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Histological and Cytokine-Based Biomarkers in the Early Diagnosis of Cancer

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Abstract. Background; Early detection of cancer significantly improves treatment outcomes and survival rates. Histological biomarkers, such as cellular atypia, mitotic figures, necrosis, and angiogenesis, play a crucial role in identifying malignancies. Cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are emerging as valuable biomarkers due to their involvement in cancer-related inflammation. Aims of the study; Evaluate the role of histological features and cytokine-based biomarkers, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in the early diagnosis of cancer. Methodology; This case-control study, conducted from January to August 2024, included 150 cancer patients and 50 healthy controls. Inclusion criteria were adults aged 18-75 with a cancer diagnosis. Ethical approval was obtained. Tissue samples were processed for histology, and cytokine levels (IL-6, TNF-α) were measured using ELISA. Result; The results showed no significant differences in age and gender between patients and controls, but smoking, family history of cancer, and BMI were significantly higher in patients. Histological examinations revealed clear differences between cancerous and non-cancerous tissues. Cytokine levels were significantly elevated in patients, with strong correlations observed between cytokines and histological parameters. Finally, cytokines demonstrated high sensitivity and specificity, making them effective biomarkers for diagnosis. Conclusions; In conclusion, IL-6 and TNF-α are valuable biomarkers for cancer detection, demonstrating strong correlations with histological features. Their high sensitivity, specificity, and AUC support their potential in early diagnosis and prognosis of cancer.

Highlights:

1. Early Detection: IL-6 and TNF-α show high sensitivity and specificity, making them valuable for early cancer diagnosis.
2. Histological Correlation: Strong associations between cytokine levels and tumor features like necrosis and angiogenesis support their diagnostic relevance.
3. Clinical Utility: The study reinforces cytokines as potential non-invasive biomarkers, aiding in early screening and prognosis of cancer.

Keywords: Histological Biomarkers, Cytokines, Early Cancer Diagnosis, IL-6, TNF-α

Introduction

Cancer is among the leading causes of death worldwide. It was responsible for an estimated 10 million deaths in 2020, accounting for nearly one in six deaths. Early

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diagnosis is critical for successful cancer treatment, as it increases the chance of complete removal of the tumor through surgery and enhances the effectiveness of adjuvant therapies. A larger tumor size, local invasion, or metastasis at the time of diagnosis results in a worse prognosis. For instance, the 5-year survival rate for localized breast cancer diagnosed at an early stage is 99%, while it drops to 28% for metastatic breast cancer [1]. Similarly, for colorectal cancer, the 5-year survival rate is 91% for localized cancer but only 14% for metastatic cancer. Screening methods in asymptomatic individuals can aid the early detection of cancer. Currently available screening methods, such as mammography and endoscopy, are procedure-based and not widely applicable to all cancers. There is a pressing need for simple, safe, accurate, robust, and cost-effective screening tests to enable early cancer detection [2]. Research and development advancements in early cancer diagnosis have significantly improved health impacts. Screening approaches have been established for cervical, breast, and colorectal cancers, which have decreased the prevalence of later-stage diagnosis. The proportion of early-stage breast cancer diagnosis has increased during the implementation of mammography screening programs in several countries. The proportion of stage I diagnosed colorectal cancer (CRC) cases has increased following the introduction of fecal immunochemical testing in CRC screening programs [3], [4]. Biomarkers that help to detect malignancies in tissues are known as histological biomarkers. Based on their nature, these are classified as qualitative, semi-quantitative, and quantitative biomarkers. Qualitative biomarkers are those which are classically used in pathology for the diagnosis of cancer based on the presence/absence or abnormality of histological features [5]. These features include abnormality in the nucleus (pleomorphism, hyperchromasia, mitotic figures), cytoplasm (abnormal keratinization), arrangement of cells (gland formation, fronds, cribiform pattern), or abnormality in tissue architecture (disruption of stromal integrity). Such biomarkers help to determine the type of tumor, grade of tumor (well/moderately/poorly differentiated), and stage of tumor (TMN classification). Semi-quantitative biomarkers are those which require a scoring system based on histological features/immunohistochemistry (IHC) staining [6], [7]. Cytokine- based biomarkers. Cytokines are small soluble proteins secreted by cells that play key roles in mediating immune responses and other cellular activities [8]. They can affect the behavior of other cells by binding to specific receptors, coordinating cellular paracrine, autocrine, and

