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.

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Letter to the Editor

Serum IFN-γ and RNAemia temporal profiles as biomarkers of severe COVID-19 in solid organ transplant and immunocompetent patients

Dear editor,

Currently, the availability of SARS-CoV-2 vaccines, despite the great worldwide differences in vaccination rates,[1] have focused the impact of the pandemic in immunodepressed patients. Therefore, we read with interest the recent meta-analysis about COVID-19 vaccine in patients with solid malignancies[2] which found that 42% and 86% of patients achieved serological response after one and two doses, respectively. Other authors have found that the pooled odds ratio for developing anti-SARS-CoV-2 spike protein IgG was higher in the control group than in solid organ transplant (SOT) recipients.[3] The infection by SARS-CoV-2 elicits an innate and specific cellular and humoral immune response. Interferons (IFN) are key in the innate immune response during the acute phase of the viral infection, as seen with plasmacytoid dendritic cells expressing high concentrations of types I and III IFNs in COVID-19 patients.[4,5] In acute COVID-19 and convalescent patients, intracellular cytokine staining after stimulation with SARS-CoV-2 peptide pools, has showed significant IFN-γ increases in CD8 + T-cells, which is associated with viral elimination, and without differences in both phases of the disease.[6,7]

In this context, to gain insight in the innate immune response in SOT recipients with COVID-19, compared with no SOT patients, we have assessed the IFN-α and IFN-γ serum levels and RNAemia at hospital admission and by days from the symptom's onset (DfSO; $\leq$1 to $\geq$15 days), as well as their association with unfavorable clinical outcomes (death and/or invasive mechanical ventilation [IMV]). With this aim, we conducted a multicentre prospective observational cohort study, including consecutive adult inpatients with confirmed COVID-19 (RT-PCR in nasopharyngeal swabs) and available samples for IFN-α/IFN-γ serum levels and RNAemia determinations (Methods, Supplementary material), from January 6th 2020 to August 13th 2021, followed until hospital discharge, death, or 30 days, whichever occurred first. The study was approved by The Ethics Committee of University Hospitals Virgen Macarena and Virgen del Rocío (C.I. 0771-N-20 and 0842-N-20).

Data were separately analyzed for SOT recipients and no SOT patients. In addition, we performed a matched cohort analysis in which patients undergoing SOT were paired with those from the no SOT cohort (1:2) according to their propensity score (PS), using callipers of a 0.01 standard deviation, to control for residual confounders. Mortality in the matched pairs was compared using Cox regression. IFN-α and IFN-γ levels were analyzed as discrete (undetectable and detectable) and continuous (pg/mL) variables. Multivariate Cox regression and logistic regression analysis were performed to identify factors independently associated with 30-day all-cause mortality and unfavorable clinical outcomes (Methods, Supplementary material).

Forty-seven (10.3%) SOT recipients and 408 (89.7%) no SOT patients (Supplementary Table 2) were recruited. The mean DfSO to hospital admission was 7.1 $\pm$ 4.3, without differences between groups. Undetectable IFN-α occurred in 8.5% and 13.5% ($p = 0.36$) of both groups, respectively (Fig. 1A), independently of the DfSO. In SOT recipients, IFN-α levels were higher with <7 DfSO than with $\geq$7 DfSO ($p = 0.015$), with a decrease from 19.5 pg/mL to 1.4 pg/mL. In no SOT, IFN-α levels were higher than in SOT recipients with $\geq$7 DfSO (Supplementary Table 3). Undetectable IFN-γ was more frequent in SOT recipients than in no SOT patients (42.6% and 19.4%, $p < 0.001$) and this difference was higher with $\geq$7 DfSO (Fig. 1A). IFN-γ levels were similar over the different time-periods, both in SOT and no SOT, and without differences between groups (Supplementary Table 3), which is consistent with other studies.[6,7] RNAemia was more frequent in SOT recipients (57.4%) than in no SOT patients (18.9%, $p < 0.001$) (Fig. 1A, Supplementary Table 2). In SOT recipients, RNAemia detection was independent of the DfSO, and in no SOT patients decreased with $\geq$11 DfSO ($p = 0.014$) (Supplementary Table 3). Mortality was higher in SOT recipients than in no SOT patients with $\geq$4 DfSO (Fig. 1A). In SOT recipients, mortality was not associated to the DfSO at admission; however, in no SOT patients, mortality was much higher in patients with $\leq$3 DfSO, decreasing to 0% in patients with $\geq$11 DfSO ($p < 0.001$) (Fig. 1A).

In the PS matched cohorts (Table 1), SOT recipients showed higher prevalence of undetectable IFN-γ than no SOT patients (39.4% *vs.* 10.6%, respectively; $p = 0.001$), lower plasma IFN-α and IFN-γ levels in those with RNAemia ($p = 0.013$ and $p = 0.001$, respectively; Supplementary Fig. 1B), higher RNAemia detection (57.6% *vs.* 13.6%; $p < 0.001$) and mortality (27.3% *vs.* 4.5%; $p = 0.003$).

In SOT recipients, the multivariate logistic regression model selected RNAemia as predictor of unfavorable clinical outcome (Supplementary Table 6). Regarding no SOT patients, in the Cox regression multivariate analysis, 30-day all-cause mortality was associated with RNAemia and undetectable IFN-γ levels (Supplementary Table 7). In the Kaplan-Meier analysis, patients with RNAemia had lower survival, both in SOT ($p < 0.0133$) and no SOT ($p = 0.001$) groups (Fig. 1B). RNAemia has been associated with COVID-19 mortality.[8] The present data confirm it, with a higher sample size and including SOT recipients, in which the RNAemia impact had not yet been analyzed. The Kaplan-Meier analysis also showed an association of undetectable IFN-γ with lower survival in SOT recipients ($p = 0.048$) (Fig. 1B). Our results, showing an association of undetectable IFN-γ in serum with mortality, support the protective role of the specific T-cells response.

