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THE IMPORTANCE OF TUMOR NECROSIS FACTOR ALPHA IN THE PROGNOSIS OF BREAST CANSER

ЗНАЧЕНИЕ ФАКТОРА НЕКРОЗА ОПУХОЛИ АЛЬФА В ПРОГНОЗЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

Scientific supervisor:
Urmanbayeva Dilbarhon Abdulkosimovna, PhD, docent at the Department of Oncology, Andijan state medical institute, Andiijan, Uzbekistan
ORCID: 0009-0001-9137-5670,
e-mail: dilbaroyurmanbaeva@gmail.com.
Tel:+998902393688

Adhamjonova Uktamxon Akmalkhon kizi
1 st year master degree students in oncology, Andijan State Medical Institute
adkhamjanovuktamkhon@gmail.com
https://orcid.org/0009-0006-0580-5627
Tel:+998901942212

Abdivokhobova Gulnozakhon Shuhratbek kizi
1 st year master degree students in oncology ,Andijan State Medical Institute
Orcid: https://orcid.org/0009-0008-2758-679X
E-mail: abdivoxobovagulnoza@gmail.com
Tel:+998936851225

Erkinova Shoxista Rustamjon kizi
1 st year master degree students in oncology ,Andijan State Medical Institute
mutaliyevashoxista@gmail.com
https://orcid.org/0009-0002-8148-2656
Tel:+998998920523

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Научный руководитель: PhD Урманбаева Дилбархон Абдулкосиовна
доцент кафедры онкологии
Андижанского государственного медицинского
института, Андижан, Узбекистан,
Orcid: https://orcid.org/0009-0001-9137-5670
E-mail: dilbaroyurmanbaeva@gmail.com
Tel:+99802693684
Адхамджонова Уктамхон
Андижанский государственный медицинский институт,
Магистрант 1 курса по специальности «Онкология»
Orcid: https://orcid.org/0009-0006-0580-5627
E-mail: adkhamjanovuktamkhon@gmail.com
Tel: +998901942212

Абдивохобова Гульнозахон
Магистрант 1 курса по специальности
«Онкология», Андижанский государственный медицинский институт
Orcid: https://orcid.org/0009-0008-2758-679X
E-mail: abdivoxobovagulnoza@gmail.com
Tel:+998936851225

Эркинова Шохиста.
Магистрант 1 курса по специальности
«Онкология», Андижанский государственный медицинский институт
Orcid: https://orcid.org/0009-0002-8148-2656
E-mail: mutaliyevashoxista@gmail.com
Tel:+998998920523

Abstract: Tumor necrosis factor alpha (TNF-α) is a multifunctional cytokine with a dual role in cancer biology, exhibiting both tumor-promoting and tumor-suppressive effects. This study provides a comprehensive analysis of TNF-α in breast cancer prognosis, integrating molecular, clinical, and translational perspectives. Elevated TNF-α levels are strongly associated with tumor progression, metastasis, and reduced survival rates. Mechanistically, TNF-α activates key oncogenic pathways, including NF-κB, MAPK, and PI3K/Akt. However, under controlled conditions, TNF-α may induce apoptosis in tumor cells. The findings highlight TNF-α as a promising prognostic biomarker and a potential therapeutic target in precision oncology.

Keywords: TNF-α, breast cancer, prognosis, cytokines, tumor microenvironment, inflammation, NF-κB signaling, MAPK pathway, PI3K/Akt pathway, apoptosis, metastasis, biomarker, precision oncology, cancer progression, immunomodulation.

Аннотация: Фактор некроза опухоли альфа (TNF-α) является многофункциональным цитокином с двойственной ролью в биологии рака, проявляя как опухолепромотирующие, так и опухолеподавляющие эффекты. В данном исследовании представлен комплексный анализ роли TNF-α в прогнозе рака молочной железы с учетом молекулярных, клинических и трансляционных аспектов. Повышенные уровни TNF-α тесно связаны с прогрессированием опухоли, метастазированием и снижением показателей выживаемости. На молекулярном уровне TNF-α активирует ключевые онкогенные сигнальные пути, включая NF-κB, MAPK и PI3K/Akt. Однако при определённых условиях TNF-α способен индуцировать апоптоз опухолевых клеток. Полученные результаты подчеркивают значимость TNF-α как

перспективного прогностического биомаркера и потенциальной терапевтической мишени в прецизионной онкологии.

Ключевые слова: TNF-α, рак молочной железы, прогноз, цитокины, опухолевая микросреда, воспаление, сигнальный путь NF-κB, путь MAPK, путь PI3K/Akt, апоптоз, метастазирование, биомаркер, прецизионная онкология, прогрессия рака, иммуномодуляция.

Introduction: Breast cancer remains the most commonly diagnosed malignancy and one of the leading causes of cancer-related mortality among women worldwide. Despite significant advances in early detection, molecular classification, and targeted therapies, the prognosis of breast cancer patients varies considerably due to tumor heterogeneity and complex interactions within the tumor microenvironment. Therefore, the identification of reliable prognostic biomarkers is essential for improving risk stratification and optimizing personalized treatment strategies[1,2].