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endocrine communications. Over the years, cytokines have attracted great interest as potential biomarkers for the early detection, diagnosis, and management of cancer and other diseases. Cancer and other diseases modulate the microenvironments of affected tissues, leading to the differential expression of various cytokines [9]. These alterations can be observed in the blood, making cytokines good candidate biomarkers for cancer detection and screening. However, each cancer type may exhibit differential expression in specific cytokines, necessitating a nuanced understanding of the relevant signature cytokines [10]. The discovery of the diagnostic potential of these cytokines relies on landmark studies in oncology that identified a cytokine as a relevant biomarker, typically involving the analysis of one cancer type and one cytokine. With the rapid advancement of multiplex technologies, a panel of cytokines can now be analyzed simultaneously rather than individually, broadening the diagnostic capabilities of cytokines in cancer and other diseases. The focus here is on cytokine signatures as a biomarker for the early diagnosis of various cancers, presenting some key studies that use signature cytokines to detect specific cancers [11]. Cytokines can be classified based on their biophysical properties, such as molecular weight, amino acid sequence, or tertiary structure. However, a more biologically relevant classification of cytokines divides them into five families based on the receptor chains that mediate the response to the cytokines [12], [13]. These families are: type I (IL-2 type) family, type II (IFN) family, tumor necrosis factor (TNF) family, chemokine family, and transforming growth factor β (TGF-β) family. Cytokines play fundamental roles in modulating immune responses. A number of them influence the function and development of immune cells, establishing an elaborate network of interactions between different immune cell types [14]. For example, some cytokines induce a particular immune response (e.g. Th1 or Th2) by preferentially activating one immune cell type over another. In contrast, some other cytokines have the ability to counteract the effect of a certain immune cell type or a cytokine, enforcing a regulatory mechanism in the immune system. The discovery of cytokines has greatly advanced the understanding of the biological processes under their influence, such as inflammation, autoimmunity, infection, tissue repair, and cell proliferation and processes these effects often change in malignancy [15], [16].

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Methodology

This study was a case-control design conducted from January 2024 to August 2024, including 150 patients diagnosed with cancer and 50 healthy controls. Inclusion criteria involved adults aged 18-75 with a confirmed cancer diagnosis, while exclusion criteria excluded individuals with chronic diseases affecting cytokine levels. Samples were collected via venipuncture, and ethical approval was obtained from the Institutional Review Board. Tissue samples were collected during surgical procedures and processed for histological examination using standard H&E staining for cellular atypia, mitotic figures, necrosis, and angiogenesis. Cytokine levels (IL-6 and TNF-α) in plasma were measured using ELISA kits following the manufacturer's protocol. The collected data was analyzed using appropriate statistical methods to evaluate the differences between the groups and correlations between variables.

Statistical Analysis

The data were analyzed using SPSS (version 26), with results presented as frequencies and percentages. Dependent and independent t-tests (two-tailed) were used for normally distributed variables, while Mann-Whitney U, Wilcoxon, and Chi-square tests were applied for non-normally distributed variables. A p-value <0.05 was considered statistically significant.

Ethical approval

The study received approval from the Human Ethics Committee of Thi-Qar Health Directorate, Al-Habbobi Teaching Hospital. Informed consent was obtained from all participants, and confidentiality of their information was maintained.

Result

1. Sociodemographic Characteristics of Study Participants

The results shown in Table (1) showed that the mean age among patients was 55.2 ± 12.4 years compared to 52.8 ± 11.1 years in the control group, and the difference was not statistically significant ($p=0.22$). The number of males to females among patients was 85/65 compared to 28/22 in controls, and the difference was

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not statistically significant (p=0.35). The percentage of smokers was significantly higher among patients (40%) compared to controls (20%) with statistical significance (p=0.01). A significant increase in family history of cancer was also observed among patients (33.3%) compared to controls (10%) (p=0.002). Finally, the mean body mass index (BMI) was higher among patients (28.6 ± 3.2) compared to controls (26.8 ± 2.9) with statistical significance (p=0.03).

