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Early Plasma Interferon- β Levels as a Predictive Marker of COVID-19 Severe Clinical Events in Adult Patients

Running title: Early IFN- β levels in COVID-19 patients

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1 *Journal of Medical Virology*

2 *Short Communication*

3 Full Title:

4 **Early Plasma Interferon- β Levels as a Predictive Marker of COVID-**
5 **19 Severe Clinical Events in Adult Patients**

6
7 **Running title:** Early IFN- β levels in COVID-19 patients

8
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27 **Abstract (187 words):**

28 We assessed relationships between early peripheral blood type I Interferons levels,
29 clinical new early warning scores (NEWS) and clinical outcomes in hospitalized
30 COVID-19 adult patients. Early IFN- β levels were lower among patients who further
31 required intensive care unit (ICU) admission than those measured in patients who did
32 not require an ICU admission during SARS-CoV-2 infection. IFN- β levels were
33 inversely correlated with NEWS only in the subgroup of patients who further required
34 ICU admission. To assess whether peripheral blood IFN- β levels could be a potential
35 relevant biomarker to predict further need for ICU admission, we performed Receiver
36 Operating Characteristic (ROC) curve analyses that showed for all study patients an
37 area under ROC curve of 0.77 growing to 0.86 ($P= 0.003$) when the analysis was
38 restricted to a subset of patients with NEWS ≥ 5 at the time of hospital admission.
39 Overall, our findings indicated that early peripheral blood IFN- β levels might be a
40 relevant predictive marker of further need for an intensive care unit admission in
41 hospitalized COVID-19 adult patients, specifically when clinical score (NEWS) was
42 graded as upper than 5 at the time of hospital admission.

43

44 **Keywords:** COVID-19, SARS-CoV-2, type I Interferons, NEWS, intensive care unit

45

46 **BACKGROUND:**

47 It is now well admitted that SARS-CoV-2 caused coronavirus disease-19 (COVID-19)
48 clinical stages evolve from early infection (stage I) towards a mild-to-moderate
49 pulmonary involvement without or with hypoxia (stage II), which can be followed by
50 an hyperinflammatory phase resulting in potential severe clinical events requiring an
51 intensive care unit (ICU) admission (clinical stage III) ¹. Pathophysiology of SARS-
52 CoV-2 infection is clearly characterized by an early viral replicative phase in
53 respiratory tract tissues associated with low viremia levels (clinical stage I) during 8
54 days after the first onset of symptoms, followed by an inflammatory phase occurring
55 from 9 to 12 days after the first onset of symptoms (clinical stages II and III).

56

57 COVID-19 inflammatory phase is characterized by a dysregulated inflammatory host
58 response with an abnormal release of proinflammatory cytokines **mediated by the**
59 **activation of cell surface or intracellular toll like Receptors (TLRs)** ²⁻⁶. Remarkably, a
60 low interferon-Beta (IFN- β) production in the peripheral blood of severe (clinical stage
61 III) COVID-19 patient was evidenced suggesting that type I IFN low production levels
62 could drive the development of clinical stages II and III during the course of the
63 SARS-CoV-2 infection⁷. Type I IFNs influence the development of innate and
64 adaptive immune responses limiting virus replication activities and preventing the
65 development of severe clinical events during viral respiratory infections^{8,9}. However,
66 patterns of type I IFNs production during SARS-CoV-2 infection, were investigated
67 only in COVID-19 patients at clinical stages II and III (9-12 days after onset of first
68 symptoms)^{7,10}. In the present time, type I IFN expression pattern in the early phase of
69 COVID-19 (clinical stage I) and its potential relationship with further development of
70 severe clinical events remains to be investigated.

71 In the present retrospective investigation, we assessed peripheral blood type I IFNs
72 and SARS-CoV-2 RNA levels at early phase (1-8 days after the first symptom onset)
73 of COVID-19 in adult patients who further required or not an ICU admission during
74 infection. Among these two subsets of patients, we assessed potential relationships
75 between early blood type I IFNs and SARS-CoV-2 RNA levels and clinical new early
76 warning scores (NEWS) at the time of hospitalisation.

