-Shabestari[31] · Sepideh Darougar[6] · Fatemeh Behmanesh[16] · Hedayat Akbari[16] · Mohammadreza Zandkarimi[17] · Farhad Abolnezhadian[32] · Abbas Fayezi[32] · Mojgan Moghtaderi[17] · Akefeh Ahmadiafshar[33] · Behzad Shakerian[26] · Vahid Sajedi[34] · Behrang Taghvaei[35] · Mojgan Safari[24] · Marzieh Heidarzadeh[36] · Babak Ghalebaghi[25] · Seyed Mohammad Fathi[37] · Behzad Darabi[38] · Saeed Bazregari[15] · Nasrin Bazargan[39] · Morteza Fallahpour[12] · Alireza Khayatzadeh[1] · Naser Javahertrash[12] · Bahram Bashardoust[6] · Mohammadali Zamani[40] · Azam Mohsenzadeh[41] · Sarehsadat Ebrahimi[9] · Samin Sharafian[9] · Ahmad Vosughimotlagh[9] · Mitra Tafakoridelbari[9] · Maziar Rahimi[9] · Parisa Ashournia[9] · Anahita Razaghian[9] · Arezou Rezaei[1,3] · Setareh Mamishi[42] · Nima Parvaneh[1,3] · Nima Rezaei[1,3] · Lennart Hammarström[2] · Asghar Aghamohammadi[1,3]

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Abstract

Background The number of inherited diseases and the spectrum of clinical manifestations of primary immunodeficiency disorders (PIDs) are ever-expanding. Molecular diagnosis using genomic approaches should be performed for all PID patients since it provides a resource to improve the management and to estimate the prognosis of patients with these rare immune disorders.

Method The current update of Iranian PID registry (IPIDR) contains the clinical phenotype of newly registered patients during last 5 years (2013–2018) and the result of molecular diagnosis in patients enrolled for targeted and next-generation sequencing.

Results Considering the newly diagnosed patients ($n = 1395$), the total number of registered PID patients reached 3056 (1852 male and 1204 female) from 31 medical centers. The predominantly antibody deficiency was the most common subcategory of PID (29.5%). The putative causative genetic defect was identified in 1014 patients (33.1%) and an autosomal recessive pattern was found in 79.3% of these patients. Among the genetically different categories of PID patients, the diagnostic rate was highest in defects in immune dysregulation and lowest in predominantly antibody deficiencies and mutations in the *MEFV* gene were the most frequent genetic disorder in our cohort.

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✉ Asghar Aghamohammadi
aghamohammadi@tums.ac.ir

Extended author information available on the last page of the article

Conclusions During a 20-year registration of Iranian PID patients, significant changes have been observed by increasing the awareness of the medical community, national PID network establishment, improving therapeutic facilities, and recently by inclusion of the molecular diagnosis. The current collective study of PID phenotypes and genotypes provides a major source for ethnic surveillance, newborn screening, and genetic consultation for prenatal and preimplantation genetic diagnosis.

Keywords Epidemiology · Iran · primary immunodeficiency · molecular diagnosis

Introduction

Primary immunodeficiency disorders (PIDs) comprise approximately 400 inherited disorders affecting the development or the function of immune system components [1]. The overall prevalence of PID has been estimated to be more than 1/600 individuals in Western countries [2–4]. However, this prediction is likely to be an underestimation in countries with a high rate of consanguineous marriages, since more than 70% of known PID-associated genes have an autosomal recessive pattern of inheritance [1]. PID patients may present with a broad spectrum of clinical manifestations and immunological complications mainly during childhood [5, 6]. Mutations in different PID genes may result in similar presentations; however, they may need also different management and therapeutic measures. Wide variations in the geographical and ethnical prevalence of PID have been reported by means of patients' registry providing invaluable information for resource allocation and health policy making [3, 4].

Since the establishment of the Iranian Primary Immunodeficiency Registry (IPIDR) in 1999, the diagnosis of the patients was mainly based on clinical parameters, affecting the process of definite diagnosis for targeted therapy and genetic counseling. Before 2014, we had reported 1661 patients in three consequential reports [7–9], but none of them included comprehensive information about the patient's genetic background. During the past 5 years, a growing number of clinical immunologists and recent advances in molecular diagnostic methods have led to an increase in the identification of genetic defects and main disease-causing gene mutations in the cohort, improving individualized therapeutic methods and the performance of prenatal diagnosis [10]. This has also resulted in an earlier diagnosis, a more precise definition of defects, reduced morbidity and mortality rates, and better long-term outcomes [10, 11].

Of note, many of the novel PID gene defects, mainly in autosomal recessive form, have been reported from the Middle East region. Therefore, continuous update on these registries has had a significant impact on our understanding of the pathogenesis of PID and also the function of the immune system [12, 13]. Here, we provide a recent update on newly diagnosed Iranian patients with PIDs and integration of molecular diagnostic outcomes based on the latest classification of PIDs by the International Union of Immunological Societies (IUIS) Expert Committee [1].

Materials and Methods

Iranian Primary Immunodeficiency Registry

This study was conducted as a cohort of patients, prospectively enrolled in the IPIDR from the "National PID Network." The IPIDR is managed by the Research Centre for Immunodeficiencies (Tehran, Iran) and its main aim is to provide epidemiological, clinical, and molecular data of PID in Iran. By March 2013, 1661 PID patients from different provinces of the country were registered in the IPIDR [7]. By the latest estimation in 2016, Iran has a population of 79,926,270 citizens (with an average annual birth rate of 1,300,000) and according to the age structure, 23.7% are less than 14 years old. This study received approval from the Ethics Committee of the Tehran University of Medical Science. Moreover, written informed consent has been obtained from all patients, their parents, or legal guardians.

Role of Participant Centers

The registry database is located in the Children's Medical Center (Tehran, Iran) which serves as a referral hospital for suspected or diagnosed cases of PID. In addition, 31 medical centers, affiliated to 26 medical science universities, collaborated in the registry program from the major provinces of the country to form the PID network (Fig. 1). All of the participating centers had access to national guidelines and necessary laboratory equipment for clinical and immunological evaluations. Subsequently, cases with suspected diagnosis were referred and re-evaluated in the Children's Medical Center for a definitive diagnosis.