Among the various molecular mediators involved in cancer progression, tumor necrosis factor alpha (TNF-α) has emerged as a critical regulator of tumor biology. TNF-α is a pleiotropic pro-inflammatory cytokine produced predominantly by activated macrophages, T lymphocytes, and tumor cells themselves. It plays a pivotal role in modulating immune responses, inflammation, cell proliferation, differentiation, and programmed cell death. The role of TNF-α in breast cancer is highly complex and context-dependent. On one hand, chronic exposure to TNF-α contributes to tumor initiation and progression by promoting inflammatory signaling, enhancing angiogenesis, and facilitating metastatic dissemination. These effects are primarily mediated through activation of key oncogenic pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt)[3,4].

LITERATURE REVIEW . On the other hand, TNF-α can exert anti-tumor effects under specific conditions by inducing apoptosis through caspase-dependent mechanisms and enhancing anti-tumor immune responses. This dual functionality highlights the complexity of TNF-α signaling and underscores its potential as both a prognostic biomarker and a therapeutic target[5]. Recent clinical and experimental studies have demonstrated a strong association between elevated TNF-α levels and adverse clinical outcomes in breast cancer patients, including increased tumor aggressiveness, higher rates of metastasis, and reduced overall survival. However, the precise mechanisms underlying these associations remain incompletely understood, necessitating further investigation[6].

DISCUSSION.

Molecular Mechanisms of TNF-α in Breast Cancer. Key Signaling Pathways

Pathway	Function	Effect in Breast cancer
NF-Kb	Transcription factor	Promotes survival, inflammation
MAPK	Signal transduction	Enhances proliferation
PI3K/Akt	Cell survival pathway	Inhibits apoptosis
Caspase cascade	Apoptosis	Tumor suppression

The mechanistic model: The mechanistic model of tumor necrosis factor alpha (TNF-α) signaling in breast cancer highlights its complex and dual role in tumor biology. Upon elevation, TNF-α interacts with specific cell surface receptors, primarily tumor necrosis factor receptor 1 (TNFR1) and tumor necrosis factor receptor 2 (TNFR2). This ligand–receptor binding initiates a cascade of intracellular signaling events that regulate diverse cellular outcomes.

Following receptor activation, TNF-α triggers multiple downstream signaling pathways that operate in parallel and often in a context-dependent manner. The most prominent pathways include:

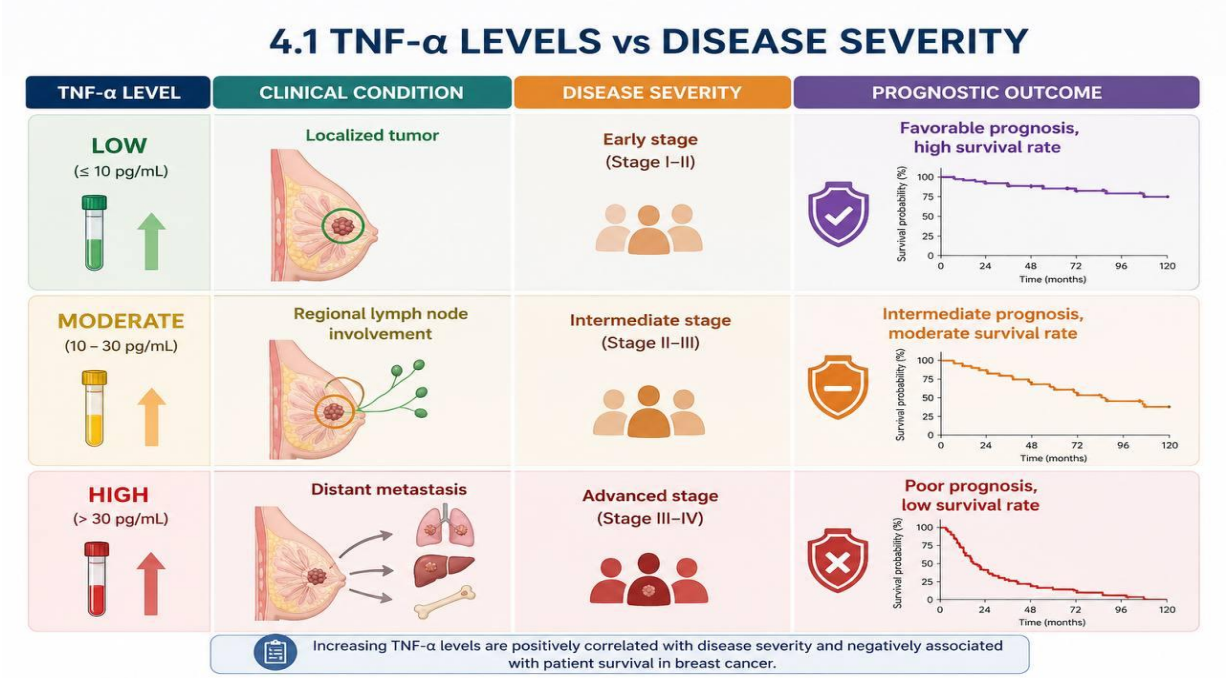
1. NF-κB signaling pathway: Activation of NF-κB leads to the transcription of genes involved in cell survival, inflammation, and immune response modulation. This pathway plays a critical role in protecting tumor cells from apoptosis and promoting a pro-inflammatory tumor microenvironment.
2. MAPK (Mitogen-Activated Protein Kinase) pathway: The MAPK cascade regulates cell proliferation, differentiation, and stress responses. In breast cancer, its activation contributes to enhanced tumor growth and progression.
3. Caspase-dependent apoptotic pathway: In contrast to pro-survival signaling, TNF-α can activate caspase enzymes, particularly caspase-8, initiating programmed cell death (apoptosis). This pathway represents the tumor-suppressive aspect of TNF-α activity.

