Ferritin levels in critically ill patients with COVID-19: A marker of outcome?

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Dear Editor,

The severe form of Coronavirus Disease 2019 (COVID-19) is a systemic disease associated with high mortality rate[1,2]. Elderly, mainly men with comorbidities, are at increased risk of death. Nevertheless, younger individuals, without underlying diseases, may also develop lethal complications (myocarditis, disseminated intravascular coagulopathy, neurological complications etc.)[3,4].

In the ICU of ATTIKON University Hospital (one of the 5 Reference Hospitals for COVID-19 in Athens, Greece), from 5 August to 30 September 2020, 16 (100%) critically ill patients with COVID-19 were admitted (median age 70.5 years, IQR 58–79). The patients were divided into survivors [Group A: 9 (56.3%)] and non-survivors [Group B: 7 (43.7%)](Table1). At the time of ICU admission, the viral load of coronavirus (expressed in Circles trough: Ct) was significantly higher in non-survivors [Group A: 23 (IQR 21–25) vs Group B: 21 (IQR 20–22), p=0.042], while ferritin levels were similar in both groups [Group A: 1290 ng/mL (IQR 550–3572) vs Group B: 980 (IQR 543–3915), p=0.71]. During ICU stay, the viral load remained permanently high in non-survivors [Group A: 32 (IQR 32–37) vs Group B: 22 (IQR 19–24), p=0.001], but it was gradually diminished among survivors [Group A: 39.1% (IQR 30.4–42.9) vs Group B: 0 (IQR -4.8–14.30), p=0.001]. In parallel, ferritin levels were increased by 109.7% (IQR 25.7–382), whatever was higher in non-survivors [Group A: 55.7% (IQR 13.3–85) vs Group B: 486.1% (IQR 137.2–761.9), p=0.007] (Table 1). The HScore, which is an indicator of macrophage activation, was higher in non-survivors [Group A: 54 (IQR 19–70) vs Group B: 87 (IQR 68–99), p=0.048)]. Finally, in this cohort, 9 (56.3%) patients survived and 7 (43.7%) died because of ARDS/Multiple Organ Failure (MOF) (one of the patients developed myocarditis).

A consistent proportion of COVID-19 patients will develop acute respiratory distress syndrome (ARDS) related to increased production of cytokines (the so-called cytokine storm) and a small subset secondary haemophagocytic lymphohistiocytosis (sHLH), a T-cell driven hyperinflammatory, 'hyperferritinemic syndrome'[5]. These are the two main causes of mortality in the severe form of COVID-19. The sHLH development reflects the ability of coronavirus to bind TLRs and to activate inflammasome through IL-1β release, but the relationship is not clear since many COVID-19 patients, even with bad prognosis, do not meet the classification criteria of HScore (Table 2)[6,7]. In light of the absence of highly increased HScore, ferritin remains high and reveals constant macrophage activation albeit not to such an extent as to be the full-blown sHLH[8-10]. In our cohort, high viral load and ferritin levels have been observed in non-survivors indicating a relation between the activity of the disease and the outcome of the patients. A future research perspective could be focused on the following three questions: a) 'Is COVID-19 a hyperferritinemic syndrome without being full-blown sHLH?'; b) 'Is there a need to revalidate sHLH and HScore cut-off limits in these patients?'; and c) 'When in the course of the COVID-19 infection may the clinicians consider starting immunomodulatory treatment?'.

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Figure 1.

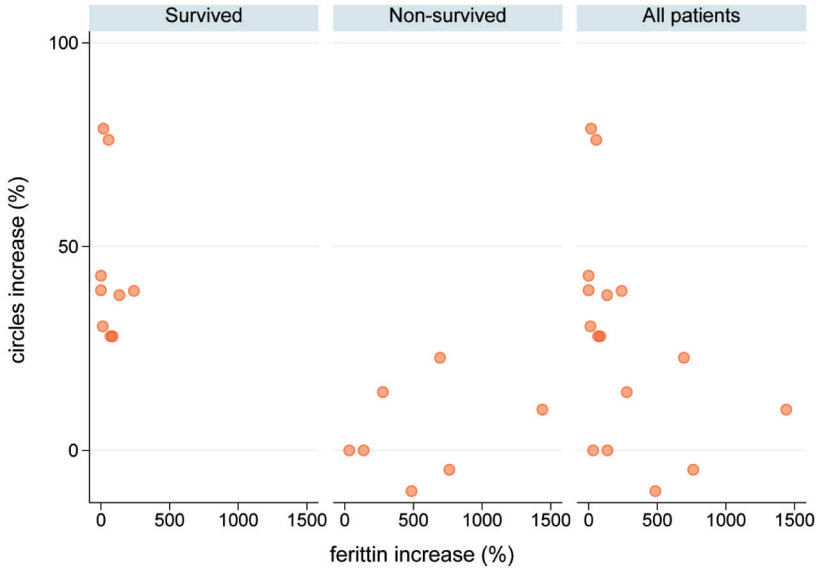

Figure 2.

