Cytokine score based on expression levels of multiple cytokines is a prognostic indicator in metastatic breast cancer patients treated with chemotherapy

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San Antonio Breast Cancer Symposium
December 9-12, 2025

Background:

The tumor immune microenvironment affects treatment response and outcomes in patients with metastatic breast cancer (MBC). Cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, play an important role in tumor progression and immune regulation, and they are associated with outcomes in patients with MBC. Although the significance of each cytokine as a prognostic factor has been reported, there is a paucity of reports on the relationship between the integrated indicator of multiple cytokines and outcomes. In this study, we established an integrated indicator of multiple cytokines and examined the relationship with patient outcomes. In addition, since inflammatory cytokines are thought to affect cancer progression and metastasis by acting on T cells, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), we also examined the relationship between the integrated cytokine indicator and immune cell profile.

Materials and Methods:

This retrospective study included 43 patients with MBC treated with chemotherapy. Baseline values for cytokine levels, including TNF-α, soluble interleukin-2 receptor (sIL-2R), IL-6, IL-8, transforming growth factor (TGF)-β, and thymidine kinase 1 (TK1), were measured in peripheral blood on the day before the first treatment with chemotherapy. Each cytokine was classified into low and high groups using cutoff values defined by ROC curves for overall survival (OS), and the progression-free survival (PFS) and OS between low and high groups were compared by Kaplan–Meier plots. CD4+ and CD8+ lymphocytes, MDSCs, and Tregs levels were determined in the blood by flow cytometry analysis.

Results:

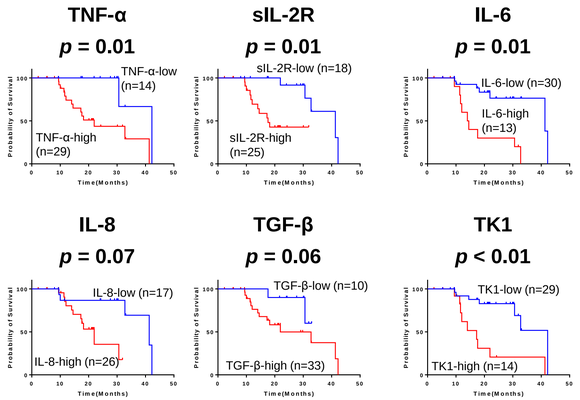
Of the patients, 46.5% (n = 20) were treated with eribulin, 9.3% (n = 4) with trastuzumab deruxtecan, 9.3% (n = 4) with paclitaxel and bevacizumab, 7.0% (n = 3) with trastuzumab emtansine, and 27.9% (n = 12) with other chemotherapeutic agents. Patients treated as first-line were 55.8% (n = 24), and those treated as second-line or later were 44.2% (n = 19). Patients with high levels of TNF-α, sIL-2R, IL-6, and TK1 showed a shorter OS compared to those with low levels (p = 0.01, 0.01, 0.01, and <0.01, respectively). IL-8 and TGF-β were not associated with OS (p = 0.07 and 0.06, respectively). Patients with high levels of sIL-2R, TGF-β, and TK1 showed a shorter PFS compared to those with low levels (p = 0.02, 0.01, and 0.04, respectively). TNF-α, IL-6, IL-8 and TK1 levels were not associated with PFS (p = 0.11, 0.10, 0.07 and 0.04, respectively). A “cytokine score” was developed based on the number of elevated cytokines among TNF-α, sIL-2R, IL-6, and TK1. Patients with 0-1 elevated cytokine were classified as low score, and those with 2-4 as high score. The high cytokine score group had shorter OS and PFS compared to the low score group (p < 0.01 and p = 0.03, respectively). Multivariable analyses revealed that cytokine score were an independent prognostic factor for both OS (p < 0.01) and PFS (p = 0.02). Furthermore, patients with high cytokine scores had lower proportions of CD4+ and CD8+ lymphocytes (p = 0.01 and 0.04, respectively), and higher levels of MDSCs (p < 0.01), with no difference in Tregs (p = 0.30).

