Virology Journal

RESEARCH

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Characterization of the epidemiology, susceptibility genes and clinical features of viral infections among children with inborn immune errors: a retrospective study

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Abstract

Background Although viral infections are one of the common clinical manifestations in patients with inborn errors of immunity (IEIs), little is known about the epidemiology, susceptibility genes, and clinical status of viral infections in patients with IEIs.

Methods The demographic information, clinical diagnoses, and laboratory findings of 931 IEI patients who underwent viral testing from January 2016 to December 2022 were collected and analyzed.

Results In total, 47.15% (439/931) patients with IEI tested positive for at least one virus during hospitalization. There were a total of 640 viral infections during the study period, mainly from EBV 131 (20.47%), HRV 102(15.94%), CMV 100(15.63%), and RV 84(13.13%). CMV and RV infections were more common in the combined immunodeficiencies (IEI_I) group during the infant stage, whereas EBV infection was more common in the immune dysregulation (IEI_IV) group during the preschool stage. Mutations in *SH2D1A* (57.14%), *PIK3CD* (56.41%) and *LRBA* (50%) make individuals susceptible to EBV infection; mutations in *WAS* (30%) make individuals susceptible to CMV infection; and mutations in *IL2RG* (56.52%) and *RAG1* (37.5%) make individuals susceptible to RV infection. Joinpoint analysis revealed trends in viral positivity in different years.

Conclusion These data suggest that it is possible to target the prevention, treatment, and management of IEI patients who are infected with a virus by accounting for the age at infection, type of IEI, and mutant genes, but special attention needs to be paid to viral infections in IEI_I and IEI_IV patients during the infant stage.

Keywords Inborn errors of immunity, Virus infection, Epidemiology, Clinical features, Gene

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Introduction

Inborn errors of immunity (IEIs) are rare diseases caused by monogenic mutations that lead to the dysfunction of immune cells and immune molecules. Infectious diseases are the most prominent clinical manifestations of IEI [1] due to pathogens including bacteria, viruses, fungi, etc. Notably, respiratory viruses are extremely common in most children with IEI. A PIDTC cohort study revealed that 21% (50/240) of severe combined immunodeficiency (SCID) patients had respiratory viral infections prior to transplantation, most commonly due to parainfluenza, followed by respiratory syncytial virus (RSV), rhinovirus, and influenza virus (IFV) [2]. Diarrhea is another common presentation in IEI patients. A prospective study revealed that norovirus (NV) infection was detected in 7 of 34 patients with combined immunodeficiency (CID). Although adenoviruses, enteroviruses (EVs) and rotaviruses (RVs) have been isolated from IEI patients with diarrhea in a single center, their true incidence is unknown [3].

IEIs can be divided into 10 categories, with different types or gene of IEIs being susceptible to different types of viruses. Cytomegalovirus (CMV) is an important cause of morbidity and mortality in IEI patients that is characterized by T- and NK-cell impairment, such as X-linked/common gamma chain deficiency (SCID) [4]. IEIs associated with Epstein–Barr virus (EBV) infection include the following categories: IEI patients that are susceptible to EBV only, IEI patients associated with hemophagocytic lymphohistiocytosis, and IEI patients susceptible to other microorganisms in addition to EBV, including those with mutations in *PIK3CD*, *PIK3R1* and *WAS* [5].

Although the risk of viral infection in IEI patients has been shown and Al-Herz et al. reported the spectrum of viral infections observed in 274 IEI patients [6], the previous studies suffer from limitations such as having a small sample size and a small number of detected pathogens (such as NV and CMV), they are often concentrated on the virologic characteristics of a single IEI disease, and they lack epidemiological characterization of viral infections in large samples. In this study, 931 hospitalized children who underwent viral testing from January 2016 to December 2022 were retrospectively analyzed to investigate the epidemiology of IEI patients with viral infection and the infection characteristics. Moreover, the prevalence of viral infection, susceptibility gene analysis, and the spectrum of viral infection in children with IEI were systematically evaluated, which may provide a comprehensive understanding of viral infection in IEI patients.

Methods

Patient data

Data were obtained from IEI patients admitted to Children's Hospital of Fudan University from January 2016 to December 2022. The study was approved by the Ethics Committee of the Children's Hospital of Fudan University. Written informed consent was acquired from every enrolled patient or their guardians. We included patients who had been definitively diagnosed with IEI and who were diagnosed with a viral infection during subsequent hospitalization.

Criteria for IEI diagnosis and classification

According to the Primary Immune Deficiency Treatment Consortium (PIDTC) published criteria for diagnosing SCID, SCID diagnosis was based on the child's clinical symptoms/immunophenotype (lymphocyte subsets): the absence or very low levels of T cells (CD3 + T-count < 500 μl) or the presence of maternally derived T cells [7]. According to The European Society for Immunodeficiencies (ESID) Registry Clinical Criteria for IEI Diagnosis, the diagnosis of partially genetically unspecified CID, hypogammaglobulinemia, and CVID is based on the clinical phenotype and immunophenotype [8]. The remaining IEIs required a combination of clinical phenotype, immunophenotype and genotype for final disease diagnosis [1]. According to the International Union of Immunological Societies (IUIS) IEI Phenotypic Classification Expert Committee 2022 classification [1], IEIs are classified into ten major categories: combined immunodeficiencies (IEI_I), combined immunodeficiencies with syndromic features (IEI_II), predominantly antibody deficiencies (IEI_III), diseases of immune dysregulation (IEI_IV), congenital defects of phagocytes (IEI_V), defects in intrinsic and innate immunity (IEI_VI), autoinflammatory diseases (IEI_VII), complement deficiencies (IEI_VIII), bone marrow failure (IEI_IX), and phenocopies of inborn errors of immunity (IEI_X).

