

## Clinicopathological Correlates of Patients with Prostate Cancer in a Tertiary Hospital in Northwestern Nigeria

Emmanuel U OYIBO, Mohammed A UMAR, Khalid ABDULLAHI, Sadiq A MUHAMMAD, Peter N AGWU

### ABSTRACT

**Background:** Worldwide, prostate cancer is a common cause of significant morbidity and mortality in ageing men. Digital rectal examination (DRE) and serum total prostate specific antigen (tPSA) are widely used tools for prostate cancer (CaP) screening and diagnosis before transrectal ultrasound (TRUS)-guided prostate biopsy. **Objectives:** This study aimed at finding the clinical, biochemical, radiological and pathological correlates in patients with an enlarged prostate and elevated serum tPSA. **Methodology:** This is a 12-month cross-sectional study of 80 male patients aged 50 years and above with lower urinary tract symptoms (LUTS), abnormal digital rectal examination and/or elevated PSA greater than 4ng/mL. Aged-matched males were also included as a negative biopsy group with serum levels of tPSA determined using ELISA methods among both groups. Clinical, procedural (TRUS guided biopsy) assessment, transrectal ultrasound-guided biopsies of the prostate for histological characterisation of all patients and Gleason score categorization for prostate in cancer group were done. The relationship between serum tPSA and Gleason score of prostate cancer patients was determined using Spearman's correlation. **Results:** The mean serum total PSA in patients with prostate cancer and the negative biopsy group was  $82.93 \pm 35.02$  and  $28.85 \pm 30.92$  ng/ml respectively. The majority of the patients in the prostate cancer group (90.0%) had suspicious findings on DRE compared to the negative biopsy group (46.2%). There is a positive correlation between serum tPSA and Gleason score in patients with prostate cancer. Serum tPSA levels were significantly lower in the negative biopsy group. The Gleason score pattern of distribution among patients with Prostate cancer showed that the majority had a score greater than 8 and ISUP Grade V. **Conclusion:** Findings of elevated total serum PSA and abnormal digital rectal examinations in patients with an enlarged prostate in our practice are predictive of high Gleason score prostate cancer on TRUS-guided biopsy of the prostate.

**Keywords:** Clinicopathological, Digital rectal examination, Gleason score, Prostate cancer, Serum total prostate specific antigen (tPSA), Transrectal ultrasound guided biopsy.

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#### Article Metrics

Date Submitted: 9 July 2022  
Date Accepted: 19 Sept 2022  
Date Published: Jan-June 2023

#### Journal Metrics

**E- ISSN:** 1115-0521  
**Website:** [www.orientjom.org.ng](http://www.orientjom.org.ng)  
**E-mail:** [editorojm@gmail.com](mailto:editorojm@gmail.com)

#### Publisher:

cPrint, Nig. Ltd  
E-mail: [cprintpublisher@gmail.com](mailto:cprintpublisher@gmail.com)



#### Access to the article

Website: <http://www.orientjom.org.ng>

DOI: 10.5281/zenodo.7126985

#### How to cite this article

Oyibo EU, Umar MA, Abdullahi K, Muhammad SA and Agwu PN. Clinicopathological Correlates of Patients with Prostate Cancer in a Tertiary Hospital in Northwestern Nigeria. *Orient J Med*, 2023;35(1-2):1-10. DOI:10.5281/zenodo.7126985

## INTRODUCTION

Prostate cancer ranks the second most common malignancy in men and the fourth most common cancer in males and females with an estimate of about 1.1 million men diagnosed with this cancer in 2012, and 70% of the diagnoses occurred in developing nations.<sup>1</sup> The incidence of prostate cancer varies worldwide, with the highest rates in Australia, New Zealand, Northern America, and Western and Northern Europe due to the widespread practice of screening for cancer using prostate specific antigen test and then a subsequent prostate biopsy.<sup>2</sup>

In men, prostate cancer is the fifth leading cause of death, and the greatest mortality has been found among men of African descent<sup>1</sup>. However, the 2012 age-standardised incidence rate for prostate cancer estimated for Nigeria was 30.7 per 100,000.<sup>3</sup> Contrary to the World Health Organization reports, several other studies indicate a higher incidence of prostate cancer in Nigerian men. Studies from Northwestern Nigeria suggest that 6.0% of male cancers are due to prostate cancer corroborated by other hospital-based studies from across other geopolitical zones of Nigeria with a rising incidence of 6.2% in certain regions to 16.5% in others.<sup>4-9</sup>

