African Journal of Laboratory Haematology and Transfusion Science

Vol 3, Issue 4, Page 297 - 302 | December 2024 | www.ajlhtsonline.org
ARTICLE DOI: doi.org/10.59708/ajlhts.v3i4.2439
DOI URL: 10.59708/ajlhts.v3i4.2439

ORIGINAL ARTICLE

Determination of Some Haemostatic Parameters and Anthropometric Indices in Cervical Cancer Patients in Port Harcourt.

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Received: 7-11-2024
Accepted: 19-11-2024
Published: 30-12-2024

ABSTRACT

Introduction: Cervical cancer is the second common female malignant tumor worldwide that seriously threatens female's health. This study was aimed at determination of some haemostatic parameters and some anthropometric indices in cervical cancer subjects in Port Harcourt. This study was a case control study. There were two groups: Group A served as a test group, women that are histologically confirmed positive for cervical cancer, while Group B served as a negative control, women that were histologically confirmed negative for cervical cancer.

Materials and Methods: A total of 40 participants (20 histologically confirmed cervical cancer positive subjects and 20 histologically confirmed cervical cancer negative subjects) within the age of 40-70 years were recruited for this study. The demography and informed consent of the study subjects was obtained with the use of a well-structured questionnaire. Four milliliters (4mls) of blood sample were collected using vacutainers from each participant. Weight was recorded with the use of a mechanical scale; height was taken using stadiometer and body mass index (BMI) was calculated. Von Willebrand Factor (vWF), thrombomodulin, FVIII, Tissue plasminogen activator and D-dimer were analysed using ELISA technique. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were analyzed using the manual method, and fibrinogen was analyzed using the coagulation method. The graph pad prism version 8.0.2.263 was used for data analysis. $P<0.05$ was considered significant. Results were presented as mean ± standard deviation (x±SD) in Tables and Figures.

Results: A statistically significant increase in the mean prothrombin time (PT) ($p=0.0002$) and APTT ($p=0.0156$) was observed among cervical cancer subjects when compared with the control subjects across all age brackets. There was also a significant increase in thrombomodulin ($p<0.0001$), tissue plasminogen activator (tPA) ($p<0.0001$), vWF ($p<0.0001$), FVIII ($p<0.0001$), and D- dimer ($p<0.0001$), in cervical cancer patients when compared with the controls.

Conclusion: This study concludes that there are coagulation and fibrinolytic derangements in subjects with cervical carcinoma.

INTRODUCTION

Cervical cancer begins on the surface of the cervix. It occurs when cells on the cervix begin to change to precancerous cells (1). The cervix is the lowest part of the uterus that connects the uterus with the vagina. It is divided into two portions: the endocervix is covered by glandular columnar cells, and the ectocervix is covered by squamous cells. It is covered in tissues made up of cells. These healthy cells can grow and change to precancer cells (1). Cervical cancer is the second most common female malignant tumor globally, which threatens female health (2). There are two types of cancer of the cervix: Squamous cell carcinomas and Adenocarcinomas. Cervical carcinoma originates in the transformation zone from the ecto or endocervical mucosa. The transformation zone is the cervix area between the old and new squamocolumnar junction (3). Most cervical cancers are caused by the virus Human Papillomavirus (HPV), the most common sexually transmitted infection that causes warts in various parts of the body (4). Persistent infection of high-risk human papillomavirus (HPV) has been clarified to be the necessary cause of cervical cancer (2). Early age at first intercourse and multiple sexual partners have been shown to exert strong effects on risk. Cervical cancer is divided into four stages based on the degree of the disease.