The Kaplan-Meier analysis did not show association of undetectable IFN-α levels with the survival at 30 days, both in SOT and no SOT groups. It has been reported that inborn errors of type I

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Table 1
Comparison of solid organ transplant (SOT) recipients matched (1:2) with no SOT patients according to propensity score.[a]

Variable	SOT recipients (n = 33)	No SOT patients (n = 66)	P value
Male sex	20 (60.6)	37 (56.1)	0.666
Age >70 years	4 (12.1)	21 (31.8)	0.033
Dyspnoea	15 (45.5)	36 (54.5)	0.394
SpO_2 <95%	17 (51.5)	26 (39.4)	0.251
Neutrophil count >7500/μL	6 (18.2)	6 (9.1)	0.327
Lymphocyte count <1000/µL	18 (54.5)	30 (45.5)	0.394
C-reactive protein >100 mg/L	9 (27.3)	20 (30.3)	0.755
Ferritin >1000 ng/mL	6 (18.2)	10 (15.2)	0.699
D-dimer >600 ng/mL	29 (87.9)	48 (72.7)	0.087
LDH >300 IU/L	14 (42.4)	33 (50.0)	0.477
IFN-α undetectable	3 (9.1)	8 (12.1)	0.747
IFN-α (pg/mL)[b]	1.43 (0.60–22.01)	11.98 (3.24–23.11)	0.163
IFN-γ undetectable	13 (39.4)	7 (10.6)	0.001
IFN-γ (pg/mL)[b]	26.14 (0.00–240.96)	145.35 (40.00–330.96)	0.347
RNAemia positive	19 (57.6)	9 (13.6)	<0.001
RNAemia (log_{10} copies/mL)[b]	2.38 (2.12–3.19)	2.36 (1.92–2.98)	0.921
CCI ≥3	25 (75.8)	37 (56.1)	0.056
CURB-65 ≥2	12 (36.4)	12 (18.8)	0.057
WHO basal score 6–9[c]	3 (9.1)	4 (6.1)	0.683
IMV	10 (30.3)	5 (7.6)	0.003
Mortality at day 30	9 (27.3)	3 (4.5)	0.003
WHO final score 7-10[c]	13 (39.4)	7 (10.6)	0.001

Data are presented as No. (%). P values are calculated by Cox regression.
Abbreviations (in order of appearance): SpO_2, peripheral capillary oxygen saturation; LDH, lactate dehydrogenase; IFN, interferon; CCI, Charlson Comorbidity Index (30); CURB-65 (31), Severity Score for Community-Acquired Pneumonia; IMV, invasive mechanical ventilation.
[a] Variables included in the propensity score were sex, dyspnea, SpO_2, neutrophil and lymphocyte counts, C-reactive protein, ferritin, D-dimer, and LDH.
[b] Median (IQR). P values are calculated by the Mann-Whitney U test.
[c] Severity rating according to the WHO Clinical Progression Scale (doi: 10.1016/S1473-3099(20)30483-7), ranged from 0 (not infected) to 10 (dead), of which scores 6–9 represent severe disease.

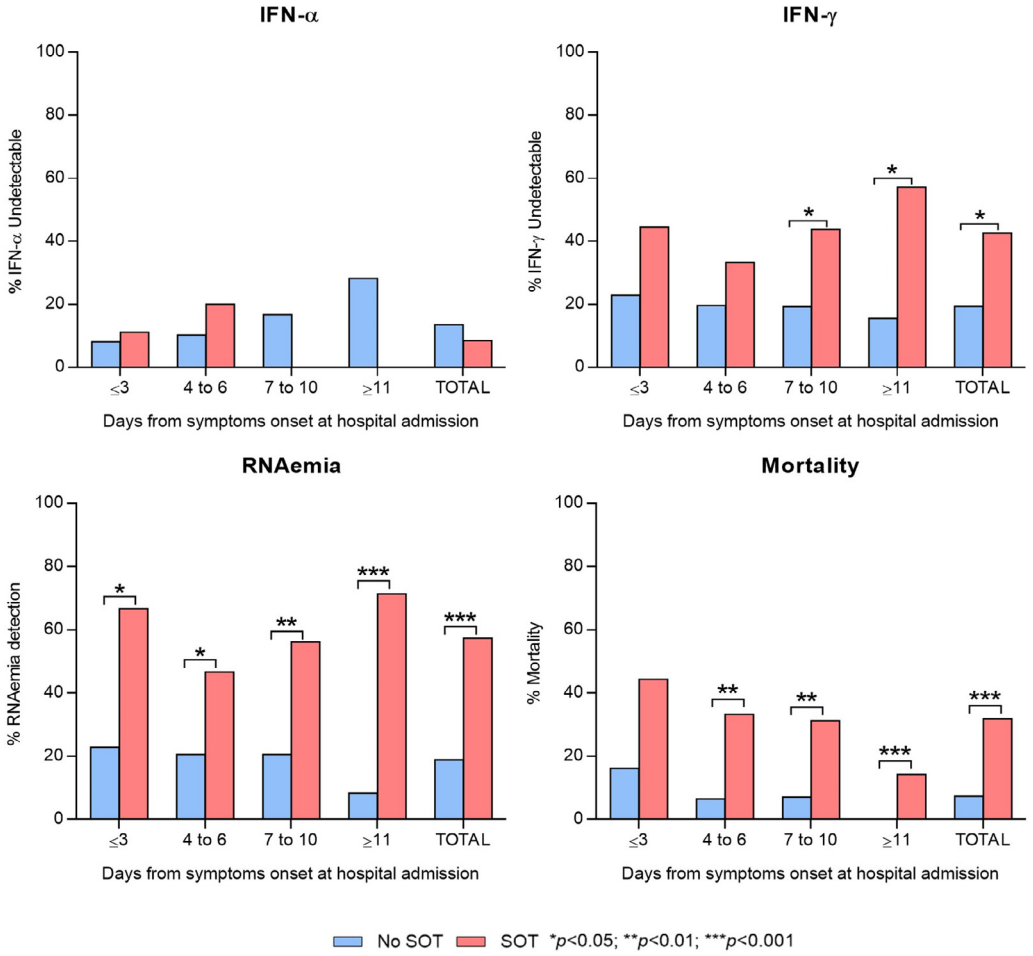

Fig. 1. SOT recipients (n = 47) comparison with no SOT patients (n=408) regarding (A) undetectable IFN-α and IFN-γ serum levels, RNAemia, and mortality, by days from symptoms onset at hospital admission, and (B) Survival Kaplan Meier analysis of patients with and without undetectable IFN-γ serum levels and RNAemia detection.

