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ORIGINAL RESEARCH ARTICLE

Genetic alterations of *APC* and *MYC* in fibroadenoma and invasive ductal adenocarcinoma: Implications for pathogenesis and personalized gene therapy

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Abstract

Breast cancer is a major public health concern, particularly among women, and its treatment remains challenging worldwide. Targeted gene therapy may offer a promising approach to reducing the disease burden and improving clinical outcomes. Hence, this study evaluates the mutation patterns of the *APC* and *MYC* genes in benign and malignant breast lesions. Ten formalin-fixed heterogeneous paraffin-embedded tissue blocks—five fibroadenomas and five invasive ductal adenocarcinomas (IDA)—from the pathological archives of Federal Teaching Hospital Ido-Ekiti were subjected to analysis. Nucleic acid extraction was performed using the Dellaporta DNA extraction protocol, followed by amplification using polymerase chain reaction (PCR). The samples were subsequently sequenced using the Applied Biosystems 3130xl Genetic Analyzer sequencer following the manufacturer's instructions. Genetic analyses were conducted using BioEdit and MEGA 6, and HGVSc, HGVSp, and variant allele frequency (%) were evaluated. Transition single-nucleotide polymorphisms (SNPs) were identified in APC for both fibroadenoma and IDA. Functional mutations in *APC* include silent and missense mutations in fibroadenoma, whereas IDA displayed only missense mutations. In the *MYC* gene, SNPs in fibroadenoma included both transversions and transitions, whereas transition and transversion SNPs, as well as insertions/deletions, were observed in IDA. Missense and silent functional mutations of *MYC* were observed in both fibroadenoma and IDA. Overall, the study demonstrated the presence of missense mutations in both *APC* and *MYC* genes in fibroadenoma and IDA.

Keywords: Targeted therapy; Precision medicine; Adenomatous polyposis coli; Myelocytomatosis; Mutation; Fibroadenoma; Invasive ductal adenocarcinoma

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1. Introduction

Breast cancer is a significant public health concern, particularly among women, and its treatment remains challenging.[1] Cancer cells typically arise from the loss or inactivation of genes responsible for inhibiting tumor development, resulting in cellular resistance

to apoptosis and uncontrolled cell proliferation.[2] Breast cancer remains a major cause of cancer morbidity and mortality, with epidemiological data highlighting its increasing burden, notably in low- and middle-income regions. Environmental factors can interact with genetic mutations to increase cancer risk. For example, Kiljańczyk *et al.*[3] showed that elevated blood lead levels increased ovarian cancer risk in *BRCA1* carriers, highlighting how environmental toxins can exacerbate genetic susceptibility. Similarly, pollutants and dietary contaminants may promote mutations in genes such as *APC* and *MYC*, driving the progression from benign breast lesions to invasive cancers. These observations underscore the importance of integrating environmental risk assessment with genetic profiling for the prevention and targeted treatment of diseases.

Recent research highlights the significance of early diagnosis through imaging modalities, including mammography and magnetic resonance imaging, combined with histopathological examination.[4,5] Breast cancer treatment has also advanced significantly, incorporating surgery, radiation, and chemotherapy, as well as targeted therapeutic approaches. Molecular profiling has become essential for guiding personalized treatment modalities, including the use of poly(ADP-ribose) polymerase inhibitors for *BRCA*-mutated tumors and anti-phosphatidylinositol 3-kinase agents for phosphatidylinositol 3-kinase pathway abnormalities.[6,7]

Early diagnosis of breast cancer is one of the most effective approaches for reducing breast cancer mortality and improving prognosis, and it can guide therapeutic decision-making or identify potential therapeutic targets within specific populations.[8,9] Invasive ductal adenocarcinoma (IDA) is a malignant tumor that originates in the breast ducts and invades surrounding tissues, with potential regional lymph node involvement and distant organs.[10] In contrast, fibroadenomas are benign tumors characterized by an admixture of stromal and epithelial tissue that arise from the lobules,[11] where glandular tissue and ducts proliferate to form a well-defined lump.[12]