Diagnosis of viral infection

Respiratory samples (nasopharyngeal aspirates/bronchoalveolar lavage), diarrhea samples (stools, anal swabs/vomit), blood and urine were collected from IEI patients. The samples were immediately sent to the Clinical Laboratory of the Children's Hospital of Fudan University for testing, as described in the supplementary methods. A total of 8 respiratory viruses, including human rhinovirus (HRV), human parainfluenza virus (HPIV), RSV, IFV, human adenovirus (HAdV), human coronavirus (HCoV), human bocavirus (HBoV) and human metapneumovirus (HMPV), were detected. Respiratory viral infection was confirmed by antigen detection or nucleic acid testing on the basis of the diagnostic samples available from the patient, including nasopharyngeal swabs and aspirates, sputum, and bronchoalveolar lavage fluid (BALF) [9]. Patients diagnosed with pneumonia presented respiratory signs and symptoms associated with imaging findings. The diagnostic criteria for gastrointestinal viral

infections included patients who presented with typical clinical signs such as fever, vomiting and diarrhea, as well as stool, anal swabs or vomit samples that tested positive for RV, NV or EV antigens or nucleic acids. The diagnostic criteria for CMV infection in patients with active CMV infection were as follows: infectious mononucleosis, pneumonia, hepatitis, retinitis, and sensorineural deafness. In addition, CMV infection was detected by polymerase chain reaction (PCR) during hospitalization via blood, alveolar lavage or positive cerebrospinal fluid specimens for CMV DNA load, and a viral load ≥ 1 × 10^3 copies/ml was considered a positive result [10]. Diagnostic criteria for EBV infection was as follows: (a) at least the following clinical signs were present: fever, tonsillopharyngitis, cervical lymphadenopathy, hepatomegaly or splenomegaly; and (b) EBV-DNA ≥ 1 × 10^3 copies/ml in blood [11–13]. The diagnosis of HSV keratitis and stomatitis, warts caused by human papillomavirus (HPV), and water and molluscum contagiosum infections was based on clinical assessment [14].

Statistical analysis

Descriptive statistics included frequency analyses for categorical variables and medians and interquartile ranges for continuous variables. Comparisons of categorical variables between groups were made via the Pearson chi-square test or Fisher's exact test. The joinpoint model (V.4.7.0.0, Statistical Research and Applications Branch, National Cancer Institute, USA) was used to describe trends from year to year. Statistical analysis was performed with R statistical software (version 4.3.1) and SPSS (version 25.0). All the statistical tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

Results

Demographic data

A total of 931 IEI inpatients were enrolled from January 1, 2016, to December 31, 2022. Among them, 669 IEI patients were from East China (Supplementary Fig. 1 and Table 1). There were 720 (77.34%) males and 211 (22.66%) females for a sex ratio of 3.41:1. The patients were categorized into 5 groups according to their age: infant (birth to 1 year), 352 cases; toddler (1–3 years), 218 cases; preschooler (3–6 years), 130 cases; older child (6–12 years), 155 cases; and adolescent (12–18 years), 76 cases. A total of 47.15% (439/931) of the patients were positive for at least one virus. These patients were younger ($p < 0.001$)

Table 1 Demographic and epidemiological characterisation of viral infections in patients hospitalised with IEI during 2016-2022

Characteristics	All patients (*N*=931)	At least one virus infection (*n*=439)	Non-virus infection (*n*=492)	*p* value
Sex, male, n (%)	720 (77.34)	350 (79.73)	370 (75.20)	0.117
Age, month, median (IQR)	21 (6-71)	16 (5-54)	28 (9-84)	<0.001
Region, n (%)				0.889
Eastern China	669 (71.86)	314(71.53)	355(72.15)	
Others	262(28.14)	125(28.34)	137 (27.96)	
Age group, n (%)				<0.001
Infant (birth to 1 year)	352(37.81)	195(44.42)	157(31.92)	
Toddler (1-3 years)	218(23.42)	104(23.69)	114(23.17)	
Preschooler (3-6 years)	130(13.96)	59(13.38)	71(14.49)	
Older child (6 -12 years)	155(16.65)	54(12.24)	101(20.61)	
Adolescent (12 -18 years)	76(8.16)	27(6.12)	49(10.00)	
IEI categories, n (%)				<0.001
IEI_I	180(19.33)	115(26.20)	65(13.21)	
IEI_II	96(10.31)	47(10.66)	49(10.00)	
IEI_III	274(29.43)	102(23.12)	172 (35.10)	
IEI_IV	46(4.94)	26(5.92)	20(4.07)	
IEI_V	214(22.99)	95(21.54)	119(24.29)	
IEI_VI	70(7.52)	36(8.16)	34(6.94)	
IEI_VII	43(4.62)	14(3.17)	29(5.92)	
IEI_VIII	1(0.11)	0(0)	1(0.20)	
IEI_IX	4(0.43)	2(0.45)	2(0.41)	
IEI_X	3(0.32)	2(0.45)	1(0.20)	
Outcome, n (%)				0.006
Death	35(3.76)	25(5.67)	10(2.04)	

Data are in n (percentage %) unless otherwise noted. Percentages may not total 100 due to rounding. IQR, interquartile spacing. IEI, inborn errors of immunity. IEI_I, combined immunodeficiencies. IEI_I, combined immunodeficiencies with syndromic features. IEI_III, predominantly antibody deficiencies. IEI_IV,diseases of immune dysregulation. IEI_V, congenital defects of phagocytes. IEI_VI, defects in intrinsic and innate immunity. IEI_VII, autoinflammatory diseases. IEI_VIII, complement deficiencies. IEI_IX, bone marrow failure. IEI_X, phenocopies of inborn errors of immunity

and had a greater proportion of IEI_I ($p < 0.001$) than did the negative patients (Table 1). A total of 16.4% (153/441) of the patients had multiple infections involving more than one viral pathogen, including 114 with two infections and 39 with three or more infections (Supplementary Fig. 2a).

