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ORIGINAL ARTICLE

Hyperproteinemia, Hematuria, and Squamous Cell Shedding in Elderly Cervical Cancer Patients and the Potential Alternative Screening Tool

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SUMMARY

Background: **In Saudi Arabia, cervical cancer, frequently caused by human papillomavirus (HPV) infection, is a common cancer. The usual procedures for screening and diagnosing cervical cancer include Pap smears and HPV tests, even though they have considerable drawbacks, particularly for older women (> 60 years) who have limited access to or compliance with these tests. Urinalysis is a simple, noninvasive test that has been suggested as an alternative procedure. This study aimed to investigate the change in urinalysis characteristics in cervical cancer patients in elderly females and the possible use of urinalysis as a screening or diagnostic tool for cervical cancer in older women.**

Methods: **This was an exploratory cross-sectional study of 190 cervical cancer patients diagnosed between January 2018 and August 2021. Based on age, the study included two groups, < 60 years and ≥ 60 years. Urinalysis characteristics, including bacterial count, blood level, protein level, and squamous epithelial cell shedding, were compared between the age groups by using the chi-squared and Kruskal-Walli tests.**

Results: **The results showed a significant difference between aged females and younger females with cervical cancer at the blood level, protein level, and squamous epithelial cell shedding in the urine. The older women (≥ 60 years) had higher incidences of increased bacterial count, blood levels, protein levels, and squamous epithelial cell shedding than the younger women (< 60 years).**

Conclusions: **The main finding of the study implies that there are significant changes in urine characteristics in cervical cancer patients including hyperproteinemia, hematuria, and squamous cell shedding in elderly patients compared to younger patients, and it proposes a potential role for urinalysis as a screening tool for cervical cancer in older women. Urinalysis could be a potential screening tool for cervical cancer in older women who have not been screened or have no screening access. Further studies are needed to validate these findings.**

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KEYWORDS

cervical cancer, urine characteristics, Saudi Arabia, elderly

INTRODUCTION

Women of all ages are susceptible to cervical cancer, a common and preventable cancer. It is often caused by persistent infection with human papillomavirus (HPV), and a Pap smear or HPV test is used to detect the virus. HPV is a group of viruses that infect the skin. More than 100 types of HPV exist, and at least 13 are consid-

ered carcinogenic because they carry a high risk or likelihood of persistent infection and are associated with precancerous lesions [1]. HPV can be transmitted sexually and is considered one of the most common causes of sexually transmitted diseases in the United States [1]. In Saudi Arabia, few data are available that indicate how common HPV infection is. According to a study by Hussain et al. in 2016, about 31% of the general population of Saudi Arabia, 80% of women with abnormal cells, and more than 92% of women with cervical cancer have an HPV infection [2]. Another study by Alhamlan et al., which followed a group of Saudi women from 2013 to 2015 in a hospital setting, found that 17% of the 400 samples tested were positive for HPV [3].

HPV infection often has no symptoms, and it usually resolves with time, but some types can persist which leads to serious health problems and causes cervical cancer [4]. Cervical cancer is reported to be the fourth most common female cancer worldwide, [4] the fourth most common cancer among non-Saudi women residing in Saudi Arabia, and the eighth most common cancer in Saudi women aged 30 to 44 years [2]. In developing countries, cervical cancer is the leading cause of morbidity and mortality among women [5]. HPV vaccines can prevent some of the most common types of HPV infection and reduce the risk of cervical cancer and other cancers. A study by Almehmadi et al. showed a lack of awareness and acceptance among the Saudi population to get the HPV vaccine, and in the same paper, they suggest the need for further education on the vaccine's importance [6]. However, some older women may not receive adequate screening or may have other risk factors that increase their susceptibility to cervical cancer. One of the significant causes of cancer death in developed countries is the lack of fair access to screening and treatment, which leads to delayed diagnosis when the cancer is already advanced [7]. The implementation of cytology has led to a decrease in the incidence of cervical cancer, even though access to cytology-based cervical cancer screening is limited, especially in rural areas and in developed countries [8].