Conclusion:

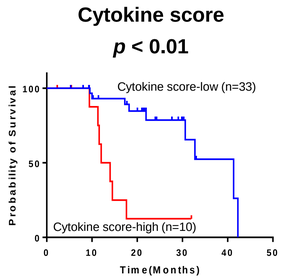
Our results show that the levels of TNF-α, sIL-2R, IL-6, and TK1 were associated with outcomes in patients with MBC treated with chemotherapy. The cytokine score, based on the number of elevated cytokines, is an important prognostic indicator for both OS and PFS. Furthermore, since a high cytokine score was associated with higher levels of MDSCs, and lower levels of CD4+ and CD8+ lymphocytes, the cytokine score might be associated with patient outcomes through immune reaction. Patients with high cytokine scores have worse outcomes, which may reflect a poor tumor microenvironment.

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Overall survival according to the levels of TNF-α, sIL-2R, IL-6, IL-8, TGF-β or TK1



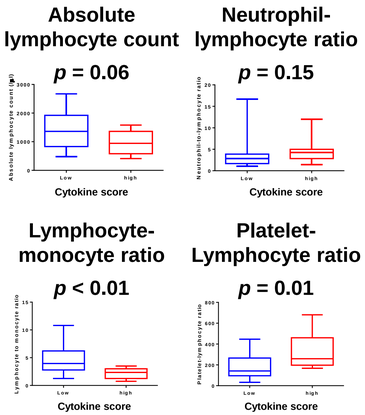
Overall survival according to the cytokine score



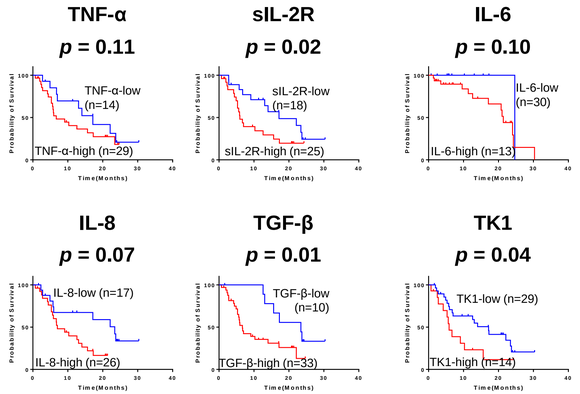
Multivariable analyses for overall survival according to cytokine scores

	Multivariable analysis HR (95% CI)	p-value
Menopausal status		
Premenopausal	1	
Postmenopausal	0.27 (0.04-1.68)	0.16
Advanced/recurrence		
Recurrence	1	
Advanced	2.05 (0.50-8.47)	0.32
Treatment lines		
1 line	1	
>2 lines	1.66 (0.33-8.24)	0.53
Estrogen receptor		
Positive	1	
Negative	2.62 (0.55-12.43)	0.23
HER2		
Positive	1	
Negative	5.17 (0.93-28.9)	0.06
Cytokine score		
Low	1	
High	15.29 (2.46-95.05)	<0.01

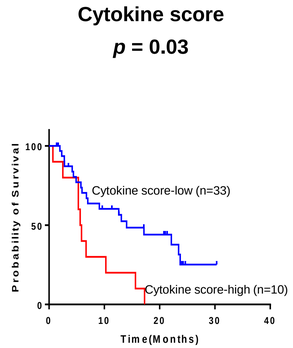
Peripheral blood inflammatory markers associated with cytokine scores



Progression-free survival according to the levels of TNF-α, sIL-2R, IL-6, IL-8, TGF-β or TK1



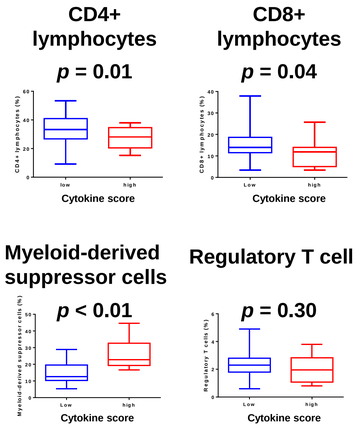
Progression-free survival according to the cytokine score



Multivariable analyses for progression-free survival according to cytokine scores

	Multivariable analysis HR (95% CI)	p-value
Menopausal status		
Premenopausal	1	
Postmenopausal	1.31	0.67
Advanced/recurrence		
Recurrence	1	
Advanced	1.02	0.97
Treatment lines		
1 line	1	
>2 lines	1.28	0.59
Estrogen receptor		
Positive	1	
Negative	0.71	0.49
HER2		
Positive	1	
Negative	1.77	0.29
Cytokine score		
Low	1	
High	3.26	0.02

Anti-tumor immunity associated with cytokine scores



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