Clinical and Immunologic Diagnoses

The clinical diagnosis of the PID patients was made according to the criteria of the European Society for Immunodeficiencies (ESID, https://esid.org/Working-Parties/Registry/Diagnosis-criteria). A questionnaire surveyed the patients' demographic information, age of disease onset, age of diagnosis, family history, detailed clinical history that included vaccination history and associated adverse reactions, recurrent infections, physical examination findings, laboratory data, and treatment history. Secondary defects of the immune system, including

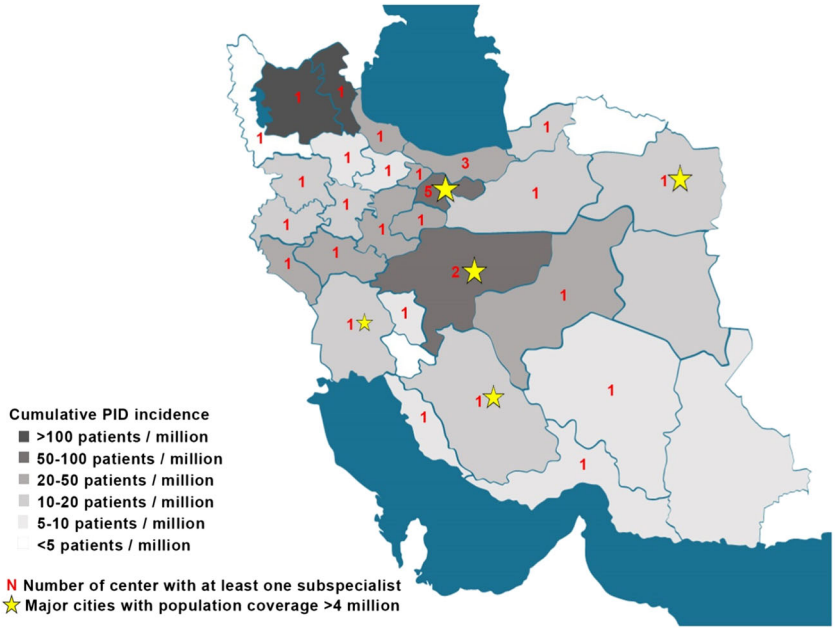

Fig. 1 Schematic map of Iran indicating the distribution of PID network centers and cumulative incidence of PID (per million) in each province

those caused by human immunodeficiency virus (HIV), were ruled out. Laboratory evaluations were performed in the study group as indicated, including complete blood and differential counts, serum protein profile and immunoglobulin (Ig) levels, serum IgG subclass levels, isohemagglutinin titers, specific antibody responses, disease-specific autoantibody measurements, flow cytometric evaluation of lymphocyte subsets, nitro blue tetrazolium dye/dihydrorhodamine test, granulocyte function and chemotaxis tests, lymphocyte transformation and T cell function tests, radiosensitivity, and measurement of complement component levels and hemolytic complement activity [14]. Microbiological, pathological, and imaging evaluations were performed for clinical diagnosis when required. A computerized database program (new registry section in http://rcid.tums.ac.ir/) was implemented for data entry. After reviewing the cases by the administrator of the system for duplicated cases, patients with incomplete diagnostic criteria were excluded. The online database was updated frequently for approved patients and all follow-up data sent by the end of the study period were included.

Genetic Analysis and Diagnoses

Genomic DNA was extracted from whole blood, as previously described [15]. For patients with classical clinical presentations suggestive of a specific PID, Sanger sequencing was performed on the panel of most likely genes (Table S1). Patients with thymic defects were examined by using fluorescent in situ hybridization (FISH) for *22q11.2* deletion and a comparative genomic hybridization array. For patients in whom Sanger sequencing failed or who had a clinical presentation resembling several genetic defects, next-generation sequencing (e.g., targeted gene sequencing [Table S2] and whole exome sequencing) was performed to detect single-nucleotide variants, insertions/deletions, and large deletions using a pipeline described previously [10, 11, 16]. Candidate variants were evaluated by the Combined Annotation-Dependent Depletion (CADD) algorithm and an individual gene cutoff given by using the mutation significance cutoff (MSC) was considered for impact predictions [17]. The Gene Damage Index (GDI) server and the Human Gene Connectome (HGC) were used to make a combined effects prediction [17]. The pathogenicity of all disease attributable gene variants was re-evaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics criteria [18, 19], considering the allele frequency in the population database, computational data, immunological data, familial segregation and parental data (confirmatory Sanger sequencing for probands and their parents), and clinical phenotyping.

Statistical Analyses

After confirmation of their clinical and genetic diagnosis, patients were classified according to the IUIS updated classification including nine categories of immunodeficiencies affecting cellular and humoral immunity (non-syndromic combined immunodeficiency or CID), combined immunodeficiencies with associated or syndromic features (syndromic CID), predominantly antibody deficiencies (PAD), diseases of immune dysregulation, congenital defects of phagocyte number or function (phagocytosis disorders), autoinflammatory

disorders, defects in intrinsic and innate immunity, complement deficiencies, and phenocopies of inborn errors of immunity [1]. A commercially available software package (SPSS Statistics 17.0.0; SPSS, Chicago, IL) was used for statistical analysis and the one-sample Kolmogorov-Smirnov test was applied to estimate whether data distribution was normal. Parametric and nonparametric analyses were performed based on the findings of this evaluation. Linear regression analysis was performed to evaluate the chronological effect of time on the different parameters. Kaplan-Meier curves and log-rank tests were used to compare different survival estimates. A p value of 0.05 or less was considered statistically significant.

Results

Newly Diagnosed Patients and Total Registry Characteristics

A total number of 1395 PID patients (824 male and 571 female) were enrolled in the study in the time period between March 2013 and March 2018. Due to an increased awareness by physicians and improved diagnostic facilities [11], an estimated incidence in this 5-year period was 0.21 cases per 1000 births. Among the newly diagnosed patients, autoinflammatory disorders were the most common group of PID, affecting 438 cases (31.4%), followed by PAD in 310 patients (22.2%), syndromic CID in 256 cases (18.6%), defects in innate immunity in 122 cases (8.7%), phagocytosis disorders in 117 cases (8.4%), non-syndromic CID in 83 cases (5.9%), diseases of immune dysregulation in 36 cases (2.6%), and complement deficiencies in 33 cases (2.3%). The median diagnostic delay was 10 months, ranging from 0 to 9.5 years. Of the 1395 cases, a diagnosis was made in 934 patients (66.9%) within 1 year from the onset of disease and within 2 years from the onset of disease in 1050 cases (75.2%). Diagnostic delay was higher than 5 years in only 153 cases (10.9%). The longest diagnostic delay was observed among patients with complement deficiency (median, 10.3 years, Table S3). Direct association between the age of the patients at the onset of disease and diagnostic delay was observed similar to our previous reports ($r = 0.02$, $p = 0.001$). However, comparison of diagnostic delay in newly diagnosed patients and old registered patients showed only a marginal difference during last 5 years ($p = 0.08$).

Accounting the newly registered cases in IPIDR, epidemiologic indexes of a total number of 3056 PID patients (1852 male and 1204 female) were evaluated. The cumulative incidence of PID in Iran during the past 10 years was estimated to be around 81 cases per 1,000,000 inhabitants. Figure 2 shows the number of registered PID patients based on the IUIS-classified group. Out of these 3056 PID patients, the majority was diagnosed with PAD (903 cases, 29.5%, Table 1). Neither cases with somatic mutations nor autoantibodies-mediated phenocopies of inborn errors of immunity were diagnosed in our cohort. Figure 1 shows the cumulative rate of clinical diagnoses of PID in different regions of the country.

