CIRCULATING LEVELS OF TYPE I, TYPE II AND TYPE III INTERFERONS AND COVID-19 SEVERITY

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Alejandro Garcia[1*], Riya Negi[1*], Camille Heckmann[1*], Grace Kenny[1], Sarah Miles[1], Dana Alalwan[1], Aoife G. Cotter[1,3], Eoin Feeney[1], John Lambert[1,3,4], Eoghan deBarra[5], Obada Yousif[2], Peter Doran[4], Patrick Mallon[1]

[1] Centre for Experimental Pathogen Host Research, University College Dublin, Ireland. [2] Wexford General Hospital, Wexford, Ireland. [3] Mater Misericordiae University Hospital, Dublin, Ireland. [4] School of Medicine, University College Dublin, [5]Beaumont Hospital, Beaumont, Dublin 9, Ireland. 6
*Authors contributed equally

Correspondence
Alejandro Garcia
Centre for Experimental Pathogen Host Research (CEPHR), Dublin, Ireland
E-mail: alejandro.garcialeon@ucd.ie

Background

- Interferons play a pivotal role as a first line of the innate immune host response to viral infections, including COVID-19[1]. Accumulating data suggests dysregulated interferon (IFN) responses in COVID-19[2]. However, the clinical relevance of circulating levels of interferon to COVID-19 disease severity remains unclear.

Objectives

- To explore associations between circulating levels of type I (IFN-α2a and IFN-β), type II (IFN-γ), and type III (IFN-λ1) Interferons and COVID-19 disease severity.

Methods

- **Participants and Study Design**: in 335 SARS-CoV-2 PCR positive subjects recruited to the All Ireland Infectious Diseases Cohort, with plasma sample collected within 10 days from onset of symptoms, levels of type I (IFN-α2a and IFN-β), type II (IFN-γ), and type III (IFN-λ1) interferons were measured. Subsequent maximum COVID-19 disease severity was classified according to World Health Organization guidance (Critical, Severe, Moderate and Mild).

- **Laboratory Methods**: Plasma was derived from EDTA whole blood tubes (centrifuged at 1500g x 10 minutes) and biobank at -80°C in individual aliquots until the day of assessment. The circulating levels in plasma of IFN-α2a, IFN-β, IFN-γ, and IFN-λ1 were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kits (Meso Scale Discovery, Rockville, USA)

- **Statistical Analysis**: Kruskal–Wallis test was used to explore differences in IFN levels between COVID-19 severity groups, and logistic regression to determine associations, adjusting for demographics (age, sex at birth, ethnicity), comorbidities (obesity, hypertension, respiratory disease, heart disease) and medical management (antibiotics, immunosuppressants, anticoagulants, invasive ventilation).

Results

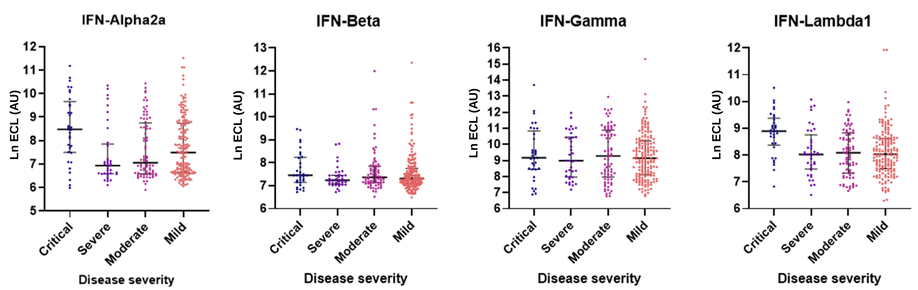
- Out of the 335 subjects with early infection and available samples, 319 had data on disease severity, 33 (10.3%) Critical, 37 (11.6%) Severe, 76 (23.8%) Moderate and 173 (54.2%) Mild. The population was predominantly Caucasian (79.3%), with a median [IQR] age of 64 [53,77] and male (52.7%). (Fig 1)

