

SUPPLEMENTAL DIGITAL CONTENT

Effect of cytomegalovirus reactivation on the time course of systemic host response biomarkers in previously immunocompetent critically ill patients with sepsis : a matched cohort study

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APPENDIX I.

Table S1. Absolute levels of host response markers during follow up by CMV reactivation status

Cytokine	Primary Comparison			Secondary Comparison		
	CMVs+	CMV+ ^a	p-value	CMVs-	CMV+ ^a	p-value
Three days after CMV reactivation (t=3)^b						
	n=26	n=26		n=29	n=23	
IL-6	3.6 (3.1-4.5)	3.8 (3.1-4.9)	0.86	4.2 (3.6-4.7)	3.6 (2.7-4.2)	0.12
IL-8	3.1 (2.6-3.7)	3.3 (2.4-4.3)	0.69	3.3 (2.8-4.6)	3.3 (2.3-4.3)	0.35
IL-18	6.1 (5.7-6.7)	6.1 (5.8-6.8)	0.85	6.1 (5.8-6.5)	6.1 (5.8-6.7)	0.92
IP-10	6.5 (5.9-6.9)	6.5 (6.0-6.9)	0.63	6.3 (6.0-6.9)	6.6 (6.0-7.4)	0.22
N-elastase	10.3 (10.1-10.9)	10.4 (10.1-10.9)	0.56	10.5 (10.2-10.8)	10.4 (10.0-11.0)	0.73
IL-10	2.1 (1.1-2.4)	2.6 (1.7-3.0)	0.06	2.2 (1.6-2.6)	2.6 (1.6-3.0)	0.15
IL-1RA	6.4 (5.8-6.8)	6.5 (5.9-6.9)	0.87	6.3 (5.8-7.0)	6.6 (5.9-6.9)	0.96
Seven days after CMV reactivation (t=7)						
	n=14	n=15		n=19	n=13	
IL-6	3.9 (3.2-4.4)	3.8 (3.0-4.4)	0.66	4.1 (3.7-5.1)	3.4 (3.0-4.0)	0.005
IL-8	3.4 (2.6-3.5)	3.5 (2.7-4.1)	0.28	3.8 (3.0-5.1)	3.5 (2.7-4.0)	0.26
IL-18	6.0 (5.6-6.4)	6.3 (5.9-6.8)	0.29	6.3 (5.9-6.7)	6.3 (5.9-6.8)	0.95
IP-10	6.2 (5.9-6.6)	6.4 (6.2-6.8)	0.32	6.6 (5.8-7.2)	6.6 (6.3-6.9)	0.55
N-elastase	10.2 (9.8-10.7)	10.5 (10.4-10.7)	0.19	10.3 (9.9-10.9)	10.6 (10.4-11.0)	0.39
IL-10	1.7 (0.7-1.8)	2.3 (1.8-2.7)	0.03	2.0 (1.4-2.6)	2.3 (1.9-2.7)	0.45
IL-1RA	6.2 (3.7-6.4)	6.2 (4.7-6.7)	0.84	6.5 (6.0-7.1)	5.9 (3.1-6.4)	0.07
Ten days after CMV reactivation (t=10)						
	n=11	n=11		n=15	n=11	
IL-6	3.7 (3.1-5.0)	4.7 (3.4-5.3)	0.22	4.4 (3.6-4.8)	4.2 (2.9-4.7)	0.36
IL-8	3.2 (2.5-3.8)	3.6 (2.0-4.4)	0.87	3.8 (2.8-4.8)	3.6 (2.0-4.4)	0.31
IL-18	6.1 (5.0-6.5)	6.4 (6.0-6.6)	0.31	6.4 (6.2-6.7)	6.2 (5.9-6.6)	0.55
IP-10	6.2 (5.8-6.9)	6.8 (6.1-7.2)	0.34	6.3 (5.7-7.3)	7.1 (6.3-7.4)	0.24
N-elastase	10.4 (9.8-10.5)	10.4 (9.8-11.0)	0.49	10.5 (9.9-10.8)	10.6 (9.8-11.1)	0.70
IL-10	1.6 (1.0-2.0)	2.7 (1.8-3.1)	0.002	1.8 (1.5-3.1)	2.7 (1.7-3.1)	0.45
IL-1RA	3.1 (3.1-6.2)	6.2 (5.8-6.7)	0.19	6.2 (5.1-6.9)	5.8 (3.1-6.3)	0.48

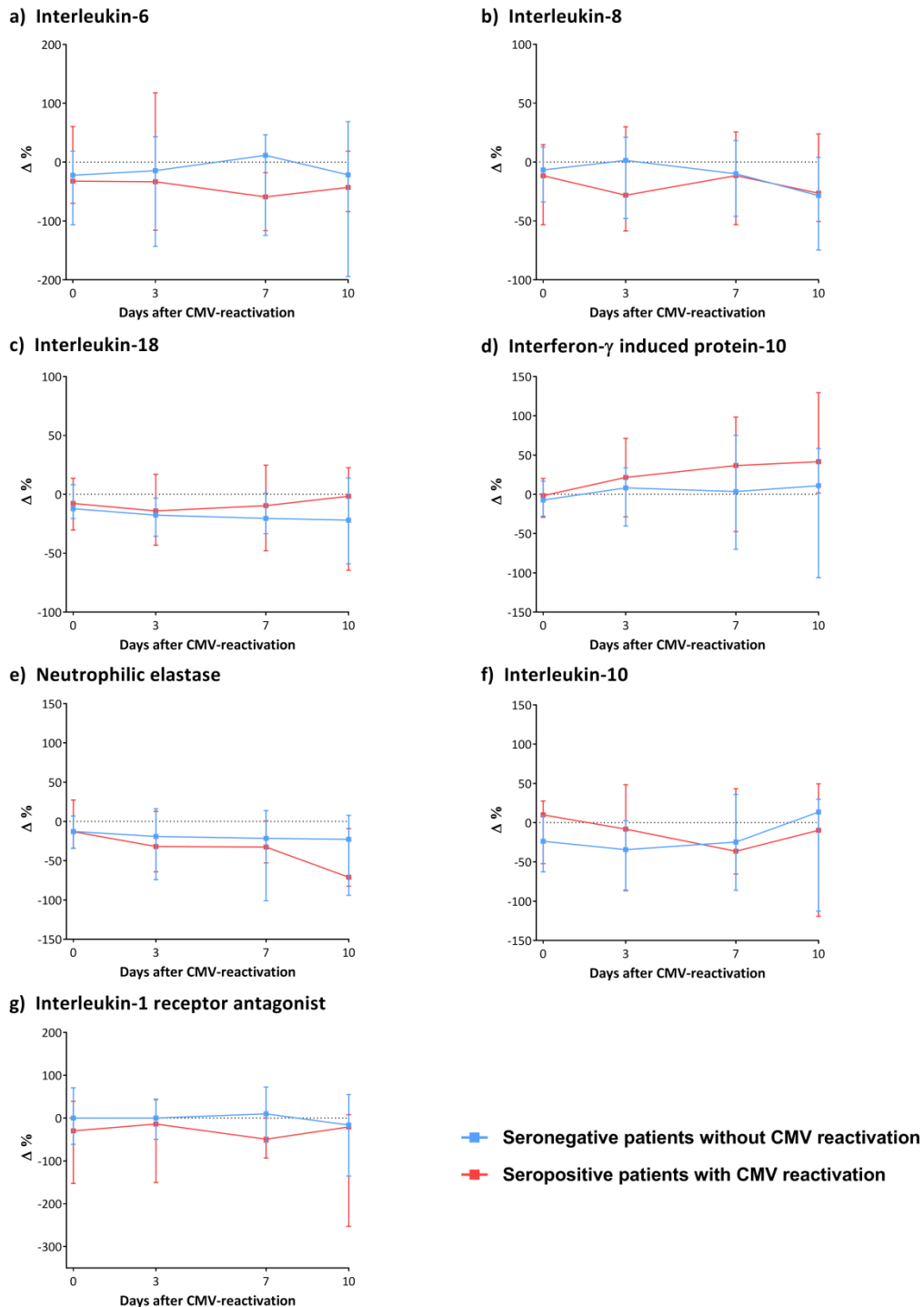
CMVs+: cytomegalovirus (CMV) seropositive without reactivation. CMV+: CMV reactivation. CMVs-: CMV seronegative. IL: interleukin. IP=interferon- γ induced protein. N: neutrophilic. RA: receptor antagonist. Biomarker levels (pg/mL) were natural log transformed and presented as median (Q1-Q3). Due to ICU discharge or death sample size decreased over time to a minimum of 11 patients per group after ten days.

^a 28 patients with CMV reactivation are included in both matched comparisons.

^b t=0 is the ICU day of CMV reactivation, this length of stay also determines t=0 in the matched patient without reactivation.

APPENDIX II.

Figure S1. Symmetric percentage differences for time trends of host response biomarkers in patients by CMV reactivation status (secondary comparison)



Levels (pg/mL) of pro-inflammatory (figure a-e) and anti-inflammatory biomarkers (figure f-g) were natural log transformed and symmetric percentage differences were calculated; $\Delta \% = (\ln(\text{value follow up measurement}) - \ln(\text{value at } t=-2)) * 100$. This measure reflects the relative difference from baseline up to the time point of interest. Results are presented as median percentage difference and Q1-Q3. Loss to follow up (death or ICU discharge) decreased the sample size with a minimum of 11 patients per group after 10 days.