



## **Evaluating Some Clinical And Laboratory Parameters for the Identification of Other Health Related Problems In Cervical Cancer Patients In Maiduguri-City, Nigeria**

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### **ABSTRACT**

The cervical cancer patients may face several other health related conditions that may complicate their disease conditions or affect the outcome of management modalities. The objectives were to assess values in laboratory parameters during care so as to identify other related emerging problems that have serious clinical implications, and to assess disease specific risk factors. A total of 66 cervical cancer patients were assessed between year 2010 and 2015 through cross sectional observation study. Demographic information were retrieved from the case note while laboratory parameters like electrolyte levels, albumin, total protein, uric acid, creatinine, urea levels, white blood cell and packed cell volume were evaluated. The mean age of patients was  $51.3 \pm 13.2$  years. Cervical cancer peaked at sixth decades and family histories were positive in 1.5% cases while 90.9% were married. The mean serum ion are  $\text{Na}^+$  ( $136 \pm 5.8$  mEq/L),  $\text{K}^+$  ( $3.7 \pm 0.94$  mEq/L),  $\text{Cl}^-$  ( $98.8 \pm 7.7$  mEq/L), and  $\text{HCO}_3^-$  ( $19.7 \pm 2.1$  mEq/L). The anion gap ranges from 1.2-49.4 mEq/L. The mean creatinine ( $237.8 \mu\text{mol/L}$ ), urea ( $7.7$  mmol/L) and uric acid ( $631.7 \mu\text{mol/L}$ ) were higher than normal range. The packed cell volumes during treatment of 85.4% patients were below normal but significantly improved ( $P < 0.05$ ) from baseline. Sodium, potassium, chloride and bicarbonate levels were below normal in 22(39.3%), 14(25.0%), 20(35.1%) and 44(77.2%) respectively. The anion gaps were high in 35 (62.5%) patients. The kidney markers like creatinine and urea were elevated in 24(51.1%) and 20(36.4%) cases respectively. Serum albumin levels were low in 19(59.4%) patients. Cervical cancer patients are prone to electrolyte abnormalities, anaemia, low albumin, and kidney damage which may have serious implication or potential for poor prognostic outcome. These findings underscore the need to always monitor the chemotherapy and other treatment procedures adopted for cervical cancer patients.

**Keywords:** Cervical Cancer, hyponitramia, packed cell volume, albumin, electrolyte imbalance

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## INTRODUCTION

The burden of cancer is not only growing but also one of the leading causes of death worldwide<sup>1</sup>. An estimated number of 10 million people are diagnosed with cancer annually with an incidence occurring at a faster rate of 48% in developed countries and 52% in developing countries<sup>2,3</sup>. About nine million people were projected to die from cancer in 2015 and 11.4 million in 2030<sup>4</sup>. The cancer epidemiological report in Africa showed 667,000 incident cases and 518,000 deaths in 2008<sup>5</sup>.

Cervical cancer is the third most common cancer in women, with an estimated 529 828 new cases and 275 128 deaths reported worldwide in 2008 where more than 85% of the global burden occurs in developing countries, which accounted for 13% of all female cancers<sup>6</sup>. Women from low and middle income countries have witnessed new cases and a growth rate of 5% per each year<sup>2</sup>. Cervical cancer occurs at the cervix due abnormal growth of cells that have the ability to invade or spread to other parts of the body<sup>7,8</sup>. The risk factors are often linked with human papilloma virus infection, smoking, Immunosuppression, chlamydia infection, diet low in fruits and vegetable, overweight, long-term use of oral contraceptives, intrauterine device use, having multiple full-term pregnancies, being younger than 17 at first full-term pregnancy, poverty, diethylstilbestrol (DES) use, having family history of cervical cancer and sexual activities<sup>9</sup>.

The diagnosis are often to very late stages particularly in developing countries due to the poor or even lack of good screening and treatment methods as opposed to the developed countries that have continuously been able to detect and treat early stages of cervical cancer mostly in the precancerous stages<sup>10</sup>. The squamous, glandular (adenocarcinoma), and other epithelial tumours including neuroendocrine tumours and undifferentiated carcinoma are often the target cells.