Patients with an enlarged prostate may present with complaints of lower urinary symptoms, necessitating physical examination and digital rectal examination(DRE), serum prostate specific antigen assay which may be elevated often culminating in prostate biopsy to reach a diagnosis and the subsequent need to provide suitable treatment.<sup>7,10-13</sup>

Early detection and improved treatment in patients with cancer of the prostate are associated with declining mortality in most Western and European countries.<sup>14</sup> However, this is contrary to what obtains in developing countries like Nigeria where no institutionalized screening protocol coupled with poor awareness, knowledge and attitude toward the disease.<sup>15-17</sup> Prostate biopsy and histology have remained the gold standard for prostate cancer

diagnosis after the detection of an anomaly on the digital rectal examination(DRE) though not the only indication for such procedure. Tumour biomarkers elaborated in the body have played a vital role in the early diagnosis, treatment and follow-up of patients with prostate cancer. These biomarkers may be present in the blood or urine samples of patients and these samples may be obtained with minimal or no complications as the sample collection is minimally invasive.<sup>18</sup>

Since the late 80s, serum prostate specific antigen assay has revolutionized the screening and diagnosing of prostate cancer. Despite the controversies surrounding its application, the introduction of PSA as a screening tool has reduced the rate of diagnosis of advanced disease and mortality from prostate cancer due to earlier detection of apparently asymptomatic stage.<sup>19,20</sup> On the other hand, the Gleason grade and score of the biopsy specimen is an objective assessment of the degree of differentiation of the malignant prostate tissue and has been applied as a surrogate indicator of the aggressiveness of the tumour.<sup>21,22</sup>

## METHODOLOGY

The study was a hospital-based prospective cross-sectional study conducted following the approval of the Health Ethics and Research Committee(HERC) of the Usmanu Danfodiyo University Teaching Hospital,Sokoto. It included consecutive patients presenting to the urology clinic of our hospital from March 2019 to February 2020 with clinical, radiological, and biochemical features suggestive of prostate cancer.

The inclusion criteria were patients aged 50 years and above with: elevated PSA and/or Lower urinary symptoms (LUTS), abnormal digital rectal examination (DRE) findings, and/or abnormal TRUS/transabdominal scan findings or those with histologically confirmed prostate cancer before the commencement of treatment.

Those patients who have had a digital rectal

examination in less than a week, a biopsy of the prostate in less than three weeks, urethral instrumentation(urethroscopy) or stones in the urethra or the bladder in less than three weeks, prostate cancer patients on 5 $\alpha$ -reductase inhibitor drugs, hormonal or radiation therapy and those who have had the previous prostatectomy for benign prostatic hyperplasia or radical prostatectomy for malignant prostatic conditions were excluded from the study.

The sample size calculation for the prospective cross-sectional study<sup>23</sup> is as follows:

$$n = \frac{[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{\beta}\sqrt{P_1(1-P_1)}]^2}{(P_1 - P_0)^2}$$

- $Z_{1-\alpha/2}$  = percentage point of the normal distribution corresponding to the required (two-sided) significance level ( $\alpha$ ) of 0.05 = 1.96.
- $Z_{\beta}$  = one sided percentage point of the normal distribution corresponding to 100% -the power, example if power = 80% (100% - power) = 20% (i.e. p- value of 0.2) = 0.84
- $P_0$  = Null hypothesis proportion (i.e. no increase expected, which means that the proportion will remain as previously obtained i.e.sensitivity of prostate specific antigen from the previous study, 89.8%.<sup>24,25</sup>=0.898
- $P_1$  = Alternative hypothesis proportion = 89.8% baseline + 10% increase = 99.8% = 0.998
- $P_1 - P_0$  = The difference (i.e. expected increase in the proportion of microseminoprotein - beta, new biomarker in the diagnosis of CaP) = 0.998-0.898 = 0.1

$$n = \frac{[1.96 \times \sqrt{0.898(1-0.898)} + 0.84\sqrt{0.998(1-0.998)}]^2}{(0.998 - 0.898)^2}$$

$n = 32.67 = 33$  Patients or subjects.