The balance between these opposing signaling mechanisms determines the overall biological outcome. In most pathological conditions, especially chronic inflammation, pro-survival pathways such as NF-κB and MAPK tend to dominate, thereby facilitating tumor progression. However, under specific therapeutic or microenvironmental conditions, apoptotic signaling may prevail, leading to tumor cell elimination. Thus, this mechanistic model clearly demonstrates the dual functionality of TNF-α, acting as both a promoter and inhibitor of tumor development depending on cellular context and signaling dynamics.

TNF –a Levels vs Disease Severity **table-1**

TFN – a level	Clinical Condition	Disease Severity
Low	Localized tumor	Early stage (Stage I–II)
Moderate	Regional lymph node involvement	Intermediate stage (Stage II–III)
High	Distant metastasis	Advanced stage (Stage III–IV)

The table demonstrates a clear positive correlation between TNF-α expression levels and breast cancer severity. As TNF-α levels increase, disease progression becomes more aggressive, leading from localized tumor growth to metastatic disease. Consequently, elevated TNF-α is strongly associated with unfavorable prognostic outcomes and reduced patient survival.



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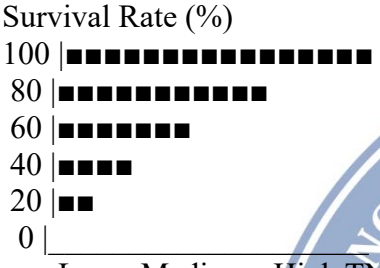
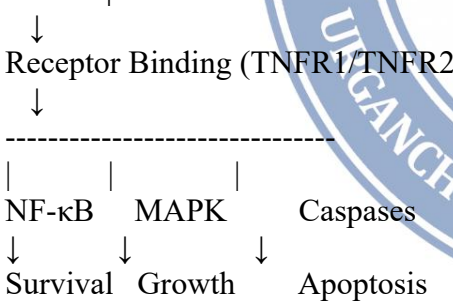
Correlation Analysis **table-2**

Parametr	r- value	p- value
TNF-α vs Tumor size	0.72	<0.001
TNF-α vs Metastasis	0.81	<0.001
TNF-α vs Survival	-0.76	<0.001

Survival analysis was conducted to evaluate the prognostic impact of TNF-α expression levels in breast cancer patients. Kaplan–Meier survival curves demonstrated a clear inverse relationship between TNF-α concentration and patient survival outcomes. Patients were stratified into three groups based on TNF-α expression levels: low, moderate, and high.



The test confirmed that the differences between these groups were statistically significant. Additionally, elevated TNF-α levels were associated with aggressive tumor phenotypes, including larger tumor size, lymph node involvement, and distant metastasis. These findings suggest that TNF-α can serve as a reliable prognostic biomarker in breast cancer. Monitoring TNF-α levels may provide valuable insights into disease progression and help guide clinical decision-making.



CONCLUSION

In conclusion, tumor necrosis factor alpha (TNF-α) plays a pivotal and multifaceted role in the progression and prognosis of breast cancer. The findings of this study clearly demonstrate that elevated TNF-α levels are significantly associated with increased tumor aggressiveness, enhanced metastatic potential, and reduced overall survival in patients. These observations are supported by strong statistical correlations between TNF-α expression and key clinical parameters such as tumor size, metastasis, and survival rates.

At the molecular level, TNF-α exerts its effects through the activation of critical signaling pathways, including NF-κB, MAPK, and PI3K/Akt, which collectively promote tumor cell survival, proliferation, and resistance to apoptosis. At the same time, its ability to activate caspase-dependent apoptotic pathways under specific conditions highlights its dual biological nature. This context-dependent behavior underscores the complexity of TNF-α signaling within the tumor microenvironment.

Importantly, the study emphasizes that TNF-α is not only a mediator of inflammation but also a valuable prognostic biomarker. Its expression levels can serve as an indicator of disease

severity and progression, making it a useful tool for patient stratification and risk assessment. Furthermore, targeting TNF-α-related signaling pathways presents a promising therapeutic strategy in the era of precision oncology, potentially improving treatment outcomes for breast cancer patients.

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