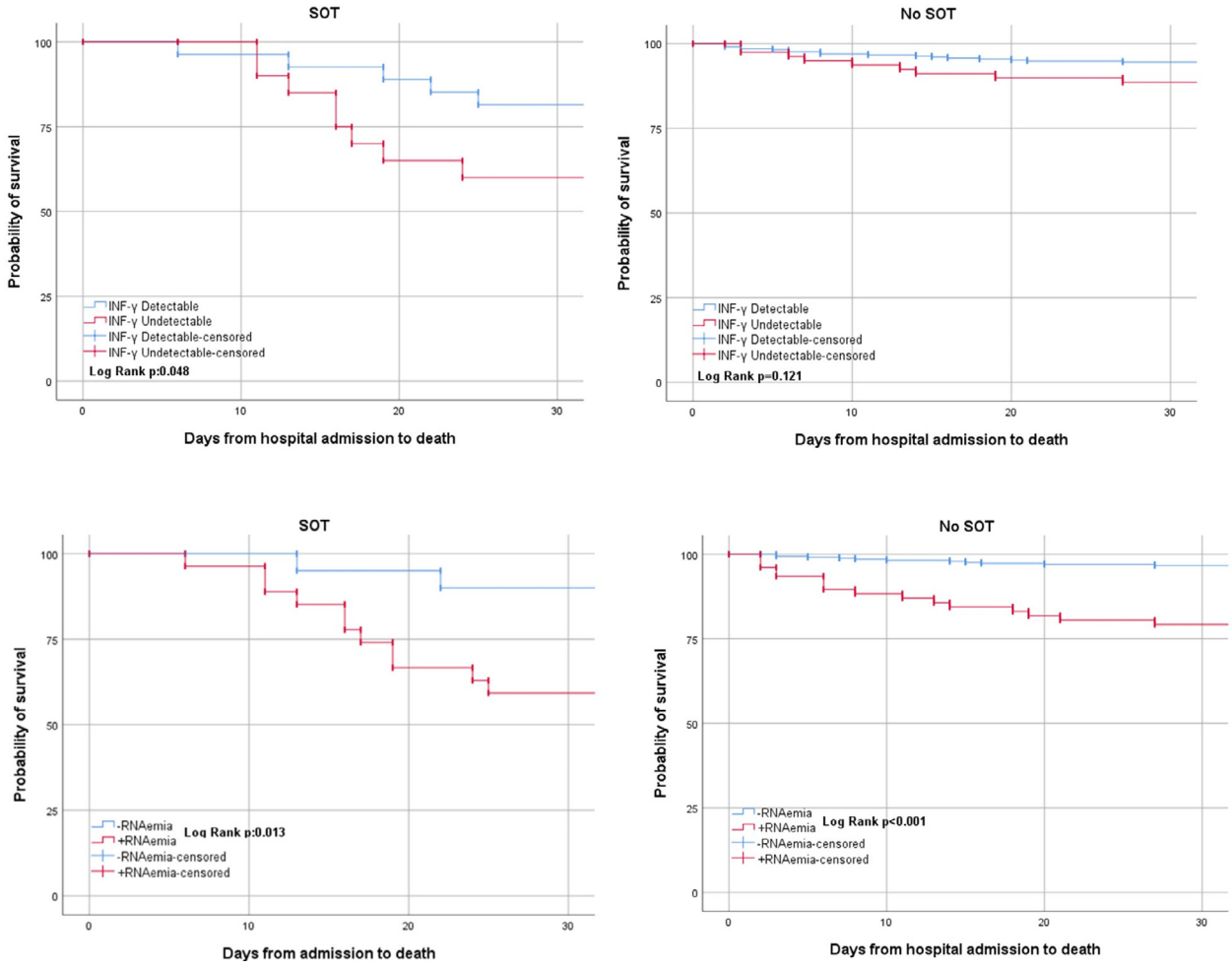

Fig. 1. Continued

IFN immunity accounts for life-threatening COVID-19 pneumonia[9] and that autoantibodies against type I IFNs increased the infection fatality rate.[10] However, we have not found association of serum undetectable IFN-α with unfavorable outcome, including immunosuppressed patients as the SOT recipients. A limitation is that we did not analyse IFN-stimulated genes to define a type I IFN signature nor interferon autoantibodies, because of our purpose was to identify easy-to-measure variables in the clinical setting.

In summary, the present results support the RNAemia and IFN-γ serum levels determinations, at hospital admission, in all adult COVID-19 patients, to guide their management and to assess the antiviral therapy efficacy in the case of RNAemia.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

Author contributions

JS-C, EC, JMC, and JP conceived and designed the study; obtained public funding from the Spanish Ministry of Economy, Industry, and Competitiveness; and took responsibility for the integrity of the data and the accuracy of its analysis. JP and SS-A did the scientific literature search. PC-M, JB-C, CI, RR-A, JA, PP-P, EG-D, CR, JPR, MJB-V, SS, RV-O, JNA, CG-G, MJB-V, DG-C, NM, GB, MAG-B, JMS, MA-G, RA-M, JG-A, JAO, ZRP-B, AP, JAL and JRB supported the inclusion of patients and the acquisition of data. JS-C, MC-L and JB-C processed the research clinical samples and obtained the data. SS-A, MC-L and JB-C processed the data, SS-A, MC-L and JP did the statistical analysis. SS-A, MC-L, JP, MA-G, JS-C and EC did the interpretation of data and wrote the draft of the manuscript. All authors critically revised the manuscript for important intellectual content and gave final approval for the version published.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.019.

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SUPPLEMENTARY MATERIAL

Serum IFN-γ and RNAemia temporal profiles as biomarkers of severe COVID-19 in solid organ transplant and immunocompetent patients

1. SUPPLMENTARY METHODS

Interferon-α and interferon-γ plasma levels

Serum samples collected from patients were stored at −80 ºC. The IFN-α (USCN Life Science & Technology Company, Missouri, TX, USA) and IFN-γ (RayBiotech, Norcross, GA, USA) were quantified by ELISA according to the manufacturer's instructions. Briefly, serum samples for IFN-α quantification were diluted 1:2 in assay diluent and incubated 1 h at 37 °C. After that, working reagent A was added, plate was incubated 1 h at 37 °C and washed 3 times before adding reagent B and let for 30 min at 37°C. Finally, plate was washed 5 times, and revealed with TMB and stop solution. For IFN-γ quantification, serum samples were also diluted 1:2 in assay diluent and incubated 2.5 h at room temperature (RT). Then, biotin antibodies were added, and plates were incubated for one hour at RT. Afterwards, streptavidin solution was incubated in the plate 45 min at RT and, at the end, the assay was revealed with TMB and stop solution. Plates were washed 4 times between each step of incubation. Optical density was measured at 450 nm using Multiskan™ GO Microplate Spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

The relative levels of IFN were analysed using a log/log fit curve using the statistical package GraphPad Prism 6. This assay was performed in duplicate for each sample. The lower limits of detection were 3 pg/ml y 2 pg/ml for IFN-α and IFN-γ, respectively. As reference values, IFN-α and IFN-γ levels were determined in 32 healthy uninfected adults, 12 males and 20 females, with a median age of 38 (IQR, 28-49; range 22-81) years, without SARS-CoV-2 infection, primary or secondary immunodeficiency, chronic underlying diseases, and any acute disease in the previous month.

SARS-CoV-2 RT-PCR in nasopharyngeal swabs, RNAemia detection and blood viral load

SARS-CoV-2 RNA was extracted from plasma samples and NP swabs using the MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche Diagnostics GmbH, Mannheim, Germany) following manufacturer recommendations. RT-PCR was conducted using the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel and the GoTaq® Probe 1-Step RT-qPCR System (Wisconsin, USA) in a LightCycler 96 Instrument (Roche, Germany) following the CDC's instructions. SARS-CoV-2 viral load quantification was calculated by the interpolation of the Ct values obtained using the Quantitative Synthetic SARS-CoV-2 RNA: ORF, E, N kit (ATCC, VA, USA) and expressed in copies/mL and $\log_{10}$ copies/mL.