Urinalysis is a simple, noninvasive test that examines urine for signs of infection, inflammation, blood, and other abnormalities. It is not a specific test for cervical cancer, but it may show some changes if the cancer has spread to the bladder or kidneys [9].

A new method of screening for cervical cancer that uses urine samples has been developed, especially for women who have difficulty accessing other modes of screening [10]. Self-sampling can help women with poor access to healthcare to be screened for cervical cancer more easily and fairly. Urine samples can be collected at home and sent to the lab with proper cooling. This method is cheaper, more acceptable, and less uncomfortable for women from low-income countries, who are more likely to get HPV-related cancers but are less likely to be screened [11].

Comparing urine and cervical samples from patients in clinics is not common in Saudi Arabian studies. Therefore, this study aimed to investigate the change in urinalysis characteristics in cervical cancer patients in elderly females and to explore the potential role of urinalysis as an alternative screening tool for cervical cancer in older women (> 60 years). We hypothesized that older women with cervical cancer would have more abnormal urinalysis results than younger women with cervical cancer, and that urinalysis might be useful for identifying cervical cancer in older women who had not been screened or had inconclusive screening results.

MATERIALS AND METHODS

Sampling and data collection

This was a cross-sectional study to compare urinalysis results between two groups of cervical cancer patients based on their age. A total of 190 cervical cancer patients who were diagnosed and treated at King Abdulaziz Hospital in Saudi Arabia between January 2018 and August 2021 were included. The study sample was divided into two groups according to the patient's age at the time of diagnosis: < 60 years old and ≥ 60 years old. The patients were matched by stage and type of cervical cancer to ensure comparability between the groups. The data were collected from the hospital database and medical records. The inclusion criteria were female gender, age 18 years or older, a confirmed diagnosis of cervical cancer by histopathology or cytology, and available urinalysis results within six months of diagnosis. The exclusion criteria were previous or concurrent bladder or kidney diseases, urinary tract infections, or other conditions that may affect urinalysis results. Parameters such as bacterial count, blood level, protein level, and squamous epithelial cell shedding in the urine were investigated. The study was performed after approval by the Ministry of Health of the Kingdom of Saudi Arabia (registration number HAP-02-T-067) and conducted according to the principles of the Helsinki declaration.

Statistical analysis

The data were analyzed using descriptive statistics and inferential statistics. Descriptive statistics were used to summarize the characteristics of the study population and the urinalysis results. Inferential statistics were used to test the hypothesis that older women with cervical cancer would have more abnormal urinalysis results than younger women with cervical cancer. The categorical variables are expressed as frequencies and percentages. To determine the difference between the two categorical variables, a chi-squared test was used where the p-value threshold for significance was 0.05. Also, we were able to analyze the data using the Kruskal-Walli test between the variables, as indicated in the graph. The statistical analysis was carried out using SPSS (Mac version 17.0) (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Mac version 16.59) (Microsoft Cop., Redmond, Washington, USA).

Table 1. Demographic characteristics of study participants.

Parameters	Patients	
Total number of participants	190 cervical cancer patients	
Age (years) (mean ± SD)	58.2 (SD 12.42)	
Age groups	< 60 years old	98 (51.57%)
	≥ 60 years old	92 (48.42%)
Nationality	non-saudi	122 (64.21%)
	Saudi	68 (35.78%)
Marital status	married	86 (45.26%)
	single	101 (52.74%)
	divorced or widowed	3 (2%)
Diabetic status	no diabetes	173 (91.05%)
	diabetes	17 (8.94%)
Smoking status	no	169 (88.94%)
	yes	21 (11.05%)
HbA1c	6.9 mmol/mol (SD 1.29)	
Urine PH	5.78 (SD 0.80)	

SD - standard deviation.

Table 2. The number of bacteria in cervical cancer patients' urine.

