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Evaluate the Seroprevalence of Human Papillomavirus Immunoglobulin IgM among Women and Its Relationship with Cervical Cancer In Diyala Governorate

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Abstract

Background: Prolonged infections caused by High-risk HPVs have the potential to cause cancer in the regions of the body where they infect cells, including the cervix or the oropharynx, which refers to the rear part of the throat.

Aims: To detection of Human Papillomavirus (HPV) -IgM , IL-10 and TNF among Iraqi women

Methods: A total of 89 blood sample were collected from females with various cervical lesions and 40 blood samples were collected from apparently healthy along with a control group of 40 healthy females. The presence of Human Papillomavirus (HPV) -IgM, IL-10 and TNF in the collected samples was assessed using the ELISA technique.

Results:

The positivity rate of HPV IgM was 13.5%. This positivity was higher among individuals aged 40 or younger who had also been diagnosed with cervical cancer. The levels of IL-10 and TNF differed between the two groups. The mean ±SD of IL-10 levels was 2.223±0.412 for patients and 2.035±0.009 for healthy females, with a significant difference ($P < 0.001$). The mean ±SD of TNF levels was 2.650±0.765 for patients and 2.384±0.011 for healthy females, with a significant difference ($P < 0.001$).

Key Words: Human papillomavirus, Immunoglobin, Cervical cancer, ELISA

INTRODUCTION

Cervical cancer remains a significant public health challenge in less developed countries, with high rates of illness and death associated with this disease. However, there are strategies that can help reduce these rates, including educational campaigns,

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regular Pap tests, and the administration of Human Papillomavirus (HPV) vaccines [2].

Cervical cancer, often abbreviated as CC, is characterized by abnormal changes in the epithelial cells of the cervix. These changes are primarily caused by infections with specific high-risk HPV serotypes, such as HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. These specific HPV serotypes are strongly associated with the formation of precancerous and cancerous intraepithelial lesions. According to a study conducted by [11]. HPV serotypes 16 and 18 alone account for roughly 80% of cervical cancer cases. Hence, it is vital to detect precancerous lesions and HPV infections early for effective intervention. Screening techniques like HPV tests and Pap smears are indispensable tools for early identification, as highlighted by [15].

HPV infection alone is not adequate for the advancement to cervical cancer and other risk conditions such as smoking, prolonged oral contraception consumption, co-infections, and multi-parity, immune-related diseases appear to lead the infection on the route of carcinogenesis [4]. Cervical cancer continues to be a major health problem in developing countries.

The goal of cervical cancer prevention programs is to achieve high detection rates. However, women in low- and middle-income countries face limited access to tests like the Pap smear. There are over 80 different HPV types, categorized into cutaneous and mucosal infections. While most HPV types are asymptomatic, some can cause warts (verrucae), and in rare cases, genital cancers. Notably, HPV 16 and 18 infections have been closely associated with an increased risk of oropharyngeal (throat) cancer, as highlighted by [6].

Human papilloma virus is the most common sexually transmitted infection worldwide. It is also the causative agent for 1/3 of all the viral induced tumors and responsible for (5%) of human cancers [8]. HPV infections spread through vaginal or anal sexual contact, or through skin-to skin contact [9]. Sexually active individuals who have multiple partners, weakened immune systems,

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or damaged skin, are more susceptible to HPV [5].

Cancers of the throat, mouth, cervix, anus, penis, and vagina are linked to HPV infections [13]. HPV is thought to be responsible for more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 60% of penile cancers, and 60% to 70% of oropharyngeal cancer" [12].

The primary mode of transmission for more than 30 to 40 different HPV strains that affect the anogenital area is through sexual intercourse. Some sexually transmitted HPV types can result in genital warts, On the other hand, other HPV types categorized as "high-risk" have the capacity to advance into precancerous lesions and ultimately invasive cancer. It's crucial to emphasize that the majority of cervical cancer cases are linked to HPV infection. However, it's worth mentioning that not all HPV infections lead to disease. For instance, HPV type 1 typically infects the soles of the feet, while HPV type 2 usually infects the palms of the hands, leading to the development of warts.

Numerous serologic procedures are available For detection of humoral antibodies, including Sabin Feldman dye test, indirect heamagglutination test, direct agglutination test, latex agglutination test, indirect fluorescent Antibody test, complement fixation test, and enzyme-linked Immunosorbent assay [1].

Since the discovery of papillomaviruses in the early 20th century, it has been confirmed that a significant percentage of cervical cancer specimens, specifically 99.7%, contain high-risk HPV DNA, as reported by [16]. This emphasizes the essential role played by high-risk HPV types in the development of cervical cancer.