Statistical analysis

A descriptive analysis of all obtained data was performed, and results were presented as crude number (%) or means ± SEM. The $\chi 2$, Fisher's exact test, Mann-Whitney U test, and Kruskal-Wallis test were used to compare between-group differences. When appropriate, continuous variables were dichotomized using data classification analysis, in accordance with their association with mortality[1,2]. Being this a contemporary and accessible cohort, we were able to recover all the necessary data for the agreed aims achievement. Hence, the small number of missing values (Supplementary Table 1) and the fact that they were missing completely at random, enabled the implementation of a complete-case analysis.

To identify bivariate correlation among IFN-α and IFN-γ levels, SARS-CoV-2 RNAemia, quantitative baseline variables, and the final WHO Clinical Progression Scale[3] at 30 days, Spearman's rank correlation coefficient ρ was calculated using Origin 2021b

(OriginLab, Northampton, MA, USA) and visualized in a heat map using the app Correlation Plot 1.30.

The outcome variables were 30-day all-cause mortality and need for invasive mechanical ventilation (IMV). The main exposures of interest, recorded at hospital admission, were IFN-α and IFN-γ serum levels and SARS-CoV-2 RNAemia at hospital admission (Methods in Supplementary material). Additional exposure variables were demographics, chronic underlying conditions, Charlson Comorbidity Index (CCI), DfSO, symptoms and signs, hemogram, liver and renal biochemistry, inflammatory biomarkers, pneumonia, CURB-65 score, quick Sequential Organ Failure Assessment (qSOFA) score, respiratory support, and COVID-19 severity according to the WHO Clinical Progression Scale[3].

Cox regression was used to analyse the impact of undetectable IFN-α/IFN-γ levels and RNAemia detection on 30-day all-cause mortality. Variables with a p value <0.10 in univariate comparisons and those considered clinically relevant were included in the multivariate models. Interaction, confusion, and collinearity were thoroughly explored. A propensity score (PS) for patients with *vs.* without RNAemia was calculated, and its predictive ability for the observed data was assessed using the area under the receiver operating characteristic curve (AUROC) with a 95% confidence interval (CI). Statistical analyses were carried out using the statistical package SPSS (SPSS 26.0, IBM Corp, Armonk, New York, USA). GraphPad Prism 9.0.0 (GraphPad Software, San Diego, CA, USA) was used for graphing and analysis of survival curves using the Kaplan-Meier method, and significance was determined using the Mantel-Cox test.

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2. SUPPLEMENTARY RESULTS, TABLES AND FIGURES

Supplementary Results

INF-α levels were higher in no SOT patients *vs.* healthy controls (p=0.042) and SOT recipients (p=0.047). IFN-γ levels were higher in no SOT patients (p<0.001) and SOT recipients (p=0.02) *vs.* healthy controls (Supplementary Fig. 1A).

The 75 patients with a WHO final score of 7-10, had more frequent RNAemia (58.7% vs. 15.8%, p<0.001) as well as higher plasma RNAemia levels (2.53 [2.18-3.17] vs. 2.05 [1.75-2.72] log10 copies/mL; p=0.0065), compared with the 380 patients with a WHO final score of 4-6 (Supplementary Fig. 2A and 2B).

The pairwise correlations heatmaps between IFN-α and IFN-γ plasma levels, SARS-CoV-2 RNAemia viral load, baseline variables, and unfavourable clinical outcome (WHO final score 7-10) for the SOT recipients and no SOT patients are detailed in Supplementary Fig. 3). As for the IFN-α, it showed positive correlation with the age, CCI, plasma creatinine, and WHO basal score, and negative correlation with lymphocytes and platelets counts in the no SOT patients. In the SOT recipients, IFN-α only showed negative correlation with the platelets count. IFN-γ had positive correlation with the platelets count in the no SOT patients; in the SOT recipients it showed positive correlation with lymphocytes count, and negative correlation with the age, CCI, and WHO basal score. SARS-CoV-2 RNAemia showed positive correlation with neutrophils, C-reactive protein, and the WHO final score in no SOT patients, and positive correlation with the heart rate, LDH, neutrophils, and platelets, and negative correlation with lymphocytes count in the SOT recipients.

Supplementary Tables

Supplementary Table 1. Missing data for the variables collected in the cohort.	
Variable	**% Missing data**
Demographics and underlying conditions	
Sex	0
Age	0
Chronic kidney disease	0.2
Chronic liver disease	0.2
SOT	0
Admission symptoms and signs	
Dyspnoea	0.7
Temperature	0.7
SpO_2	4.4
HR	13.8
Admission image and laboratory findings	
Infiltrates on chest X-rays	2.2
Neutrophil count	5.3
Lymphocyte count	2.2
Platelets	1.5
Creatinine	3.1
C-reactive protein	4.8
Ferritin	11.2
D-dimer	16.7
LDH	11.2
IFN alpha	0
IFN gamma	0
RNAemia	0
Admission scores	
CCI	0.4
CURB-65	3.1
qSOFA	2.9
WHO basal score [a]	0.2
Outcomes	
IMV	0
Mortality at day 30	0
WHO final score [a]	0

Abbreviations (in order of appearance): SOT, solid organ transplant; SpO_2, peripheral capillary oxygen saturation; HR, heart rate; LDH, lactate dehydrogenase; IFN, interferon; CCI, Charlson Comorbidity Index; CURB-65, Severity Score for Community-Acquired Pneumonia; qSOFA, quick Sequential Organ Failure Assessment score; IMV, invasive mechanical ventilation.

[a] WHO Clinical Progression Scale, doi: 10.1016/S1473-3099(20)30483-7.

Supplementary Table 2. Demographics, underlying chronic diseases, clinical features, IFN-α, IFN-γ, RNAemia, and outcomes in all, SOT recipients, and no SOT patients.