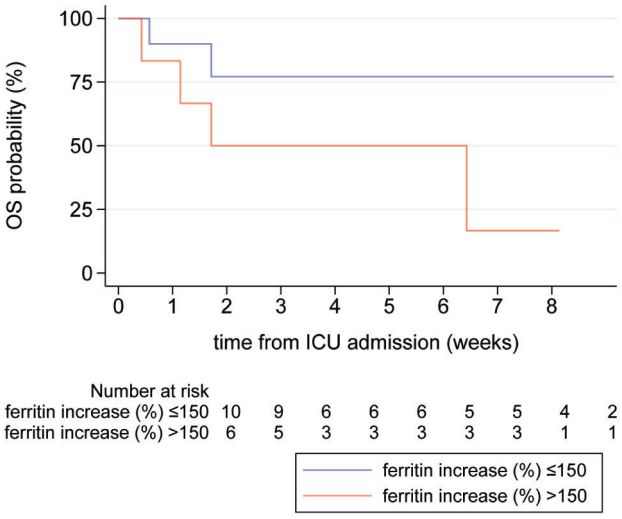

Figure 3.

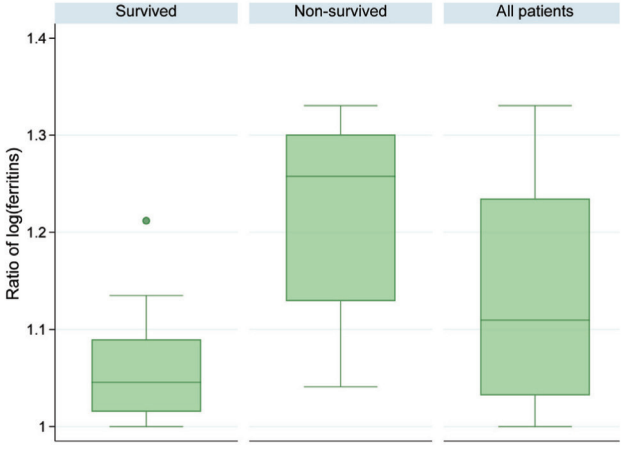

Table 1. Demographics, clinical and laboratory data of all patients, survivors and non-survivors (N=16)

Parameters	All patients	Survivors N=9 (56.3%)	Non-survivors N=7 (43.7%)	p
Age (years)	70.5 (58–79)	75 (54–79)	67 (62–79)	0.92
Gender				0.55
Male	13 (81.3)	8 (88.9)	5 (71.4)	
Female	3 (18.7)	1 (11.1)	2 (28.6)	
Comorbidities				
Hypertension	12 (8)	6 (66.7)	6 (85.7)	0.59
Cardiovascular disorders	7 (43.8)	6 (66.7)	1 (14.3)	0.06
Diabetes II	4 (3)	1 (11.1)	3 (42.9)	0.26
COPD	4 (25)	2 (22.2)	2 (28.6)	>0.99