Demographic Data and Follow-up Outcome

The cohort that underwent registration was assigned to three main ethnicities according to the reference population for the Greater Middle East (GME, http://igm.ucsd.edu/gme/) including Central Asia (80.3%) and Turkish (17.1%) and Arabian (2.6%) Peninsulas. A family history of PID was found in 641 cases (20.9%). Family history of recurrent infections without a known diagnosis of PID was positive in 389 cases (12.7%). In 737 cases (24.1%), a positive family history of death at an early age was documented. A history of diagnosed cancer was reported in the family of 322 patients (10.5%), and 208 individuals (6.8%) revealed a positive family history of autoimmune disorders. Consanguineous marriage was observed in the parents of 1837 cases (60.1%). There was a significant difference between the consanguinity rates of various types of PID, with the highest rate in patients with immune dysregulation (72 cases, 94.7%) and the lowest rate in patients with complement deficiencies (25 cases, 40.3%).

From 3056 patients, 1318 cases (43.0%) were confirmed to be dead (827 male and 491 female) and 528 patients (17.2%) could not be located during the last 6 months of the study period. Beside the specific disorders with a frequency of less than 10 cases, the mortality rate was highest in non-syndromic CID (157 severe CID cases and 57 less profound CID) with a mortality rate of 57.2% (214 out of 374 cases) and lost to follow-up rate of 9.3% (35 out of 374 cases). Cardiopulmonary failure due to severe pneumonia and sepsis was the main cause of death in 70.3% of the cases. Figure 3 compares the mortality rate in different PID categories presenting the lowest survival rate in patients with a CID (mainly due to severe CID) during the first 5 years of life (< 50% survival, significantly different compared to complement deficiencies [$p = 0.02$], immune dysregulations [$p = 0.03$], and autoinflammatory diseases [$p = 0.045$]).

Genetic Diagnosis and Diagnostic Yield

According to the estimated prevalence of PIDs (1/600), the expected prevalence of PIDs in Iran would be more than 130,000 individuals. To date, 3056 clinically diagnosed patients of PIDs (2.3% of expected patients) have been diagnosed, and a definite diagnosis, defined by mutation analysis, was made in 1014 individuals (among 1457 evaluated patients, 69.5% diagnostic yield). As a result, 33.1% of the total number of registered patients has been diagnosed at a molecular level. Table 1 shows the frequency of patients in each category of PID who are genetically diagnosed in Iran.

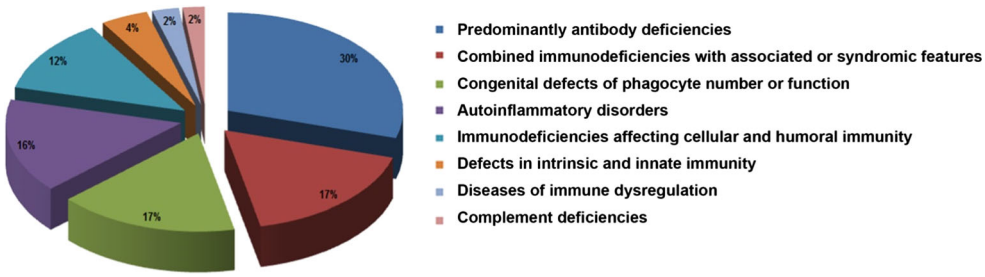

Fig. 2 Distribution of the frequencies of PIDs according to IUIS categories in 3065 Iranian patients in the study

Experimental data and the results of functional assays on 921 patients with genetic diagnosis have been published previously (Table 2). Of note, the cohort has had a great impact on novel PID gene discovery including finding mutations in the *HAX1*, *G6PC3*, *ELA2*, *JAGN1*, *CARD9*, *IFNGR2*, *DOCK8*, *STK4*, *LRBA*, and *CD70* genes. The majority of the patients ($n = 805$, 79.3%) had an autosomal recessive disorder (75.9% homozygous and 3.4% compound heterozygous). X-linked disorders comprised 12.8% of the genetic diagnoses ($n = 130$) and 7.8% of patients had an autosomal dominant disease ($n = 79$), where 76 mutations were de novo based on segregation analysis and Sanger sequencing of the parents (Fig. 4).

The probable prevalence of non-syndromic CID has been reported to be 1/50,000 using both clinically diagnosed patients and newborn screening methods [20, 21]. Considering the total population of Iran, the expected frequency of patients would be 1600 individuals. Until now, there have been 374 patients with a clinical diagnosis of non-syndromic CID and among them, 122 individuals have had a definite diagnosis with known mutations. As a result, 23.3% of the expected patients have been recognized and 32.4% of them have been molecularly diagnosed. Based on the estimated prevalence of syndromic CID (1/100,000) [20], 800 individuals would be expected to be diagnosed in this PID group. Until now, 529 patients have been clinically diagnosed with syndromic CID (66.1% of the expected frequency) and 117 patients (22.1%) were diagnosed using mutation analysis. The estimated prevalence of PAD is > 1/650 [20, 22], which results in an expected frequency of more than 123,000 individuals considering the total population of Iran. It should be noted that approximately 70% of the estimated individuals are expected to be asymptomatic and have no significant clinical complications as a cause of selective IgA deficiency or other specific antibody defects. Only 903 PAD patients, 0.7% of the total expected frequency, have been clinically diagnosed. Among them, 111 patients (12.2%) have had a definite diagnosis by molecular techniques.

Regarding diseases of immune dysregulation and their expected prevalence (< 1/1,000,000 [20]), 95% of these patients have been registered by clinical diagnosis (76 of 80 expected patients) and 68 patients (89.4%) were genetically diagnosed by identifying mutated genes. Since the country is located in the eastern Mediterranean region, the probable prevalence of autoinflammatory disorders is more than 1/10,000 [20], and the expected frequency of patients with these disorders would be approximately 8000 individuals. To date, only 476 (5.9%) defined patients, mostly with a clinical diagnosis of familial Mediterranean fever, have been reported and 418 individuals (87.8%) have been definitely diagnosed by molecular techniques. Complement deficiencies were expected with a prevalence of 1/50,000 [20]; however, only 62 patients (3.8% of the expected frequency) and 2 patients (3.2% of registered patients) were diagnosed clinically and genetically, respectively.

