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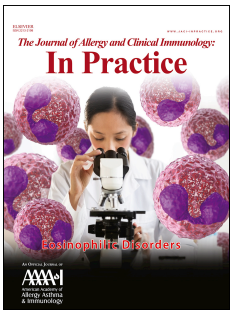

Clinical outcome, incidence and SARS-CoV-2 infection fatality rates in Italian patients with Inborn Errors of Immunity.

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Clinical outcome, incidence and SARS-CoV-2 infection fatality rates in Italian patients with Inborn Errors of Immunity.

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Conflict of interest

All Authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Clinical Implications statement

SARS-CoV-2 positive IEI patients showed a similar infection fatality rate, a lower incidence in peadiatric age, and a younger age at death than the SARS-CoV-2 positive Italian population. The fatality rate was lower than previously reported from other IEI cohorts. Antibody deficiencies showed a long-lasting SARS-CoV-2 positivity.

Early reports described an unexpected low number of patients affected by IEI with SARS-CoV-2 infection. However, the incidence and mortality rates in IEI are still a matter of speculation, and a detailed figure is lacking since cohorts of IEI patients were not compared with the general population in a given country.[1-2] Due to the high burden of COVID-19 in Italy, we evaluated the impact of the pandemic on IEI patients enrolled by 21 Centres in the IPINet national registry (www.ipinet.org) [3] with the aim to assess SARS-CoV-2 incidence, and infection fatality rate in different IEI entities in a cohort of 3263 adult and pediatric patients for which we have the exact figure available thanks to the Italian registry for each nosological entity, to quantify the length of time of SARS-CoV-2 positivity, and to verify if a condition of lymphopenia might be a possible predictor of COVID-19 outcome. All data were compared to the data of the SARS-CoV-2 positive Italian population.

IEI patients diagnosed according to the ESID criteria were considered SARS-CoV-2 positive if confirmed by PCR. PCR was repeatedly tested in each patient, according to the rule to test for SARS-CoV-2 every time a patient is attending a hospital site. In SARS-CoV-2 positive patients, PCR was tested every 10 days until negative. The cumulative incidence, and infection fatality rate was calculated by age and by diagnosis. We used the Italian NIH report on SARS-CoV-2 pandemic in Italy to obtain national estimates, and we compared data by Student's t-test for continuous variables by STATA 10 (Stata-Corp, College Station, TX). A *P* value of <.05 indicates statistical significance.

In the one-year study period, 131 cases of SARS-CoV-2 infection were notified among 3263 IEI patients, 33 of them ≤18 years. According to WHO criteria 2020,[4] patients might be stratified in asymptomatic, mild, moderate, and severe COVID-19. The asymptomatic condition, revealed by the screening of patients attending the hospital sites, and of household contacts, was reported in 36.3% of patients ≤18 years, and 24.5% of patients >18 years. Mean age was similar in asymptomatic, mild/moderate or severe COVID-19 patients, and in patients who died for COVID-19, with the exception of asymptomatic adult patients who were younger than severe COVID-19 adult patients (*P* <0.003). (Table I). IEI patients with severe COVID-19 and patients who later died to COVID-19 had a limited spectrum of IEI diagnosis: CVID, Del 22q11 and Good's syndrome.

At the end of February 2021, the cumulative incidence per 100,000 of confirmed infections was 4.01 in IEI patients and 5.22 in the general population (Table II). Only the incidence in pediatric age was significantly lower in IEI patients (2.36) in comparison to the Italian pediatric population (4.11, *P*<0.001), a finding possibly due to the continuous patients' education on protection procedures our patients have been following since diagnosis. The highest number of SARS-CoV-2 infected