Variable	All cohort (n = 455)	SOT recipients (n = 47)	No SOT patients (n = 408)	*P* value [e]
Demographics and underlying conditions				
Male sex	261 (57.4)	28 (59.6)	233 (57.1)	0.746
Age >70 years	157 (34.5)	11 (23.4)	146 (35.8)	0.091
Chronic kidney disease [a]	42 (9.3)	7 (15.2)	35 (8.6)	0.173
Chronic liver disease [b]	13 (2.9)	1 (2.2)	12 (2.9)	1.000
Admission symptoms and signs				
Dyspnoea	231 (51.1)	20 (44.4)	211 (51.8)	0.346
Temperature ≥37.5ºC	129 (28.5)	8 (17.8)	121 (29.7)	0.092
DBP <60 mmHg	21 (5.9)	3 (8.6)	18 (5.6)	0.449
SpO_2 <95%	203 (46.6)	19 (43.2)	184 (46.9)	0.636
HR >100 bpm	117 (29.8)	12 (31.6)	105 (29.7)	0.806
RR >30 bpm	7 (5.3)	2 (15.4)	5 (4.2)	0.140
Admission image and laboratory findings				
Infiltrates on chest X-rays	403 (88.6)	35 (74.5)	368 (90.2)	0.001
Neutrophil count >7500/μL	85 (19.7)	7 (16.7)	78 (20.1)	0.600
Lymphocyte count <1000/μL	224 (50.3)	26 (61.9)	198 (49.1)	0.115
Platelets <130 000/μL	62 (13.8)	12 (27.9)	50 (12.3)	0.005
Creatinine >1.3 mg/dL	105 (23.8)	30 (71.4)	75 (18.8)	<0.001
C-reactive protein >100 mg/L	151 (34.9)	14 (35.0)	137 (34.9)	0.986
Ferritin >1000 ng/mL	88 (21.8)	7 (19.4)	81 (22.0)	0.722
D-dimer >600 ng/mL	224 (59.1)	28 (84.8)	196 (56.6)	0.002
LDH >300 IU/L	189 (46.8)	16 (41.0)	173 (47.4)	0.448
IFN-α undetectable	59 (13.0)	4 (8.5)	55 (13.5)	0.337
IFN-α (pg/mL) [c]	15.52 (3.45–29.48)	3.74 (0.60–22.99)	16.79 (5.29–32.72)	0.231
IFN-γ undetectable	99 (21.8)	20 (42.6)	79 (19.4)	<0.001
IFN-γ (pg/mL) [c]	111.90 (7.20–305.51)	26.14 (0.00–180.00)	120.71 (12.33–350.70)	0.247
RNAemia positive	104 (22.9)	27 (57.4)	77 (18.9)	<0.001
RNAemia (log_{10} copies/mL) [c]	2.39 (1.88–3.08)	2.43 (2.17–3.23)	2.37 (1.87–3.03)	0.282
Admission scores				
CCI ≥3	258 (57.0)	35 (77.8)	223 (54.7)	0.003
CURB-65 ≥2	108 (24.5)	16 (35.6)	92 (23.2)	0.069
qSOFA ≥2	13 (2.9)	2 (5.9)	11 (2.7)	0.264
WHO basal score 6–9 [d]	32 (7.0)	4 (8.5)	28 (6.9)	0.761
Outcomes				
IMV	35 (7.7)	13 (27.7)	22 (5.4)	<0.001
Mortality at day 30	45 (9.9)	15 (31.9)	30 (7.4)	<0.001
WHO final score 7-10 [d]	75 (16.5)	21 (44.7)	54 (13.2)	<0.001

Data are presented as No. (%). P values are calculated by χ^2 or Fisher's test, as appropriate.

Abbreviations (in order of appearance): SOT, solid organ transplant; DBP, diastolic blood pressure; SpO_2, peripheral capillary oxygen saturation; HR, heart rate; RR, respiratory rate; LDH, lactate dehydrogenase; IFN, interferon; CCI, Charlson Comorbidity Index; CURB-65, Severity Score for Community-Acquired Pneumonia; qSOFA, quick Sequential Organ Failure Assessment score; IMV, invasive mechanical ventilation.

[a] Kidney transplant recipients are excluded from this category.

[b] Liver transplant recipients are excluded from this category.

[c] Median (IQR). P values are calculated by the Mann-Whitney U test.

[d] Severity rating according to the WHO Clinical Progression Scale (doi: 10.1016/S1473-3099(20)30483-7), ranged from 0 (not infected) to 10 (dead), of which scores 6–9 represent severe diseases.

[e] Comparisons between SOT recipients and no SOT patients.

Supplementary Table 3. IFN-α, IFN-γ, and RNAemia detection and plasma levels, and mortality rates by days from symptoms onset (DfSO), in SOT recipients and no SOT patients.				
DfSO at hospital admission	**Total cohort (N = 455)**	**SOT recipients (N =47)**	**No SOT patients (N = 408)**	**p value**
IFN-α				
≤ 3	76/83 (91.5) *	8/9 (88.9)	68/74 (91.9)	0.567
		14.2 (2.1-24.1) **, #	23.5 (13.8-52.7)	0.054
4 to 6	108/122 (88.5)	12/15 (80)	96/107 (89.7)	0.236
		19.5 (3.9-40.4)	20.7 (9.7-39.4)	0.358
7 to 10	146/172 (84.8)	16/16 (100)	130/156 (83.3)	0.064
		1.4 (0.5-20.4)	18.9 (9.6-31.4)	0.001
≥ 11	66/78 (84.6)	7/7 (100)	59/71 (71.8)	0.295
		1.03 (0.7-5.8)	15.2 (6.05-30.0)	0.004
TOTAL	396/455 (86.8)	43/47 (91.48)	353/408 (86.5)	0.360
		4.9 (0.75-23.4)	19.98 (10.74-37.98)	**0.000**
IFN-γ				
≤ 3	62/83 (74.7) *	5/9 (55.5)	57/74 (77.1)	0.159
		55.9 (36.34-197.1) **	134.4 (71.1-399.8)	0.194
4 to 6	96/122 (78.7)	10/15 (66.7)	86/107 (80.4)	0.187
		187.4 (77.5-375.8)	179.8 (70.6-377.4)	0.792
7 to 10	135/172 (78.5)	9/16 (56.2)	126/156 (80.7)	0.031
		158.3 (35.9-543.4)	155.18 (61.8-369.7)	0.853
≥ 11	63/78 (80.7)	3/7 (42.8)	60/71 (84.5)	0.023
		187.9 (144-2-188)	265.96 (70.29-506.98)	0.570
TOTAL	356/455 (78.02)	27/47 (57.4)	329/408 (80.6)	0.000
		172.27 (52.3-303.8)	164.83 (69.06-410.74)	0.834
RNAemia				
≤ 3	23/83 (27.7) *	6/9 (66.7)	17/74 (22.9) ##	0.012
		3.3 (2.11-4.04) ***	2.7 (2.3-3.4)	0.609
4 to 6	29/122 (23.7)	7/15 (46.7)	22/107 (20.5)	0.047
		2.8 (2.7-3.2)	2.6 (2.2-3.3)	0.263
7 to 10	41/172 (23.8)	9/16 (56.2)	32/156 (20.5)	0.003
		3.3 (2.5-3.9)	2.5 (3.14-3.7)	0.841
≥ 11	11/78 (14.1)	5/7 (71.4)	6/71 (8.4)	0.000
		2.9 (2.9-4.25)	2.3 (1.8-2.9)	0.052
TOTAL	104/455 (22.8)	27/47 (57.4)	77/408 (18.9)	0.000
	2,89 (2,41-3,61)	2,95 (2,71-3,71)	2,87 (2,39-3,57)	0.154
Mortality				
≤ 3	15/83 (18.1) *	4/9 (44.4) ###	12/74 (16.2) ####	0.064
4 to 6	12/122 (9.8)	5/15 (33.3)	7/107 (6.5)	0.006
7 to 10	15/172 (8.7)	5/16 (31.3)	11/156 (7.1)	0.008
≥ 11	1/78 (1.3)	1/7 (14.3)	0/71 (0.0)	0.089
TOTAL	43/455 (9.5)	15/47 (31.9)	30/408 (7.4)	<0.001