Table 1 Comparison of expected versus observed clinical diagnoses in different types of PID in Iran and the rate of molecular diagnosis in the registered patients

Category	Presumed prevalence	Number of expected cases	Clinically diagnosed (*N*; %)	Genetically diagnosed (*N*; %)
Immunodeficiencies affecting cellular and humoral immunity	1/50,000	1600	374 (23.3)	122 (32.4)
Combined immunodeficiencies with associated or syndromic features	1/100,000	800	529 (66.1)	117 (22.1)
Predominantly antibody deficiencies	> 1/650	> 123,000*	903 (0.7)	111 (12.2)
Diseases of immune dysregulation	< 1/1,000,000	80	76 (95.0)	68 (89.4)
Congenital defects of phagocyte number or function	1/250,000	320	507 (158.4)	117 (23.0)
Defects in intrinsic and innate immunity	<1/1,000,000	80	134 (167.5)	59 (44.0)
Autoinflammatory disorders	1/10,000	8000	476 (5.9)	418 (87.8)
Complement deficiencies	1/50,000	1600	62 (3.8)	2 (3.2)
Total	≥ 1/600	≥ 130,000	3056 (2.3)	1014 (33.1)

*It is estimated that 70% of patients with predominantly antibody deficiencies are asymptomatic

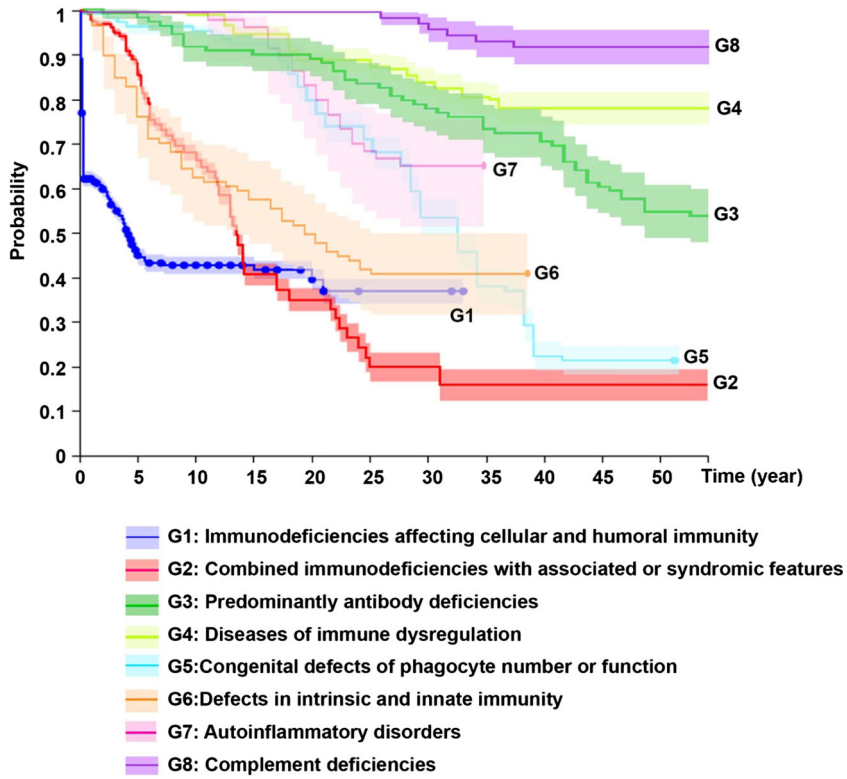

Fig. 3 Kaplan-Meier curve showing overall survival in the 3065 studied patients within the 8 categories of PIDs

Interestingly, the observed prevalence of phagocytosis disorders and defects in innate immunity was higher than their expected rate (1/250,000 and < 1/1,000,000, respectively [20]). There have been 507 clinically diagnosed patients with phagocytosis disorders (58% over than the estimated frequency) and 134 patients with defects in innate immunity (67% over than the estimated frequency). Among these patients, genetic mutations were identified in 117 (23.0%) from the former and 59 (44.0%) from the latter disease groups. Table 2 summarizes the number of cases with different mutations associated to PIDs reported in the cohort.

Discussion

Despite improved diagnostic techniques and molecular characterization of different types of PID, the majority of patients in worldwide registries are still without a definite genetic diagnosis. According to the findings of the updated analysis in our registry and the estimated prevalence rates for different forms of PID to date, only 2.3% of the expected (asymptomatic and symptomatic) patients have been diagnosed clinically, and a molecular diagnosis has only been identified in 33.1% of the registered cases. The rate of diagnosis at the molecular level is comparable with well-known registries around the world. Modell et al. at 2018 registered 102,097 patients from 86 countries spanning six continents, documented in the Jeffrey Modell Foundation Network registry. The most prevalent PID group was predominantly antibody deficiencies, accounting for almost half of the globally diagnosed patients. The most prevalent symptomatic PID entity was IgA deficiency, followed by common variable immunodeficiency (CVID) and DiGeorge anomaly [23]. Although this network was involved in several gene discoveries in the field of PID, less than 35% of the reported patient had a confirmed genetic defect [23].

The United States Immunodeficiency Network (USIDNET) provides advanced scientific research in the field of PID and epidemiologic indexes of patients registered in the largest national database with 6584 participants. They also reported PAD in 31.8% of household members with a specific diagnosis for PID followed by chronic granulomatous disease (8%) and thymic defect (DiGeorge anomaly, 7.8%). Genetic diagnosis also was ascertained in 36.5% of patients mainly with mutations in X-linked genes including *BTK*, *CYBB*, and *WAS* (https://usidnet.org [3]). The ESID registry also contains more than 20,000 patients where PAD represents the most common category (56.8%), where CVID is the main PID entity (21%). The PID genetic cause was known in approximately 36% of all registered patients and mutations in *BTK*, 22q11.2, and *ATM* were the most frequent recorded defects in this multinational registry (https://esid.org/Working-Parties/Registry/ESID-Database-Statistics [4]). Analysis of genetic diagnosis data from 4530 patients in the United Kingdom PID (UKPID) registry showed that 27% have a recorded genetic mutation affecting mainly *BTK*,

Table 2 Distribution of different genetic defects among patients with primary immunodeficiencies in Iran