MATERIALS AND METHODS

Specimens' collection

The sample included (89) Iraqi women patients with cervical diseases with ages ranging between 17 to 80 years who attended Baghdad Teaching Hospital in Medical City and private clinical in Baqubah City from October 2022 to January 2023 .The blood samples have been taken from the vein and serum was obtained after

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separation of blood by centrifuge according to standard procedure.

Ethical consideration

This study conducted according to the principles of Helsinki declaration.

A full explanation of the purpose of this study to all participants before starting. Dully filled consent form obtained from all participants.

Approval of an ethical review committee of Biology department, college of Science, Diyala University, Iraq, taken before initiation into the work.

Results

Table 1: Distribution of Anti-HPV Ab positivity rate between study groups.

			Groups		*P* value
			Cervical cancer Patients (89)	**Healthy (40)**	
HPV IgM	+ve	N.o.	19	0	< 0.001
		%	21.3 %	0 %	
	-ve	N.o.	70	40	
		%	78.7 %	100 %	

Table 2: Distribution of IL-10 and TNF-α level Concentration between study groups

Groups		**N**	**Mean**	**Std. Deviation**	**Std. error**	***P* value**
IL-10	**Patients**	89	2.223	0.412	0.043	< 0.001
	Healthy	40	2.035	0.009	0.001	
TNF-α	**Patients**	89	2.650	0.765	0.081	< 0.001
	Healthy	40	2.384	0.011	0.001	

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Table 3: ROC curve, sensitivity, and specificity of IL-10, TNF and HPV IgM.

Variables	AUC	Std. Error	*P* value	Sensitivity %	Specificity %
IL-10	.994	.004	< 0.000	99 %	93 %
TNF	.920	.032	< 0.000	86 %	93 %
HPV IgM	.984	.010	< 0.000	100 %	97 %

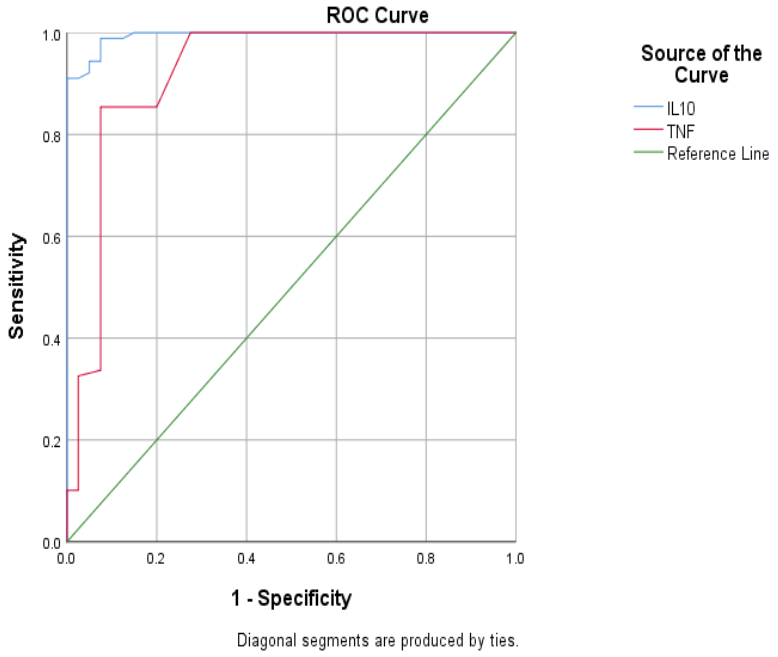

Figure 1: ROC curve of IL-10 and TNF

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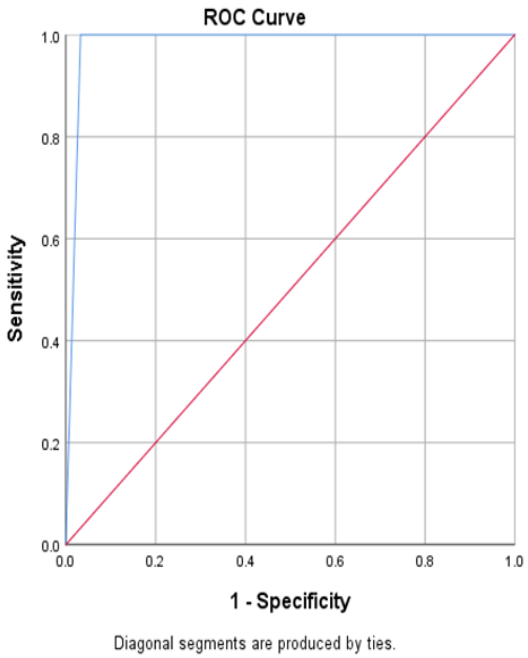

Figure2: ROC curve of HPV IgM

Discussions

Detection of HPV by ELISA method

Diagnosis of Human papillomavirus (HPV) anti HPV IgM by ELISA

In the current study, the findings indicated a 21.3% positivity rate of HPV IgM ($P < 0.001$). These results align with earlier research conducted in southeastern China, which reported a 18.34% positivity rate for HPV IgM among participants, with an overall HPV positivity rate of 20.16% [7]. It's worth noting that several factors have been suggested as conducive to HPV infection, including genetic susceptibility, sexual behavior (such as an earlier age of sexual activity and having multiple sexual partners), long-term use of contraceptives, and lifestyle [14]. These factors can contribute to the prevalence of HPV infections in populations.