The sample size includes attrition of 20% {that is 6.30 approximately 7}. The minimum sample size for this research was forty(40). Out of the eighty patients(80) recruited, forty(40) patients returned

with adenocarcinoma of the prostate on histology while the remaining forty(40) patients had a negative biopsy. All the patients had TRUS-guided biopsy of the prostate. A structured proforma was used to collect relevant data, including demographics, clinical history, physical examination, clinicopathological variables, results of the relevant investigation and prostate biopsy findings on TRUS examination. The data were entered into the Statistical Package for the Social Sciences (IBM SPSS) for Windows, Version 20.0. Armonk, NY: IBM Corp, 2011. The mean of serum total prostate-specific antigen (tPSA) in both groups was determined and compared using the Students' t-test. The relationship between serum levels of total prostate-specific antigen (tPSA) and Gleason scores of patients with prostate cancer was calculated using Spearman's correlation. The level of significance was set at  $p < 0.05$ . After informed consent, under aseptic conditions, 4mls of the venous blood sample was collected from the upper extremity and put into plain red top venipuncture tubes without additives and anticoagulants. The assay for total PSA(tPSA) was done using the enzyme-linked immunosorbent assay (ELISA) method based on the manufacturer's (Monobind Inc- AccuBind ELISA Microwells Product Code:2125-300) instruction.

### Prostate Biopsy

Transrectal ultrasound(TRUS) guided prostate biopsy was done using Mindray Digi/Prince®(DP-6600)-Germany 2007/2008 for all patients recruited. The frequency of the transrectal probe was set at 6.5 MHz to scan the prostate and for biopsy. Twelve (12) biopsy cores were obtained from lateral to medial parts of each prostate lobe, targeting suspicious nodules visualized on TRUS. The specimen was appropriately labelled and sent in 10% formaldehyde to the Histopathologist. Haematoxylin and Eosin (H&E) slides were prepared and examined under the microscope (Olympus BX51 with low power X40 and medium power X200) for tissue diagnosis. The histopathologist determined the histology and the Gleason grade/score of the benign and malignant prostate tissue respectively.

## RESULTS

Forty men with histological diagnosis of prostate cancer and forty age-matched adult males with negative biopsy were recruited for this study.

Patients' age distribution in the CaP group ranged from 50 to 89 years, with a mean of  $69.38 \pm 8.08$  years. The peak age incidence in the CaP group was in the 8<sup>th</sup> decade (71-80 years). Similarly, patients' age range in the negative biopsy group was 50 to 99 years, with a mean of  $65.43 \pm 9.68$  years). There was a statistically significant difference in the age distribution of both groups ( $p=0.003$ ).

**Table 1: Clinical parameters of study participants**

Variables	Prostate Cancer Group n=40(%)	Negative biopsy Group n=40(%)	p-value
<b>LUTS</b>			
Yes	30(75.0)	34(85.0)	0.264
No	10(25.0)	6(15.0)	
<b>Family history of Prostate cancer</b>			
Negative	4(10.0)	11(27.5)	0.898
Positive	2(5.0)	2(5.0)	
<b>Digital rectal examination</b>			
Unaware	34(85.0)	27(67.5)	<0.001
Benign	4(10.0)	22(53.8)	
Suspicious	36(90.0)	18(46.2)	

**Table 2: Procedural (TRUS Guided biopsy) assessment**

Variables	Prostate Cancer Group n=40(%)	Negative biopsy Group n=40(%)	p-value
<b>Prostate capsule Integrity</b>			
Intact/Uniform	6(15.0)	22(55.0)	
Breach/Irregular	34(85.0)	18(45.0)	
<b>Prostatic Nodules</b>			
Yes	31(77.5)	15(37.5)	<0.001
No	9(22.5)	25(62.5)	
<b>Echogenicity of Prostate</b>			
Hyperechoic	0(0.0)	5(12.5)	0.003
Hypoechoic	22(55.0)	11(27.5)	
Isoechoic	5(12.0)	14(35.0)	
Mixed	13(32.5)	10(25.0)	
<b>TRUS Prostate Volume(g)</b>	67.32±52.50	57.19±34.06	0.382

### Serum Total PSA Levels and Histopathological Characteristics of Study Participants

Among the Prostate cancer patients, the serum total PSA ranged from 6.25 to 114.67 ng/ml with a mean of  $82.93 \pm 35.02$ , while the serum total PSA in the negative biopsy group ranged from 0.88 to 115.17 ng/ml with a mean of  $28.85 \pm 30.92$  which was significantly lower than the CaP group ( $p < 0.001$ ). The majority of the CaP group patients (34, 90%) had PSA values greater than 20 ng/ml.