The early stage of cervical cancer is characterized by dysplasia; stages 1 to 3 are characterized by pre-invasive changes in the cervix called cervical intraepithelial neoplasia (CIN), and stage 4 of invasive cancer within or outside of the cervix (1). Most cases of invasive cervical cancers are due to squamous cell carcinomas. Although early stages of cervical cancer present with no symptoms. At an advanced stage, it may cause symptoms such as pelvic pain and vaginal bleeding during intercourse, bleeding outside of the periods for cycling women and after menopause (1). Haemostatic parameters, including coagulation factors and fibrinolytic markers, play a crucial role in tumor angiogenesis, metastasis, and cancer-associated thrombosis (4).

Understanding the intricate interplay among these diverse factors may provide valuable insights into the pathophysiology of cervical cancer and contribute to the development of more effective diagnostic and therapeutic strategies. Cervical cancer remains a significant global health concern, with a high incidence and mortality rate among women, particularly in developing regions (5). The complexity of cervical cancer necessitates a comprehensive understanding of the underlying molecular, inflammatory, and hematological aspects to improve diagnostic and prognostic approaches. This study recognizes the multifaceted nature of cervical cancer, incorporating an expansive array of parameters to unravel the intricate connections between cancer biology and haemostatic alterations. Integrating these diverse aspects aims to provide a holistic understanding of the disease, offering potential avenues for developing targeted therapeutic interventions and personalized medical approaches.

Haemostatic measurement is vital in the effective management of cancer patients. Alteration ranging from subtle abnormalities in laboratory tests to clinically avert thrombosis and disseminated intravascular coagulation is seen in most cancers (6). Up to 50% of all cancer patients and 90% of those with metastases exhibit haemostatic abnormalities (6). Cancer induces changes in haemostatic parameters. In a study by (7), plasma levels of D-Dimer, von Willebrand Factor, and fibrinogen were assayed in 66 patients with cervical carcinoma and in 67 healthy women as controls. D-Dimer and fibrinogen levels were significantly higher in patients with stage Ib-IIa cervical carcinoma than in controls, respectively) (7). A further increase of DD, but no significant increase of fibrinogen concentrations, was observed in stages II and

III of the disease. Von Willebrand Factor levels in patients with early-stage cervical carcinoma were in the normal range, while in patients with advanced cancer, they were significantly higher.

MATERIALS AND METHODS

Study Design

This is a case-control study. There were two groups: Group A and Group B. Group A served as a test group, women that have been histologically confirmed positive for cervical cancer, while Group B served as a negative control, women that were histologically confirmed negative for cervical cancer.

Study Area

This research was conducted in Rivers State University Teaching Hospital (RSUTH), Port Harcourt, Nigeria. Rivers State occupies 11,077 km ^{2} (4,277 sq mi). It was created on 27th May 1967, and it is located in the Southern part of Nigeria (Old Eastern Region), with 23 Local Government Areas. Port Harcourt is the capital and largest city in Rivers State, Nigeria, with its geographical coordinates as latitude: 4˚46′38″ N, longitude: 7˚00′48″ E, and elevation above sea level: 16m (52ft). It lies along the Bonny Stream and is located in the Niger Delta (Encyclopedia.com, 2022).

Study Population

Forty (40) participants between the ages of 18-70 years were enrolled for this study. Twenty (20) participants were those who were histologically diagnosed with cervical cancer, while the other 20 participants were those negative for cervical cancer in Rivers State University Teaching Hospital (RSUTH). The demography and informed consent of the study subjects were obtained using a well-structured questionnaire. The purpose of the research was explained to the participants to decide voluntarily to partake in the research, and those who consented were recruited for the study. Information relating to the biological and demography of the subjects was recorded.

Informed Consent and Ethical Clearance

Individuals recruited as participants in this study gave informed consent before sample collection began. Before commencing the study, ethical clearance was obtained from the Rivers State University Teaching Hospital Research and Ethics Committee.

Eligibility Criteria

Inclusion Criteria

Women between the age of 18-70 years, without other health challenges, and women who are not yet on chemotherapy treatment and who did not decline to give consent were included in this study.

Exclusion Criteria

Women less than 18 years and above 70 years of age with other health challenges, women who were already on chemotherapy treatment, and who declined to give consent were excluded from this study.