Sample interpretation	Number of bacteria in the urine	Total percentage of positive and negative samples	Total number of patients	Aged < 60 years	Aged ≥ 60 years	chi-square	p-value
Positive	1+	98 (51.57%)	21 (11.05%)	9 (42.85%)	12 (51.14%)	0.639	0.423
	2+		15 (7.89%)	8 (53.33%)	7 (46.44)	0.018	0.891
	3+		21 (11.05%)	13 (61.90%)	8 (38.09)	0.896	0.343
	4+		41 (21.57%)	16 (39.02%)	25 (60.97%)	9.83	0.00171 *
Negative	Nil	92 (48.42%)	92 (48.42%)	52 (56.52%)	40 (43.47)	0.89	0.342

chi-squared test * - Significant p-value < 0.05.
1+: few bacteria; less than 10 CFU/mL.
2+: moderate bacteria; 10 to 100 CFU/mL.
3+: many bacteria; more than 100 CFU/mL.
4+: high number of bacteria; more than 500 CFU/mL.

RESULTS

The total number of participants in this cross-sectional study was 190 patients diagnosed with cervical cancer, and the mean age was 58.2 years (12.42). The number of participants < 60 years old was 98 (51.57%), and the number of participants ≥ 60 was 92 (48.43%). The study included 122 (64.21%) non-Saudi participants and 68 (35.78%) Saudi participants. Regarding marital status, the majority were single (52.74%), 45.26% were married, and the rest were divorced or widowed (2%). The number of participants without diabetes was 173 (91.06%), and the number of participants with diabetes was 17 (8.94%). The average HbA1c was 6.9 mmol/mol. Regarding smoking status, approximately 11.06% reported smoking cigarettes, and the remaining 169 participants (88.94%) were non-smokers. The mean urine PH was 5.78 (0.80). The demographic data are summarized in Table 1. A urinalysis of 190 females diagnosed with cervical cancer was conducted to examine

Table 3. The amount of blood in cervical cancer patients' urine.

Sample interpretation	Blood in urine	Total percentage of positive and negative samples	Number of patients	Aged < 60 years	Aged ≥ 60 years	chi-square	p-value
Positive	1+	118 (62.11%)	27 (14.21%)	11 (40.74%)	16 (59.25%)	1.108	0.29
	2+		53 (27.89%)	22 (41.50%)	31 (58.49%)	4.223	0.03 *
	3+		38 (20%)	10 (26.31%)	28 (73.68%)	5.215	0.02 *
Negative	Neg	72 (37.89%)	72 (37.89%)	55 (76.38%)	17 (23.61%)	5.383	0.02 *

chi-squared test * - Significant p-value < 0.05.
1+: a small amount of blood that might make urine look slightly pinkish.
2+: a moderate amount of blood that makes urine look red or tea-colored.
3+: a large amount of blood that makes urine look very red or dark brown.

Table 4. The protein level in cervical cancer patients' urine of two different age groups.

Sample interpretation	Protein level in urine	Total percentage of positive and negative samples	Number of patients out of total (n = 190)	Aged < 60 years	Aged ≥ 60 years	chi-square	p-value
Positive	1+	90 (47.36%)	54 (28.42%)	10 (18.51%)	44 (81.48%)	11.33	0.0007 *
	2+		16 (8.42%)	5 (31.25%)	11 (68.75%)	4.87	0.027 *
	trace		20 (10.52%)	12 (60%)	8 (40%)	1.75	0.185
Negative	neg	100 (52.63%)	100 (52.63%)	71 (71%)	29 (29%)	1.32	0.24

chi-squared test * - Significant p-value < 0.05.
1+: This means there is a small amount of protein in the urine, about 30 mg/dL or more.
2+: This means there is a moderate amount of protein in the urine, about 100 mg/dL or more.
Trace: This means there is a very small amount of protein in the urine, less than 30 mg/dL.
Negative - This means there is no detectable protein in the urine.

Table 5. The presence of squamous epithelial cell shedding in cervical cancer patients' urine of two different age groups.