Squamous cell carcinomas account for 70%–80% of cervical cancers and adenocarcinomas for 10%–15%. Human Papillomavirus has been recognized as the most important etiologic factor in cervical cancer. Squamous cell carcinomas and their precursor, intraepithelial squamous lesions, are related to HPV infection in almost all the cases and the presence of HPV 18 DNA is associated with poor prognosis. Endocervical adenocarcinoma of usual type and its precursor, the adenocarcinoma in situ are also positive for HPV in nearly 90-100% of cases although HPV 18 is more common in adenocarcinomas and adenosquamous carcinomas than in squamous cell carcinomas<sup>11</sup>. HPV16/18 account for at least two thirds of cervical carcinomas in all continents; HPV 31, 33, 35, 45, 52, and 58 are the next most common types in cancers globally and that several markers identified along the carcinogenetic pathways includes; EGFR, HER2, VEGS,

COX-2, and c-myc which serves as prognostic or predictive factors. Chlamydia trachomatis, herpes simplex virus type-2, immunosuppressant, and certain dietary deficiencies are known to be associated risk factors for HPV infection<sup>12</sup> but sexually transmitted infectious such as gonorrhoea, Chlamydia, syphilis, and Herpes simplex virus type 2, were considered to be the causative agents for cervical cancer<sup>13</sup>. Chemicals substances in the cigarettes have also been detected in cervical mucus therefore aiding in development of cervical cancer by causing damage on DNA around the cervical cells<sup>14</sup>. Cervical cancer mortality rates in low resource countries are nearly three times as high as rates experienced in high resource settings<sup>15</sup>.

Quality of life is most compromised among patients with inoperable cervical cancer treated by radiotherapy, with a majority reporting deterioration in physical, emotional, social, and economic support and the highest risk for long-term dysfunction of bladder, bowels and psychosocial consequences<sup>16</sup>. The costs for return hospital visits, pathology reports, and subsequent treatment are beyond the resources of the majority of women in these settings<sup>17</sup>.

The cervical cancer patients may face several other health related conditions that may complicate their disease conditions or affect the outcome of management modalities. It is desirable to assess these conditions in order to outline comprehensive care plan and monitoring so as to institute appropriate measures and to improve the quality of life of patients.

The objectives were to assess values in laboratory parameters during care so as to identify other related emerging problems that have serious clinical implications, and to assess the risk factors for cervical cancer in patients.

## MATERIALS AND METHOD

The research was conducted at the Oncology unit of the University of Maiduguri Teaching Hospital, Borno State. The tertiary health institution is located in Jere Local Government area of the state and lies between latitude 11.5 North and 13.5 East in the Sudan Savannah. The research protocol was approved by Ethic Committee of the Teaching Hospital prior to the commencement of the study. The study design was retrospective involving review of cervical cancer patients' folders attending oncology clinic. Patients' demographic information such as age, gender, occupation, religion and ethnic group were retrieved from their case notes. Laboratory parameters like sodium, potassium, chloride, albumin, total protein, uric acid, creatinine, urea levels, white blood cell and packed cell volume were assessed with chemotherapy progression. A total of 73 breast cancer cases were assessed between year 2010 and 2015. Only cervical cancer cases were reviewed and other forms of cancer were excluded. The drug combination regimens

used to treat various patients were documented. Descriptive statistics using the Statistical Package for Social Sciences (SPSS) version 20 was used to analyse the results. Odds values were determined where appropriate.

## RESULTS AND DISCUSSION

The mean age of patients with cervical cancer was  $51.3 \pm 13.2$  years. Cervical cancer cases peaked in those in their sixth decades of life before progressively declining (Table 1). The family history for breast cancer was positive in only 1.5% cases. Majority of patients (90.9%) with cervical cancer are married women. The assessment of risk factors for cervical cancer indicated that family history, obesity, advancing age, contraceptive use and multiple sex partner occurred in 1.5%, 15.2% 57.6%, 1.5% and 6.2% respectively (Table 2). The major symptoms reported were vagina bleeding 56(84.8%), 25(37.9%), 7(11.9%) and 51(77.3%) (Table 3). The mean packed cell volume at diagnosis and during treatment was significantly different ( $P <$ ). There were no significant changes in the white blood count at diagnosis and during treatment. The mean serum electrolyte values were Na ( $136 \pm 5.8$  mEq/L), K ( $3.7 \pm 0.94$  mEq/L), Chloride  $98.8 \pm 7.7$  mEq/L), and bicarbonate ( $19.7 \pm 2.1$  mEq/L). The mean anion gap was  $21.02 \pm 7.88$  mEq/L. The kidney function markers like mean creatinine and urea levels as well as uric acid levels were higher than the normal being  $237.8 \mu\text{mol/L}$ ,  $7.7 \text{ mmol/L}$  and  $631.7 \mu\text{mol/L}$  respectively suggesting defects in kidney functions of some patients. The mean albumin level ( $34.2 \text{ g/L}$ ) was slightly lower than normal but the mean total protein ( $68.0 \text{ g/L}$ ) is within the normal range. The mean systolic and diastolic blood pressures were 121.6 and 75.6 mmHg respectively (Table 4).