77

78

79

80 **CLINICAL SAMPLES and METHODS:**

81 *Study design:*

82 From November 2020 to March 2021, peripheral blood EDTA-plasma samples taken
83 from adult patients had been stored at -80°C in Reims University Hospital (Grand-Est,
84 France) until processing for anti SARS-CoV-2 IgM or IgG antibodies detection assays.
85 This biobank was declared as a biological specimen's research collection and was
86 registered by the French Ministry of High Education and Research (number DC-
87 2020-4052).

88 From this research biobank samples (n=4704 sampled patients), we retrospectively
89 selected samples taken from adult patients (i) hospitalized in medicine wards for
90 COVID-19 (n=1116) ; (ii) with a time delay less than 9 days between sample
91 collection and onset of COVID-19 symptoms (n= 183); (iii) with full clinical data
92 available from a registered clinical data bank (Reims University Hospital GDPR
93 number RMR004-061120) elaborated for an internal purpose between March 1st
94 2020 and March 31rd 2021 and focusing on COVID-19 adult patients (n=143).
95 Patients who required palliative care or hospitalized directly in ICU were excluded
96 from the study.

97 Finally, only 43 COVID-19 adult patients with available frozen EDTA-plasma samples
98 and with full registered clinical data were included in this retrospective investigation.

99

100 *Demographic, clinical and medical data collection:*

101 For each selected patient, the following data had been previously registered in a
102 declared database (RMR004-061120) during their hospital stage: sex, age,
103 comorbidities, immunocompromised state, date of symptoms onset, new early
104 warning score (NEWS) graded at the time of hospital admission¹¹, computerized

105 tomography chest scan results (CT-chest scan), drugs prescription and further need
106 for intensive care unit admission (ICU) and in-hospital mortality. Demographic and
107 clinical characteristics of study patients are depicted in Table 1.

108

109 *Ethical approval:*

110 The Institutional Ethics Committee (IEC), University hospital of Reims (Grand-Est,
111 France) waived the requirement of informed consent and approved all methods and
112 protocols. The study was conducted in accordance with the Declaration of Helsinki
113 Ethical Principles and Good Clinical Practices. Patients did not provide individual
114 consent because of the retrospective and non-interventional nature of this study, in
115 accordance with French legislation. No patient raised an opposition to the use of their
116 recorded medical data or their samples collected at the time of hospitalization for
117 COVID-19. Data confidentiality was preserved during this internal study (Reims
118 University Hospital GDPR register number RMR004-061120), and research
119 collection of biological specimens was registered in French Ministry of Higher
120 Education and Research as number DC-2020-4052.

121

122 *Peripheral blood type I interferons and SARS-CoV-2 RNA load*

123 Using our research biological samples (registered research biobank), peripheral
124 blood levels of Interferon-alpha (IFN- α), Beta (IFN- β) were determined on plasma
125 samples using ELISA (*enzyme-linked immunosorbent assay*) (Biotechne, France)
126 according to the manufacturer's instructions. In parallel, SARS-CoV-2 RNA load in
127 EDTA plasma samples were quantified using droplet based digital PCR (dd-PCR)
128 (MOBICYTE technical platform, Reims, France), as previously described⁷, with Bio-
129 Rad SARS-CoV-2 dd-PCR kit (Bio-Rad, France). Viral RNA was extracted using

130 QIAmp viral RNA mini kit (Qiagen) according to the manufacturer's guidelines. Viral
131 concentration results (copies/ml, cp/ml) were calculated considering the extraction
132 volumes of plasma (140 µl).

133

134 *Statistical analyses:*

135 Quantitative variables expressed as median [range] were compared using the Mann
136 Whitney U-test. Qualitative variables expressed as percentages were compared
137 using Fischer's exact test or Pearson Chi-2 if applicable. When linear regression was
138 performed, slopes were compared using Spearman test. When Receiver operating
139 characteristic (ROC) curve analysis was performed, Area under ROC Curve,
140 Standard Error and P value were calculated using the trapezoid rule, the Hanley
141 Method and Z ratio respectively. A *P* value<0.05 was considered statistically
142 significant. Statistical analyses were performed using GraphPad Prism 8 (GraphPad)
143 and SAS version 9.4 (SAS Institute Inc).

