Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endogenous IFNβ expression predicts outcome in critical patients with COVID-19

Although the subject of intensive preclinical and clinical research, controversy on the protective versus deleterious effects of endogenous and therapeutic IFN on COVID-19 remains. Some apparently conflicting results are most likely due to the intricacy of IFN subtypes (ie, type I: interferon alfa and interferon beta, type III: interferon lambda), timing and mode of administration (ie, nebulised or subcutaneous), and clinical groups that are targeted (ie, patients with asymptomatic, mild, moderate, or severe or critical COVID-19).

A phase 2 clinical trial reporting the use of peginterferon lambda achieved its primary clinical outcome (ie, change in clinical condition on the WHO Ordinal Scale for Clinical Improvement) in patients with COVID-19 who were admitted to hospital.[1] Another phase 2 clinical trial reporting the use of interferon beta-1a achieved its virological outcome (ie, proportion of patients who were negative for SARS-CoV-2 RNA on day 7 after the injection) in ambulatory patients with COVID-19.[2] As set forth previously,[3] understanding the different kinetics of endogenous IFN production in patients with mild and severe COVID-19, relative to viral replication, will help to identify the therapeutic window. Thus, endogenous IFNs add complexity to the COVID-19 IFN conundrum but have been understudied in patients who are of critical status in intensive care units (ICUs).

Within a prospective COVID-19 clinical trial (NCT04327570), we

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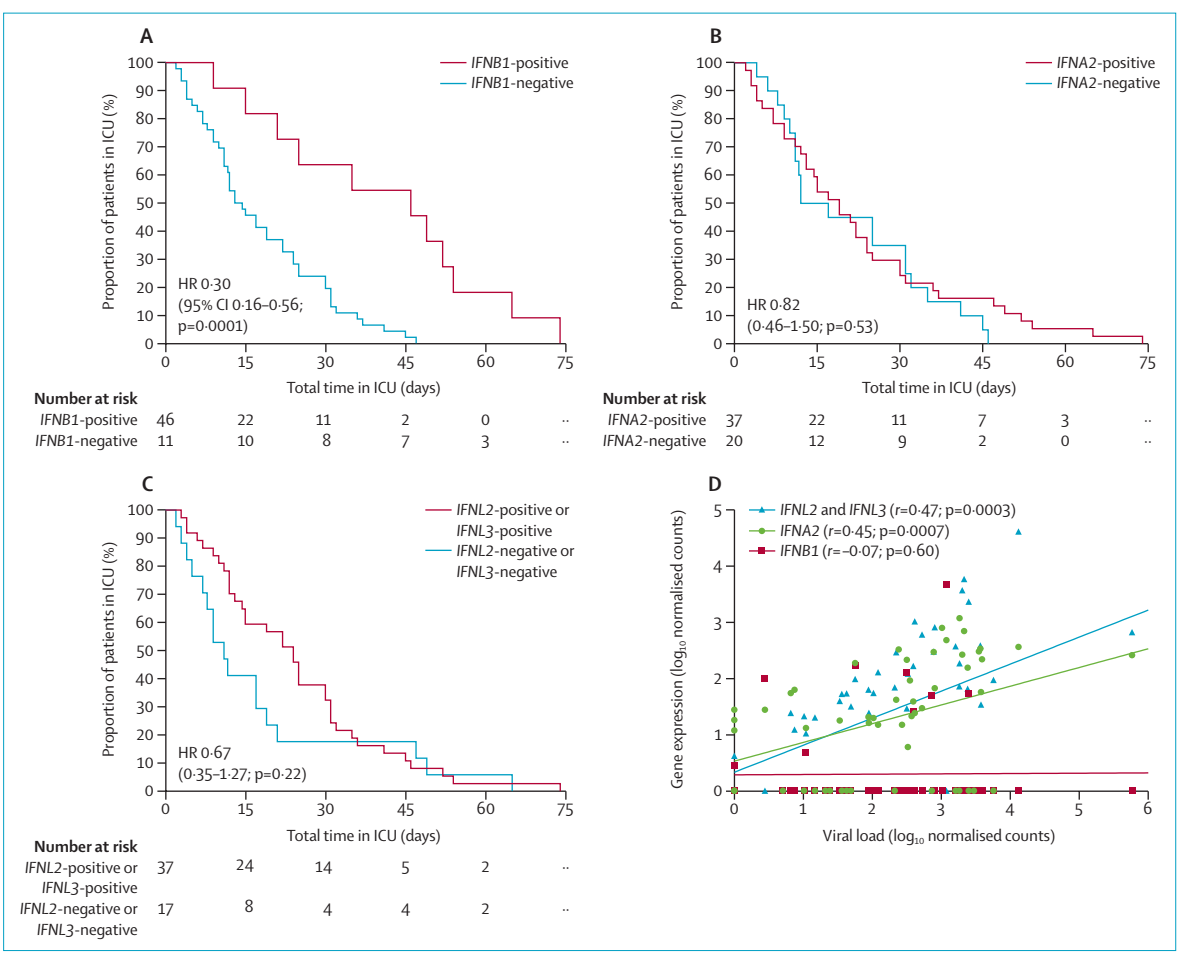