Patterns of specific positivity for viral pathogens in IEI patients

Overall, a total of 640 incidents of viral infection were detected during the hospitalization of IEI patients with viral infections (Supplementary Fig. 2b). Next, we selected 9 common viruses for subsequent analysis (Table 2). RV had the highest percentage of positive detection (17.32%), followed by HRV (15.77%), EBV (15.47%), CMV (12.48%), HPIV (11.86%) and RSV (7.51%). The rate of positive virus infection was 48.61% (350/720) in males and 42.18% (89/211) in females($p > 0.05$). All patients were divided into 5 groups according to age. The results revealed that the positivity rates of the infant group and the toddler group were significantly higher than those of the other groups ($p < 0.001$). Among all detected viruses, EBV (31.67%) was more common in the preschool group ($p < 0.001$). Additionally, the rate of CMV infection (22.22%) was greater in the infant group ($p < 0.001$). Moreover, the rates of HPIV were higher in the infant group and toddler group ($p = 0.001$), with values of 15.79% and 15.86%, respectively. The rate of RSV infection (12.76%) was also greater in the infant group ($p < 0.001$). The rates of HPIV were higher in the infant group and toddler group ($p < 0.001$), at 25.44% and 17.70%, respectively. In terms of the seven IEI group classifications, the difference in the positivity rate of IEI virus infection among the seven groups was significant ($p < 0.001$). The rate of EBV positivity was higher in the IEI_IV group (44.44%) than in the other groups ($p < 0.0001$); the rate of CMV infection (19.64%) was higher in the IEI_I group than in the other groups, but there was no statistical difference ($p > 0.05$); the rates of HPIV positivity were higher in the IEI_I and IEI_VII groups ($p = 0.002$), at 19.11% and 25.00%, respectively; the percentages of RV positivity were greater in the IEI_I and IEI_VI groups ($p = 0.002$), at 26.76% and 25.00%, respectively; and the rate of EV positivity (7.23%) was greater in the IEI_III group ($p < 0.001$) (Table 2).

Patterns of gene-specific positivity rates

Gene sequencing analysis of the 439 IEI patients with virus infections revealed that 375 patients had pathogenic mutations(Fig. 1a). To analyze the genotypes of multiple susceptible viruses, we selected intersections on the basis of genes associated with six viruses (CMV, EBV, HRV, HPIV, RSV, and RV) and identified seven overlapping genes from IEI_I, IEI_II, IEI_III, IEI_IV, IEI_V, and IEI_VI (*RAG1*, chromosome 22q11.2 deletion syndrome, *STAT3*, *CYBB*, *IL12RB1*, *ELANE* and *IL2RG*) infected with these six viruses (Fig. 1b). We then analyzed the genes for each viral susceptibility trait on the basis of the number of genes in these six categories with IEIs greater than 7 or the two genes ranked in each category of IEIs. Viruses were most commonly detected in patients with chromosome 22q11.2 deletion syndrome (80%), followed by patients with mutations in *IL2RG* (77%), *PIK3CD* (69%), *RAG1* (65%) and *SH2D1A* (57%). The highest detection rates of RV were found in patients with mutations in *IL2RG* (57%), followed by *RAG1* (38%) and *IL12RB1* (30%). The highest detection rate of CMV was found in patients with mutations in *WAS* (30%), followed by *RAG1* and *IFNGR1* (29%). The highest detection rate of HPIV was found in patients with mutations in *IL2RG* (27%), followed by patients with chromosome 22q11.2 deletion syndrome (22%). The highest detection rate of EBV was found in patients with mutations in *SH2D1A* (57%), followed by *PIK3CD* (56%), *LRBA* (50%), and *STAT1* (31%). The highest detection rate of HRV was found in patients with mutations in *SH2D1A* (40%), followed by *IFNGR1* (33%) and *PIK3CD* (31%) (Fig. 1c and Supplementary Table 1).

Temporal trends and seasonality

No consistent trends in positivity rates for the tested viruses were observed between 2016 and 2022. The HRV positivity rate increased annually; however, the rate of EV positivity tended to increase but then decreased (Supplementary Fig. 3). By applying the joinpoint model, a significant increase in the HRV positivity rate was found between 2016 and 2018 (annual percent change (APC) = 354.07) and between 2018 and 2022 (APC = 22.38). For EVs, a decreasing trend was detected in 2018 (APC = -27.90) (Fig. 2). The main detected viruses display seasonal variations at the same time. For example, the rate of positivity for HRV was greater in the summer ($p = 0.024$); the rate of RSV positivity was greater in the spring ($p = 0.003$); the IFV positivity rate was greater in spring ($p < 0.001$); and the rate of RV positivity was greater in the summer ($p = 0.02$). The positivity rates of several pathogens, such as CMV, EBV, HPIV, HAdV and EV, did not significantly differ among seasons in our study (Table 3).