Disease	Disease subcategory	Genetic defect	Patients (*n*)	Ref.
Immunodeficiencies affecting cellular and humoral immunity				
T−B− severe combined immunodeficiency	RAG1 deficiency	*RAG 1*	17	[11, 27, 28]†
	RAG2 deficiency	*RAG 2*	12	[11, 27, 29]†
	Adenosine deaminase (ADA) deficiency	*ADA*	6	[11, 28]†
	Artemis deficiency	*DCLRE1C*	5	[11]†
	Cernunnos/XLF deficiency	*NHEJ1*	2	[11, 30]†
	DNA ligase IV deficiency	*LIG4*	1	†
T−B+ severe combined immunodeficiency	IL7Rα deficiency	*IL7R*	4	[11, 27, 28]†
	CD3ε deficiency	*CD3E*	1	[11]
	CD3ζ deficiency	*CD3D*	1	[11]
	γc deficiency	*IL2RG*	5	[11, 28, 31]†
	JAK3 deficiency	*JAK3*	4	[11]†
	CD45 deficiency	*PTPRC*	1	[11]
Less profound combined immunodeficiencies	DOCK2 deficiency	*DOCK2*	1	[32]
	CD40 ligand (CD154) deficiency	*CD40LG*	23	[11, 33]†
	ICOS deficiency	*ICOS*	3	[11]†
	ZAP70 deficiency	*ZAP70*	3	[11]†
	MHC class II deficiency	*CIITA*	1	[11]
		RFX5	1	†
		RFXANK	7	[11, 34] †
	DOCK8 deficiency	*DOCK8*	17	[11, 35, 36]†
	MST1 deficiency	*STK4*	3	[11, 37]
	MALT1 deficiency	*MALT1*	3	[11]†
	IL-21 receptor deficiency	*IL21R*	1	†
Combined immunodeficiencies with associated or syndromic features				
Immunodeficiency with congenital thrombocytopenia	Wiskott-Aldrich syndrome (X-linked thrombocytopenia)	*WAS*	18	[11]†
DNA repair defects syndromes	Ataxia telangiectasia	*ATM*	38	[11, 38]†
	Immunodeficiency with centromeric instability and facial anomalies	*DNMT3B*	10	[11]†
		ZBTB24	5	[11]
Thymic defects with additional congenital anomalies	DiGeorge anomaly (chromosome 22q11.2 deletion syndrome)	*TBX1*	13	[11]
Immune-osseous dysplasia	Schimke syndrome	*SMARCAL1*	1	[11]

Table 2 (continued)

Disease	Disease subcategory	Genetic defect	Patients (*n*)	Ref.
Hyper IgE syndromes (HIES)	AD-HIES (Job syndrome)	*STAT3*	20	[11]†
	Phosphoglucomutase 3 deficiency	*PGM3*	3	[11]†
	Comel-Netherton syndrome	*SPINK5*	1	[11]
Dyskeratosis congenita (DKC)	XL-DKC due to dyskerin deficiency	*DKC1*	1	[11]
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	EDA-ID, X-linked (NEMO deficiency)	*IKBKG*	1	[11]
Other syndromic CID defects	Purine nucleoside phosphorylase (PNP) deficiency	*PNP*	3	[11, 39]†
	Vici syndrome	*EPG5*	1	[11]
	Immunodeficiency with multiple intestinal atresias	*TTC7A*	3	[11]
Predominantly antibody deficiencies				
Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells, agammaglobulinemia	BTK deficiency (X-linked agammaglobulinemia)	*BTK*	58	[40, 41]†
	μ heavy-chain deficiency	*IGHM*	6	[40, 41]†
	Igα deficiency	*CD79A*	1	[40, 42]
	λ5 deficiency	*IGLL1*	1	†
	E47 transcription factor deficiency	*TCF3*	3	†
	BLNK deficiency	*BLNK*	2	[10]
Severe reduction in at least 2 serum immunoglobulin isotypes with a normal or low number of B cells, CVID phenotype	TACI deficiency	*TNFRSF13B*	4	[10]
	BAFF receptor deficiency	*TNFRSF13C*	5	[10]†
	IKAROS deficiency	*IKZF1*	1	[10]
	NFKB1 deficiency	*NFKB1*	3	[10]
	NFKB2 deficiency	*NFKB2*	3	[10]†
	PIK3CD gain-of-function	*PI3KCD*	5	[10, 23]†
	PIK3R1 deficiency	*PI3KR1*	7	[10, 23]†
	CD19 deficiency	*CD19*	1	†
Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells, hyper IgM	Activation-induced cytidine deaminase deficiency	*AICDA*	8	[43, 44]†
Isotype, light chain, or functional deficiencies with generally normal numbers of B cells	CLEC16A deficiency	*CLEC16A*	1	[10]
	CARD11 gain-of-function	*CARD11*	1	†
	VAV1 deficiency	*VAV1*	2	[10]†
Diseases of immune dysregulation				
Familial hemophagocytic lymphohistiocytosis (FHL syndromes)	Munc13–4 deficiency (FHL3)	*UNC13D*	1	†
	Munc18-2 deficiency (FHL5)	*STXBP2*	1	[45]
FHL syndromes with hypopigmentation	Griscelli syndrome, type 2	*RAB27A*	15	[46–48]†
	Hermansky-Pudlak syndrome, type 2	*AP3B1*	1	[49]
Regulatory T cell defects	Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX)	*FOXP3*	4	†
	LRBA deficiency	*LRBA*	22	[50, 51]†

Table 2 (continued)

Disease	Disease subcategory	Genetic defect	Patients (*n*)	Ref.
Autoimmunity with or without lymphoproliferation	ITCH deficiency	*ITCH*	2	†
	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy/dysplasia (APECED)	*AIRE*	1	†
Immune dysregulation with colitis	IL-10 Rβ deficiency	*IL10RB*	1	†
Susceptibility to EBV and lymphoproliferative conditions	XIAP deficiency (XLP2)	*XIAP*	2	[10]†
	SH2D1A deficiency (XLP1)	*SH2D1A*	1	[52]
	CD27 deficiency	*CD27*	6	[11, 53]†
	CD70 deficiency	*CD70*	2	[54]
	ITK deficiency	*ITK*	2	[55]
	MAGT1 deficiency (XMEN)	*MAGT1*	1	†
	PRKCD deficiency	*PRKCD*	6	[10]†
Congenital defects of phagocyte number or function				
Congenital neutropenias	Elastase deficiency (SCN 1)	*ELANE*	6	[56, 57]†
	Kostmann disease (SCN 3)	*HAX1*	14	[56–58]†
	G6PC3 deficiency (SCN 4)	*G6PC3*	5	[56, 57, 59, 60]
	JAGN1 deficiency	*JAGN1*	2	[61]
Defects of motility	Leukocyte adhesion deficiency type 1 (LAD1)	*ITGB2*	32	[62–66]†
	Rac 2 deficiency	*RAC2*	3	[10, 67]
Defects of respiratory burst	X-linked chronic granulomatous disease (CGD), gp91phox	*CYBB*	16	[62, 68–70]
	Autosomal recessive CGD p22phox	*CYBA*	31	[62, 71–74]†
	Autosomal recessive CGD p47phox	*NCF1*	2	[62, 75]
	Autosomal recessive CGD p67phox	*NCF2*	6	[74, 76]
Defects in intrinsic and innate immunity				
Mendelian susceptibility to mycobacterial disease (MSMD)	IL-12 and IL-23 receptor β1 chain deficiency	*IL12RB1*	24	[77–79]†
	IL12p40 deficiency	*IL12B*	10	[80, 81]†
	IFN-γ receptor 2 deficiency	*IFNGR2*	1	[82]
	IFN-γ receptor 1 deficiency	*IFNGR1*	1	†
	ISG15 deficiency	*ISG15*	5	[83]†
	STAT1 deficiency	*STAT1*	2	[62, 84]
	Tyk2 deficiency	*TYK2*	6	[11, 85]†
Epidermodysplasia verruciformis (HPV)	WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome gain-of-function	*CXCR4*	2	[86, 87]
Predisposition to fungal diseases	CARD9 deficiency	*CARD9*	6	[88–90]