subjects was in the group 19-49-years for IEIs and the general population. The overall infection fatality rate was 3.81% in IEIs, compared to 3.28% in the Italian population (*P*=0.61), and 5.10% in IEI adult patients compared to 3.68% in the adult general population (*P*=0.5). Nonetheless, the fatality rate among IEI Italian patients is lower than previously reported from other IEI cohorts, ranging from 9.57[1] to 25.[2] IEI patients showed a younger age at death (median age: 52 years, range: 30-59, vs 83 years, range: 0-109), and did not have those comorbidities predisposing to a severe COVID-19 in the not-immunocompromised population[5]. Pre-existing comorbidities associated to COVID-19 severity were described in only 6/11 IEI patients with severe COVID-19 (1 hypertension, 2 cardiomyopathy, 3 chronic lung diseases) and in only 2/5 IEI patients who died to SARS-CoV-2 infection (hypertension and obesity).

Distribution of SARS-CoV-2 infected patients by IEI entities and by children and adult populations are shown in Figure E1A,B,C. Del 22q11 and CVID accounted for the most affected IEI in the pediatric and adult age, respectively. The cumulative incidence, and infection fatality rate by type of IEI and by age are shown in Table II. Given the low numbers among different IEI entities, a higher SARS-CoV-2 incidence was found only by comparing CVID to SIgAD (*P*=0.04). The fatality rate was high in Good's Syndrome and in Del 22q11, both conditions associated with a T-cell defect. A condition of lymphopenia and CD4 lymphopenia was detected in the pre-SARS-CoV-2 period in about 10% and 20% of IEI, respectively, mainly in Del22q11 and CVID patients. However, this was not a risk factor for the subsequent COVID-19 severity. As reported in non-immunocompromised adult patients,[6] Neutrophil/Lymphocyte ratio (NLR) was higher in patients with severe COVID-19 than in asymptomatic patients (7.3 ± 7.4 vs 2.0 ± 0.9, *P*=0.008), and in mild/moderate disease patients (3.3 ± 3.9, *P*=0.04)..

Since IEI patients might struggle with clearing the infection, we calculated the time from the first SARS-CoV-2 positive PCR to the first SARS-CoV-2 negative PCR. One third of patients with antibody deficiencies were SARS-CoV-2 positive for more than 3 weeks, representing a possible risk factor for viral spreading[7]. A similar length was observed in patients with Agammaglobulinemia (56.4 ± 38.1 days), CVID (47.6 ± 20.9 days), SIgAD (52.5 ± 71.2 days). Shorter times were described in patients with Del 22q11 (29.1 ± 33.9 days, *P*<0.01) (Figure E2).

The long time of observation might have helped correct some initial conclusions also from our group [8], since patients with Agammaglobulinemia and ARA might also show a severe COVID-19, even if none died. Our study has a major limitation of possible underestimation, but less relevant than that described in the general population [9], as we started our study at the early stages of the pandemic, and we followed our patient rigorously. The purely descriptive data set on IEI patients

might be the basis for a comparison over time of the trend of SARS-CoV-2 infection in this population as is for data on the trend of SARS-CoV-2 infection in the general population.

Acknowledgments

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TABLE I. Demographic data, and disease severity of SARS-CoV-2 positive IEI patients

SARS-Cov-2 positive	%	mean age
≤18 years	**25.1**	**9.6 ± 5.7**
male	**60.6**	
asymptomatic	**36.3**	**6.2 ± 2.9**
mild/moderate	**60.6**	**5.6 ± 4.2**
severe	**3.03**	**1**
death	**0**	
> 18 years	**74.8**	**43.9 ± 15.8**
male	**58.2**	
asymptomatic	**24.5**	**38.0 ±17.0 ***
mild/moderate	**55.1**	**41.6 ±16.8**
severe	**15.8**	**50.9 ±14.8**
death	**5.1**	**48.5 ±13.0**

*mean age asymptomatic vs severe COVID-19 > 18 years: *P*<0.03

TABLE II. Cumulative incidence per 100,000, and infection fatality per cent for IEI by diagnosis. Comparison of IEI (total, pediatric and adult age) to data (total, pediatric and adult) of the Italian population