144

145 *Data availability:*

146 The datasets generated and/or analysed during the current study are not publicly
147 available according to French law guidelines and registrations but are available from
148 the corresponding author on reasonable request.

149

150 **RESULTS**

151 **Early peripheral blood IFN- β , SARS-CoV-2 RNA levels and further need for**
152 **intensive care unit admission in COVID-19 adult patients**

153 Type I Interferons (IFNs) and SARS-CoV-2 RNA load were assessed in peripheral
154 blood samples taken from adult patients after a median time delay of 5 [1-8 days
155 after the onset of symptoms] (Table1). Among the 43 selected patients, early
156 peripheral blood IFN- β were detected in all the study patients with values ranging
157 from 40 to 929 pg/ml, whereas peripheral blood IFN- α were detectable in only 86% of
158 the study patients with values ranging from non-detectable to 326 pg/ml (Figure 1A).
159 Because low type I IFN production levels could drive the development of COVID-19
160 induced inflammatory phase, we segregated our patient group into two subsets
161 according for their further need for an ICU admission during infection. Remarkably,
162 levels of IFN- β appeared to be significantly lower among the subset of patients who
163 further required ICU admission than the subset of patients who did not further require
164 ICU admission ($P=0.001$) (Figure 1B). For IFN- α levels, no significant differences
165 between patient subsets requiring or not ICU admission was evidenced at the time of
166 hospitalization (Figure 1C). In addition, the plasma SARS-CoV-2 RNA load appeared
167 to be significantly higher in patients who further required ICU admission than those
168 measured in samples of patients who did not further required ICU admission ($P=$
169 0.03) (Figure 1D).

170

171 **Associations between early peripheral blood IFN- β levels, SARS-CoV-2 RNA**
172 **loads and clinical new early warning scores**

173 Because clinical new early warning scores (NEWS) had been previously associated
174 with further ICU admission events in COVID-19 adult patients¹¹, we first sought for a

175 potential association between NEWS and IFN- β concentrations and then between
176 NEWS and SARS-CoV-2 RNA load according to a further need for ICU admission.
177 Among the subset of patients who further required an ICU admission, a significant
178 negative correlation between NEWS and IFN- β concentrations ($P= 0.045$; $R^2= 0.226$)
179 was observed (Figure 2A, left panel). By contrast a non-significant positive
180 correlation was observed between NEWS and IFN- β concentrations among the
181 subset of patients who did not require further ICU admission ($P= 0.182$; $R^2= 0.075$)
182 (Figure 2A, right panel). No significant correlation was evidenced between NEWS
183 and SARS-CoV-2 RNA load among the two subsets of study patients (Figure 2B).
184 Remarkably, when the analysis was restricted to a subset of patients with a NEWS \geq
185 5 at hospital admission we observed a significant negative correlation between blood
186 IFN- β level and plasma SARS-CoV-2 RNA load in the subset of COVID-19 patient
187 who did not further require an ICU admission. Such a correlation was not observed
188 among patients who further require ICU admission (supplementary Figure 1).

189

190 **Early Blood IFN- β concentrations accuracy to predict the need for a further ICU** 191 **admission**

192 To assess whether peripheral blood IFN- β levels could be a relevant biomarker to
193 predict further need for ICU admission, we performed Receiver Operating
194 Characteristic (ROC) curve analyses (Figure 3). Including all study patients, the
195 sensitivity and specificity were respectively of 88% and 50% with an area under the
196 receiver operating characteristic curve (AUC) of 0.77 (Figure 3A). Remarkably, the
197 area under the ROC curve of blood IFN- β level grew to 0.86 when the analysis was
198 restricted to a subset of patients with a NEWS ≥ 5 at hospital admission indicating a
199 relevant predictive value of early IFN- β levels among the most clinically severe study

200 patients. Among the subset of patients with NEWS \geq 5 at hospital admission,
201 peripheral blood IFN- β levels below 107.6 pg/ml were associated to a further ICU
202 requirement with a specificity of 100% and a sensitivity of 60% (Figure 3B).