Sample Collection, Processing, and Preservation

A rubber tourniquet was applied for less than one minute, and the site was punctured and disinfected with 70% methylated spirit. Using a vacuum cleaner, 4mls of whole blood were taken from each patient by standard phlebotomy into sample tubes. Two milliliters (2mls) of blood were obtained in a 3.2% trisodium citrate anticoagulant bottle, and 2mls of blood were also obtained in a plain bottle.

Samples in 3.2% trisodium citrate bottles were spun at 3500rpm for 5 minutes, and the plasma separated and stored in a plain bottle, which was used to assay fibrinogen, prothrombin

time (PT) and activated partial thromboplastin time (APTT) analysis. The samples in plain bottles were also spun for 5 minutes at 3,000rpm, and the serum was separated and stored in a plain bottle, which was used to assay for factor V111, vWF, thrombomodulin, and tissue plasminogen activator. The blood samples taken were immediately transported to the laboratory. The samples were stored in the freezer at -20°C until analysis. This helped to keep the protein matrix of the sample for a longer period.

Sample Analysis

Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) using Elabscience Biotechnology was employed for Thrombomodulin, tissue plasminogen activator, Fibrinogen, von Willibrand Factor, Factor VIII, and D-dimer. As described by Nilsson et al. (2018), the manual method was employed for PT and APTT—coagulation method using Atlas Medical FIB Liquid Kit for Fibrinogen.

Statistical Analysis

The Graph-Pad Prism 8.0.2.263 version statistical package was used to obtain the mean and standard deviation of the study groups. The student t-test determined the statistical difference between the two means. The level of significance was set at $P<0.05$. Results were presented as mean ± standard deviation (X±SD) in Tables and Figures.

RESULTS

There was a statistically significant increase in PT (16.2 ± 0.8s), APTT (38.2 ± 1.3s), Thrombomodulin, tPA, VWF, FVIII, and D-dimer in cervical cancer patients compared with control subjects. There was also a statistically significant decrease in fibrinogen concentration in cervical cancer patients compared with control subjects. Other parameters recorded no statistical significance. Details are shown in Table 1.

Table 1: Comparison of Mean ($\bar{x}$) ± Standard Deviation of Haemostatic Parameters and Some Anthropometric Parameters in Cervical Cancer Subjects and Control Subjects

Parameters (Units)	Cerv ($\bar{x}$ ± SD) N = 20	Control ($\bar{x}$ ± SD) N = 20	p-value	Remark
PT (s)	16.2 ± 0.8	15.0 ± 1.0	0.0002	S
APTT (s)	38.2 ± 1.3	37.2 ± 1.0	0.0156	S
Thrombomodulin (ng/mL)	31.8 ± 5.2	21.8 ± 4.6	<0.0001	S
tPA (ng/mL)	53.6 ± 5.5	21.2 ± 4.7	<0.0001	S
Fibrinogen (ng/mL)	233.2 ± 68.6	527.2 ± 67.6	<0.0001	S
vWF (%)	313.5 ± 53.1	105.0 ± 25.5	<0.0001	S
FVIII (%)	272.1 ± 45.9	98.1 ± 16.9	<0.0001	S
D-dimer (ng/mL)	434.8 ± 71.1	253.7 ± 51.1	<0.0001	S

Weight (Kg)	82.2 ± 9.2	71.7 ± 5.3	<0.0001	S
Height (cm)	158.2 ± 16.4	160.2 ± 12.4	0.6591	NS
BMI	31.9 ± 4.3	28.4 ± 4.8	0.0219	S

Key: PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; tPA = Tissue Plasminogen Activator; vWF = von Willebrand Factor; FVIII = Factor VIII, BMI=Body Mass Index

Table 2 showed no statistically significant difference in all haemostatic parameters of cervical cancer subjects when their body mass index was compared.