	Number of SARS-Cov-2 positive patients	Number of IEI patients enrolled	Cumulative incidence (per 100,000)	Infection fatality rate (%)
CVID	74	1161***	6.4	4.05
XLA	13	148	8.8	0
ARA	3	17	17.6	0
SIgAD	7	961	0.7	0
Good's syndrome	3	24	12.5	33.3
Del 22q11	12	527	2.3	8.3
WAS	0	5	0	0
CGD	0	66	0	0
AT	2	54	3.7	0
HIE syndrome	0	50	0	0
ALPS	1	12	8.3	0
CD4 lymphopenia	2	26	7.7	0
APDS	2	2	*	0
Aicardi-Goutiers	1	1	*	0
Prolidase deficiency	1	1	*	0
MyD88 deficiency	1	1	*	0
NBAS deficiency	1	1	*	0
XIAP	0	1	*	0
Neutropenia	2	39	5.1	0
Post-HSCT, post-gene therapy and post-thymic transplant	6	162	3.70	0
IEI (total number)	**131**	**3263**	**4.01**	**3.81**
<18 years	33	1396**	2,36	0
>18 years	98	1867	5,25	5,10
Italian population (IP:total number)	**3,123,368**	**59,816,655**	**5.22**	**3.28**
<18 years	417,752	10,160,000	4.11	0,005
>18 years	2,705,616	49,656,655	5.45	3,68

*This figure cannot be calculated as we do not have a disease register for these rare IEI and we do not know the possible number of affected patients in Italy

**IEI <18 years vs IP <18 years: p<0.001

*** SARS-Cov-2 positive CVID vs SARS-CoV-2 positive SIgAD: p=0.04

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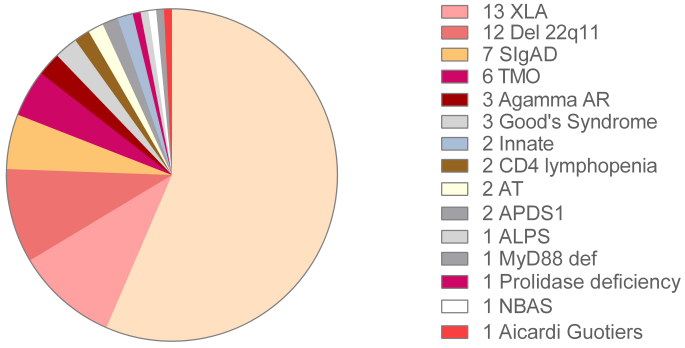

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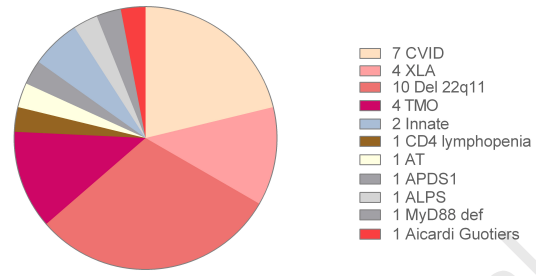

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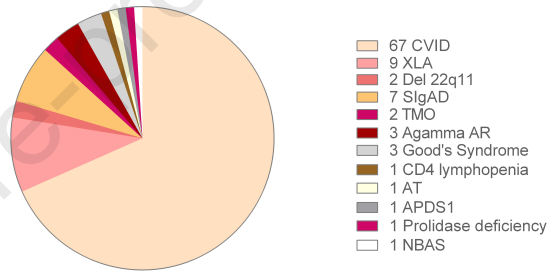

