

**Supplementary Table S1.**

<b>2004-HLH Criteria</b>
<b>Must fulfill five out of eight criteria below</b>
<b>1) Fever</b>
<b>2) Splenomegaly</b>
<b>3) Cytopenia</b> (affecting $\geq 2$ of 3 lineages in peripheral blood) i.e. hemoglobin $< 90$ g/L platelets $< 100$ K/mm <sup>3</sup> , neutrophils $< 1.0$ K/mm <sup>3</sup>
<b>4) Hypertriglyceridemia and/or hypofibrinogenemia</b> Fasting triglycerides $\geq 265$ mg/dL Fibrinogen $\leq 150$ mg/dL
<b>5) Hemophagocytosis</b> in bone marrow, spleen or LNs
<b>6) Low NK activity</b> (local laboratory reference)
<b>7) Ferritin</b> $\geq 500$ ng/mL
<b>8) Soluble CD25</b> $\geq 2,400$ U/mL

**Supplementary Table S1. Criteria to diagnose HLH, as reported in literature [4].**

**Supplementary Table S2.**

<b>2014-H score</b>
<b>Best cut off value to diagnose secondary HLH is 169</b>
<b>Known underlying immunosuppression</b> 0 (no) or 18 (yes)
<b>Temperature (°C)</b> 0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
<b>Organomegaly</b> 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
<b>No. of cytopenias</b> 0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
<b>Ferritin (ng/ml)</b> 0 (>2,000), 35 (2,000–6,000), or 50 (>6,000)
<b>Triglyceride (mmoles/liter)</b> 0 (<1.5), 44 (1.5–4), or 64 (>4)
<b>Fibrinogen (gm/liter)</b> 0 (>2.5) or 30 (<2.5)
<b>Serum AST (IU/liter)</b> 0 (<30) or 19 (>30)
<b>Hemophagocytosis features on bone marrow aspirate</b> 0 (no) or 35 (yes)

**Supplementary Table S2. Criteria to calculate the H Score, as reported in literature [24].**

**Supplementary Table S3.**

2016-MAS Criteria
<b>Must fulfill</b>
<ul style="list-style-type: none"><li>- Fever</li><li>- Ferritin &gt; 684 ng/mL</li></ul>
<b>AND any 2 of the following</b>
<ul style="list-style-type: none"><li>- Platelet count <math>\leq</math> 181 K/mm<sup>3</sup></li><li>- AST &gt; 48 U/L</li><li>- Triglycerides &gt; 156 mg/dL</li><li>- Fibrinogen <math>\leq</math> 360 mg/dL</li></ul>

**Supplementary Table S3. Criteria to diagnose MAS, as reported in literature [5].**

**Supplementary Table S4.**

	Normal range	All COVID	Clinical Consensus		Odd Ratio	<i>p</i> -value
			No Storm	Storm		
<b>Fibrinogen</b>	200-385 mg/dL	491 ± 148	493 ± 141	483 ± 182	0.937	n.s.
<b>Triglycerides</b>	< 150 mg/dL	177 ± 207	182 ± 221	152 ± 81	0.796	n.s.
<b>AST</b>	15-37 UL	54 ± 92	50 ± 80	82 ± 145	1.249	0.028
<b>WBC</b>	4 -11 K/mm <sup>3</sup>	7.86 ± 4.5	7.7 ± 4.6	8.8 ± 3.6	1.199	n.s.
<b>Platelets</b>	150-450 K/mm <sup>3</sup>	224 ± 87	226 ± 87	215 ± 88	0.882	n.s.
<b>Monocytes</b>	0-0.8 K/mm <sup>3</sup>	0.58 ± 0.28	0.58 ± 0.28	0.58 ± 0.27	0.978	n.s.
<b>Neutrophils</b>	1.8-7.8 K/mm <sup>3</sup>	6 ± 3.6	5.8 ± 3.6	7.23 ± 3.5	1.4	0.004
<b>Hemoglobin</b>	12.3-15.3 g/dL	12.4 ± 2.1	12.5 ± 2	11.8 ± 2.3	0.717	0.01
<b>Ferritin</b>	8 - 388 ng/mL	945 ± 2592	835 ± 2223	1638 ± 4192	1.211	0.01
<b>CRP</b>	0 - 0.4 mg/dL	7.2 ± 6.4	6.9 ± 6.4	9.1 ± 6.1	1.341	0.016

**Supplementary Table S4. Laboratory parameters indicative of HLH and MAS do not predict the Cytokine Storm in patients with COVID-19 infection.** Average and Standard deviation of the laboratory parameters associated with the criteria of HLH and MAS, as collected up to the 24 hours within reaching the clinical consensus of cytokine storm or in the first 7 days of hospitalization in COVID-19 patients who never reached the clinical consensus of storm. Odd Ratios and *p*-values were calculated by logistic regression. Normal range of values are shown for our laboratory as reference. Abbreviations: AST aspartate aminotransferase, WBC white blood cells, CRP C-reactive protein.

**Supplementary Table S5.**

COVID-CS new criteria					Consensus Storm	
	N	%	LoS (days)*	Mortality (%)*	NO	YES
<b>NO</b>	172	67	4.7 ± 3.7	4.2	160	12
<b>YES</b>	86	33	15.5 ± 10	33.7	59	27
					SP=0.73	SE=0.69
						ACC=0.72

**Supplementary Table S5. Validation of the novel criteria of COVID-CS in the second cohort.** The new COVID-CS criteria were applied to the second cohort of 258 COVID-19 patients (*left*) and to the same patients divided according to the clinical consensus of cytokine storm (258, 39 patients who reached and 219 who did not reach the clinical consensus of COVID cytokine storm). (*right*). SP is Specificity, SE is Sensitivity and ACC is Accuracy. The new criteria identified patients with significantly greater Length of Stay (LoS) and mortality. (\*)  $p < 0.0001$ .