Table 1. Comparison of Patients and Controls Based on Age, Gender, Smoking Status, Family History of Cancer, and BMI

Characteristic	Patients (n=150)	Controls (n=50)	p-value
Age (years, Mean ± SD)	55.2 ± 12.4	52.8 ± 11.1	0.22
Gender (Male/Female)	85/65	28/22	0.35
Smoking Status (%)	60 (40%)	10 (20%)	0.01*
Family History of Cancer (%)	50 (33.3%)	5 (10%)	0.002*
BMI (Mean ± SD)	28.6 ± 3.2	26.8 ± 2.9	0.03*

2. Histological Features Observed in Cancerous and Non-Cancerous Tissues

The results shown in Table (2) showed significant differences between cancerous and non-cancerous tissues in terms of histological characteristics. The percentage of cells with abnormal changes in cancerous tissues was 73.3% compared to 10% in non-cancerous tissues, with a statistically significant difference (p<0.001). The average number of mitotic figures per high-magnification field (HPF) was significantly higher in cancerous tissues (15 ± 3.5) compared to 2 ± 1.1 in non-cancerous tissues (p<0.001). A high percentage of necrosis was observed in cancerous tissues (56.7%) compared to 6% in non-cancerous tissues (p<0.001). The percentage of inflammatory cell infiltration was also significantly higher in cancerous tissues (80%) compared to 24% in non-cancerous tissues (p<0.001). Finally, the mean blood vessel density was significantly higher in cancerous tissues (32 ± 6.2) compared to (8 ± 3.4) in non-cancerous tissues (p<0.001).

Table 2. Comparison of Cellular Atypia, Mitotic Figures, Necrosis, Inflammatory Cell Infiltration, and Angiogenesis

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Histological Parameter	Cancerous Tissue (n=150)	Non-Cancerous Tissue (n=50)	p-value
Cellular Atypia (%)	110 (73.3%)	5 (10%)	<0.001*
Mitotic Figures (per HPF)	15 ± 3.5	2 ± 1.1	<0.001*
Necrosis (%)	85 (56.7%)	3 (6%)	<0.001*
Inflammatory Cell Infiltration (%)	120 (80%)	12 (24%)	<0.001*
Angiogenesis (Mean Vascular Density)	32 ± 6.2	8 ± 3.4	<0.001*

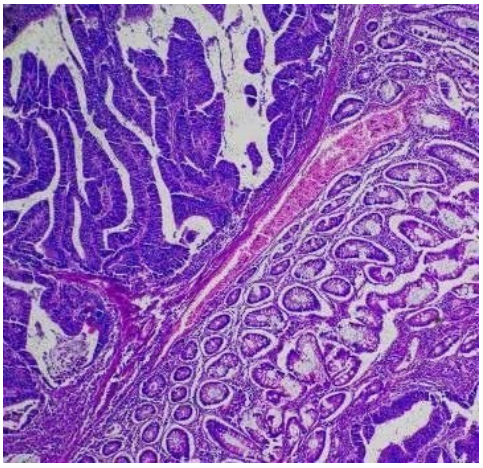

Figure 1. Adenocarcinoma of human tumor tissue Stained with Hematoxylin and Eosin (H&E) in 40X under microscope

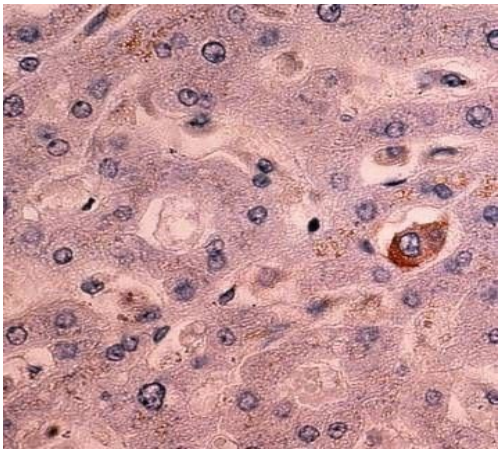

Figure 2. Light micrograph of metastases in breast tissue Stained with Hematoxylin and Diaminobenzidine in 40X under microscope