SOT: solid organ transplantation; * n/N (%); ** pg/mL (median [IQR]); *** log_{10} copies/mL (median [IQR]); # IFN-α levels alongside the four time-periods (p=0.015, Kruskal-Wallis test); ## RNAemia rates alongside the four time-periods (p=0.014); ### Mortality rates alongside the four time-periods in SOT (p=0.346); #### Mortality rates alongside the four time-periods in no SOT (p=0.001).

Supplementary Table 4. Demographics, underlying chronic diseases, clinical features, and outcomes of patients with COVID-19 according to the presence of RNAemia.

Variable	RNAemia (n = 104)	No RNAemia (n = 351)	*P* value
Demographics and underlying conditions			
Male sex	63 (60.6)	198 (56.1)	0.45
Age >70 years	33 (31.7)	124 (35.1)	0.50
Chronic kidney disease [a]	11 (10.7)	31 (8.8)	0.57
Chronic liver disease [b]	5 (4.9)	8 (2.3)	0.18
SOT	29 (27.9)	20 (5.7)	<0.001
Admission symptoms and signs			
Dyspnoea	62 (61.4)	169 (48)	0.01
Temperature ≥37.5 ºC	30 (29.4)	100 (28.4)	0.83
DBP <60 mmHg	7 (9.3)	14 (5)	0.17
SpO_2 <95%	54 (54.5)	149 (44)	0.07
HR >100 bpm	30 (34.1)	87 (28.4)	0.32
RR >30 bpm	5 (15.6)	2 (2)	0.01
Admission image and laboratory findings			
Infiltrates on chest X-rays	92 (91.1)	282 (81.3)	0.02
Neutrophil count >7500/μL	22 (22.2)	63 (18.9)	0.48
Lymphocyte count <1000/μL	68 (67.3)	157 (45.4)	<0.001
Platelets <130 000/μL	20 (19.6)	42 (12.1)	0.06
Creatinine >1.3 mg/dL	36 (36.4)	69 (20.1)	<0.001
C-reactive protein >100 mg/L	50 (51.5)	102 (30.2)	<0.001
Ferritin >1000 ng/mL	26 (29.2)	62 (19.6)	0.05
D-dimer >600 ng/mL	51 (64.6)	174 (57.6)	0.27
LDH >300 IU/L	61 (67)	128 (40.6)	<0.001
IFN-α undetectable	17 (16.3)	42 (12.0)	0.24
IFN-α (pg/mL) [c]	15.73 (0.75-45.42)	15.52 (5.06-25.48)	0.15
IFN-γ undetectable	28 (26.9)	71 (20.2)	0.15
IFN-γ (pg/mL) [c]	140.34 (0.00-222.85)	103.29 (11.00-360.47)	0.94
Admission scores			
CCI ≥3	66 (64.1)	193 (54.8)	0.10
CURB-65 ≥2	34 (34)	74 (21.6)	0.01
qSOFA ≥2	5 (5.2)	8 (2.3)	0.17
WHO basal score 6–9 [d]	17 (16.5)	14 (4)	<0.001
Outcome			
IMV	25 (24.0)	10 (2.8)	<0.001
Mortality at day 30	32 (30.8)	13 (3.7)	<0.001
WHO final score 7-10 [d]	44 (42.3)	31 (8.8)	<0.001

Data are presented as No. (%). *P* values are calculated by χ^2 or Fisher's test, as appropriate.

Abbreviations (in order of appearance): SOT, solid organ transplant; DBP, diastolic blood pressure; SpO_2, peripheral capillary oxygen saturation; HR, heart rate; RR, respiratory rate; LDH, lactate dehydrogenase; IFN, interferon; CCI, Charlson Comorbidity Index; CURB-65, Severity Score for Community-Acquired Pneumonia; qSOFA, quick Sequential Organ Failure Assessment score; IMV, invasive mechanical ventilation.

[a] Kidney transplant patients are excluded from this category.

[b] Liver transplant patients are excluded from this category.

[c] Median (IQR). P values are calculated by the Mann-Whitney U test.

[d] Severity rating according to the WHO Clinical Progression Scale (doi: 10.1016/S1473-3099(20)30483-7), ranged from 0 (not infected) to 10 (dead), of which scores 6–9 represent severe disease.

Supplementary Table 5. Analytical data of patients with COVID-19 according to the presence of RNAemia.				
Variable	**Total cohort (n = 455)**	**RNAemia (n = 104)**	**No RNAemia (n = 351)**	***P* value**
Neutrophil count, $x10^3/\mu L$	5.43 (3.32)	5.44 (3.25)	5.43 (3.35)	0.98
Lymphocyte count, $x10^3/\mu L$	1.17 (0.73)	0.98 (0.65)	1.22 (0.74)	0.004
Platelets, $x10^3/\mu L$	216.9 (99.8)	178.1 (64.9)	228.4 (105.3)	<0.001
Creatinine, mg/dL	1.21 (1.02)	1.41 (1.15)	1.15 (0.97)	0.03
C-reactive protein, mg/L	92.3 (92.2)	116.0 (83.6)	85.5 (93.6)	0.004
Ferritin, ng/mL	705.7 (775.9)	914.0 (857.4)	646.8 (742.2)	0.004
D-dimer, ng/mL	610.0 (1390.1)	892.0 (907.9)	1110.0 (1489.3)	0.22
LDH, IU/L	318.5 (130.1)	366.8 (145.8)	304.4 (121.8)	<0.001

Data are presented as Mean (SD) or Median (IQR). *P* values are calculated by Student t-test or Mann-Whitney test, as appropriate. LDH: lactate dehydrogenase; IFN: interferon.