Figure: **Upper respiratory tract *IFN* transcript expression and length of ICU stay for critical patients with COVID-19**
Nasal swabs were obtained from 57 critical patients with COVID-19 on admission to ICU or at first bronchoscopy. RNA was extracted and normalised counts for IFNβ (*IFNB1*), IFNα (*IFNA2*), and IFNλ (*IFNL2* and *IFNL3*) mRNA were quantified by nCounter (Nanostring) as previously described.[4] Viral load (ie, total SARS-CoV-2 transcripts corresponding to surface glycoprotein, nucleoprotein, envelope protein, membrane protein, ORF1ab, ORF3a, and ORF7a) was quantified as described.[5] Kaplan-Meier curves of patients in ICU who were positive versus negative for *IFNB1* (A), positive versus negative for *IFNA2* (B), and positive versus negative for *IFNL2 or IFNL3* (C) were compared by use of Log-rank test. Viral load did not predict length of ICU stay (HR 1·13 [95% CI 0·35–1·27; p=0·22]; data not shown). (D) Viral load was correlated to *IFNB1*, *IFNA2*, *IFNL2*, and *IFNL3* transcripts (Spearman correlation). Viral load and *IFNL2* and *IFNL3* data were missing for three patients (n=54). HR=hazard ratio. ICU=intensive care unit.

For more on **nCounter** see https://www.nanostring.com

quantified type I (*IFNA2* and *IFNB1*) and type III IFN (*IFNL2* and *IFNL3*) transcripts in nasal mucosa of 57 patients with critical COVID-19, by use of digital transcriptomics technology (nCounter) that was previously validated in a large cohort of patients with acute respiratory infection.[4] All patients in ICUs received standard-of-care treatment (ie, corticosteroids, anticoagulants, vasopressors, antibiotics, or a combination, in addition to ventilation or extracorporeal membrane oxygenation) but none received IFN treatment.

IFNB1 transcript expression, but not *IFNA2*, *IFNL2*, or *IFNL3* transcript expression nor viral load (not shown), predicted the length of ICU stay (figure A–C). Multivariate regression suggests *IFNB1* expression (β=0·45 [95% CI 0·24–0·67]; p=0·0002) and Acute Physiology and Chronic Health Evaluation II score (β=1·06 [0·49–1·65]; p=0·0009) as independent predictors, whereas viral load, age, gender, body-mass index, or Charlson Comorbidity Index were not. Moreover, *IFNB1* expression also predicted worse clinical outcome measured by maximal WHO ordinal scale (Mann-Whitney, p=0·027) or maximal oxygen support (Mann-Whitney, p=0·0068) and a composite score (ie, discharge to rehabilitation centre, hospital stay >60 days, or death; Mann-Whitney p=0·040). Notably, 45% (5 of 11) of patients who were positive for *IFNB1* required extracorporeal membrane oxygenation versus 9% (4 of 46) of patients who were negative for *IFNB1*. Total days on extracorporeal membrane oxygenation was also higher in patients who were positive for *IFNB1* (median 24·0 days *vs* 10·5 days; Mann-Whitney p=0·016). *IFNB1* expression also predicted multiorgan involvement, another hallmark of critical COVID-19 (median Sequential Organ Failure Assessment score 7 for patients who were negative for *IFNB1 vs* 12 for patients who were positive for *IFNB1*; Mann-Whitney p=0·0072). Surprisingly, *IFNB1* expression was not correlated to viral load (figure D), in contrast to *IFNA2* (*r*=0·45; p=0·0007) and *IFNL2* and *IFNL3* (*r*=0·47; p=0·0003).

In conclusion, endogenous IFNβ production in the nasal mucosa predicts clinical outcome, independent of viral replication or Acute Physiology and Chronic Health Evaluation II score, and should be considered as a prognostic tool in a precision medicine approach of IFN therapy in clinical management of COVID-19.

We declare no competing interests. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication .The funder of the study had no role in study, design, data collection, data analysis, data interpretation, or writing the report.

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