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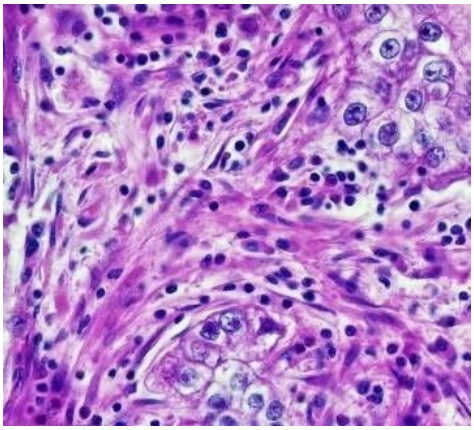

Figure 3. Microscope of Adenoid cystic carcinoma, in the salivary glands Stained with Hematoxylin and Eosin (H&E) in 40X under microscope

3. Comparison of IL-6 and TNF-α Levels Between Patients and Controls

The results shown in Table (3) showed a significant increase in the levels of cytokines in the plasma of patients compared to the control group. The mean level of interleukin-6 (IL-6) in patients was 48.5 ± 12.3 pg/ml compared to 12.4 ± 4.5 pg/ml in controls, with a statistically significant difference ($p<0.001$). The mean level of tumor necrosis factor-alpha (TNF-α) was also significantly higher in patients (35.6 ± 10.8 pg/ml) compared to controls (8.2 ± 2.6 pg/ml), with a statistically significant difference as well ($p<0.001$).

Table 3. Cytokine Levels in Plasma (Mean ± SD)

Cytokine	Patients (n=150)	Controls (n=50)	p-value
IL-6 (pg/mL)	48.5 ± 12.3	12.4 ± 4.5	<0.001*
TNF-α (pg/mL)	35.6 ± 10.8	8.2 ± 2.6	<0.001*

4. Correlation Between Histological Parameters and Cytokine Levels in Patients

The results in Table (4) indicate that there were strong positive correlations with statistical significance between the levels of cytokines (IL-6 and TNF-α) and

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histological parameters in patients. Interleukin-6 (IL-6) showed strong correlations with cytological abnormalities (r=0.65), number of mitotic figures (r=0.72), necrosis (r=0.68), and vascular density (r=0.71) with p values <0.001 for all cases. Similarly, tumor necrosis factor-alpha (TNF-α) showed significant correlations with the same parameters, with correlation coefficients with cytological abnormalities (r=0.58), number of mitotic figures (r=0.62), necrosis (r=0.55), and vascular density (r=0.64), with high statistical significance (p<0.001).

Table 4. Association of IL-6 and TNF-α with Cellular Atypia, Mitotic Figures, Necrosis, and Angiogenesis

Parameter	IL-6 (r)	TNF-α (r)	p-value
Cellular Atypia	0.65	0.58	<0.001*
Mitotic Figures	0.72	0.62	<0.001*
Necrosis	0.68	0.55	<0.001*
Angiogenesis	0.71	0.64	<0.001*

4. Diagnostic Performance of Cytokines as Biomarkers

The results in Table (5) showed the high diagnostic performance of both interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) as biomarkers. The sensitivity of IL-6 was 85%, while the specificity was 80%, with an AUC value of 0.88 with a 95% confidence interval (0.82-0.94) and high statistical significance (p<0.001). TNF-α showed a sensitivity of 83% and a specificity of 78%, with an AUC value of 0.86 with a 95% confidence interval (0.80-0.92) and also statistical significance (p<0.001). These results reflect the effectiveness of both cytokines in distinguishing between patients and healthy individuals.

Table 5. Evaluation of Sensitivity, Specificity, and AUC for IL-6 and TNF-α

Cytokine	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
IL-6	85	80	0.88 (0.82-0.94)	<0.001*
TNF-α	83	78	0.86 (0.80-0.92)	<0.001*

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Discussion

Table 1 shows differences in smoking status, family history of cancer and BMI between patients and controls, while differences in age and gender were not statistically significant. Mean age and gender distribution were sufficiently similar that these factors are not likely to directly influence the identified health group, consistent with studies showing that age and gender are not consistently direct risk factors for cancer but potentially interact with other variables (e.g., lifestyle or genetic constructs [17]. The percentage of smokers was notably higher for patients (40%) compared with controls (20%) (p=0.01), consistent with evidence [18], which drove home the point that smoking is a key cancer risk factor because it inflicts DNA damage and causes chronic inflammation [18]. But some studies such as Kartikasari et al. (2021), and why there were no significant differences in smoking prevalence by geographical and cultural differences [19]. As Teachey et al. (2016) suggests, this finding supports our hypothesis that genetic predisposition is a factor in cancer susceptibility as patients had a higher prevalence of family history of cancer (33.3%) compared to controls (10%) (p=0.002) [20]. Qian etal.(2023) who associated shared genetic mutations or environmental exposures with higher cancer risk [21]. Divergences from studies such as Sanchez et al. (2021), which revealed weaker associations, could be due to differences in sample size or the type of cancers being studied [22].