Table 2 (continued)

Disease	Disease subcategory	Genetic defect	Patients (*n*)	Ref.
Predisposition to mucocutaneous candidiasis	IL-17RA deficiency	*IL17RA*	1	†
Autoinflammatory disorders				
Defects effecting the inflammasome	Familial Mediterranean fever (autosomal recessive form)	*MEFV*	403	[62, 91, 92]†
	Mevalonate kinase deficiency (hyper IgD syndrome)	*MVK*	4	[93]†
	Familial cold autoinflammatory syndrome 2	*NLRP12*	1	†
	NLRP1 deficiency	*NLRP1*	1	†
	PLAID (PLCγ2-associated antibody deficiency and immune dysregulation)	*PLCG2*	4	†
Non-inflammasome-related conditions	Blau syndrome/NOD2 deficiency	*CARD15*	3	[94]
	Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	*PSTPIP1 (C2BP1)*	2	[95]†
Complement deficiencies				
Hereditary angioedema	C1 inhibitor deficiency	*SERPING1*	2	†

† Unpublished data from the Iranian Primary Immunodeficiency Disease Registry

RAG, recombinase-activating gene; *DCLRE1C*, DNA cross-link repair 1C; *NHEJ1*, non-homologous end joining factor 1; *XLF*, XRCC4-like factor; *JAK3*, Janus kinase 3; *PTRPC*, protein tyrosine phosphatase, receptor type C; *DOCK*, dedicator of cytokinesis; ICOS, inducible T cell COStimulator; *ZAP70*, zeta-chain-associated protein kinase 70; *MHC*, major histocompatibility complex; *CIITA*, class II MHC trans activator; *RX5*, regulatory factor X5; *RFXANK*, regulatory factor X-associated ankyrin-containing protein; *STK4*, serine/threonine kinase 4, *MST1*, macrophage stimulating 1; *DNMT3B*, DNA methyltransferase 3 beta; *ZBTB24*, zinc finger and BTB domain-containing 24; *TBX1*, T-box transcription factor; *SMARCAL1*, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A like; *STAT*, signal transducer and activator of transcription; *SPINK5*, serine peptidase inhibitor Kazal type 5; *NEMO*, nuclear factor kappa B essential modulator; *IKBKG*, inhibitor of nuclear factor kappa B kinase subunit gamma; *EPG5*, ectopic P-granules autophagy protein; *TTC7A*, tetratricopeptide repeat domain 7A; *BTK*, Bruton tyrosine kinase; *IGLL1*, immunoglobulin lambda-like polypeptide 1; *TCF3*, transcription factor 3; *BLNK*, B cell linker protein; *TACI*, transmembrane activator and CAML interactor; *TNFRSF*, tumor necrosis factor receptor superfamily; *BAFF*, B cell activating factor; *IKZF1*, IKAROS family zinc finger1; *NFKB*, nuclear factor kappa B kinase; *PIK3CD*, phosphoinositide-3-kinase catalytic subunit delta; *PIK3R1*, phosphoinositide-3-kinase regulatory subunit 1; *CLEC16A*, C-type lectin domain-containing 16A; *CARD11*, caspase recruitment domain-containing protein 11; *Munc*, mammalian homolog of *C. elegans* uncoordinated gene; *STXBP2*, syntaxin binding protein 2; *RAB27A*, Ras-related protein Rab-27A; *AP3B1*, AP-3 complex subunit beta-1; *FOXP3*, forkhead box P3; *LRBA*, lipopolysaccharide (LPS)-responsive and beige-like anchor protein; *AIRE*, autoimmune regulator; *XIAP*, X-linked inhibitor of apoptosis; *XLP*, X-linked lymphoproliferative syndrome; *SH2D1A*, SH2 domain-containing 1A; *ITK*, IL2 inducible T cell kinase; *MAGT1*, magnesium transporter 1; *PRKCD*, protein kinase C delta type; *HAX1*, HCLS1-associated protein X-1; *G6PC3*, glucose-6-phosphatase catalytic subunit 3; *JAGN1*, Jagunal Homolog 1; *ITGB2*, integrin subunit beta 2; *RAC2*, Rac family small GTPase 2; *CYB*, cytochrome B-245; NCF, neutrophil cytosolic factor; *TYK2*, tyrosine kinase 2; *CXCR4*, C-X-C motif chemokine receptor 4; *NLRP*, NLR family pyrin; *PLCG2*, phospholipase C gamma 2; *PSTPIP1*, proline-serine-threonine phosphatase interacting protein 1