**Table 1: Demographic characteristics of patients**

Description	Variables	Frequency n (%)	Description	Variables	Frequency n (%)
Age range of patients	Below 20	0 (0)	Marital Status	Single	0 (0)
	20-29	1 (1.5)		Married	60 (90.9)
	30-39	11 (16.7)		Divorced	1 (1.5)
	40-49	10 (15.2)		Widow	4 (6.1)
	50-59	22 (33.3)		Unknown	1 (1.5)
	60-69	15 (22.7)	TOTAL	66 (100)	
	70-79	6 (9.1)	Ethnic group	Kanuri	34 (51.5)
	>80	1 (1.5)		Fulani	2 (3.0)
TOTAL	66 (100)	Shuwa		8 (12.1)	
Gender	Female	66 (100)	Marghi	2 (3.0)	
Occupation	Unknown	1 (1.5)	Hausa	5 (7.6)	
	House wife	62 (93.9)	Babur	1 (1.5)	
	Civil servant	2 (3.0)	Others	14 (21.2)	

Cervical cancer family history	Artisan	1 (1.5)	Religion	TOTAL	66 (100)
	TOTAL	66 (100)		Christian	11 (16.7)
	Positive	1 (1.5)		Islam	54 (81.8)
	Negative	65 (98.5)		Unknown	1 (1.5)
	TOTAL	66 (100)		TOTAL	66 (100)

**Table 2: Risk Factors for Cervical Cancer**

Risk factors	Presentn (%)	Not Present n (%)	Total N (%)	Odds of Present to not present
Family history	1 (1.5)	65 (98.5)	66 (100)	5.60
Obesity	10 (15.2)	56 (84.8)	66 (100)	0.56
Older age	38 (57.6)	28 (42.4)	66 (100)	1.36
Contraceptive use	1 (1.5)	65 (98.5)	66 (100)	0.02
Multiple sex partner	4 (6.2)	62 (93.8)	66 (100)	0.06

**Table 3: Major Reported symptoms**

Reported symptoms	Experienced n (%)	Not experienced n (%)	Odds of experience to not experience
Vagina bleeding	56 (84.8)	10 (15.2)	5.60
Pain at the pelvis/lower belly	25 (37.9)	41 (62.1)	0.61
Coitus pain	7 (11.9)	59 (89.1)	0.19
Vagina discharge	51 (77.3)	15 (22.7)	3.4

**Table 4: Mean, standard deviation and Range of some laboratory parameters**

Laboratory parameters	Mean values	Std dev	Range	Unit
PCV at diagnosis (n=66)	26	± 0.08	0.11-0.39	%
PCV during Treatment (n=48)	0.31	± 0.06	0.17-0.50	%
WBC at diagnosis (n=34)	7.0	± 3.0	3.0-12.8	x 10 <sup>9</sup> /c
WBC during Treatment (n=11)	7.0	± 2.7	3.7-11.5	x 10 <sup>9</sup> /c
Sodium level (n=56)	136.0	± 5.8	120-149	mEq/L
Potassium level (n=52)	3.7	± 0.94	2.7-7.5	mEq/L
Chloride level (n=57)	98.8	± 7.7	80-110	mEq/L
Bicarbonate level (n=57)	19.7	± 2.1	15-25	mEq/L
Albumin level (n=32)	34.2	± 9.5	15-60	g/L
Creatinine level (n= 47)	237.8	± 328.5	48-1657	µmol/L
Uric acid level (n=21)	631.7	± 432.2	58-1551	µmol/L
Urea level (n=55)	7.7	± 5.0	2.9-27.8	mmol/L
Total protein (n=28)	68.0	± 10.1	40-86	g/L
Systolic Blood Pressure (n=66)	121.6	± 23.3	90-210	mmHg
Diastolic Blood Pressure(n=66)	75.5	± 15.6	40-110	mmHg
Anion gap (n=56)	21.02	± 7.88	1.5-49.5	mEq/L