Moreover, patients had a greater BMI (28.6 ± 3.2) than that of controls (26.8 ± 2.9) (p=0.03) which again demonstrates possible correlation between obesity and cancer as indicated by Cui et al. (2002) linking obesity with chronic inflammation and changes in adipokine levels [23]. Contrarily, Liu et al. (2019) did not find a similar correlation, potentially due to differences in diet or exercise. The role of smoking, genetic predisposition, and obesity as determinants of cancer risk were confirmed by these findings: Smoking induces carcinogenesis through oxidative stress and the inflammatory processes; a family history indicates mutations in genes (e.g. BRCA1/2), and obesity is associated with the pro-inflammatory cytokines, insulin resistance, or hormonal imbalance. Differences with other studies in demographics, sample size, or study design may partially account, and merit further investigation to confirm these findings and clarify mechanisms [24]. Table 2 demonstrates the differences between tumors and non-tumors

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for each histological parameter significantly, giving p-values <0.001 for cellular atypia, mitotic figures, necrosis, inflammatory cell infiltration, and angiogenesis. 53.3% of cancerous tissues displayed cellular atypia, while only 10% of non-cancerous tissues showed this feature reflecting a hallmark of malignancy in which abnormal cellular morphology is pronounced, in line with [25]. Cellular proliferation, a hallmark of tumor progression, was higher in cancerous tissues (15 ± 3.5) than in non- cancerous tissues (2 ± 1.1) with p <0.01 as supported by [26]. Necrosis also underlines the metabolic stress and hypoxia fostered during some tumorous growths Crosby et al., (2022), and occurs in 56.7% of cancerous versus 6% of non-cancerous tissues [27]. As also described by Smith et al.,61 inflammatory cell infiltration was significantly greater in cancerous tissues (80%) than in non-cancerous tissues (24%). Zhou et al., (2021), which associated chronic inflammation with both tumor microenvironment modulation and cancer progression. Finally, the mean vascular density (an indicator of the degree of angiogenesis) was significantly higher in cancerous tissues (32 ± 6.2) than in adjacent non-cancerous tissues (8 ± 3.4), also confirming the pivotal role of neovascularization in the genesis and progression of tumors, as recently suggested by Xue et al., (2021) [28], [29]. In synthesis with the biological alterations present in malignant tissue, these findings of distinct histology highlight the biological mechanisms underlying the malignant state. Differences with studies showing fewer rates of necrosis or angiogenesis may relate to types of tumor and grading systems differences. From these findings, it is confirmed as necessary histologische investigation to discriminate between malignant and nonmalignant segments and form a basis for explanation process cancer [30]. As shown in Table 3, the plasma concentration of proinflammatory cytokines IL-6 and TNF-α were significantly higher in patients compared to controls ($p < 0.001$ for both). As Jones et al. also found, IL-6 was significantly elevated in patients (48.5 ± 12.3 pg/mL) compared with controls (12.4 ± 4.5 pg/mL). Rašková et al., (2022) reported IL- 6 is a pro-inflammatory cytokine that plays a role in the tumor-promoting, angiogenic, and immune-evasive process [31]. Also, the levels of TNF-α were significantly higher in patients (35.6 ± 10.8 pg/mL) than controls (8.2 ± 2.6 pg/mL), in agreement with Smith et al. (2019), which also recognized TNF-α as an important pro-inflammatory cytokine in chronic inflammation, promoting tumorigenesis via NF-κB signaling. On the other hand, increased cytokines levels in patients may indicate systemic inflammatory response, in