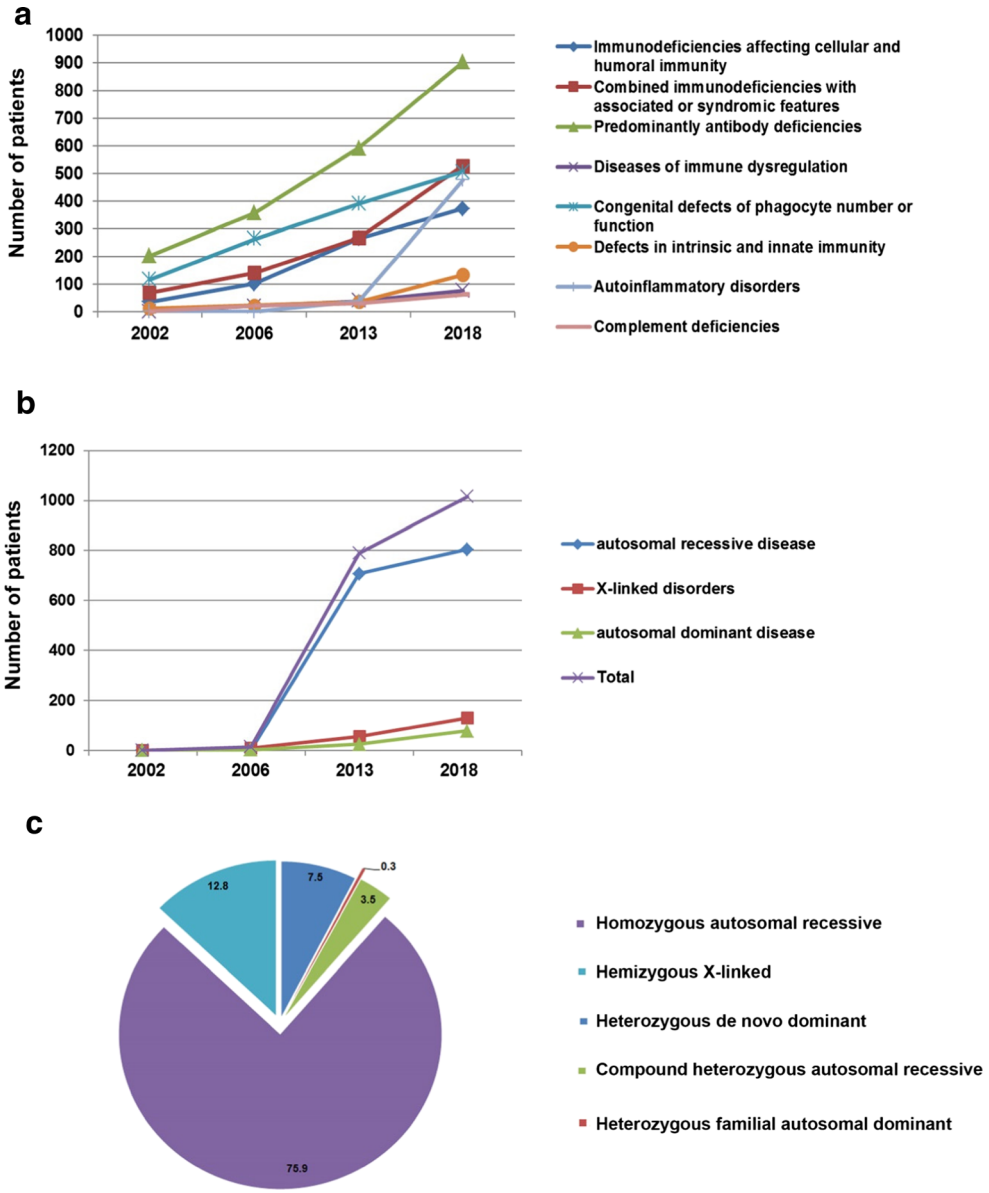

Fig. 4 Trend of the frequency of different PIDs (**a**) and the inheritance pattern in patients with definite molecular diagnosis (**b**–**c**) in the IPIDR registry during 2002–2018 [7–9]

22q11.2, and *CYBB* (http://www.piduk.org [24]). Based on the updated report of the Latin American Society for Immunodeficiencies (LASID), this registry contains 6646 PID patients from 15 countries with an increased frequency of antibody deficiency compared to other registries (62.9%). Even though defects in *BTK*, 22q11.2, and *CYBB* are estimated to be the main genetic diagnosis form in this continent registry, the genetic composition remains unknown (http://imunodeficiencia.unicamp.br:8080/estatistica mensal.html [25]). Although PAD was the main clinical diagnosis in our patients (29.5%) with a prominent increasing rate of diagnosis compared to other forms of PID (Fig. 4), its proportion is slightly lower than that in Western countries, a phenomenon which is observed in many countries within the Middle East region and Asia [26]. In contrast to all of the above-mentioned studies, the three main causes of PID in the current study were *MEFV*, *BTK*, and *ATM*, out of which two have an autosomal recessive mode of inheritance, probably owing to the high rate of parental consanguinity in the genetically diagnosed patients. Indeed, many defective genes with autosomal respective inheritance that underlie PIDs were firstly described in the patients originated from the Middle East area with high rate of parental consanguinity. The DiGeorge anomaly is reported as one of the most common genetic defects in PID patients in most Western countries; in contrast, only 13 patients were identified in our study (~8% versus 1.2% of genetically diagnosed patients, respectively) [23]. The difference in our study may partly have been due to the obligatory presence of immunologic profile alterations for consideration of patients as PID. Moreover, a lack of referring patients with prominent non-infectious features (e.g., congenital heart disease, hypocalcemia, facial abnormalities) for immunologic

evaluation may result in a lower rate of DiGeorge syndrome discovery. Furthermore, the role of genetic ethnicity should be considered as we observed among patients with X-linked PIDs a similar pattern of dominancy of *BTK* mutations (84.5% in our agammaglobulinemic patients compared to ~90% in Western cohorts), while a less frequent proportion of mutations in *IL2RG* (8.4% of our severe CID patients compared to ~60% in Western cohorts) and *CYBB* (29% of our chronic granulomatous disease patients compared to ~70% in Western cohorts) genes [3, 4].

The proportion of patients with a genetically definite diagnosis varied between 89.4% in patients with immune dysregulations and 3.2% in the cases with complement deficiencies. This wide spectrum might be due to the natural history of the disease, unknown underlying genetic defects, or complex disease pathogenesis including multigenetic or epigenetic/non-genetic etiologies. Of note, the patients with a lower genetic diagnostic yield also had the lowest percentage of clinically diagnosed cases signifying mild manifestations or non-infectious presentation. Our recent studies using enhanced techniques of detection of immunological abnormalities, mainly by targeted panel sequencing and whole exome sequencing, have led to earlier and more precise diagnosis of patients in both categories of antibody deficiency (improved from 7.8 to 12.2%) [10] and combined immunodeficiency (from 7.9 to 32%) [11]. A definite diagnosis of a PID allowed genetic screening and counseling in more than half of our patients' cohort with the molecular diagnosis. Moreover, carrier detection and preimplantation testing in conjunction with in vitro fertilization helped more than 20 families to plan for their next child.

For the first time, we now report the comparative survival analysis on the 20-year follow-up of different categories of PID. Not surprisingly, CID patients had the highest mortality rate compared to other registered patients [11]. Despite an improvement in our national practice for therapeutic and prophylactic antibiotics for infections and the most common treatment options for PID patients including Ig replacement therapy and immune modulators (e.g., interferon-gamma, granulocyte colony-stimulating factor, and monoclonal antibodies), hematopoietic stem cell transplantation (HSCT) which is the mainstay of curative treatment in CID patients is available only for a limited number of patients due to restrictions in expertise and financial resources. Of the patients requiring HSCT, less than 100 patients (~3%) are under or awaiting therapy. Although the resources for HSCT in Iran are limited and no national program for newborn screening is ongoing, genetic diagnoses are pivotal for confirming clinical diagnoses, identifying new genetic carriers of CID genes, and diagnosing of pre-symptomatic individuals.