Viral infection manifestations and clinical outcomes in IEI patients

The most common presentation of viral infection was respiratory infection (42.83%), followed by viremia (34.21%) and gastrointestinal infection (16.96%). The most common cause of viraemia was EBV, followed by CMV. The most common virus causing pneumonia was HRV, followed by HPIV and RSV. The most common

Table 2 Virus-positive detection rates among IEI hospitalised patients during 2016-2022

Characteristics	Total	EBV	CMV	HRV	HPIV	RSV	IFV	HAdV	RV	EV
Overall cases	47.15%(439/931)	15.47%(131/847)	12.48%(100/801)	15.77%(105/666)	11.86%(79/666)	7.51%(51/679)	2.34%(16/683)	2.50%(17/679)	17.32%(84/485)	4.65%(24/516)
Sex										
Male	48.61%(350/720)	14.99%(97/647)	12.95%(79/610)	15.01%(80/553)	11.93%(66/533)	8.49%(46/542)	2.21%(12/544)	2.77%(15/542)	17.71%(71/401)	4.46%(19/426)
Female	42.18%(89/211)	17.00%(34/200)	10.99%(21/191)	18.80%(25/133)	9.77%(13/133)	3.65%(5/137)	2.88%(4/139)	1.46%(2/137)	15.48%(13/84)	5.56%(5/90)
p value	1	0.493	0.475	0.284	0.437	0.055	0.64	0.381	0.623	0.654
Region										
Eastern China	46.94%(314/669)	15.76%(96/609)	13.41%(77/574)	16.67%(80/480)	12.71%(61/480)	7.54%(37/491)	2.63%(13/494)	2.65%(13/491)	16.52%(57/345)	4.61%(17/369)
Others	47.71%(125/262)	14.71%(35/238)	10.13%(23/22)	13.44%(25/186)	9.68%(18/186)	7.45%(14/188)	1.59%(3/189)	2.13%(4/188)	19.29%(27/140)	4.76%(7/147)
p value	0.831	0.752	0.205	0.344	0.290	1.00	0.576	0.792	0.508	1.00
Age group										
Infant (birth to 1 year)	55.11%(194/352)	1.25%(4/319)	21.60%(70/324)	14.74%(42/285)	15.79%(45/285)	12.76%(37/290)	2.76%(8/290)	2.41%(7/290)	25.44%(58/228)	3.39%(7/213)
Toddler (1-3 years)	48.17%(105/218)	17.56%(36/205)	8.81%(17/193)	17.83%(26/145)	15.86%(23/145)	6.76%(10/148)	2.00%(3/150)	4.05%(6/148)	17.70%(20/113)	5.83%(7/120)
Preschooler (3-6 years)	45.38%(59/130)	31.67%(38/120)	4.63%(5/108)	13.79%(12/87)	5.75%(5/87)	3.30%(3/91)	44.40%(4/91)	2.20%(2/91)	7.14%(4/56)	7.69%(5/65)
Older child (6 -12 years)	34.84%(54/155)	25.36%(35/138)	3.20%(4/125)	16.84%(16/95)	4.21%(4/95)	1.05%(1/95)	1.03%(1/97)	2.11%(2/95)	11.69%(1/59)	5.26%(4/76)
Adolescent (12 -18 years)	35.53%(27/76)	27.69%(18/65)	7.84%(4/51)	16.67%(9/54)	3.70%(2/54)	0(0/55)	0(0/55)	0(0/55)	3.45%(1/29)	2.38%(1/42)
p value	< 0.001	< 0.001	< 0.001	0.893	0.001	< 0.001	0.413	0.562	< 0.001	0.528
IEI categories										
IEI_I	63.89%(115/180)	7.65%(13/170)	19.05%(32/168)	16.56%(26/157)	19.11%(30/157)	9.49%(15/158)	3.45%(2/158)	0.63%(1/158)	26.76%(38/142)	3.55%(5/141)
IEI_II	48.96%(47/96)	12.50%(11/88)	16.28%(14/86)	23.08%(15/65)	7.69%(5/65)	7.69%(5/65)	1.54%(1/65)	1.54%(1/65)	10.64%(5/47)	4.08%(2/49)
IEI_III	37.23%(102/274)	16.67%(38/228)	9.31%(19/204)	16.39%(30/183)	5.46%(10/183)	6.56%(12/183)	2.72%(5/184)	3.83%(7/183)	7.30%(10/137)	7.23%(12/166)
IEI_IV	58.52%(26/46)	44.44%(20/45)	10.26%(4/39)	17.14%(6/35)	5.71%(2/35)	2.86%(1/35)	0(0/36)	0(0/35)	21.43%(3/14)	0(0/20)
IEI_V	44.39%(95/214)	14.85%(30/202)	9.33%(18/193)	10.59%(18/170)	13.53%(23/170)	7.43%(13/175)	2.82%(5/177)	4.00%(7/175)	17.43%(19/109)	3.96%(4/101)
IEI_VI	51.43%(36/70)	20.90%(14/67)	10.61%(7/66)	18.92%(7/37)	13.51%(5/37)	9.76%(4/41)	7.32(3/41)	0(0/41)	25.00%(5/20)	0(0/22)
Others [a]	35.29%(18/51)	10.63%(5/47)	13.33%(6/45)	15.79%(3/19)	21.05%(4/19)	4.54%(1/22)	0(0/22)	4.54%(1/22)	25.00%(4/16)	0(0/16)
p value	< 0.001	< 0.001	0.066	0.369	0.002	0.875	0.434	0.242	0.001	0.005

