SARS-CoV2 infection in patients with IEI: an international survey

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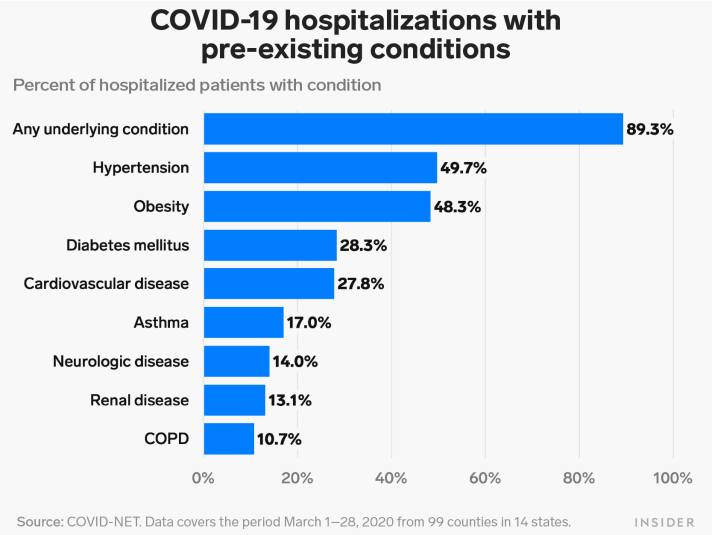
All physicians who contributed

Background: March 2020

- How to advise patient population (and their physicians)?
- Emerging data from secondary ID patient groups
- Null hypothesis: no increased risk?
- Are comorbidities important ? >> IEI patients more at risk?
- Specific inborn errors of immunity predisposing to severe COVID19?
  - Cfr Severe Flu: IRF7, IRF9, TLR3, GATA2, IFNAR1, …
- Early March: birth of the survey > ESID – IPOPI – IUIS
- AIM: to assess impact of COVID19 in IEI



Outcome of SARS-CoV2 infection in PID: a global survey (methods and results)

- Monkey Survey– started March 16
- Basic questionnaire on condition, outcome, treatment
- No identifying data, IRB approved
- PCR proven / serology proven infection
- Data on 94 patients collected
  - Argentina, Belgium, Brazil, Chile, France, Germany, Italy, Mexico, Netherlands , Spain, Turkey, UK, USA
- 32 children, 62 adults

Patients with inborn errors of immunity						General Population				
Age groups (94 cases)	M:F	COVID-19 cases per age group in our cohort N (%)	Deaths in our cohort N (%)	ICU admission N (%)	Age groups general pop (1 320 488 total cases)	COVID-19 cases per age group (general pop %)		Deaths (general pop) %		ICU admission (general pop) %
0-2 yrs	6:1	7 (7.4%)	1/7 (14%)	3/7 (43%)	0-9 yrs	1.5[A]	4.2[B]	0.1[A]	0[C]	0.7 [A]
3-12 yrs	12:5	17 (18%)	0/17	2/17 (12%)						
13-18 yrs	4:4	8 (8.5%)	1/8 (10%)	4/8 (50%)	10-19 yrs	3.7	7.8	0.1	0.2	0.4
19-24 yrs	4:0	4 (4.2%)	0/4	0/4	20-29 yrs	13.8	20.0	0.1	0.2	0.5
25-34 yrs	10:3	13 (13.8%)	0/13	0/13	30-39 yrs	16.3	17.8	0.4	0.2	0.9
35-44 yrs	9:6	15 (16%)	2/15 (13%)	3/15 (20%)	40-49 yrs	16.6	14.4	1.0	0.3	1.5
45-54 yrs	8:1	9 (9.5%)	0/0	1/9 (11%)	50-59 yrs	17.9	12.7	2.4	0.8	2.5
55-64 yrs	5:5	10 (10.6%)	2/10 (20%)	3/10 (30%)	60-69 yrs	13.6	7.6	6.7	2.7	4.1
65-74 yrs	0:5	5 (5.3%)	0	0	70-79 yrs	8.0	5.3	16.6	8.0	5.6
>75 yrs	2:3	5 (5.3%)	3 (60%)	2 (40%)	>80 yrs	8.7	10.0	28.7	16.0	3.6
All patients	65:35 (1.8:1)	NA	10 (10%)	20 (20%)	All			5.4% (1-20%)		2.3%

Individual IEI

- Antibody deficiency 53

CVID: 29

XLA (*BTK*): 6

AR Agamma: 2

NFKB1: 2

NFKB2: 2

X-SCID [gene therapy]: 1

- Immune dysregulation

APECED (*AIRE*): 1 / mild disease

ALPS: 2 ; LRBA (1); CTLA4 (2); XIAP: 1

- Phagocytic defects: 4 CGD

- Combined immunodeficiency: 14

- Syndromic: Trisomy 21: 3; DiGeorge: 2

- Auto-inflammatory: Aicardi-Goutieres: 3

FMF (*MEFV*): 2

- Bone marrow failure

GATA2 (1), *DNAJC21* (1)

- Innate

IFNGR2 deficiency (1), GOF STAT1 (1)

Outcome: asymptomatic infection and mild disease in 35/94!