**Table 5: The distribution of status of laboratory values of patients with cervical cancer**

Laboratory parameters	Laboratory Values Status			Total (%)	Odds BNR:WNR
	BNR (%)	WNR (%)	ANR (%)		
PCV at diagnosis (n=66)	61 (92.4)	5 (7.6)	0 (0)	66 (100)	12.2
PCV during Treatment (n=48)	41 (85.4)	6 (12.5)	1 (2.1)	48 (100)	6.8
WBC at diagnosis (n=35)	5 (14.3)	23 (65.7)	7 (20.0)	35 (100)	0.2
WBC during Treatment(n=11)	2 (18.2)	7 (63.6)	2 (18.2)	11 (100)	0.3
Sodium level (n=56)	22 (39.3)	32 (57.1)	2 (3.6)	56 (100)	0.7

Potassium level (n=52)	14 (25.0)	33 (63.5)	5 (9.5)	52 (100)	0.4
Chloride level (n=57)	20 (35.1)	26 (45.6)	11 (19.3)	57 (100)	0.8
Bicarbonate level (n=57)	44 (77.2)	13 (22.8)	0 (0)	57 (100)	3.4
Albumin level (n=32)	19 (59.4)	11 (34.4)	2 (6.3)	32 (100)	1.7
Creatinine level (n= 47)	1 (2.1)	22 (46.8)	24 (51.1)	47 (100)	0.05
Uric acid level (n=21)	2 (9.5)	6 (28.6)	13 (61.9)	21 (100)	0.3
Urea level (n=55)	2 (3.6)	33 (60.0)	20 (36.4)	55 (100)	0.1
Total protein (n=28)	9 (32.1)	18 (64.2)	1 (3.6)	28 (100)	0.5
Systolic BP (n=66)	1 (1.5)	57 (86.4)	8 (12.1)	66 (100)	0.02
Diastolic BP (n=66)	5 (7.6)	46 (69.7)	15 (22.7)	66 (100)	0.1
Anion gap (n=56)	6 (10.7)	15 (26.8)	35 (62.5)	56 (100)	0.4

Key: BNR= Below normal range; WNR= Within normal range; ANR= Above normal range

PCV= Packed cell volume; WBC=White blood count

The packed cell volumes during treatment of majority of patients (85.4%) were below normal range but not significantly different ( $P>0.05$ ) from baseline with Z-score analysis (Table 5). Sodium, potassium, chloride and bicarbonate levels were below the normal range in 22(39.3%), 14(25.0%), 20(35.1%) and 44 (77.2%) proportion of patients respectively. The anion gaps were higher than normal range in 35 (62.5%) patients. The odds of patients with low evaluated data are below normal range to those within normal range were high for PCV during treatment, bicarbonates and albumin. The kidney markers like creatinine and urea were elevated in 24 (51.1%) and 20 (36.4%) cases respectively. Similarly uric acid levels were higher than normal range in 13 (61.9%) patients. Serum albumin levels were below the normal range in 19 (59.4%) patients while in 32.1% (n=9), the total protein levels were low. The systolic and diastolic blood pressures were within the hypertensive range in 8 (12.1%) and 15 (22.7%) cases respectively (Table 5).

Cervical cancer is one of the cancers that can be treated successfully when it is detected or diagnosed early. The condition can also be detected early particularly when regular pap tests are conducted. In our study, family history, obesity and long term use of oral contraceptive were the identified risk factors for cervical cancer in the region. Many other risks factors such as human papilloma virus infection, smoking, immunosuppression, chlamydia infection, intrauterine device, multiple full term pregnancies and poverty are however reported<sup>13</sup>. It is also likely that risk factor such as early sexual exposure or having first full term baby before the age of 17 years may be an influential risk factor since early marriages are common in the region and has been reported as a contributing factor in study conducted in a near-by region<sup>18</sup>. The mean age of women with cervical cancer (51.3 years) is a little higher than the mean age reported in most other part of northern Nigeria<sup>19, 20, 21</sup> but similar to the mean age of presentation in developed

countries. The peaked age for CC is similar to the peaked age reported in India<sup>22</sup>. There were no cases of cervical cancer identified in those below 20 years while about 22% of patients with cervical cancer are 60 years and above. A high proportion of cases were also observed in those in their midlife age or below 50 years. These findings are consistent with the literatures<sup>13</sup>. Similarly, the symptoms reported by several patients in this study are also consistent with symptoms associated with cervical cancer.