All the patients in the study group had a histological diagnosis of adenocarcinoma of the prostate. The Gleason score of CaP patients in this study ranged from 6 to 10, with a modal score of 6. Twenty-one (52.5%) of these patients had a score of 8 and above (Figure 1). The least Gleason score was 6, accounting for 13(32.5%) men in the CaP group.

**Table 3: Gleason score distribution and ISUP Grading among patients with Prostate Cancer.**

Variable	Frequency	Percentage	
<b>Gleason Score</b>	6	13	32.5
	7	6	15.0
	8	6	15.0
	9	12	30.0
	10	3	7.5
<b>Total</b>	<b>40</b>	<b>100</b>	
<b>ISUP Gleason Categories</b>	I	13	32.5
	II(3+4)	1	2.5
	III(4+3)	5	12.5
	IV(8)	6	15.0
	V( $\geq 9$ )	15	37.5
<b>Total</b>	<b>40</b>	<b>100</b>	

ISUP: International Society of Urological Pathology

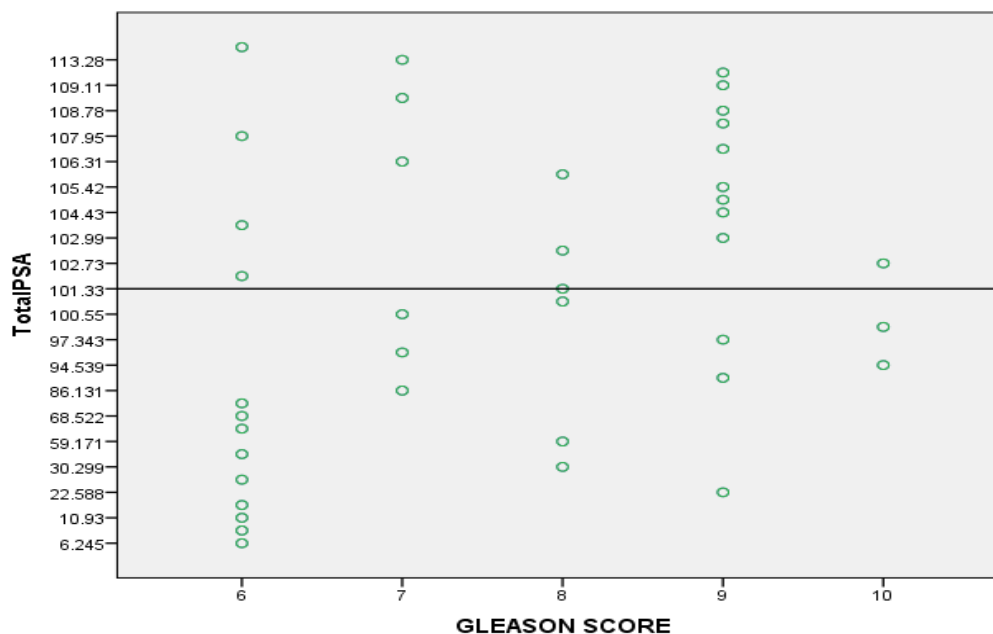
Correlation between Serum levels of Total Prostate Specific Antigen (tPSA) to Gleason Score in patients with Prostate Cancer.

Forty (40) study patients with adenocarcinoma of the prostate had an assessment of their Gleason's score (Mean =  $7.65 \pm 1.41$ ) and assayed serum levels of prostate-specific antigen (PSA) (Mean =  $82.93 \pm 35.02$ ). Spearman's correlation analysis showed a moderate positive correlation ( $r_s = 0.442$ ) between Gleason's score and assayed serum levels of total prostate-specific antigen (tPSA). Therefore, there was a strong positive association between Gleason score and assayed serum levels of total PSA and was statistically significant ( $p = 0.004$ ).