In order to improve the coverage of genetic testing for PID patients, several parameters should be considered including clinical investigation of the probands, and cost of the test, the probability of incidental findings, and the effects on relatives of the index patient. Therefore, a stepwise clinical, immunological, and genetic approach must be designed and used for different entities of PID. Integration of medical and family histories, findings of the physical examination and laboratory data, and confirmatory evidence for pathogenicity of the candidate gene variants would be important for decision making by clinical immunologists and immunogenetics experts. The approximate number of diagnosed PID cases was reported to be 7 per year in the 1980s, 30 per year in the 1990s, 58 per year in 2000–2006, 104 per year in 2007–2013, and 279 per year afterwards until the March of 2018 (Fig. 4). Although the definite molecular diagnostic rate of PID in Iran is almost similar to that in the developed countries, introduction of newborn sequencing for PID, increasing the rate of clinical diagnoses, providing more laboratory facilities and diagnostic modalities, and specialized immunogenetic centers for PID, in addition to improvement of current national PID network, should still be considered.

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Compliance with Ethical Standards

This study received approval from the Ethics Committee of the Tehran University of Medical Science. Moreover, written informed consent has been obtained from all patients, their parents, or legal guardians.

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

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Affiliations

Hassan Abolhassani[1,2,3] · Fatemeh Kiaee[1,3] · Marzieh Tavakol[4] · Zahra Chavoshzadeh[5] · Seyed Alireza Mahdaviani[6] · Tooba Momen[7] · Reza Yazdani[1,3] · Gholamreza Azizi[8] · Sima Habibi[1,3] · Mohammad Gharagozlou[9] · Masoud Movahedi[9] · Amir Ali Hamidieh[10] · Nasrin Behniafard[11] · Mohammamd Nabavi[12] · Mohammad Hassan Bemanian[12] · Saba Arshi[12] · Rasol Molatefi[13] · Roya Sherkat[14] · Afshin Shirkani[15] · Reza Amin[16] · Soheila Aleyasin[16] · Reza Faridhosseini[17] · Farahzad Jabbari-Azad[17] · Iraj Mohammadzadeh[18] · Javad Ghaffari[19] · Alireza Shafiei[20] · Arash Kalantari[21] · Mahboubeh Mansouri[22] · Mehrnaz Mesdaghi[22] · Delara Babaie[5] · Hamid Ahanchian[17] · Maryam Khoshkhui[17] · Habib Soheili[23] · Mohammad Hossein Eslamian[24] · Taher Cheraghi[25] · Abbas Dabbaghzadeh[18,43] · Mahmoud Tavassoli[26] · Rasoul Nasiri Kalmarzi[27] · Seyed Hamidreza Mortazavi[28] · Sara Kashef[16] · Hossein Esmaeilzadeh[16] · Javad Tafaroji[29] · Abbas Khalili[30] · Fariborz Zandieh[20] · Mahnaz Sadeghi-Shabestari[31] · Sepideh Darougar[6] · Fatemeh Behmanesh[16] · Hedayat Akbari[16] · Mohammadreza Zandkarimi[17] · Farhad Abolnezhadian[32] · Abbas Fayezi[32] · Mojgan Moghtaderi[17] · Akefeh Ahmadiafshar[33] · Behzad Shakerian[26] · Vahid Sajedi[34] · Behrang Taghvaei[35] · Mojgan Safari[24] · Marzieh Heidarzadeh[36] · Babak Ghalebaghi[25] · Seyed Mohammad Fathi[37] · Behzad Darabi[38] · Saeed Bazregari[15] · Nasrin Bazargan[39] · Morteza Fallahpour[12] · Alireza Khayatzadeh[1] · Naser Javahertrash[12] · Bahram Bashardoust[6] · Mohammadali Zamani[40] · Azam Mohsenzadeh[41] · Sarehsadat Ebrahimi[9] · Samin Sharafian[9] · Ahmad Vosughimotlagh[9] · Mitra Tafakoridelbari[9] · Maziar Rahimi[9] · Parisa Ashournia[9] · Anahita Razaghian[9] · Arezou Rezaei[1,3] · Setareh Mamishi[42] · Nima Parvaneh[1,3] · Nima Rezaei[1,3] · Lennart Hammarström[2] · Asghar Aghamohammadi[1,3]

[1] Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2] Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden

[3] Iranian Primary Immunodeficiencies Network (IPIN), Tehran University of Medical Science, Tehran, Iran

[4] Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

[5] Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[6] Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[7] Department of Allergy and Clinical Immunology, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

[8] Department of Laboratory Medicine, Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran

[9] Division of Allergy and Clinical Immunology, Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center, Tehran, University of Medical Sciences, Tehran, Iran

[10] Hematology, Oncology and Stem Cell Transplantation Research Centre, Tehran University of Medical Sciences, Tehran, Iran

[11] Department of Allergy and Clinical Immunology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[12] Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

[13] Department of Pediatrics, Bo-Ali children's Hospital of Ardabil University of Medical Sciences, Ardabil, Iran

[14] Acquired Immunodeficiency Research Center, lsfahan University of Medical Sciences, Isfahan, Iran

[15] Allergy and Clinical Immunology Department, Bushehr University of Medical Science, School of Medicine, Bushehr, Iran

[16] Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[17] Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[18] Noncommunicable Pediatric Diseases Research Center, Amirkola Hospital, Babol University of Medical Sciences, Babol, Iran

[19] Department of Pediatrics, Mazandaran University of Medical Sciences, Sari, Iran

[20] Department of Immunology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran

[21] Department of Immunology and Allergy, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[22] Immunology and Allergy Department, Mofid Children's Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

[23] Department of Pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran

[24] Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran

[25] Department of Pediatrics, 17th Shahrivar Children's Hospital, Guilan University of Medical Sciences, Rasht, Iran

[26] Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[27] Cellular & Molecular Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

[28] Department of Pediatrics, Kermanshah University of Medical Sciences, Kermanshah, Iran

[29] Department of Pediatrics, Qom University of Medical Sciences, Qom, Iran

[30] Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[31] Department of Immunology and Allergy, Tabriz University of Medical Sciences, Tabriz, Iran

[32] Department of Immunology and Allergy, Ahvaz University of Medical Sciences, Ahvaz, Iran

[33] Mousavi Hospital, Zanjan University of Meical Sciences, Zanjan, Iran

[34] Department of Immunology and Allergy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[35] Department of Immunology and Allergy, Semnan University of Medical Sciences, Semnan, Iran

[36] Department of Immunology and Allergy, Kashan University of Medical Sciences, Kashan, Iran

[37] Department of Immunology and Allergy, Qazvin University of Medical Sciences, Qazvin, Iran

[38] Department of Immunology and Allergy, Ilam University of Medical Sciences, Ilam, Iran

[39] Department of Immunology and Allergy, Kerman University of Medical Sciences, Kerman, Iran

[40] Department of Immunology and Allergy, Shahrekord University of Medical Sciences, Shahrekord, Iran

[41] Department of Pediatrics, Lorestan University of Medical Sciences, Khorramabad, Iran

[42] Pediatric Infectious Diseases Research Center, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

[43] Department of Allergy and Clinical Immunology, Pediatric Infectious Diseases Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran