

Appendix 4: Study of prognostic value of cytokines level in ascites fluid

Cytokine and no. of studies	Study author	Prognostic Value						
		OS			PFS			Cut-off value
		effect	univariate analysis	multivariate analysis	effect	univariate analysis	multivariate analysis	
IL-10	Matte et al., 2012	NS	NS	NS	Patients with high levels of IL-10 in ascites (> 24 pg/ml) showed shorter PFS with a median PFS of 14 months for high IL-10 levels versus 36 months for patients with low IL-10 (P = 0.002)	HR= 3.1 (1.4-6.7) p = 0.002	NS	median IL-10 24 pg/ml (range 0-488)
	Chen et al., 2015	Ascites level of IL-10 is not significantly associated with OS	HR 1.3 (0.60–2.50), p=0.41	NS	NS	NS	NS	median 5.8 (0.6–83.3) pg/ml
	Lane et al., 2015	NS	NS	NS	Ascites level of IL-10 is not significantly associated with PFS	p = 0.11	NS	median 97,5 (23–186)

IL-6	Dalal et al., 2018	NS	NS	NS	significantly reduced progression free survival (log rank test, $p \leq 0.041$) was observed in patients having higher IL-6 (≥ 9585.25 pg/ml) levels than patients having low IL-6 levels (< 9585.25 pg/ml).	$p \leq 0.041$	NS	≥ 9585.25 pg/ml
	Chen et al., 2015	Ascites level of IL-6 is not significantly associated with OS	1.9 (0.96–3.82) $p=0.06$	NS	NS	NS	NS	median 942.5 (0.5–15 600.0) pg/ml
	Lane et al., 2015	NS	NS	NS	Patients with low ascites IL-6 levels had a median PFS of 12 months compared to patients with high levels who had a PFS of 28 months ($P = 0.0004$, log rank test).	$p = 0.0004$		median 1820 (279–4327) pg/ml
	Kolomeyevskaya et al., 2015	there was no univariate relationship of OS and IL-6.	$p=0.779$	NS	there was no univariate relationship of PFS and IL-6.	$p = 0.510$	NS	we stratified the level of each cytokine at the observed median value to form low and high level sets. Median IL-6: 4741.6 pg/ml

		Combination of high IL-6 and high TNF- α were associated with shorter OS	p=0.0278	NS	Combination of high IL-6 and high TNF- α were associated with shorter PFS	p=0.00015	NS	
		Combination of high IL-6 and low TNF- α were associated with higher OS	p=0.0101	NS	Combination of high IL-6 and low TNF- α were associated with higher PFS	p=0.016	NS	
		Combination of high IL-6 and high or low TNF- α were associated with higher OS	p=0.0175	NS	Combination of high IL-6 and high or low TNF- α were associated with higher PFS	p=0.000193	NS	
		three combination of high level of three cytokines (IL-6, IL-8, and TNF- α) associated with shortened OS	p = 0.779 (3 cytokines)	NS	three combination of high level of three cytokines (IL-6, IL-8, and TNF- α) associated with shortened PFS	p=0.01 (3 cytokines)	NS	
VEGF	Liang et al., 2013	high ascites VEGF-C concentration (P 0.001) were independent predictor variables of a shortened overall survival.	p<0.0001	HR 1.622–2.385; p<0.001	NS	NS	NS	median 10,250 [8655–13,525] ng/L

	Dalal et al., 2018	NS	NS	NS	there was significantly shorter progression free survival (log rank test, $p \leq 0.023$) in EOC patients having higher VEGF-A levels (≥ 5263.29 pg/ml) in the ascitic fluid compared to patients having low VEGF-A levels (< 5263.29 pg/ml)	$p \leq 0.023$	NS	≥ 5263.29 pg/ml
	C. Rudlowski et al., 2006	OS were significantly reduced in patients with enhanced VEGF levels in tumor ascites	$P < 0.001$	NS	PFS were significantly reduced in patients with enhanced VEGF levels in tumor ascites	$P < 0.001$	NS	median VEGF level of 2575 pg/mL
IFN- γ	Chen et al., 2013	high IFN- γ expression levels in cancer-associated ascites have poorer clinico-pathological characteristics and shorter OS than low IFN- γ expression levels	NS	2.8 (95% CI: 1.05–7.52) $p < 0.04$	high IFN- γ expression levels in cancer-associated ascites have poorer clinico-pathological characteristics and shorter DFS than low IFN- γ expression levels	NS	4.4 (95% CI 2.27–8.65)	The IFN- γ expression levels were divided into tertiles (low, ≤ 1.4 pg/mL; medium, 1.4–16.0 pg/mL; and high: > 16.0 pg/mL) for analysis.

TNF- α	Kolomeyevskaya et al., 2015	TNF- α had a significant association with worse OS	HR = 2.8, 95% CI: 1.1-7.0, p = 0.0255	NS	TNF- α had a significant association with worse PFS (HR = 2.9, 95% CI: 1.2-6.7, p = 0.0154)	HR = 2.9, 95% CI: 1.2-6.7, p = 0.0154	NS	we stratified the level of each cytokine at the observed median value to form low and high level sets. Median TNF- α 38.5 pg/ml
	Chen et al., 2015	Ascites level of TNF- α is not significantly associated with OS	p = 0.691	NS	NS	NS	NS	median 2.9 (0.6-77.1)
IL-8	Kolomeyevskaya et al., 2015	there was no univariate relationship with OS for IL-8.	p = 0.691	NS	there was no univariate relationship with PFS for IL-8.	p = 0.933	NS	