203

204

205

206 **DISCUSSION**

207 Investigation of peripheral blood type I IFN production patterns in SARS-CoV-2
208 infected adult patients is of major interest for understanding COVID-19
209 pathophysiology and clinical courses of infection^{7,10}. Herein, we assessed
210 relationships between early peripheral blood Interferon-Beta (IFN- β) levels, clinical
211 new early warning scores (NEWS) and clinical outcomes in SARS-CoV-2 infected
212 adult patients hospitalized from 1 to 8 days after the first symptom onset (clinical
213 stage I).

214

215 Among the 43 selected patients, anti-SARS-CoV-2 total antibodies were not detected
216 and interleukin 6 (IL6) and tumour necrosis factor-alpha (TNF- α) were not measured
217 at significant levels in peripheral blood (data not shown). These results were
218 associated with detectable SARS-CoV-2 RNA load confirming that study patients
219 were at the viral phase of COVID-19 (Figure 1D). Interestingly, early peripheral blood
220 IFN- β were detected in all the study patients, whereas IFN- α were detectable only in
221 86% of the study patients (Figure 1A). Because low type I IFN production levels
222 could drive the development of COVID-19 induced inflammatory phase (clinical
223 stages II and III), we segregated our patient group into two subsets according for
224 their further need for an ICU admission. Interestingly, our findings indicated for the
225 first time that patients who further required ICU admission demonstrated significant
226 lower peripheral blood IFN- β levels and higher SARS-CoV-2 RNA load than those
227 observed in patients who did not require ICU admission (Figure 1). Low early IFN- β
228 concentration levels in patient could be related to inter-individual sequences
229 variability in human genes implicated into the regulation of type I IFN innate
230 immunity¹², but also to the translation of SARS-CoV-2 nonstructural proteins

231 inhibiting the IFN- β promoter activation¹³ or to preexisting peripheral blood auto-
232 antibodies directed against human type I IFNs¹⁴.
233 Among the subset of COVID-19 patients who further required ICU admission, a
234 negative correlation between peripheral blood IFN- β concentrations and clinical
235 NEWS was evidenced, whereas no significant association was observed between
236 clinical scores and SARS-CoV-2 RNA levels (Figure 2). These findings were
237 completed by ROC analyses and results indicated that early peripheral blood IFN- β ,
238 but not SARS-CoV-2 RNA load, might be a relevant biomarker of a further ICU
239 admission, specifically among patients with a NEWS \geq 5 at the time of hospital
240 admission (Figure 3B). Overall, these findings supported the concept that an early
241 IFN- β treatment in COVID-19 adult patients hospitalized at phase I of SARS-CoV-2
242 infection might be of therapeutic benefit improving the clinical outcomes. However,
243 these findings remain to be fully investigated in further prospective large multicenter
244 clinical investigations.

245 **Conclusions**

246 Even if our study is a limited retrospective monocentric investigation conducted
247 before large anti-SARS-CoV-2 vaccination campaigns in general population and
248 before the emergence of new Delta or Omicron viral variants, our original findings
249 revealed a significant association between early low peripheral blood IFN- β levels
250 and high clinical scores (NEWS) during SARS-CoV-2 clinical phase I. Overall, our
251 findings indicated that early peripheral blood IFN- β levels might be a relevant
252 predictive marker of further need for an intensive care unit admission in COVID-19
253 adult patients, specifically when clinical score (NEWS) was graded as upper than 5 at
254 hospital admission.

255

256

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289

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295

296 **Author's contribution**

297 L.A, Y.N'G and F.B designed the study. L.A, F.B and Y.N'G wrote the manuscript.
298 L.A , BN. P and Y.N'G established the research biobank, the clinical data bank and
299 supervised the data collection. F.B and Y.N'G analyzed the data and designed the
300 table and the figures. D.C helped for data collection. F.B, Y.N'G, L.A, D.C, A-L.L,
301 M.G, L.H, F.B-S and BN. P provided valuable input to interpretation of the data and
302 critically reviewed the manuscript. All these authors approved the final version of the
303 present manuscript.

304

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307 research teams from the University of Reims Champagne-Ardenne.

308

309 ***Conflict of interest***

310 The authors report no conflict of interest.

311

312 ***Data availability:***

313 The datasets generated and/or analyzed during the current study are not publicly
314 available according to French law guidelines and registrations but are available from
315 the corresponding author on reasonable request.

