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Letter to the Editor

Trends of thrombo-inflammation biomarkers after Tocilizumab predict treatment failure better than scores in patients with severe SARS-CoV2 related respiratory failure

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Dear editor

Cytokine antagonists are now concrete therapeutic options in patients with severe SARS-CoV2 respiratory failure. The Interleukin-6 (IL-6) inhibitor tocilizumab (TCZ) has shown to significantly reduce the 30-day mortality risk and the risk of mechanical ventilation, without increasing the risk of infection and/or adverse events [1]. However, 30-day mortality in patients treated with TCZ remain of about 25% [1]. Predictors of tocilizumab failure in SARs-CoV2 patients are uncertain. To tail treatment on single patient based on his or her inflammatory status could improve the rate of success, as highlighted by Levi M in a recent issue of European Journal of Internal Medicine [2]. Evidence shows that the response to TCZ in this context is associated with restoration of thrombo-inflammation biomarkers after its administration [3], while persistence of high biomarkers after TCZ administration seems to be associated with poor outcome [4]. Recently, Emre Eskazan A. et al. found that platelets count $\leq 147 \times 10^9$/L, procalcitonin ≥ 0.35 ng/mL, room air oxygen saturation $\leq 91.5\%$, D-Dimer ≥ 2520 microg/L and time from symptoms to TCZ administration > 12 days are independent variables associated with 28-day mortality. Therefore they proposed the CERRAHPASA score, ranging from 0 to 107 points, as a prognostic tool aimed to predict 28-day mortality in severe COVID-19 treated by TCZ with an area under receiver operating characteristics curve (AUROC) of 0.954 (95% CI: 0.908–0.999) [5]. In another study, Mussini C et al. identified sex, paO_2/FiO_2 ratio (P/F) after 96 h from TCZ administration, platelets count and C-reactive protein (CRP) as independent risk factors for TCZ failure and associated with 28-day mortality and mechanical ventilation [6]. Combining these variables, the Authors proposed a predictive score with an AUROC of 0.80 [6]. External validations of CERRAHPASA score and the score proposed by Mussini C et al. lack, therefore we retrospectively analyzed data records of patients admitted in non intensive wards of our hospital and suffering from severe respiratory failure who were treated by TCZ aimed to provide evidence about this issue and to evaluate whether these scores were superior to biomarkers of thrombo-inflammation measured after a time ranging from 72 to 96 h from TCZ administration. Our study population was composed by one hundred and seven patients (77 males and 30 females) with mean age ± SD 64.5 ± 12.8 years. Seventeen patients (15.8%) died during hospital stay, while ten patients received oro-tracheal intubation. Mean age and mean procalcitonin values at hospital arrival in patients who died were significantly higher compared with that of survivors, while mean room air oxygen saturation at hospital arrival was significantly lower in patients who died compared with patients who did not. No difference between groups was found in sex and in the means of P/F ratio at hospital admission and at the time of TCZ administration, time from symptoms onset to TCZ administration, mean CERRAHPASA and MUSSINI scores, mean Neutrophils to Lymphocytes (Neu/Lym) ratio, D-Dimer and CRP at hospital admission (Table 1). After 72–96 h from TCZ administration, mean values of CRP were significantly lower compared with those at hospital admission, both in died patients and in survivors, while no significant difference was found in mean Neu/Lym ratio and D-Dimer values between hospital admission and after 72–96 h from TCZ. At this time, mean Neu/Lym ratio was significantly higher in patients who died compared with that of survivors, while no significant difference between died patients and survivors was found for D-Dimer and CRP values (Table 2). Predictive power of CERRAHPASA and MUSSINI scores as mortality prognosticators were low with an AUROC of 0.517 (95%CI: 0,417–0,615) and 0.613 (95% CI: 0.495–0.723) respectively (difference between areas 0.0668, $p = 0.5575$). No difference was found in the predictive power of CERRAHPASA score when compared with those of Neu/Lym ratio, D-Dimer and CRP measured at hospital admission, while the predictive power of CERRAHPASA score was significantly lower compared with those of Neu/Lym ratio (AUROC 0.802, 95%CI: 0,713 to 0,873; difference between areas 0.285, 95% CI: 0.120–0.451, $p = 0.0007$) and D-Dimer (AUROC 0.697, 95%CI: 0,600–0,783; difference between areas 0.181, 95% CI: 0.00162–0.360, $p = 0.0480$), but not CRP (AUROC 0.579, 95% CI: 0.479–0.674; difference between areas 0.0621, 95% CI: −0.121–0.245, $p = 0.5049$) measured after 72–96 h from TCZ administration. No significative difference was found between MUSSINI score and biomarkers measured after 72–96 h from TCZ administration, despite Neu/Lym ratio and D-Dimer showed higher predictive power compared with MUSSINI score. At this time, the predictive power of Neu/Lym ratio was significantly higher compared

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Table 1
Characteristic of study population.

	Total	Dead	Alive	p
Number	107	17	90	
F/M	30/77	5/12	25/65	1.000
Mean age ± SD (years)	64.5 ± 12.8	74.0 ± 9.0	62.7 ± 12.7	0.0002
Mean room air oxygen saturation (%) ± SD	91.0 ± 4.3	88.6 ± 6.4	91.5 ± 3.6	0.0095
Mean P/F at hospital admission ± SD	260.0 ± 71.4	246.0 ± 73.0	264.2 ± 71.0	0.3420
Mean P/F at the TCZ administration ± SD	134.8 ± 36.2	120.3 ± 38.8	137.2 ± 35.4	0.0728
Mean time from symptoms to TCZ administration ± SD (days)	7.9 ± 3.2	7.9 ± 2.7	7.9 ± 3.3	1.000
Mean Neu/Lym ratio ± SD at hospital admission	13.8 ± 38.1	13.7 ± 23.1	13.9 ± 40.5	0.9841
Mean Neu/Lym ratio ± SD after 72–96 h from TCZ	8.49 ± 10.8	18.6 ± 20.4	6.5 ± 6.2	<0.0001
Mean D-Dimer ± SD at hospital admission (microg/L)	1212.3 ± 2577.4	1123.8 ± 677.6	1228.9 ± 2797.3	0.8784
Mean D-Dimer ± SD after 72–96 h from TCZ (microg/L)	2906.35 ± 6554.0	2787.5 ± 3346.8	2928.8 ± 7010.2	0.9356
Mean CRP ± SD at hospital admission (mg/dL)	8.72 ± 5.34	9.0 ± 6.0	8.6 ± 5.2	0.7771
Mean CRP ± SD after 72–96 h from TCZ (mg/dL)	1.24 ± 1.49	1.34 ± 1.35	1.22 ± 1.52	0.7621
Mean procalcitonin ± SD at hospital admission (ng/mL)	0.28 ± 0.73	0.78 ± 1.71	0.20 ± 0.33	0.0045
Mean platelets count ± SD at hospital admission x 10^{-3}/μL	207.1 ± 79.8	182.6 ± 73.4	211.8 ± 80.5	0.1679
Mean CERRAHPASA score	19.9 ± 18.0	22.0 ± 19.3	19.5 ± 17.9	0.6020
Mean MUSSINI score	10.2 ± 3.9	11.5 ± 3.6	10.1 ± 3.9	0.1727

Table 2
Comparison of thrombo-inflammation biomarkers at hospital arrival and after Tocilizumab administration.

	Total			Dead			Survivors		
	At hospital admission	After 72-96 h from TCZ administration	p	At hospital admission	After 72–96 h from TCZ administration	p	At hospital admission	After 72–96 h from TCZ administration	p
Mean Neu/Lym ratio ± SD	13.8 ± 38.1	8.49 ± 10.8	0.2555	13.7 ± 23.1	18.6 ± 20.4	$p =$ 0.3678	13.9 ± 40.5	6.5 ± 6.2	$p =$ 0.0953
Mean D-Dimer ± SD (microg/L)	1212.3 ± 2577.4	2906.35 ± 6554.0	0.2974	1123.8 ± 677.6	2787.5 ± 3346.8	$p =$ 0.0585	1228.9 ± 2797.3	2928.8 ± 7010.2	$p =$ 0.3283
Mean CRP ± SD (mg/dL)	8.72 ± 5.34	1.24 ± 1.49	<0.0001	9.0 ± 6.0	1.34 ± 1.35	$p <$ 0.0001	8.6 ± 5.2	1.22 ± 1.52	$P <$ 0.0001

Table 3
Predictive power of CERRAHPASA and MUSSINI scores compared with thrombo-inflammation biomarkers measured after 72–96 h from TCZ administration.

	At hospital admission			After 72–96 h from TCZ administration		
Variable	AUROC	Standard Error	95% CI	AUROC	Standard Error	95% CI
CERRAHPASA score	0,517	0,0734	0,417–0,615			
MUSSINI score				0.613	0.0913	0.495–0.723
D-DIMER	0.578	0.0828	0,478–0,673	0,697	0,0626	0,600–0,783
C-reactive protein	0.505	0.0848	0,406–0,603	0,579	0,0672	0,479–0,674
Neu-Lym ratio	0.505	0.0784	0,406–0,604	0,802	0,0560	0,713–0,873

with that of CRP (difference between AUROCS 0.223, 95% CI: 0.0921–0.354, $p = 0.0008$) (Table 3).

Predicting the response to TCZ in SARS-CoV2 patients suffering from severe respiratory failure is of utmost importance in clinical practice. Despite CERRAHPASA and MUSSINI scores promise to be good prediction tools, in our study population their predictive power resulted low and lower compared with those of Neu/Lym ratio and D-Dimer measured after 72–96 h from TCZ administration.

Monitoring thrombo-inflammation biomarkers after TCZ administration could be useful for risk stratification of patients treated by TCZ. Further prospective studies are warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Luo L, Luo T, Du M, Mei H, Hu Y. Efficacy and safety of tocilizumab in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Infect 2021;(21): S0163–4453. https://doi.org/10.1016/j.jinf.2021.11.013. 00557-0.

[2] Levi M. Tocilizumab in severe COVID-19: a promise fulfilled. Eur J Intern Med 2022; 95:38–9. https://doi.org/10.1016/j.ejim.2021.11.015.

[3] Di Nisio M, Potere N, Candeloro M, et al. Interleukin-6 receptor blockade with subcutaneous tocilizumab improves coagulation activity in patients with COVID-19. Eur J Intern Med 2021;83:34–8. https://doi.org/10.1016/j.ejim.2020.10.020.

[4] Lakatos B, Szabo BG, Bobek I, et al. Laboratory parameters predicting mortality of adult in-patients with COVID-19 associated cytokine release syndrome treated with high-dose tocilizumab. Acta Microbiol Immunol Hung 2021. https://doi.org/10.1556/030.2021.01526.

[5] Eşkazan AE, Balkan İİ, Demirbaş KC, et al. Tocilizumab in COVID-19: the Cerrahpaşa-PREDICT score. J Infect Chemother 2021;27:1329–35. https://doi.org/10.1016/j.jiac.2021.05.007.

[6] Mussini C, Cozzi-Lepri A, Menozzi M, et al. Development and validation of a prediction model for tocilizumab failure in hospitalized patients with SARS-CoV-2 infection. PLoS One 2021;16:e0247275. https://doi.org/10.1371/journal.pone.0247275.

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