However, there was a moderate positive correlation between serum total PSA and the Gleason score among men with CaP with higher total PSA levels found

\* Correlation is significant at the 0.05 level (2- tailed)

Figure 1 : Correlation between serum level of Total PSA and Gleason Score in Patients with Prostate cancer.



among men with higher Gleason scores (Table 4) ( $R^2=0.442$ ,  $p=0.004$ ).

## DISCUSSION

The manifestation of prostate disease is usually amongst the middle-aged and elderly groups. The development of adenocarcinoma of the prostate increases with age, peaking at 60-69 and 70-79 years, respectively.<sup>26, 27</sup> The highest incidence of prostatic diseases in this study was in the 6th and 7th decades but among patients with negative biopsy occurred a decade earlier than the Prostate cancer group. This is because prostate diseases occur in the elderly population. These findings were similar to global surveys and studies in other parts of Nigeria, Ghana and South Korea.<sup>28-31</sup>

The serum total PSA was significantly higher in patients with prostate cancer than in those with negative biopsy. This finding is comparable to

studies by Prcic *et al.*<sup>32</sup>, Froehner *et al.*<sup>33</sup> and Orakwe *et al.*<sup>34</sup>, where the malignant prostate tumour group had a significant increase in the mean serum level of total prostate-specific antigen(PSA) compared with the controls( $p<0.0001$ ). This is due to the abnormal leakage of PSA into the circulation further influencing its expression in malignant epithelium following a distorted prostatic glandular architecture.<sup>35</sup>

In this study, prostate cancer patients had a Mean Gleason's Score and tPSA of  $7.65 \pm 1.41$  and  $82.93 \pm 35.02$ , respectively. Amongst the CaP group, twenty-one (52.5%) patients with a Gleason score of 8 and above, with thirteen (32.5%) patients having a Gleason score of 6 and below. This study showed a high Gleason score in most patients, similar to a survey by Okolo *et al.*, Nakandi *et al.* and Jalloh *et al.*<sup>36</sup> reporting that prostate cancer patients in sub-Saharan countries have high Gleason scores when compared to those in developed countries. The high Gleason score found in

the current study underscores the more aggressive behaviour of prostate cancer in men of African descent irrespective of place of birth or residence and this observation may be due to the genetic susceptibility of people of this race to the disease.<sup>37</sup> However, it may just be due to the peculiar cultural and religious practices leading to late presentation to the hospital for treatment.<sup>16</sup>

In this study, a moderate positive correlation ( $r_s=0.442$ ) was observed between Gleason's score and assayed serum levels of total prostate-specific antigen among patients with CaP. This moderate positive correlation was statistically significant ( $p=0.004$ ). This finding is in keeping with a previous study by Okolo *et al.*<sup>38</sup> from Ibadan-South western Nigeria, who also observed a moderate positive correlation ( $r_s=0.400$ ) between Gleason's score and assayed serum levels of PSA, which was also statistically significant at  $p=0.001$ .

Patients presenting with suspicious findings were more likely to have a histopathological diagnosis of prostate cancer. Most of the patients in the CaP group had suspicious DRE findings ( $p<0.001$ ), giving a cancer detection rate of 90% when compared to studies by Lee *et al.*<sup>39</sup> and Cooner<sup>40</sup> with a detection rate of 43.8% and 32.6% respectively. Thus the value of DRE in detecting prostate cancer in this study was higher than in previous studies which may be a result of the late presentation among our patients with advanced disease. Although 46.2% of the patients in the negative biopsy group had suspicious findings on DRE, a previous study had explained similar occurrences with a significant proportion of patients with DRE findings suggestive of malignancy turning out to be negative for malignancy after histological evaluation.<sup>41</sup>

This study supports the utility of DRE as an important and simple adjunctive bedside or office procedure in the diagnostic workup of patients with an enlarged prostate. This may be a trigger for

prostate biopsy and thus a diagnosis of prostate cancer as has been reported from other parts of the world among family care physicians.<sup>42-44</sup>

Digital rectal examination may thus be a handy tool for the general practitioner and the urologists, especially in most Sub-Saharan Africa hospitals, where there are no organized screening programs or advanced diagnostic tools for the detection of prostate cancer. This observation is pertinent as most patients in the region of study present late with advanced disease that induce changes in the prostate adjourning and rectal mucosa are usually remarkable and can easily be detected during DRE.