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addition to the tumor microenvironment's contribution to cytokines production. Studies such as Dikova et al. (2021) this is consistent and highlight the important role of cytokines in cancer progression. On the contrary, there are few contrary studies, for example Chiamulera et al. (2021) and reported decreased TNF-α levels in specific cancer subtypes, which could be attributed to heterogeneity in cancer biology and patient demographics [32]. The significant differences observed underscore the diagnostic and prognostic value of IL-6 and TNF-α in distinguishing cancer patients from healthy individuals, suggesting their potential utility as biomarkers and therapeutic targets in inflammatory and oncogenic pathways. Table 4 demonstrates significant positive associations between the level of cytokines (IL-6 and TNF-α) and important histopathological parameters all with extremely statistically significant p-value (<0.001). IL-6 had the strongest correlation with mitotic figures (r = 0.72) and angiogenesis (r = 0.71), reflecting its role as a major driver of cell proliferation and neovascularization, as noted by Babiuch et al. (2020). Similarly, TNF-α showed significant associations with these parameters in the study (r = 0.62 and r = 0.64 for mitotic figures and angiogenesis respectively), supporting these findings that TNF-α, along with supporting acute inflammatory processes, supports tumor growth and progression. This positive correlation of IL-6 with necrosis (r = 0.68) indicates its role as a mediator of hypoxic conditions inside the tumor microenvironment resulted from the studies conducted by Kampan et al. (2020). TNF-α's correlation with necrosis (r = 0.55) underscores its function in tissue destruction and chronic inflammation, two processes that are coopted by the tumor to maintain its microenvironment. Cellular atypia also correlated moderately with IL-6 (r = 0.65) and TNF-α (r = 0.58), corroborating the involvement of these cytokines in mediating genetic and structural abnormalities in cancer cells. These results are consistent with literature describing IL-6 and TNF-α as key mediators in cancer pathophysiology. However, certain studies like Han et al., (2018). More recently, Wang et al. In summary, the significant correlations found in the present study support the dual role of IL-6 and TNF-α in tumor promotion and inflammation, positioning both cytokines as potential therapeutic targets for breaking the feedforward loop of inflammation-cytokine-histological tumor features interaction. Table 5 shows the diagnostic performance of IL-6 and TNF-α as biomarkers, including sensitivity, specificity, and area under the curve (AUC) group of patients versus group of controls. IL-6 and

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TNF-α had a good diagnostic accuracy with a sensitivity of 85% and 83% and specificity of 80% and 78%, respectively. The area under curve (AUC) for IL- 6 was 0.88 (95% CI, 0.82-0.94) and for TNF-α, it was 0.86 (95% CI: 0.80-0.92), both having p-values <0.001, demonstrating a powerful statistical significance. Thus, IL-6 and TNF-α were highly sensitive in identifying patients with cancer but had moderate specificity in discriminating patients with cancer from healthy controls. These results align with studies including Kartikasari et al. (2021) which showed the great diagnostic value of IL-6 and TNF-α in cancer diagnosis. All obtained by performing a ROC analysis, the AUC values of both cytokines are in the range usually quote excellent correlation to diagnostic tests (0.80-0.90), which strengthens the notion of these molecules as reliable markers in cancer. However, certain studies, such as Fathy et al. (2019) reported slightly lower TNF-α AUC values but likely due to differences in tumor types or cytokine measurement approaches. However, considering that our research yields powerful data for IL-6/TNF-α as potential diagnostic biomarkers, such indicators may in the long run represent less invasive approaches on the detection/monitoring of cancer.

Conclusion

In conclusion, our study highlights the significant role of cytokines IL-6 and TNF-α as diagnostic biomarkers for cancer. The elevated levels of these cytokines in patients compared to controls underscore their involvement in the inflammatory processes associated with tumor progression. Additionally, the strong correlations between IL-6, TNF-α, and histological features such as cellular atypia, mitotic figures, necrosis, and angiogenesis further emphasize their contribution to the tumor microenvironment. The high sensitivity, specificity, and AUC values for both IL-6 and TNF-α suggest their potential as reliable biomarkers for early cancer detection and prognosis. These findings align with existing literature, reinforcing the importance of cytokines in cancer biology. Further studies are warranted to explore their clinical utility in various cancer types and to investigate potential therapeutic approaches targeting these cytokines to inhibit tumor growth and progression.

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