Continued

Table 1. Continued

Parameters	All patients	Survivors N=9 (56.3%)	Non-survivors N=7 (43.7%)	p
Malignancy	3 (18.8)	1 (11.1)	2 (28.6)	0.55
Epilepsy	2 (12.5)	2 (22.2)	0 (0)	0.48
Obesity	1 (6.3)	1 (11.1)	0 (0)	>0.99
Renal failure	1 (6.3)	0 (0)	1 (14.3)	0.44
Thrombophilia	1 (6.3)	1 (11.1)	0 (0)	>0.99
Admission				0.63
Directly from ER	6 (37.5)	4 (44.4)	2 (28.6)	
From clinical floor	10 (62.5)	5 (55.6)	5 (71.4)	
Time to ICU admission (days)	3.5 (0–7)	1 (0–7)	4 (0–5)	0.87
APACHE II admission	20 (18.5–21.5)	20 (18–21)	21 (19–24)	0.33
SOFA score	13.5 (11.5–15)	13 (12–14)	15 (11–15)	0.23
Ferritin (admission), ng/mL	1046.5 (546.5–3748.5)	1290 (550–3572)	980 (543–3915)	0.71
Ferritin (ICU stay), ng/mL	2295 (1503.5–6366.5)	1735 (1289–4058)	2538 (1895–36940)	0.19
Ferritin levels increase	109.7 (25.7–382)	55.7 (13.3–85)	486.1 (137.2–761.9)	0.007*
Time of highest ferritin levels (day since admission)	12.5 (5.5–23.5)	10 (5–23)	16 (6–24)	0.75
Viral load (Ct) **admission**	21.5 (20.5–24)	23 (21–25)	21 (20–22)	0.042*
Viral load (Ct)[a]	29.5 (22–33)	32 (32–37)	22 (19–24)	0.001*
Viral load reduction (Ct) (%)	28 (5–39.2)	39.1 (30.4–42.9)	0 (-4.8–14.3)	0.001*
Temperature (°C)[a]	38.1 (37.3–38.9)	38 (37.7–38.5)	38.4 (36–40.5)	0.71
PaO2/FiO2[a]	123.5 (114–159)	125 (115–195)	122 (53–156)	0.56
WBC ($x10^9$/L)[a]	14600 (10200–17900)	13200 (9300–15900)	16900 (11980–27580)	0.19
Neutrophils (%)	81 (77.5–88)	81 (80–83)	87 (61–89)	0.67
Neutrophils absolute number	10380 (7530–14450)	10000 (7460–13200)	13600 (7600–15100)	0.32
Lymphocytes (%)	7 (5–12)	10 (6–11)	6 (5–26)	0.75
Lymphocytes absolute number	780 (695–1262)	770 (640–920)	790 (750–1290)	0.47
Hb[a]	11.3 (9.3–13)	11.5 (11–13)	11 (8.5–13)	0.63
Platelets ($x10^9$/L)[a]	258 (224–317)	252 (208–318)	258 (249–289)	0.96
Cytopenia[a]	5 (31.3)	2 (22.2)	3 (42.9)	0.60
Fibrinogen[a]	502.5 (426–775.5)	484 (456–782)	626 (396–769)	0.87
AST (µKat/L)[a]	87 (39.5–244.5)	115 (33–168)	59 (41–548)	0.71
LDH[a]	449.5 (365–627)	399 (330–521)	596 (378–628)	0.19
HS score[a]	69.5 (50.5–87)	54 (19–70)	87 (68–99)	0.048*
Inotropic agents	13 (81.3)	6 (66.7)	7 (100)	0.21
CRRT	2 (14.3)	1 (11.1)	1 (20)	>0.99
Length of ICU stay (days)	37 (8.5–52.5)	52 (29–57)	12 (4–45)	0.033*

Values are expressed as number (%) or median (IQR). IQR: interquartile range. Patients presented more than one comorbidity. AST: Aspartate Aminotransferase. APACHE II: Acute Physiology And Chronic Health Evaluation II. COPD: Chronic Obstructive Pulmonary Disease. CRRT: Continuous Renal Replacement Treatment. HS score: hemophagocytic syndrome. LDH: Lactate Dehydrogenase. SOFA: Sequential Organ Failure Assessment. WBC: White Blood Cells count. a On day of highest ferritin levels. *p<0.05 statistically significant.

Table 2. Haemophagocytic lymphohistiocytosis (HLH)-2004 diagnostic criteria[11] and HScore (HS)[12]

HScore			
Parameter	**Number of points**	**Parameter**	**Number of points**
Temperature (°C)		**Fibrinogen** (g/L)	
<38.4	0	>2.5	0
38.4-39. 4	33	≤2.5	30
>39.4	49	**Ferritin** (ng/mL)	
Organomegaly		<2.000	0
None	0	2.000-6.000	35
Hepatomegaly or splenomegaly	23	>6.000	50
Hepatomegaly and splenomegaly	38	**Serum Aspartate aminotransferase** (IU/L)	
Number of cytopenias		<30	0
One lineage	0	>30	19
Two lineages	24	**Haemophagocytosis on bone marrow aspirate**	
Three lineages	34	No	0
Triglycerides (mmol/L)		Yes	35
<1.5	0	**Known immunosuppression**	
1.5–4.0	44	No	0
>4.0	64	Yes	18

A. A molecular diagnosis consistent with HLH
B. Al least five of the following criteria should be met
1. Fever
2. Splenomegaly
3. Cytopenia (affecting ≥2 or 3 lineages in the peripheral blood Haemoglobin <90 g/L (in infants < 4 weeks haemoglobin <100 g/L) Platelets <100 x 10^9/L Neutrophils <1.0 x 10^9/L
4. Hypertriglyceridaemia and / or hypofibrinogenaemia Fasting triglycerides ≥3.0 mmol/L Fibrinogen ≤1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymh nodes. No evidence of malignancy
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥500 mg/L
8. sCD25 ≥2400 U/mL

HScore: HS >169 is 93% sensitive and 86% specific for HLH. NK: natural killer. sCD25: soluble CD25.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethics approval and informed consent were not required for this study.

PROVENANCE AND PEER REVIEW

Not commissioned; internally peer reviewed.

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