Proportions may not total 100 because of rounding. IEI, inborn errors of immunity. IEI_I, combined immunodeficiencies. IEI_II, combined immunodeficiencies with syndromic features. IEI_III, predominantly antibody deficiencies. IEI_IV,diseases of immune dysregulation. IEI_V, congenital defects of phagocytes. IEI_VI, defects in intrinsic and innate immunity. IEI_VII, autoinflammatory diseases. IEI_VIII, complement deficiencies. IEI_IX, bone marrow failure. IEI_X, phenocopies of inborn errors of immunity. a, sum of IEI_VII, IEI_VIII, IEI_IX and IEI_X. EBV, epstein-barr virus. CMV, cytomegalovirus, HRV, human rhinovirus. HPIV, human parainfluenza virus. RSV, respiratory syncytial virus. IFV, influenza viruses. HAdV, human adenovirus. RV, rotavirus. EV, enterovirus

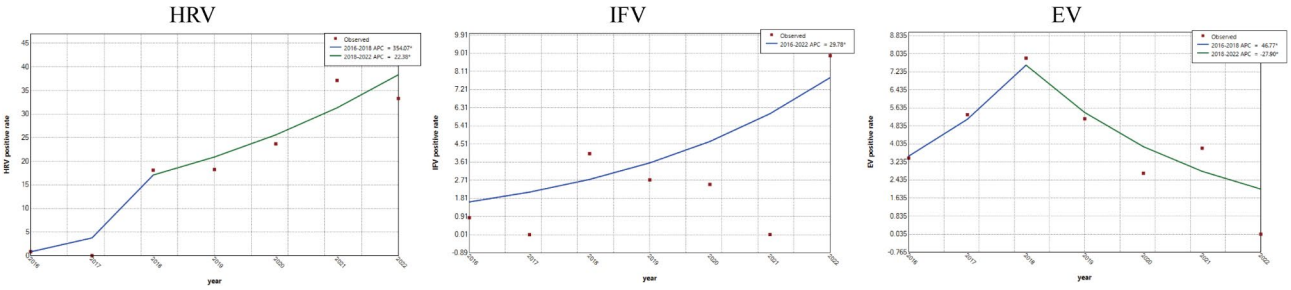

Fig. 1 Patterns of gene-specific positivity for common viruses. (**A**) Genotyping of IEI patients in the six most common categories. (**B**) Venn diagram analysis of the overlapping hub genes with common viruses. (**C**) Heatmap visualization of different gene detection rates for common viruses