316

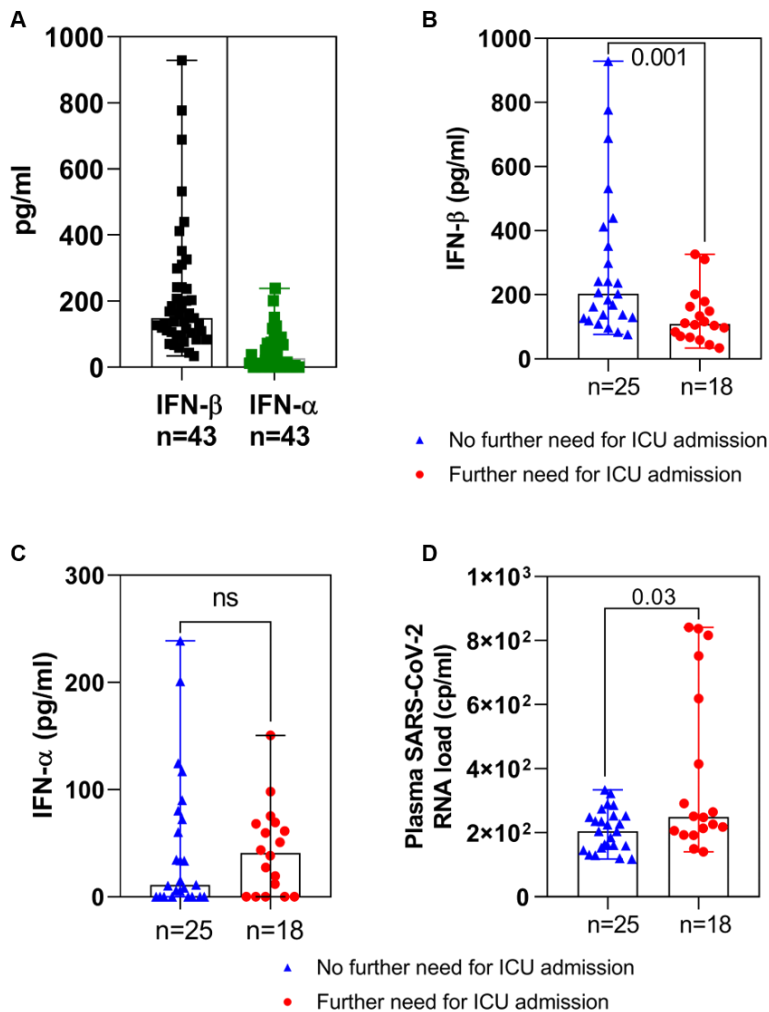
317 ***Reims Covid-19 Study group.*** Collaborators included the following: Dr Ezekiel
318 Bankole, Dr Loïs Bolko, Dr Michel Bonnivard, Dr Nelly Bourse, Dr Aurélie Brunet, Dr
319 Sandy Carazo Mendez, Dr Clement Chopin, Dr Joël Cousson, Dr Sophie Demotier,
320 Pr Gaetan Deslee, Dr Vincent Dupont, Dr Thierry Floch, Dr Julien Gautier, Dr
321 Guillaume Giordano Orsini, Dr Sophie Giordano Orsini Dr Antoine Goury, Dr Marie
322 Laure Gross, Dr Valentin Houannou, Dr Claire Lepouse, Dr Gauthier Lejeune, Dr
323 Natacha Noël, Pr Jeanne Marie Perotin, Dr Juliette Romaru, Dr Jerome Tassain. Pr.
324 Bruno Mourvillier.

325 **TABLE AND FIGURES**326 **Table 1:** Demographic and clinical characteristics COVID-19 adult patients according to their further need for ICU admission.