Sample interpretation	squamous epithelial cell shedding in urine	Total percentage of positive and negative samples	Number of patients out of total (n = 190)	Aged < 60 years	Aged ≥ 60 years	chi-square	p-value
Positive	few	40 (21%)	13 (6.84%)	1 (7.69%)	12 (92.30%)	8.20	0.004 *
	modrate		27 (14.21%)	7 (25.92%)	20 (74.07%)	4.97	0.025 *
Negative	nil	150 (79%)	150 (78.94%)	90 (60.00%)	60 (40.00%)	3.20	0.073

chi-squared test * - Significant p-value < 0.05.

our hypothesis. In the beginning, healthy women were selected of the same ages (> 60 years old) as controls to test the hypothesis. However, this design showed a big contrast in urine features between the cancer and healthy groups. The healthy group had no significant changes in urine features. Therefore, we compared the cancer groups of different ages (> 60 years old and < 60 years old) instead. Table 2 shows that around 48.00% of

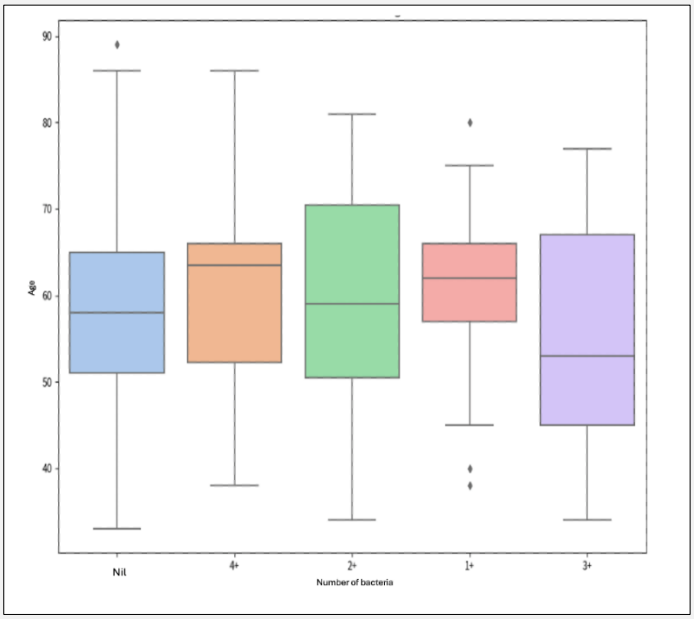

Figure 1. The box plot visualizes the age distribution for the number of bacteria in the urine.

The bottom and top of each box represent the first (Q1) and third (Q3) quartiles, respectively. The line inside the box indicates the median. The whiskers extend to 1.5 times the interquartile range (IQR) above Q3 and below Q1. Points outside the whiskers are considered outliers.

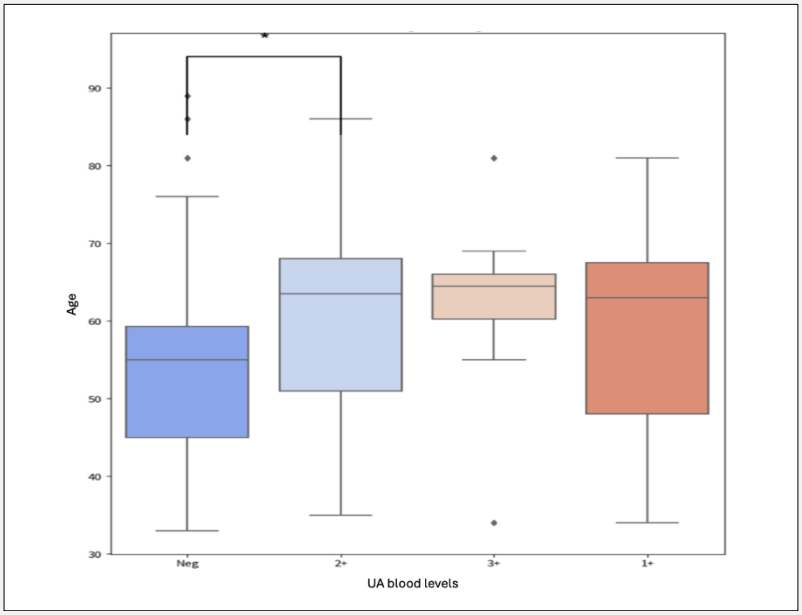

Figure 2. Box plot visualizes the age distribution for each blood level in the urine.

The bottom and top of each box represent the first (Q1) and third (Q3) quartiles, respectively. The line inside the box indicates the median. The whiskers extend to 1.5 times the interquartile range (IQR) above Q3 and below Q1. Points outside the whiskers are considered outliers.