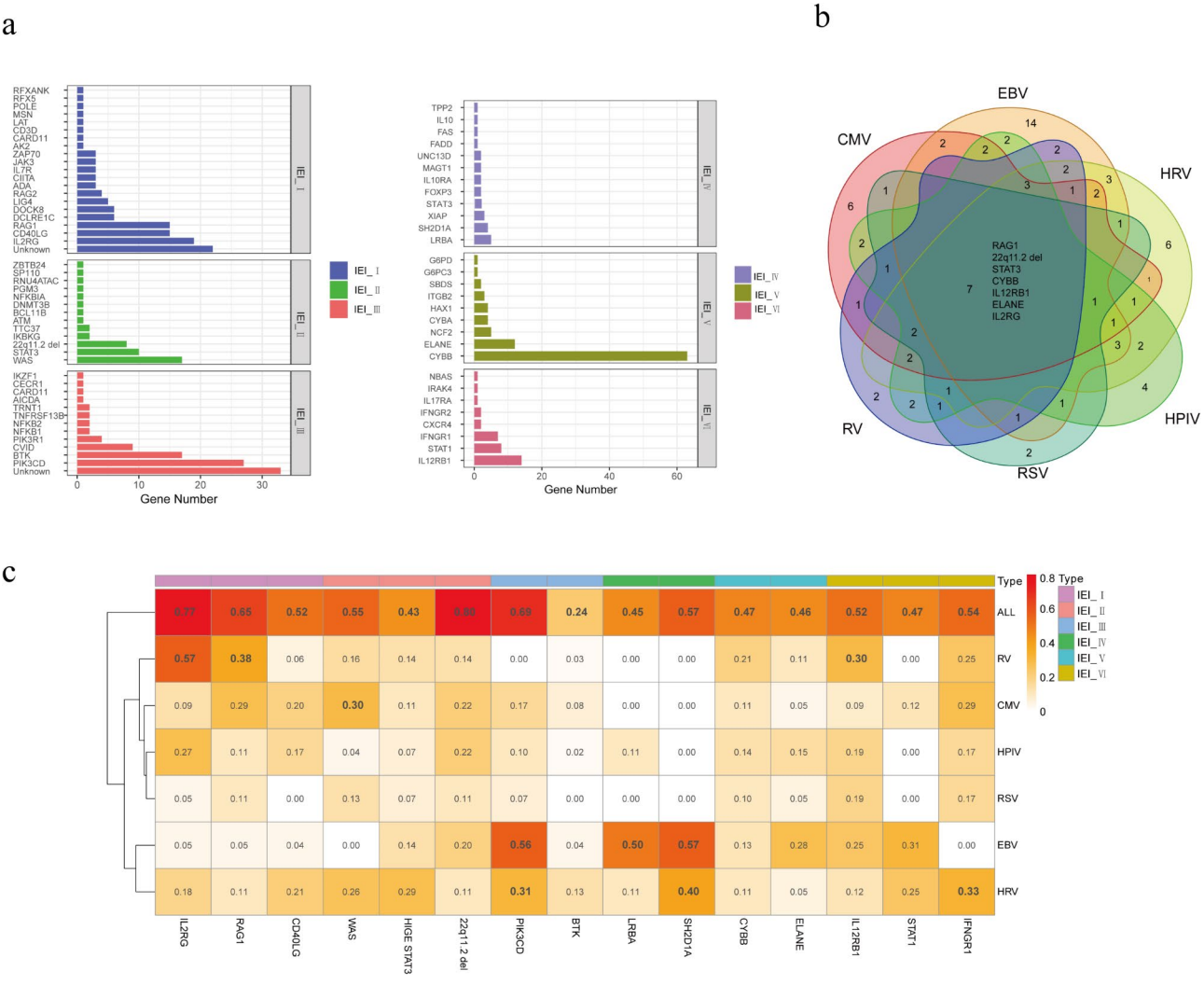

Fig. 2 Joinpoint regression analyses of positivity rates in different years. (**a**) HRV, (**b**) IFV, and (**c**) EV. HRV, human rhinovirus; IFV, influenza virus; and EV, enterovirus. The red dots indicate the mean positivity rate of the patients in different age groups, and the colored curves indicate the fitting patterns for the different age groups. The annual percentage change (APC) values are given for each virus fitting curve. * Indicates that the APC is significantly different from zero at $p < 0.05$

cause of gastrointestinal infections was RV, followed by EV. The virus that caused retinitis was CMV (Supplementary Fig. 4). The most common clinical manifestations of viral infection in IEI patients were cough, enlarged lymph nodes, and fever. The rates of cough, diarrhea and retinitis were significantly higher in children in the IEI_I group than in those in the other groups ($p < 0.05$) (Table 4). The rates of fever and abnormal liver function were

Table 3 Comparison of positive detection rates for common viruses in different quarters

Virus	Spring	Summer	Autumn	Winter	*p* value
CMV	12.74%(20/157)	14.29%(28/196)	12.83%(28/226)	11.26%(24/222)	0.762
EBV	15.73%(28/178)	15.58%(31/199)	15%(36/240)	15.58%(36/231)	0.997
HRV	8.72%(13/149)	15.53%(25/161)	15.82%(31/196)	21.18%(36/170)	0.024
HPIV	9.40%(14/149)	13.66%(22/161)	11.83%(22/186)	11.76%(20/170)	0.713
RSV	13.33%(20/150)	2.41%(4/166)	6.35%(12/189)	8.62%(15/174)	0.003
IFV	7.95%(12/151)	1.18%(2/169)	1.06%(2/189)	0%(0/174)	<0.001
HAdV	1.33%(2/150)	2.41%(4/166)	3.70%(7/189)	2.30%(4/174)	0.574
RV	19.30%(22/114)	25.00%(30/120)	10.48%(13/124)	14.96%(19/127)	0.02
EV	2.42%(3/124)	4.31%(5/116)	6.99%(10/143)	4.51%(6/133)	0.362

EBV, epstein-barr virus. CMV, cytomegalovirus, HRV, human rhinovirus. HPIV, human parainfluenza virus. RSV, respiratory syncytial virus. IFV, influenza viruses. HAdV, human adenovirus.RV, rotavirus. EV, enterovirus

Table 4 Clinical manifestations of patients with IEI virus infection and differences in clinical manifestations between groups

Clinical manifestation	Total *n* = 441	IEI_I *n* = 115	IEI_II *n* = 47	IEI_III *n* = 102	IEI_IV *n* = 26	IEI_V *n* = 95	IEI_VI *n* = 36	Others [a] *n* = 18	*p* value
Cough	314(71.20%)	100(87.07%)	32(68.09%)	65(63.73%)	15(59.26%)	67(70.53%)	22(61.11%)	11(61.11%)	0.001
Enlarged lymph nodes	264(59.86%)	64(55.17%)	23(48.94%)	55(53.92%)	17(62.96%)	60(63.16%)	31(86.11%)	14(77.78%)	0.006
Abnormal liver function	114(25.85%)	44(37.93%)	17(36.17%)	11(10.78%)	10(37.04%)	21(22.11%)	5(13.89%)	6(33.33%)	<0.001
Fever	239(54.20%)	69(60.37%)	23(48.94%)	38(37.25%)	17(66.67%)	59(62.11%)	17(47.22%)	14(77.78%)	0.001
Hepatomegaly	145(32.88%)	42(36.21%)	10(21.28%)	29(28.43%)	11(40.74%)	30(31.58%)	16(44.44%)	7(38.89%)	0.263
Retinitis	38(8.62%)	19(16.38%)	6(12.77%)	1(0.98%)	1(7.41%)	7(7.37%)	1(2.78%)	2(11.11%)	0.002
Splenomegaly	131(29.71%)	32(27.59%)	9(19.15%)	33(32.35%)	9(33.33%)	29(30.53%)	14(38.89%)	5(27.78%)	0.571
Diarrhea	133(30.16%)	50(43.10%)	10(21.18%)	17(16.67%)	8(29.63%)	32(33.68%)	9(25.00%)	7(38.89%)	0.002
Expectoration	163(36.96%)	48(41.38%)	18(38.30%)	40(39.22%)	7(29.63%)	34(35.79%)	10(27.78%)	5(27.78%)	0.627
Dysplasia	39(8.84%)	8(6.90%)	7(14.89%)	13(12.75%)	3(11.11%)	4(4.21%)	2(5.56%)	2(11.11%)	0.245