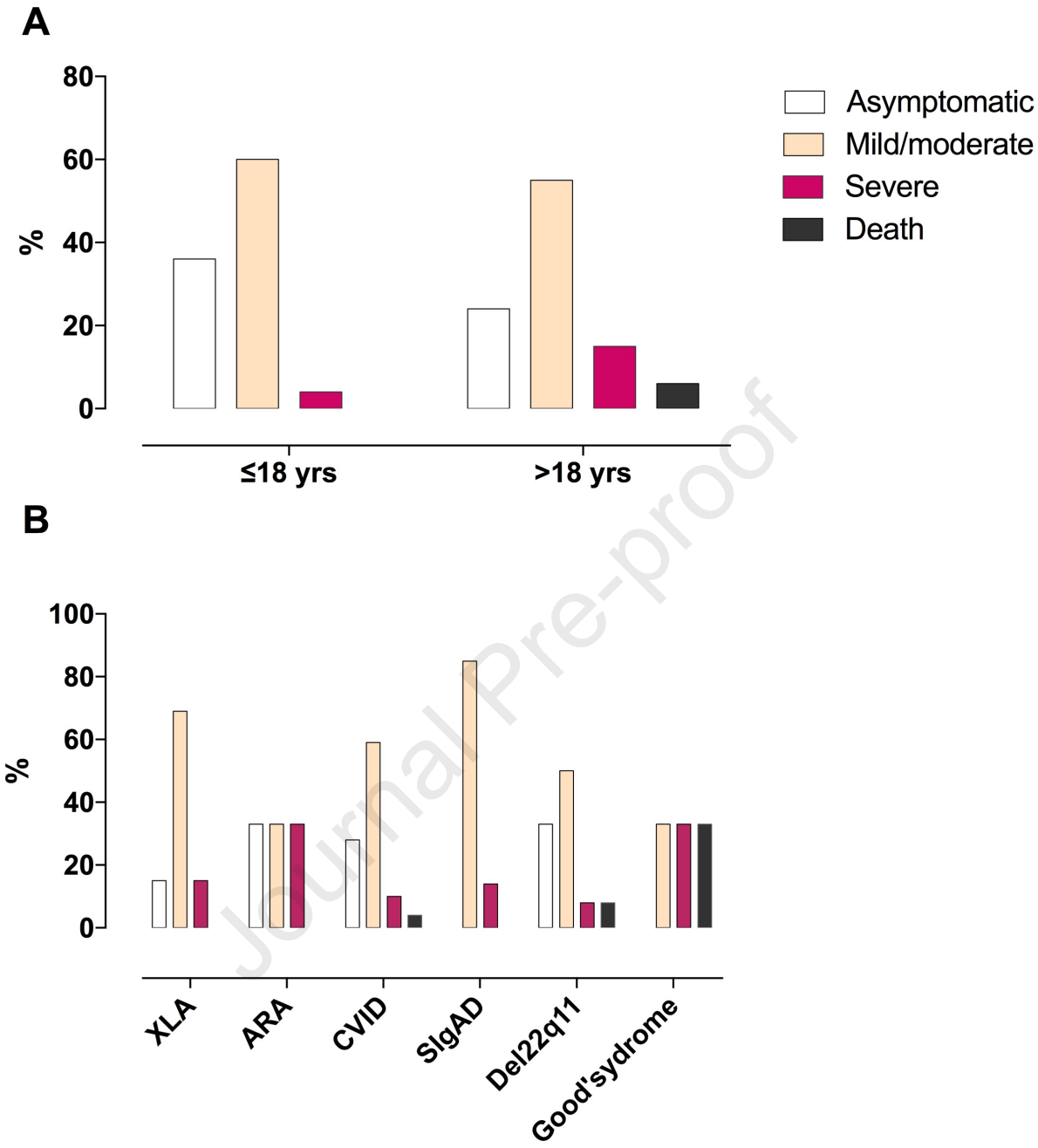

Legend to Figures

Figure E1. Distribution of SARS-Cov-2 infected patients by IEI entities (panel A) and by children (panel B) and adult populations (panel C).

Figure E2. COVID-19 disease severity by age (panel A) and by IEI entity (panel B) in the Italian IEI cohort.