Transrectal ultrasonography (TRUS) since its introduction into clinical practice four decades ago has been an important armamentarium in the evaluation of the patient with a symptomatic enlarged prostate as it enables the assessment of prostate volume, echotexture, capsular integrity, changes in the urinary bladder as well as a tool for guided biopsy.<sup>45,46</sup>

This study revealed a mean prostate volume of 67.32g with a range of 13.0-282g with the majority of patients having hypoechoic echogenicity (55.0%). Ahmed *et al.*<sup>47</sup> in Zaria-Nigeria found a mean prostate size of 66.8g with a range of 15-219g while Isiwele *et al.*<sup>48</sup> reported a mean prostate volume of 88.5cm<sup>3</sup> with a range of 13.0cm<sup>3</sup> 376.0 cm<sup>3</sup>. These were at variance with a similar study done in Norway by Eric *et al.*<sup>49</sup> with a mean prostate volume of 58.0g and a range of 26.6164.8g. In this study, lower prostate volumes were noted in the negative biopsy compared with the prostate cancer group, which is at variance with a previous study<sup>50</sup> however it was not statistically significant ( $p>0.005$ ). Therefore, it is logical to take a higher number of core biopsies in larger prostates to detect cancerous foci as prostate cancer may coexist with benign prostate hyperplasia. TRUS is the most commonly available and utilized imaging modality in the diagnosis of prostate cancer with sonographic features such as hyperechoic, isoechoic and

hypoechoic though malignancy mostly demonstrates hypoechoic lesions, especially in the peripheral zone.<sup>46, 51, 52</sup> More than half of the CaP group patients had prostate glands with hypoechoic features, followed closely by mixed echogenic elements. The highest proportion (55.0%) of patients with hypoechoic nodules had CaP compared with none and 32.5% (hyperechoic and mixed echogenicity) respectively. The highest predictive value in detecting prostate cancer is associated with peripherally located hypoechoic nodules.<sup>53</sup> The correlation of hypoechoic nodules to the histological diagnosis of CaP was noted in a previous study.<sup>48</sup> This was corroborated by a study done by Ahmed *et al.*<sup>47</sup> and Lee *et al.*<sup>39</sup> with hypoechoic lesions correlating more with a histologic diagnosis of CaP however, this current study revealed that all the hyperechoic lesions were benign. Performing a biopsy of only hypoechoic lesions would have misdiagnosed 27.5% of the patients with prostate cancer whose results were negative on histology.

A higher proportion of patients with an irregular prostate outline have CaP than 15.0% of those with intact/uniform capsules. This implies that the presence of irregular prostate outlines on TRUS strongly suggests the presence of CaP. The majority of the patients in the CaP group had a TRUS diagnosis of prostate cancer, giving a cancer detection rate of 77.5%. In a similar study by Lopes *et al.*<sup>54</sup> in Brazil, most of the patients with suspicious nodules in the CaP group had a malignant prostate on histology with a positive predictive value of 74%. A similar study by Gupta *et al.*<sup>55</sup> in India confirms identical inferences.

## CONCLUSION

There is a significantly higher serum total PSA and Gleason score in the patients with prostate cancer in our population. Furthermore, suspicious findings on digital rectal examination and TRUS-guided biopsy were suggestive of malignancy in patients with prostate cancer suggesting the role of DRE in an

environment like ours.

## Limitations of the Study

Some of the patients included in the negative biopsy group may have prostate cancer despite the negative TRUS biopsy result.

## Declarations

Ethical approval and patient consent to participate in the study were sought from the institution's health and research committee and a copy is attached. All authors have their signatures appended.

**Availability of data and material for the study:** The datasets used and/or analyzed during the current study are available from the corresponding author on request.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** No source of funding.

**Authors' contributions:** EUO conceptualized the study, and analyzed and interpreted the patient data regarding prostatic diseases and biopsy. UA/KA/ASM/NPA thoroughly reviewed the manuscript and made corrections.

All authors read and approved the final manuscript.

**Acknowledgements:** I want to acknowledge Drs. KJ Awosan, Bilkisu Gulma and Ijapa Adamu for their assistance concerning statistical analysis. Mr Kabiru and Mr Mustapha assisted with the laboratory analysis.

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