IEI, inborn errors of immunity. IEI_I, combined immunodeficiencies. IEI_II, combined immunodeficiencies with syndromic features. IEI_III, predominantly antibody deficiencies. IEI_IV,diseases of immune dysregulation. IEI_V, congenital defects of phagocytes. IEI_VI, defects in intrinsic and innate immunity. IEI_VII, autoinflammatory diseases. IEI_VIII, complement deficiencies. IEI_IX, bone marrow failure. IEI_X, phenocopies of inborn errors of immunity. [a], sum of IEI_VII, IEI_VIII, IEI_IX and IEI_X

significantly greater in children in the IEI_IV group than in those in the other groups ($p < 0.05$) (Table 4). In addition, four cases of immunodeficiency-related vaccine-derived poliovirus (iVDPV) infection, two each in groups IEI_I and IEI_III, with varying degrees of paralysis, were identified during our study period (Supplementary Table 2). By the end of this study, 35/931 (3.76%) patients had died, 25 (71.42%) of whom were found to have a viral infection during hospitalization. IEI patients with viral infection had a higher mortality rate ($p = 0.006$) than those who tested negative for viral infection (Table 1). The most common viral infections were caused by HPIV (9 patients), RV (9 patients), RSV (6 patients) and CMV (6 patients). Among them, there were 16 cases in IEI_I (mainly 3 cases of *IL2RG* mutations, 3 cases of *LIG4* mutations, 2 cases of *DCLRE1C* mutations and 2 cases of *RAG2* mutations), 1 cases of *WAS* mutations, 1 cases of *AICDA* mutation, 1 cases of *BTK* mutation, 1 cases of *FOXP3* mutation, and 1 cases of *IL10RA* mutation, 5 cases of *CYBB* mutation. However, the main causes of death in these cases are severe pneumonia, respiratory failure, MODS and sepsis caused by infection (Supplementary Table 3).

Discussion

This study included 931 IEI patients from which data was taken from January 2016 to December 2022 who were subgrouped according to the IUIS guidelines to analyze their epidemiological and clinical characteristics. Patients with IEIs were exposed to a range of viral infections during their hospitalization.

In this study, 47.15%(439/931) of hospitalized IEI patients were positive for at least one virus, which is higher than the previous percentage found of 31.75% (84/274). Previous studies of IEI patients revealed their susceptibility to CMV, HADV, and EBV infection [6]. The highest detection rates of RV, HRV, EBV and CMV were found in hospitalized IEI patients in this study, at 17.32%, 15.77%, 15.47% and 12.48%, respectively. This may be because different sampling techniques, detection methods, clinical patient characteristics, and geographic regions can greatly affect virus detection rates. Etsuro et al. reported an IEI national survey study in which the prevalence of RV in hospitalized patients was 1.1% (10/910) [15], which is much lower than our findings (17.32%, 84/485). One of the reasons for the high RV detection rate in this study is that the samples were collected for viral testing only after the IEI patients in this

study developed gastrointestinal symptoms. Notably, HRV was detected in 15.77% of the IEI patient samples, which could be due to commensalization or prolonged viral shedding in the nasopharynx. This may also explain the high detection rate of HRV in nasopharyngeal swabs. In our study, CMV (19.05%) and RV (26.76%) infections were more common in the combined immunodeficiency group, a finding that has been previously reported [16, 17]. EBV was more common in patients with immune dysregulation, an observation that has been well documented [18, 19]. In addition, we found the highest EV detection rate in patients with predominant antibody deficiencies, and among the 24 patients with EV infection, four had iVDPV infection, two had combined immunodeficiencies, and one had predominant antibody deficiencies. Currently, humoral immunity is considered the main mechanism of protection against EV infection, while the risk of IEI patients developing iVDPV infection is increased by approximately 3,000-fold [20]. Although the WHO maintains a registry of known vaccine-derived poliovirus cases (detected mainly via acute flaccid paralysis (AFP) surveillance), the global prevalence of asymptomatic vaccine-derived poliovirus excretions remains uncertain [21]. Therefore, we need to carefully ask patients about their history with other live attenuated vaccines and be aware of the possibility that the patients may have had poliovirus.

Furthermore, virus detection rates vary among different age groups, with the overall positivity rates being highest in infants and lowest in older children. This may be correlated with the onset of combined immunodeficiency in patients in this age group. Overall, CMV, HPIV, RSV, and RV had the highest positive detection rates in infancy. However, for EBV, the highest detection rate was found in children aged 3–6 years (preschoolers), and these trends were similar to the age distribution of normal children [22–24]. We used IEI virus infection data from 2016 to 2022 to construct a joinpoint model, and the results revealed that HRV and IFV infection showed overall increasing trends, whereas EV infection first tended to increase but then decreased. This may be related to the use of vaccines and the presence of viral variants. In the present study, the peak of HRV infection occurred in the winter, which is different from the findings of other studies [25]. RSV detection rates were highest in the spring, similar to the findings of a general population study [26]. This study is the first to report the age distribution and temporal flow trends of viral infections in IEI patients, although the general trends are consistent with those of the general pediatric epidemic, which can help to implement the active surveillance and treatment of IEI patients during viral epidemics.