10 patients were asymptomatic

ALPS-like

AGS (2)

STAT1 GOF

WAS

AR CGD

XLA (adult)

AR agammaglobulinemia

hypogammaglobulinemia (adult)

CID

(4 had chronic lung disease)

25 patients were mildly ill and treated as outpatient

14 with predominantly Ab deficiency (11 with CVID, of whom 7 had one or more comorbidities);

1 X-SCID patient post GT

1 with activated PI3 kinase syndrome (*PIK3R1* mutation)

1 with CID with multiple autoimmune features

3 with HIES due to *PGM3* (1) or *STAT3* LOF (2) including one with chronic lung disease;

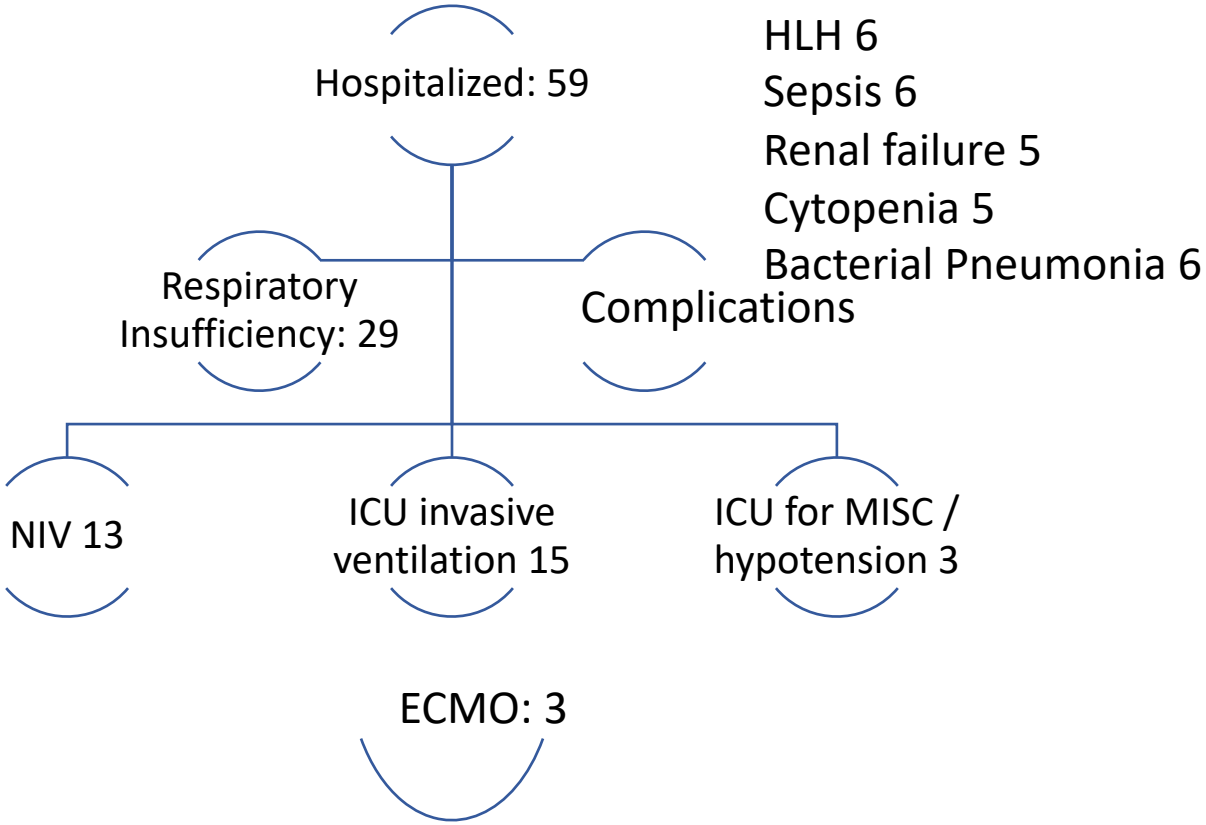
2 with *MEFV* mutations,

1 with AGS (P83, *SAMHD1* mutation),

1 with CGD due to *CYBB* mutation

1 with an unspecified phagocyte defect

Hospitalisation – ICU admission



4 female

T21 <2y, CVID 55-64y (2), hypogamma >75y

11 male

1 aged 0-2 years [X-CGD]

2 aged 3-12 years [trisomy 21]; [*WAS*]);