The adenomatous polyposis coli (*APC*) gene is a well-established tumor suppressor that plays a critical role in the Wnt/β-catenin signaling pathway, a pathway pivotal for regulating cellular proliferation, differentiation, and apoptosis. Recent evidence suggests the implication of *APC* mutations in breast tissue malignancies,[13] underscoring the importance of studying these alterations across different breast pathologies. Myelocytomatosis (*MYC*) is a well-characterized proto-oncogene[14] that modulates transcriptional control over key genes influencing cellular growth, metabolism, and survival.[15] Deregulation of *MYC*, through gene mutations or amplification, is often a hallmark of aggressive tumor phenotypes.[16]

Recent advances in breast cancer research have highlighted the growing potential of immunotherapy and the need for robust biomarkers to enable patient stratification. Shi *et al.*[17] characterized immunogenic cell death-dependent subtypes in triple-negative breast cancer and demonstrated that tumors with "hot" immune microenvironments, reflected by higher immunogenic cell death scores, showed a better prognosis and may respond more favorably to immune checkpoint blockade. Given that early molecular events may influence later therapeutic responses, understanding mutations in *APC* and *MYC* in benign and malignant breast lesions could provide insights into the timeline of tumor evolution and identify early markers for therapy selection. Although data on alternative primary therapies are sparse, and some studies suggest poor outcomes when standard treatments are delayed or omitted, other studies[18,19] have reported that alternative or targeted therapies offer better results compared to conventional therapies.

These findings underscore the importance of molecular stratification, even in early-stage or benign lesions, to identify initial tumorigenic events, avoid misclassification of potentially pathogenic mutations, and prevent delays in appropriate treatment. Thus, profiling genetic alterations in *APC* and *MYC* in fibroadenomas versus IDAs may offer valuable insights into the timeline of breast tumor progression and potentially inform therapeutic decision-making. Given the proven effectiveness of alternative and targeted therapies in patients with specific molecular abnormalities, this pilot study aims to assess *APC* and *MYC* gene mutation patterns in benign and malignant breast lesions, emphasizing the need to integrate molecular diagnostics into clinical practice.

2. Materials and methods

2.1. Sample collection and histological confirmation

The pilot study utilized 10 processed tissue blocks obtained from the pathology archive at the Department of Histopathology, Federal Teaching Hospital, Ido-Ekiti, Ekiti, Nigeria. They were confirmed as either fibroadenoma or IDA samples. Histological confirmation for all cases was conducted using hematoxylin and eosin staining, followed by microscopic examination to validate the diagnosis. Fibroadenoma was characterized by stromal and glandular proliferation without cellular atypia, whereas IDA was confirmed by irregular glandular structures invading the stromal tissue. Thin sections were cut using a microtome and dewaxed with xylene. Clinical data were excluded to maintain patient confidentiality, as the study was

retrospective. Three main procedures were employed in this study: DNA extraction, polymerase chain reaction (PCR), and DNA sequencing. These methods were supplemented by spectrophotometric analysis, DNA purification, and isolation of the gene of interest as described and modified by Olukayode *et al.*[11]

2.2. DNA extraction and spectrophotometric analysis

DNA was extracted from the tissue sections using a modified Dellaporta protocol. The extraction process involved cell lysis, protein removal, DNA precipitation, and resuspension in Tris-ethylenediaminetetraacetic acid buffer. DNA quality and concentration were verified using a NanoDrop spectrophotometer (ThermoFisher Scientific, United States). The purity of the DNA was assessed by measuring the absorbance ratios at 260/280 nm and 260/230 nm, with ratios of 1.8–2.0 indicating high-quality DNA. The concentrations ranged from 50 to 200 ng/μL, confirming sufficient yields for downstream applications.

2.3. PCR

PCR of target genes was performed using a 25 μL reaction volume containing 1× PCR buffer, 2.0 mM magnesium chloride, 0.2 mM dNTPs, 0.5 μM of each primer, 1 U Taq DNA polymerase (Inqaba Biotech, South Africa), and 100 ng of template DNA. The primers were designed to target specific exons of the *APC* and *MYC* genes. The primer sequences and nucleotide positions are as follows:

(i) *APC* forward: 5'-AGCTTGCTGTCATTG-3' (chr5:112,707,448–112,707,462)
(ii) *APC* reverse: 5'-TGGTTTCTGCTTGC-3' (chr5:112,707,580–112,707,594)
(iii) *MYC* forward: 5'-GGAGCTGGACTGGAA-3' (chr8:128,748,315–128,748,329)
(iv) *MYC* reverse: 5'-GTCGTGCTGAGGG-3' (chr8:128,748,445–128,748,458).