Characteristics of COVID-19 patients	No further need for ICU admission (n=25)	Further need for ICU admission (n=18)	P-Value
Male gender n (%)	13 (52.0)	10(55.5)	0.81
Median age (years) [range]	68 [28-92]	63 [44-78]	0.14
Comorbidities n (%) [#]	20 (80.0)	12 (66.6)	0.32*
Immunocompromised state n (%) ^{##}	6 (24.0)	4 (22.2)	0.89*
Median time delay between symptoms/admission in Covid-19 medicine ward (days) [range]	5 [0-10]	5 [0-11]	0.22
Median New Early Warning Score [range] ⁽¹¹⁾	3 [0-11]	7 [2-11]	0.0005
Median maximal lung involvement observed on CT- chest scan (%) [range]	25 [0-75]	50 [25-75]	0.001
Corticosteroids treatment n (%)	14 (56.0)	17 (94.4)	0.01*
Antibiotics n (%)	17 (68.0)	18 (100.0)	0.02*
Anticoagulation therapy n (%)	24 (96.0)	18 (100.0)	0.99*
Isocoagulant heparin therapy n (%)	10 (40.0)	7 (38.8)	0.99*
Optiflow nasal high flow therapy n (%)	0 (0.0)	6 (33.3)	0.007*
Mechanical ventilation n (%)	0 (0.0)	11 (61.1)	<0.0001*

In-hospital mortality n (%)	0 (0.0)	6 (33.3)	0.007*
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327 * Fischer's exact test; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus type 2; RT-PCR: Reverse Transcriptase
328 Polymerase Chain Reaction; CT-chest Scan: Computerized Tomography chest scan; # Comorbidities: Arterial Hypertension,
329 Diabetes mellitus, Coronary artery disease, Heart Failure, Obesity, Chronic Kidney Failure, Chronic obstructive Pulmonary Disease
330 or unbalanced Asthma; ## Immunocompromised state: cases of neoplasia (cancers), antineoplastic chemotherapy or previous
331 corticosteroids or immunosuppressive treatments.
332 ⁽¹¹⁾: Covino, M. *et al.* Predicting intensive care unit admission and death for COVID-19 patients in the emergency department using
333 early warning scores. *Resuscitation* 156, 84–91 (2020).



335

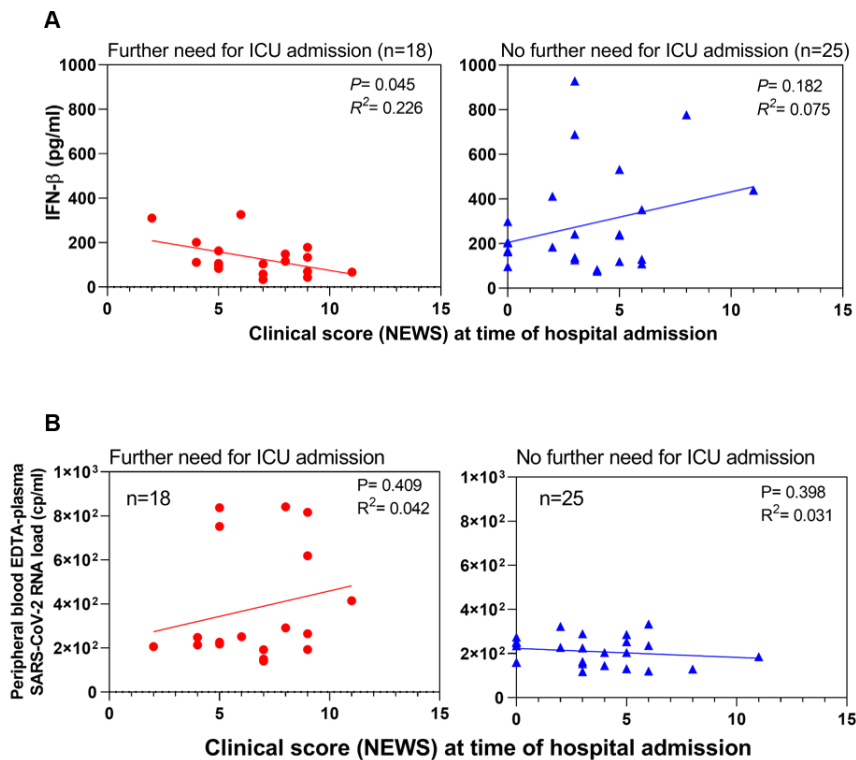
336 **Figure 1: Early peripheral blood type I IFN levels, SARS-CoV-2 RNA load and**
 337 **clinical new early warning scores in COVID-19 adult patients requiring or not**
 338 **further intensive care unit admission**