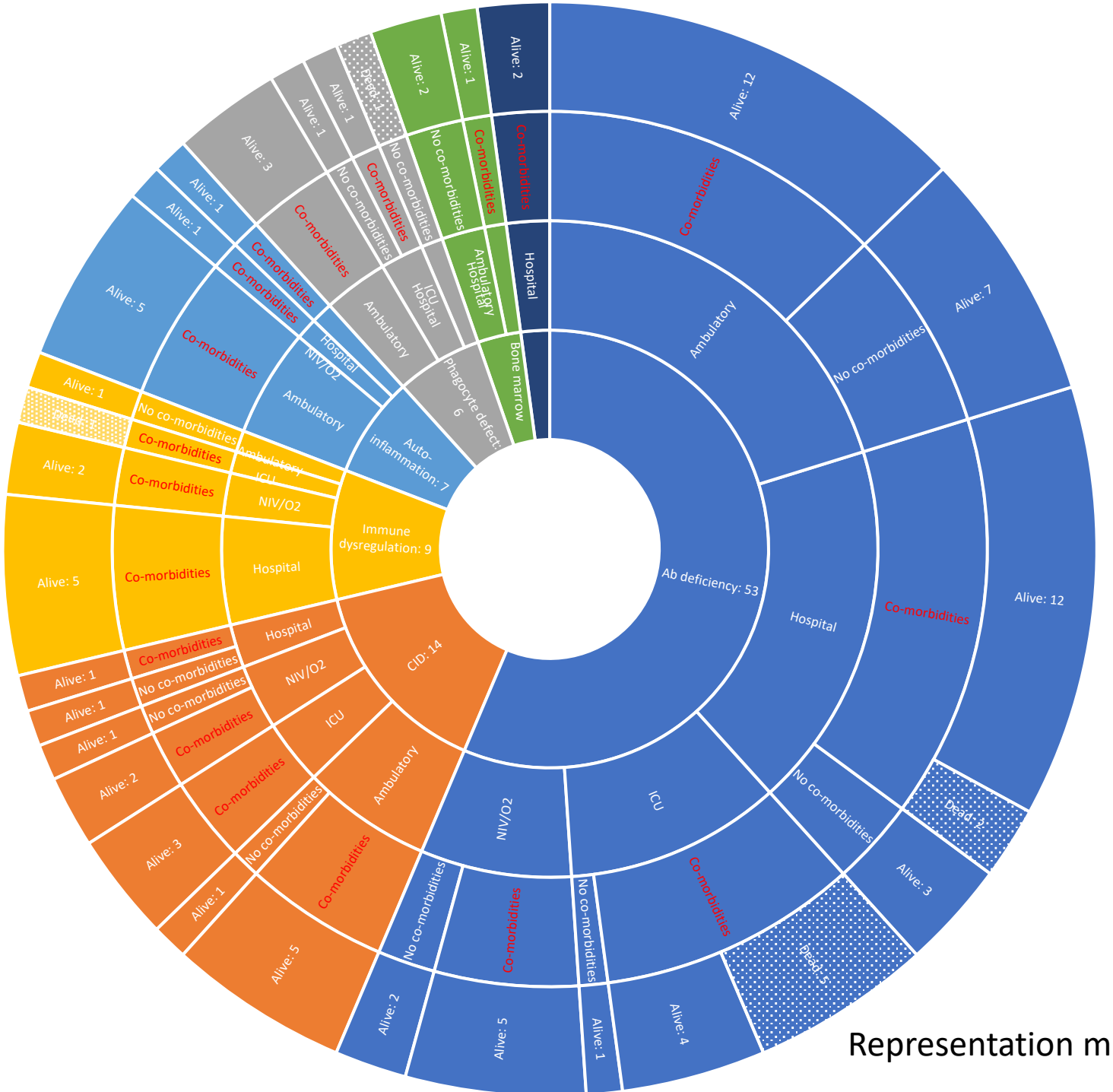
2 aged13-18 years [*NFKB2*] [*XIAP*]

3 aged 35-44 years [*NFKB2*] [agammaglobulinemia] [syndromic primary Ab deficiency]

1 aged 45-54 years with CVID

1 aged 55-64 years with CVID

1 aged ≥75 years [IgG2/IgA deficiency]



Representation mimics distribution of patients in large registries

9 patients succumbed

4 males

- 0-2 years: n=1 (X-CGD)
- 13-18 years: n=1 (XIAP post-hsct)
- 35-44 years: n=1
- 75 years: n=1

5 females (35-44 years: n=1; 55-64 years: n=2 ; ≥75 years: n=2)

CVID / Antibody deficiency with co-morbidities

Conclusions: bias!