Supplementary Table 6. Multivariate logistic regression analysis of risk factors associated with unfavourable outcome [a] in SOT recipients (n = 47)

Variable	B coefficient	Standard error	Wald	Degree of freedom	Adjusted analysis [b]	
					OR (95% CI)	*P* value
IFN alpha undetectable	-0.621	1.503	0.171	1	0.537 (0.028–10.232)	0.680
IFN gamma undetectable	1.678	0.985	2.901	1	5.353 (0.777–36.899)	0.089
Days from symptoms onset ≤10	2.197	1.284	2.927	1	8.995 (0.726–111.412)	0.087
Presence of RNAemia	1.816	0.858	4.479	1	6.147 (1.144–33.046)	0.034
CCI ≥3	0.545	1.058	0.265	1	1.724 (0.217–13.720)	0.607
CURB-65 ≥2	0.846	0.897	0.891	1	2.331 (0.402–13.524)	0.345
Constant	-4.791	1.844	6.749	1	0.008	0.009

Abbreviations (in order of appearance): SOT, solid organ transplant; OR, odds ratio; IFN, interferon; CCI, Charlson Comorbidity Index; CURB-65, Severity Score for Community-Acquired Pneumonia.

[a] Invasive mechanical ventilation and/or death (Final WHO score 7-10).

[b] The area under the receiver operating characteristic (AUROC) curve of the model was 0.84 (95% CI, 0.72–0.97), p<0.001, and no interactions were identified.

Supplementary Table 7. Multivariate analyses of risk factors associated with 30-day all-cause mortality using Cox regression in the no SOT patients (n = 408)

Variable	Adjusted analysis [a]		Adjusted by PS [b]	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
IFN alpha undetectable	1.773 (0.662–4.750)	0.255	0.981 (0.176–5.478)	0.983
IFN gamma undetectable	1.073 (0.441–2.607)	0.877	3.860 (1.046–14.238)	0.043
Days from symptoms onset ≤3	2.048 (0.931–4.506)	0.075	3.805 (0.906–15.983)	0.068
Presence of RNAemia	5.331 (2.381–11.937)	<0.001	8.457 (2.009–35.598)	0.004
CCI ≥3	3.378 (0.880–12.968)	0.076	2.715 (0.419–17.595)	0.295
CURB-65 ≥2	3.352 (1.320–8.515)	0.011	2.703 (0.676–10.803)	0.160
Propensity score [b]	…	…	0.137 (0.001–16.421)	0.415

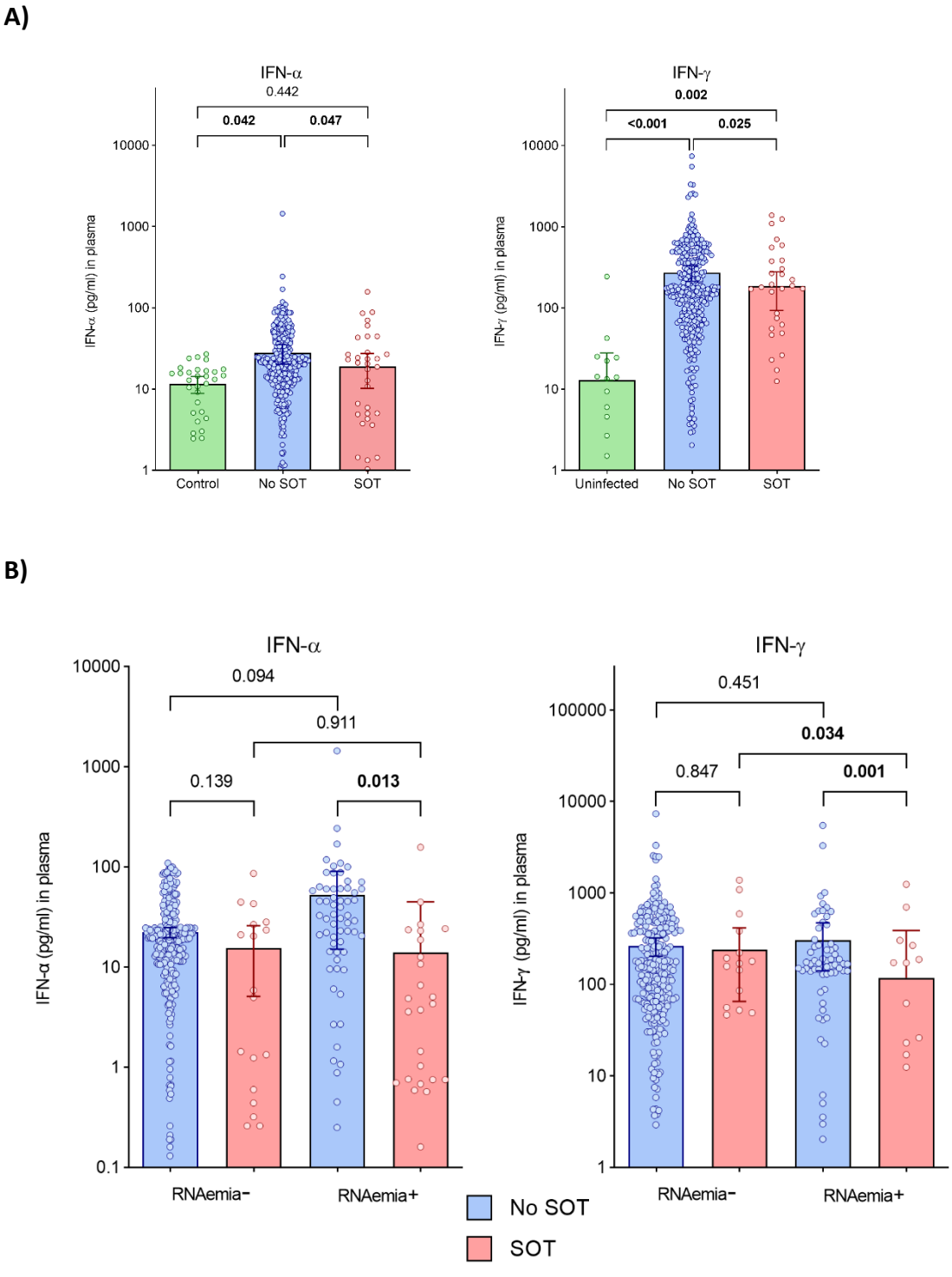
Abbreviations (in order of appearance): SOT, solid organ transplant; PS, propensity score; HR; hazard ratio; CI, confidence interval; IFN, interferon; CCI, Charlson Comorbidity Index; CURB-65, Severity Score for Community-Acquired Pneumonia.

[a] The area under the receiver operating characteristic (AUROC) curve of the model was 0.84 (95% CI, 0.80–0.91), p<0.001, and no interactions were identified.

[b] The variables included in the propensity score were sex, dyspnoea, peripheral capillary oxygen saturation, neutrophil and lymphocyte count, C-reactive protein, ferritin, D-dimer, and lactate dehydrogenase. The AUROC curve of the PS model was 0.84 (95% CI, 0.75–0.93), p<0.001.