339 At the time of hospital admission type I interferon (IFN) and SARS-CoV-2 RNA load
 340 were measured in the peripheral blood of patients who further required (red circle,
 341 n=18) or not (blue triangle, n= 25) further Intensive Unit Care (ICU) admission; **A)**
 342 IFN- β (black square) and IFN- α (green square) were measured using ELISA
 343 (*enzyme-linked immunosorbent assay*) in the peripheral blood of 43 COVID-19
 344 patients. **B, C)** IFN- β and IFN- α levels were measured using a referenced ELISA; **D)**
 345 Plasma SARS-CoV-2 RNA loads were assessed by a referenced digital PCR assay.
 346 Data indicated median values. *P* values were determined using Mann-Whitney test
 347 by two-way comparisons. ns: non-significant.

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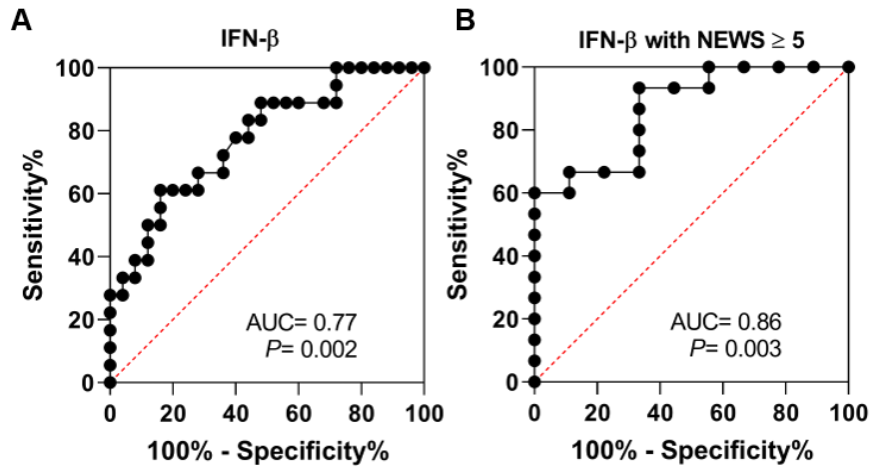
352 **Figure 2: Association of early peripheral blood type I IFN levels, SARS-CoV-2**
 353 **RNA load with clinical new early warning scores in COVID-19 adult patients**
 354 **requiring or not further intensive care unit admission**

355 **A)** Correlation analyses between clinical scores (NEWS: New Early Warning Score)
 356 and IFN- β levels in the peripheral blood of Covid-19 adult patients at the time of
 357 hospital admission: left panel with red circles (n=18) represent patients who further
 358 required an ICU admission; right panel with blue triangles (n=25) represent patients
 359 who did not further require an ICU admission. Linear regression analyses were
 360 performed using Spearman tests, $P=0.045$; $R^2=0.226$ and $P=0.182$; $R^2=0.075$,
 361 respectively. **B)** Correlation analyses between clinical scores (NEWS: New Early
 362 Warning Score) and peripheral blood plasma SARS-CoV-2 RNA load in COVID-19
 363 patients at the time of hospital admission: left panel with red circles (n=18) represent
 364 patients who further required an ICU admission and right panel with blue triangles
 365 (n=25) represent patients who did not further require an ICU admission. Linear
 366 regression analyses were performed using Spearman tests, $P=0.409$; $R^2=0.042$ and
 367 $P=0.398$; $R^2=0.031$, respectively.

368

369

370



371

372 **Figure 3: Receiver Operating Characteristic (ROC) curve of IFN-β for relevance**
 373 **to predict coronavirus disease 2019 (COVID-19) severity.**

374 **A)** ROC curve of blood IFN-β levels among study Covid-19 patients who further
 375 require or not an ICU admission; Area under the receiver operating characteristic
 376 (AUC)= 0.77, *P*= 0.002. **B)** ROC curve Blood IFN-β levels of Covid-19 patients who
 377 further required or not an ICU admission when the analysis was restricted to patients
 378 with a NEWS ≥ 5 at admission. Area under the receiver operating characteristic
 379 (AUC)= 0.86, *P*= 0.003.

380