Figure 1 - Subjects characteristics by severity group

		Critical (N=33)	Severe (N=37)	Moderate (N=76)	Mild (N=173)	P*
Age: median [IQR]		73 (62-79) (33/33)	64 (53-75) (37/37)	59 (53-76) (76/76)	59 (34-74) (173/173)	0.0029
Gender (n)	Male	20 (60.6%)	20 (54.1%)	42 (55.3%)	86 (49.7%)	0.6426
	Female	13 (39.4%)	17 (45.9%)	34 (44.7%)	87 (50.3%)	
	Unknown	-	-	-	-	
Ethnicity (n)	Caucasian	23 (69.7%)	26 (70.3%)	57 (75%)	147 (85%)	0.0473
	Other	10 (30.3%)	11 (29.7%)	19 (25%)	26 (15%)	
Smoking (n)	Smoker/Ex-smoker	13 (39.4%)	16 (43.2%)	19 (25%)	51 (29.5%)	0.1113
	Non smoker	15 (45.4%)	15 (40.5%)	44 (58.9%)	102 (59%)	
	Unknown	5 (15.2%)	6 (16.2%)	13 (17.1%)	20 (11.6%)	
Obesity (n)	Yes	5 (15.2%)	9 (24.3%)	11 (14.5%)	19 (11%)	0.3709
	No	24 (72.7%)	24 (64.9%)	56 (73.7%)	113 (65.3%)	
	Unknown	4 (12.1%)	4 (10.8%)	9 (11.8%)	41 (23.7%)	
Respiratory disease (n)	Yes	11 (33.3%)	14 (37.8%)	24 (31.6%)	31 (17.9%)	0.0749
	No	18 (54.5%)	19 (51.4%)	43 (56.6%)	101 (58.4%)	
	Unknown	4 (12.1%)	4 (10.8%)	9 (11.8%)	41 (23.7%)	
ICU admission (n)	Yes	14 (51.5%)	2 (5.4%)	3 (3.9%)	5 (2.9%)	<0.0001
	No	14 (42.4%)	30 (81.1%)	67 (88.2%)	148 (85.5%)	
	Unknown	2 (6.1%)	5 (13.5%)	6 (7.9%)	20 (11.6%)	
Outcome (n)	Discharged	9 (27.3%)	30 (81.1%)	72 (94.7%)	162 (93.6%)	<0.0001
	Death	23 (69.7%)	5 (13.5%)	2 (2.6%)	3 (1.7%)	
	Other	1 (3%)	2 (5.4%)	2 (2.6%)	8 (4.6%)	

- There was a significant difference between the 4 groups for the levels of Type I IFN-α2a (p=0.0028) and Type 3 IFN-λ1 (p=0.0001), both being higher in the critical group. (Fig 2).

Figure 2 – Circulating levels of Interferon by severity group.



Results (cont)

- In adjusted analyses higher levels of Type I IFN-α2a but not Type 3 IFN-λ1 remained significantly associated with the development of Critical COVID-19 (Odds Ratio: 5.911 / 95% CI: 0.608, 52.388 / p=0.029). (Fig 3).

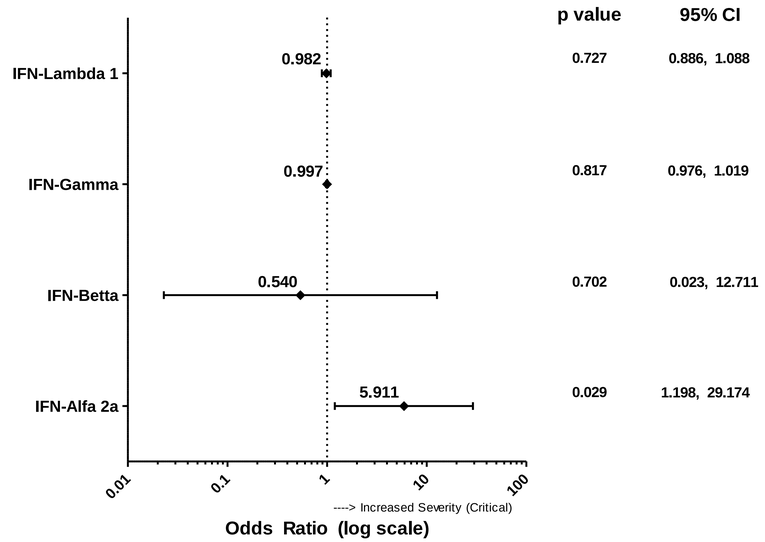


Figure 3. Forest Plot: Association between the interferons and a Critical COVID-19 disease status. Adjusted for demographics (age, sex at birth, ethnicity), comorbidities (obesity, hypertension, respiratory disease, heart disease) and medical management (antibiotics, immunosuppressants, anticoagulants, invasive ventilation). Odds Ratios, p-values and 95% confidence are shown for the 4 Interferons. Type I (IFN-α2a and IFN-β), type II (IFN-γ), and type III (IFN-λ1).

Conclusions

- Increased circulating Type I IFN-α2a, but not other IFN classes, measured in the early stages of SARS-CoV-2 infection was associated with higher odds of Critical COVID-19 infection. These data point to specific differences in host responses that may lead to more targeted interventions to prevent development of severe COVID-19 infection.

References & Acknowledgments

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