Table 2: Comparison of Mean($\bar{x}$) ± Standard Deviation of Haemostatic Parameters in Cervical Cancer Subjects Based on Body Mass Index

Parameters (Units)	Overweight 25.0 to 29.9 (a); n = 7 $\bar{x} \pm SD$	Obese Class I 30.0 to 34.9(b); n = 8 $\bar{x} \pm SD$	Obese Class II 35.0 to 39.9(c); n = 5 $\bar{x} \pm SD$	F-value	p-value	TMC
PT (s)	16.0± 0.7	16.3 ± 0.9	16.4 ± 0.7	0.262	0.7722^{NS}	N/A
APTT (s)	38.6 ± 1.4	37.9 ± 1.4	38.1 ± 1.0	0.524	0.6010^{NS}	N/A
Thrombomodulin (ng/mL)	30.4 ± 3.8	32.9 ± 5.2	32.2 ± 7.7	0.385	0.6862^{NS}	N/A
tPA (ng/mL)	52.3 ± 3.6	52.9 ± 6.3	55.8 ± 6.7	0.514	0.6071^{NS}	N/A
Fibrinogen (ng/mL)	510 ± 68	557 ± 74	502 ± 41	1.418	0.2694^{NS}	N/A
vWF (%)	319 ± 39	324 ± 72	287 ± 27	0.806	0.4628^{NS}	N/A
FVIII (%)	281 ± 55	269 ± 48	263 ± 31	0.214	0.8089^{NS}	N/A
D-dimer (ng/mL)	456 ± 71	425 ± 81	418 ± 60	0.504	0.6128^{NS}	N/A

KEY: N/A = Not Applicable because there is no difference between groups.

TMC = Tukey's Multiple Comparison between Groups. PT = Prothrombin Time;

APTT = Activated Partial Thromboplastin Time; tPA = Tissue Plasminogen Activator; vWF = von Willebrand Factor; FVIII = Factor VIII.

DISCUSSION

This research showed a statistically significant increase compared to their controls in the mean prothrombin time and activated partial thromboplastin time among cervical cancer subjects across all age brackets. This is in agreement with the work done by Okwesili *et al* (8). This study indicates a significant increase as against their controls in thrombomodulin, tissue plasminogen activator (tPA), von Willebrand Factor (vWF), factor VIII (FVIII), D-dimer, Weight and BMI in cervical cancer patients. There was a significant decrease against the control in Fibrinogen. These findings imply that, in patients with cervical carcinoma there is an activation of blood coagulation and fibrinolysis. This agrees with the work carried out by Almukhtar, & Alaraji (9) and that of Yang *et al* (10). Increased D-dimer levels can be associated with high levels of fibrin degradation products (FDPs). This elevation agrees with the findings of Okwesili *et al* (8), who reported a marked increase in the level of D-dimer in patients with cervical cancer disease. From this study, in comparison of hemostatic parameters in cervical cancer based on body mass index (BMI), when compared between the different groups, it was observed that there was no statistically significant difference in all hemostatic parameters of cervical cancer subjects. This is in agreement with the work of Okwesili *et al* (8).

CONCLUSION

This study revealed that cervical cancer is becoming a burden in Port Harcourt. Cervical cancer has a significant impact on some haemostatic parameters. The study showed that overweight is a risk factor for cervical cancer. Continuous monitoring of haemostatic parameters and early intervention of alterations are very important to reduce the mortality rate of cervical cancer patients.

Financial support and sponsorship: This study was self-sponsored.

Conflicts of interest: There are no conflicts of interest.

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How to cite this article:
Isomah AC, Ken-Ezihuo SU, Eze EM, Jeremiah ZA. Determination of Some Haemostatic Parameters and Anthropometric Indices in Cervical Cancer Patients in Port Harcourt. *Afr J Lab Haem Transf Sci* 2024; 3(4): 297 - 302
DOI: https://doi.org/10.59708/ajlhts.v3i4.2439