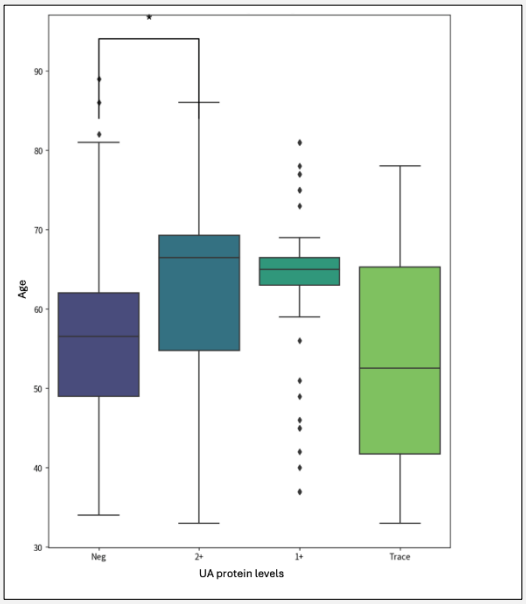

Figure 3. The box plot visualizes the age distribution for each protein level in the urine.

The bottom and top of each box represent the first (Q1) and third (Q3) quartiles, respectively. The line inside the box indicates the median. The whiskers extend to 1.5 times the interquartile range (IQR) above Q3 and below Q1. Points outside the whiskers are considered outliers.

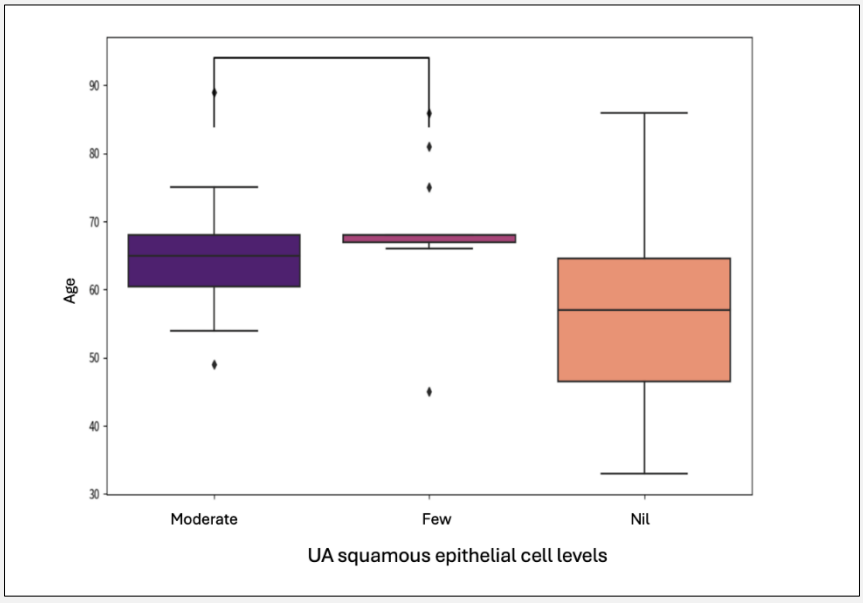

Figure 4. Box plot visualizes the distribution of age for each level of squamous epithelial cells in the urine.

The bottom and top of each box represent the first (Q1) and third (Q3) quartiles, respectively. The line inside the box indicates the median. The whiskers extend to 1.5 times the interquartile range (IQR) above Q3 and below Q1. Points outside the whiskers are considered outliers.

the cervical cancer patients did not have bacteria in their urine, while 52% showed the existence of bacteria in different amounts; 21.57% of the cervical cancer patients had high bacterial counts (i.e., > 500 CFU/mL) (4+).

We found a statistically significant increase ($p < 0.05$) in the number of participants aged ≥ 60 years having bacteria > 500 CFU/mL (4+) in their urine compared to the younger individuals as shown in Table 2 (chi-square) and Figure 1 using Kruskal-Walli test. However, there was no significant difference in the urine of the participants ≥ 60 years having bacteria < 500 CFU/mL (from 1+ to 3+) compared to the younger individuals.