Another distinguishing feature of this study is the reporting of the susceptibility of IEI patients to viral infections. The susceptibility genes for HRV in this study were *PIK3CD* (31.03%) and *SH2D1A* (40%). This may be related to the decrease in memory B cells and insufficient antibody production in these individuals. The susceptibility genes for common RV infection in this study were *IL2RG*, *RAG1* and *IL12RB1*. Resolution of RV infection involves both CD8 cytotoxic T lymphocyte (CTL) and antibody responses, as demonstrated in *RAG1* knockout mice [27, 28]. Klinkenberg et al. reported a case of a patient with an *IL2RG* mutation, due to the fact that persistent RV shedding may have been an important cause of the patient's death [29]. We reported in our previous study that *IL12RB1* is also associated with *Talaromyces marneffei* infection, salmonellosis, and candidiasis [30, 31]. In vivo animal experiments confirmed that *IL12RB1* mutations impairing IFN-γ (IFN-γ) production fail to inhibit RV replication. *IL12RB1* mutation impairs IFN-gamma (IFN-γ) production [32]. Children with severe T-cell defects are also susceptible to systemic viral infections. CMV is a recognized cause of morbidity and mortality in IEIs characterized by T-cell and NK-cell damage, such as X-linked/common gamma-chain-deficient SCID [4]. Previous studies have shown that patients with *WAS* mutations are at increased risk of recurrent infection by members of the herpesvirus family, including CMV [33, 34], and that antiviral drugs do not control such infections [35]. The susceptibility genes for the common CMV strains identified in this study were *WAS* and *RAG1*. Notably, for the first time, the *IFNGR1* gene was reported to be associated with CMV infection in our study. EBV-infected B cells are controlled mainly by NK cells, CD4 + T cells and CD8 + T cells [36, 37]. The susceptibility genes for the common EBV strains identified in this study were *SH2D1A*, *PIK3CD* and *LRBA*, similar to previous studies.

We found that the distribution of virus infections in IEI patients largely supported previous findings. However, the frequency of respiratory infections in this study was higher than that previously reported, with HRV infections being the most frequent, followed by HPIV [6]. However, the top three pathogens for common respiratory viral infections in our center between 2010 and 2020 were RSV, HPIV, and HAdV, with detection rates of 9.8% (543/5544), 5.3% (294/5544), and 2.0% (111/5544), respectively [38]. The clinical symptoms of IEI patients with viral infection range from mild to death. In our clinical characterization of patients with viral infections, there were differences between the different IEI types. Interestingly, an increased risk of comorbid retinitis was found in CMV-infected IEI patients in our study. CMV retinitis (CMVR) is an organ- and vision-threatening invasive manifestation of CMV infection in immunodeficient or immunocompromised patients, such as HIV patients, solid organ transplant recipients, hematopoietic

stem cell transplant (HSCT) recipients, and patients receiving immunosuppressive therapy [39]. CMVR is also progressive and can lead to blindness if left untreated [40]. CMVR is rare in IEI patients and has been reported only in patients with mutations in *WAS*, *DOCK8* and SCID [41–43], which may be related to impaired T-cell function. This is also confirmed by the fact that CMVR infection was more prevalent in the IEI_I group than in the other groups in our study. The results showed that all IEI patients who died had higher rates of virus detection during hospitalization (especially HPIV, RV, HRVand CMV). Because respiratory diseases are the main reason why patients with IEI are admitted to hospital. Al-Herz et al. have shown that sepsis and pneumonia are the most common causes of death in patients with IEI [44]. However, death in patients with IEI is caused by multiple factors, and viral infection may be one of the triggers, which requires further prospective research. These infections should be treated early and aggressively to avoid serious complications leading to death.

This study has several limitations. However, our study has some important limitations. First, (a) data from a single-center hospital system; (b) the small number of patients with several types of IEI is under-representative; and (c) some patients may have been pretreated with antiviral medications or treated outside of the hospital, which may have led to an underestimation of the overall detection rate of the selected viruses. Second, although representative of children with IEI from different cities in East China, it may not be representative or generalizable to children with IEI in China as a whole (e.g., differences in ethnicity and regional distribution between our data on children with IEI and the country as a whole). Third, it should be taken into account that some viruses (e.g., respiratory viruses, rotaviruses) can be transmitted long after infection or discovery of asymptomatic carriers, and there is no follow-up to assess long-term outcomes. In the future, we will plan to conduct a multicenter prospective study to include children with IEI in different regions to further validate the results.

In conclusion, our study provides a more comprehensive understanding of IEI patients with viral infections, as well as the age distribution, sex differences, annual trends, seasonal variations, and common susceptibility gene patterns of viral infections in IEI patients. These data help to identify the major virus types in clinical practice, may assist in optimizing the prevention, control, early diagnosis, and treatment of viral infections in IEI patients and provide a basis for future epidemiological studies of viral infections in IEI patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02697-8.

Supplementary Material 1

Acknowledgements
The authors thank the study investigators, nursing staff, and patients for contributing to this research.

Author contributions
Xiaochuan Wang, Bijun Sun and Haiqiao Zhang designed the research; Haiqiao Zhang performed the data analysis and wrote the article; Bijun Sun and Xiaochuan Wang provided critical revision of the article. Wenjie Wang, Qinhua Zhou, Jia Hou, Wenjing Ying, Xiaoying Hui, Jinqiao Sun, Lipin Liu, Luyao Liu, Chenhao Wang and Hai Zhang diagnosed, treated and managed these patients.

Funding
This study was supported by grants from the Shanghai Municipal Science and Technology Major Project (ZD2021CY001) and the "Sailing Program" of Shanghai Science and Technology Committee (23YF1403400).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This retrospective study received ethical approval from the institutional review board of ethics committee of the Children's Hospital of Fudan University. The data access was also provided by Children's Hospital of Fudan University. The committee waived informed consent because the study was retrospective, there was no risk of harm to the subjects, and all patients were anonymous.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 February 2025 / Accepted: 6 March 2025
Published online: 02 April 2025

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