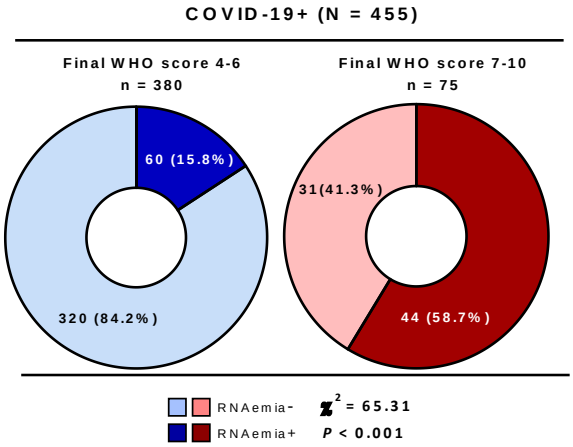
Supplementary Figures

Supplementary Figure 1. IFN-α and IFN-γ plasma levels (means ± SEM) in (A) healthy uninfected controls *vs.* no SOT and SOT recipients and (B) patients without *vs.* with RNAemia in no SOT and SOT recipients.

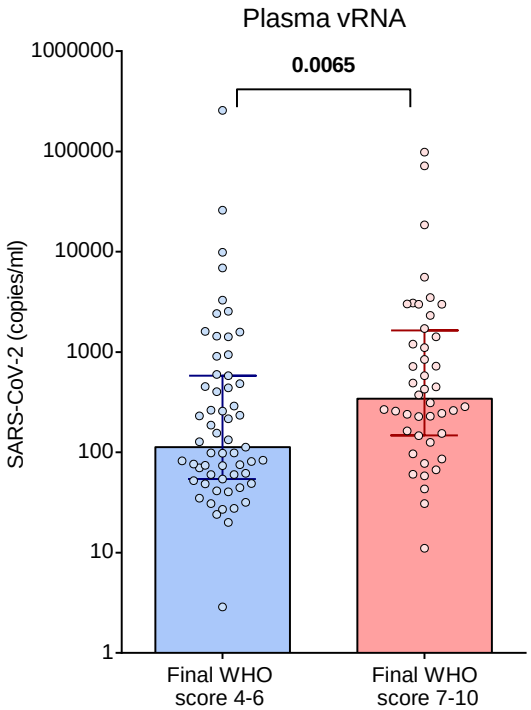


Supplementary Figure 2. SARS-CoV-2 RNAemia rates (A) and plasma viral load (median, IQR) (B) regarding the Final WHO Clinical Progression Scale (33) in all cohort (n=455).

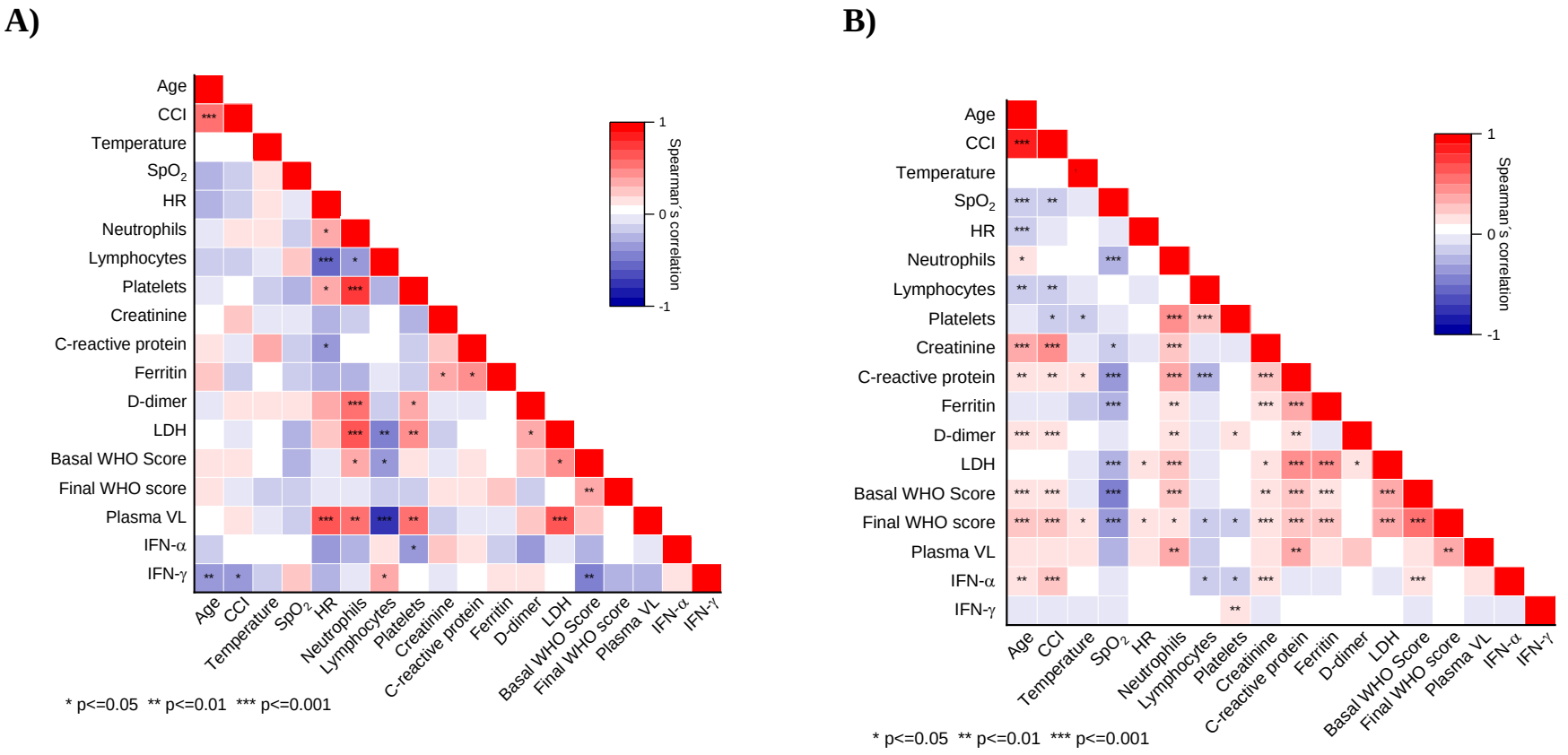
A)



B)



Supplementary Figure 3. Pairwise correlation heatmaps between IFN-α and IFN-γ plasma levels and SARS-CoV-2 RNAemia at hospital admission and baseline factors (Spearman's rank correlation coefficient) in (A) SOT recipients (n=47) and (B) no SOT patients (n=408). CCI, Charlson Comorbidity Index; SpO_2, capillary oxygen saturation; HR: heart rate; LDH, lactate dehydrogenase; Plasma VL: RNAemia (copies/mL); IFN: interferon.



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