Table 3 shows that around 62.11% of all participants had blood in their urine (hematuria) at different concentrations, and 37.89% of cervical cancer patients did not have blood in their urine. In addition, around 20.00% of the participants had a large amount of blood, making their urine a dark brown color. We found a statistically significant increase ($p < 0.05$) in the number of participants aged ≥ 60 years having a large amount of blood (3+ and 2+) in their urine compared to the younger individuals, as shown in Figure 2 and Table 3. However, there was no significant difference in the participants aged ≥ 60 years having slight to moderate amounts of blood (from 1+) in their urine compared to the younger individuals.

The data in Table 4 show the protein levels in the participants' urine. Around 52.63% showed no protein in their urine, while the remaining participants (47.36%) showed 1+ or 2+ trace protein levels in their urine. Table 4 and Figure 3 show a significant difference ($p < 0.05$) between the protein level in urine and the age group ≥ 60 years for the 1+ and 2+ categories compared to the participants aged < 60 years, as their p-values were < 0.05. This means that the incidence of 1+ and 2+ protein levels in urine differs between the two age groups. However, there was no significant association between the protein level in urine and the age group for the trace and negative categories. The squamous epithelial cell shedding results are presented in Table 5 and Figure 4, revealing a statistically significant difference ($p < 0.05$) between the squamous epithelial cells in urine and age group for the few and moderate categories. However, there was no significant association between the squamous epithelial cells in urine and the age group for the nil category, as its p-value was > 0.05.

DISCUSSION

The results of this study showed that age ≥ 60 years increased the incidences of bacterial counts, blood levels, protein levels, and squamous epithelial cell shedding in the urine of cervical cancer patients. Based on the results, older patients with cervical cancer have a higher potential to come to the clinic with severe urinary tract infections, hematuria, proteinuria, and squamous cell shedding in urine than younger patients. These findings are consistent with previous studies that reported a positive association between age and the risk of cervical cancer [12,13]. The possible mechanisms for this association include the accumulation of genetic mutations, the persistence of high-risk human papillomavirus (HPV) infection, the decline of immune system function, and exposure to other risk factors, such as smoking, sexual activity, and hormonal changes [12]. Therefore, screening and monitoring older patients with cervical cancer for these urinary abnormalities is important, as they may indicate a poor prognosis or a need for a more aggressive treatment [14]. Further studies are needed to confirm these results and to explore the causal relationship between age and urinary parameters in cervical cancer patients.

In line with a study by Tranberg et al., this study speculates that urine analysis can be a potential alternative to cervical samples for cervical cancer screening, especially for women who are reluctant to undergo clinician-based screening or vaginal self-sampling and who experience the side effects of Pap smears, such as discomfort, anxiety, and bleeding [14]. Although in Tranberg et al. paper, urine cytology or an HPV DNA test was used to detect the presence of HPV in urine, our retrospective study showed that squamous epithelial cells are found in the urine, which will increase the chance of detecting the virus in the urine. In addition, squamous epithelial cells in urine need further examination to indicate their source and to check that they are not due to contamination.

The findings of this study have implications for clinical practice and public health policy, such as improving the awareness and accessibility of cervical cancer screening for older women, developing new or alternative screening methods based on urinalysis, and optimizing the treatment and follow-up of cervical cancer patients according to their age and urinalysis results.

This study has some limitations that should be acknowledged. First, it was a retrospective study that relied on secondary data from a hospital database, and access to some information like vaccination HPV was hard to include, and some data were not included due to missing values. Second, it was a single-center study that may not represent the general population or other settings. Third, it did not include other types of urine tests that may be more sensitive or specific for cervical cancer, such as urine cytology or HPV DNA tests.

CONCLUSION

In conclusion, this study implies that there are significant changes in urine characteristics in cervical cancer patients including hyperproteinemia, hematuria, and squamous cell shedding in elderly patients compared to younger patients, and it proposes a potential role for urinalysis as a screening tool for cervical cancer in older women. Further studies are needed to confirm these re-

sults and to explore the causal relationship between age and urinary parameters in cervical cancer patients.

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Declaration of Interest:
The work was not previously presented at any conference. The author has no conflict of interest to declare.

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