One of the major laboratory findings associated with cancer of any kind (CC inclusive) is decrease in packed cell volume. Low PCV can also develop or further complicated with chemotherapy or surgical procedures. Surgery, chemotherapy, or radiotherapy; and increased loss of RBCs caused by blood loss from the tumour, surgery, or haemolysis can result to anaemia<sup>23, 24</sup>. Some researchers have also reported that people with cervix cancer who are anaemic may have worse treatment outcome to chemotherapy<sup>25, 26</sup>. In this study, there are evidences from biomarkers results that the kidney status of some patients may be affected. Chronic kidney disease may complicate anaemia due to low level of erythropoietin production. Low levels of PCV always require medical attention through transfusion or administration of erythropoietin hormonal preparation in order to prevent complications. The result of this study underscores the need for keen monitoring of blood level and to identify patients with potential interaction of drug regimen.

Electrolyte imbalances are commonly features in nearly all types of cancer cases<sup>27, 28, 29</sup> and may arise due to the glowing tumor, inadequate intake from diet or absorption, vomiting associated with cancer or due to chemotherapy<sup>28</sup>. Hyponitramia and hypokalemia were observed in this study in close to two-fifth and one quarter of patients respectively. The proportion of patients with hyponitramia is higher than the prevalence rate of 15-30% range commonly reported<sup>30</sup> and also lower than the report of Gills and colleagues<sup>31</sup> but lower than results reported solid cancer types by some researchers<sup>32, 33</sup>. The hypokalaemia cases as high as 43-64% range are reported in other cancer types<sup>34</sup>. It is noteworthy to know that cervical cancer medication like cisplatin can also induce hyponitramia in some patients either through the stimulation of arginine vasopressin (AVP) to cause syndrome of inappropriate antidiuretic hormone (SIADH) or through direct damage to renal tubules to cause interference with sodium absorption<sup>35</sup>. Hyponatremia is also a recognised negative prognostic factor in many cancer types<sup>36, 37, 38, 39, 40</sup>. Because untreated electrolytes imbalances can be life-threatening as well as affect treatment outcome in conditions considered to be terminal disease, there is always the need to identify these imbalances and institute appropriate intervention measures with aim of improving the quality of life of patients.

The low anion gap in one-tenth of the patients whose anion gap were determined confirmed hypoalbuminaemia in such patients while the high anion gap may suggest varying degrees of metabolic acidosis or alkalosis.

Another critical area to watch for in the pharmaceutical care of patients with cervical cancer is co-morbidity that may result particularly those involving kidney disorders. Many markers for renal damage may be elevated in most cancer cases. For instance, in 71.2% cervical cancer cases whose renal status were evaluated in this study, a little above average of this number had high creatinine values and the urea values of the 83.3% of patients evaluated indicated high values in more than one quarter of such patients. There may be potential and actual drug therapy problems that may be presented with these patients. Malignancy or its treatment can produce varieties of renal diseases <sup>41</sup> and this renal failure can be multifactorial. However, acute and chronic kidney disease and electrolyte abnormalities are the most common, but nephrotic syndrome, isolated proteinuria, and other syndromes can occur <sup>42</sup>. This calls for great concern during pharmaceutical care services since many drugs indicated for cancer and non-cancer cases may require adjustment in doses, withdrawal or may necessitated being used with caution. For instance NSAIDs are often recommended for pain management in cancer. Similarly hyperuricaemia which occurred in more than half of the 31.8% patients with cervical cancer cases evaluated in this study would require caution in the use of agents that are elimination unchanged through the renal route if treatment is so required.

Serum albumin is often used to assess the nutritional status, severity of disease, disease progression and prognosis. Low albumin levels could arise from malnutrition which can lead to several clinical consequences, including deteriorated quality of life, decreased response to treatment, increased risk of chemotherapy-induced toxicity and a reduction in cancer survival <sup>43</sup>. This may imply that the low albumin levels observed in more than half of the 32 patients evaluated in this study may have serious pharmacokinetic implications and therefore calls for caution since most drugs are bound to plasma albumin. Low pre-treatment albumin levels are also prognostic predictive factors for survival in many chronic disease conditions <sup>44</sup>. Low serum albumin levels in many patients have caused in-hospital mortality, increase the length of stay (LOS), and nosocomial infection <sup>45, 46, 47, 48</sup>.

## CONCLUSION

Because untreated electrolytes imbalances can be life-threatening as well as affect treatment outcome in conditions considered to be terminal disease, there is always the need to identify

these imbalances and institute appropriate intervention measures with aim to improve the quality of life of patients. The low anion gap in one-tenth of the patients whose anion gap were determined confirmed hypoalbuminaemia in such patients while the high anion gap may suggest varying degrees of metabolic acidosis or alkalosis.

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