Inclusion bias

Diagnostic bias (regional testing priorities)

Already strict isolation and precautions may cause additional bias

> Physician preferences in precautions: specific attention to patients with severe viral infections

MIS-C not differentiated (not described yet)

Several conditions not identified as IEI yet

Treatment bias (regional differences, differences in timing etc)

True explanation may be different! >> Autoantibodies against type I IFN? (Zhang Q et al Science - Bastard P et al Science 2020)

Conclusions

Presentation and risk factors: similar to non-IEI population ?
Younger male patients (9<35y) critically ill ?

Role of protective antibodies? CVID more critically ill than Agammaglobulinemia patients (Isabella Quinti, J Allergy Clin Immunol 2020 146:211)

All patients with CID survived!

5/6 patients with phagocyte defects had a mild course

Conclusions

- 7/7 with auto-inflammation survived
- The role of IL-6 in hyperinflammatory response to SARS-CoV2 confirmed?
  - Mild disease in STAT3 LOF (n=2, of whom 1 with CLD)
  - XLA ?
- GATA2 deficient patient with prolonged disease
- AGS had mild course

UK Cohort (J Allergy Clin Immunol, accepted)

- Individuals with primary immunodeficiency (n=60) had an overall infection fatality ratio of 20.0%, a Case fatality ratio of 31.6% and inpatient mortality of 37.5%
- 8/12 deaths: CVID

- Individuals with symptomatic secondary immunodeficiency (N=33) infection fatality ratio of 33.3%, case fatality ratio of 39.2% and an inpatient mortality of 44.0%
- 7 auto-inflammatory disorders

- Only 70/100 had lab test confirming the infection!

Iranian cohort (J Clin Immunol Dec 2020 Delavari S et al)

- 2754 patients on monthly follow-up
- SARS-CoV2 swab if triade of fever, cough, dyspnea
- 19 patients tested + 7 females, median age 106 months
- 47% had CID
- 8 patients died

A patient with CGD, survived (Montravadi et al J Clin Immunol Dec 2020)

Table 1 Epidemiologic characteristics, genetic diagnosis and outcomes of COVID-19 infection in the patients with different types of primary immunodeficiencies

Primary immunodeficiency categories	Total patients in the registry	Alive patients during the pandemic	Number of COVID-19 patients (%)	Monogenic defects of patients with COVID-19	Mortality due to COVID-19, N (%)	Mortality rate due to COVID-19
Combined immunodeficiencies	1392	630	10 (1.5)	–	6 (60.0)	0.009
Non-syndromic combined immunodeficiencies	576	247	6 (2.4)	–	5 (83.3)	0.020
Severe combined immunodeficiency	355	113	5 (4.4)	–	4 (80)	0.035
Less profound combined immunodeficiencies	221	134	1 (0.7)	STK4	1 (100)	0.007
Syndromic combined immunodeficiencies	816	383	4 (1.0)	–	1(25)	0.002
Wiskott-Aldrich syndrome	74	59	1 (1.7)	WAS	–	–
Ataxia-telangiectasia	292	86	1 (1.1)	ATM	–	–
Other syndromic combined immunodeficiencies	450	238	2 (0.8)	DNMT3B (n = 2)	1 (50)	0.004
Predominantly antibody deficiencies	1391	1002	4 (0.4)	–	–	–
Agammaglobulinemia	208	147	1 (0.6)	BTK	–	–
Common variable immunodeficiency	599	352	1 (0.2)	–	–	–
Hyper immunoglobulin M syndrome	102	86	1 (1.1)	–	–	–
Selective IgA deficiency	193	185	1 (0.1)	–	–	–
Other antibody deficiencies	285	232	0	–	–	–
Congenital defects of phagocytes	782	426	2 (0.4)	–	–	–
Chronic granulomatous disease	385	217	2 (0.9)	CYBA (n = 1)	–	–
Other phagocytosis defects	397	209	0	–	–	–
Diseases of immune dysregulation	117	90	2 (2.2)	–	1 (50)	0.011
Familial hemophagocytic lymphohistiocytosis	44	37	1 (2.7)	RAB27A	1 (100)	0.027
Susceptibility to EBV and lymphoproliferation	50	34	1 (2.9)	CD70	–	–
Other immune dysregulations	23	19	0	–	–	–
Autoinflammatory disorders	734	389	1 (0.2)	–	1 (100)	0.002
Non-inflammasome-related conditions	45	40	1	IL1RN	1 (100)	0.025
Other autoinflammatory disorders	689	549	0	–	–	–
Other primary immunodeficiencies*	302	217	0	–	–	–
Total	4718	2754	19 (0.68)	–	8 (42.1)	0.003

We need to learn more!

- More national and regional data coming up, individual cases published
- Ongoing registration effort: COPID19 dsp.institutimagine.org/copid … ESID …
- In depth analysis (WES) of previously healthy severe COVID19 patients!

Thank you!

All physicians who contributed!!

ESID - CIS - LASID – ASID – APSID – ASCIA - JMF

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