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The concentration of IL-10 and TNF-α was measured between the study groups using the ELISA method

The findings indicated that the average ± standard deviation (SD) of IL-10 levels were elevated in patients when compared to healthy individuals. Specifically, the values were 2.223 ± 0.412 for patients and 2.035 ± 0.009 for healthy individuals. This disparity was statistically significant ($P < 0.001$). Similarly, the mean ± SD of TNF levels were also higher in patients than in healthy individuals, with values of 2.650 ± 0.765 for patients and 2.384 ± 0.011 for healthy individuals. This difference was also statistically significant ($P < 0.001$).

In a study conducted by [1], they documented comparable alterations in cytokine expression when researching immune responses in cervical cancer patients in Hawler City, Iraq. Their study also revealed significantly elevated levels of IL-10 and TNFα among the subjects, mirroring the findings of this study.

InterLeukine-10 is a significant anti-inflammatory cytokine with characteristics such as anti-angiogenic and immunosuppressive properties. Numerous studies have explored variations in IL-10 levels in cervical cancer, with some reporting increases and others decreases. Given the high prevalence and mortality of cervical cancer, your study underscores the importance of expanding efforts in disease prevention and advocating for regular gynecological check-ups.

While Human Papillomavirus (HPV) undoubtedly plays a critical role in the development of cervical cancer, it's important to recognize that other factors also influence the formation of squamous intraepithelial lesions (SIL), which may or may not progress to cervical cancer. In this context, Interleukin 10 (IL-10) is highlighted as a significant anti-inflammatory factor that contributes to immune system evasion by promoting immunosuppression.

Within the cervical microenvironment during various stages of HPV infection, multiple cell sources come into play. These sources include infected keratinocytes, dendritic cells, tumor-associated

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macrophages, T regulatory cells, and tumor cells. These cells collectively induce and sustain the production of IL-10. IL-10, in turn, exerts diverse effects on different cell populations. These effects encompass the inhibition of proinflammatory cytokine production, influence on dendritic cell differentiation and antigen presentation, and the modulation of T-helper 1 polarization. These intricate interactions within the cervical microenvironment illustrate the complex dynamics involved in the development and progression of cervical lesions and cancer [3].

The role of IL-10 in cancer is still controversial and not fully understood, but it tends to increase in parallel with SIL development and is even higher within cervical tumors. The interaction between HPV and IL-10 can create a cycle favoring an immunosuppressive microenvironment in the cervix, potentially facilitating the progression of HPV infection to SIL or cervical cancer [3].

TNF-α is a cytokine with both anti-tumor and tumor-promoting functions. While it has antitumor, antiviral, and immune-enhancing properties, it has also been associated with tumor development. Tumor tissue secreting TNF-α can promote tumor cell growth, stimulate angiogenesis, and accelerate cancer onset and progression [10].

Based on ROC analysis, IL-10 and TNF exhibited high sensitivity and specificity (99%, 93%) and (86%, 93%), respectively, in distinguishing patients from controls, with a significant difference ($P < 0.001$). As for HPV IgM, the test demonstrated a sensitivity and specificity of 100% and 97%, respectively, with an area under the curve of 0.984 and a significant difference ($P < 0.001$) for diagnosing patients with HPV.

CONCLUSION

- In conclusion IL-10 and TNF levels were higher in patients than healthy with significant difference.
- Correlation between TNF and IL-10 but these correlations were not significant.
- IL-10, TNF -α level, anti-HPV IgM were have high sensitivity

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and specificity in diagnosis by ELISA.

RECOMMENDATIONS

- The summary of the results and interpretations of this study should be informed to the Directory of Hospitals of ministry of Health particularly the Women's hospitals and cancer centers to make benefits of them.
- Adoption of continuous program of health education toward the prevention and control of HPV in general and specially against the newly emerged routes of transmission such as nightclubs and sex practices and not allowing foreign arrivals and workers except after conducting medical examinations.
- We recommend larger studied , in different Iraqi cities, so that establishing the prevalent virus type will help to recommend the most effective vaccine, as in our study the quadrivalent vaccine is the most suitable option.

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Conflicts of interest

The authors declare that they have no potential conflict of interest concerning the authorship or publication of this article.

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