The PCR cycling conditions were as follows: Initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 45 s, with a final extension at 72°C for 7 min. Amplified products were verified on a 1.5% agarose gel stained with ethidium bromide, visualized under ultraviolet transillumination, and compared against a 100 bp DNA ladder.

2.4. PCR optimization and primer specificity

Primers were designed using Primer3 and checked for specificity with NCBI BLAST against the human genome. Primer pairs were validated by gradient PCR to determine the optimal annealing temperatures and by agarose gel electrophoresis to confirm the presence of single, correctly sized amplicons. PCR amplicons were Sanger-sequenced to verify target identity. Negative (no template) and positive control samples were included in all amplification experiments to monitor contamination and assay performance.

2.5. DNA purification and sequencing

Amplified PCR products were purified using ethanol precipitation to remove residual reagents. The DNA pellets were washed, air-dried, and resuspended in sterile distilled water. Purified DNA was verified on a 1.5% agarose gel and quantified using a NanoDrop spectrophotometer. DNA sequencing was performed using the Applied Biosystems Genetic Analyzer 3130xl with the BigDye Terminator v3.1 cycle sequencing kit (ThermoFisher Scientific, United States). Sequences were obtained using both forward and reverse primers for accuracy.

2.6. Data analysis

The obtained sequences were aligned to the human reference genome (hg38) using BioEdit software (version 7.2). Sequence alignment and variant calling were performed using the MEGA 6 software. Mutations were classified as pathogenic or benign using the ClinVar database, which provided information on clinical significance and population frequency. The mutation frequency was compared between fibroadenoma and IDA cases. Statistical analysis was conducted using the Statistical Package for the Social Sciences software version 25, with significance set at $p<0.05$.

2.7. Ethical consideration

Ethical approval was obtained from the ethics committee at Federal Teaching Hospital, Ido (protocol number: ERC/2023/04/26/958B).

3. Results

Mutations identified in the *APC* and *MYC* genes, which include missense, silent, and insertion/deletion (indel) mutations observed at various gene locations using HGVSc, HGVSp, and variant allele frequencies (%), are shown in Tables 1-3. The analysis indicated that mutations within the *APC* and *MYC* genes occur at varying frequencies in fibroadenoma and IDA, suggesting potential roles in tumorigenesis. The observed mutations included transitions, transversions, indels, missense, and silent mutations, reflecting the genetic diversity and complexity of these breast lesions.

Figure 1 illustrates the frequencies of *APC* single-nucleotide polymorphisms (SNPs), *APC* functional mutations, and *APC* mutations in IDA and fibroadenoma,

Table 1. Clinical characteristics of patients

Diagnosis/specimen	Age range (years)	Gender	Histology	Confirmed mutation (s)
Invasive ductal adenocarcinoma	45–55	Female	Confirmed via H&E	*APC*, *MYC*
Fibroadenoma	25–35	Female	Confirmed via H&E	*APC*, *MYC*

Abbreviation: H&E: Hematoxylin and eosin.

Table 2. Details of mutations in the *APC* gene

Gene	Specimen	Chromosome position	Mutation type	HGVSc	HGVSp	VAF (%)
APC	IDA	Chr5:112175	Transition	c. 162A>G	p.Asn54Ser	70
	IDA	Chr5:112586	Transition	c. 573G>A	p.Ala191Thr	80
	FA	Chr5:112638	Transition	c. 625T>C	p.Tyr208Tyr	20
	IDA	Chr5:112778	Transition	c. 765A>G	p.Glu255Gly	90
	FA	Chr5:112915	Transition	c. 902C>T	p.Pro301Ser	60

Abbreviations: FA: Fibroadenoma; IDA: Invasive ductal adenocarcinoma; Indel: Insertion/deletion; VAF: Variant allele frequency.

Table 3. Details of mutations in the *MYC* gene

Gene	Specimen	Chromosome position	Mutation type	HGVSc	HGVSp	VAF (%)
MYC	IDA	Chr8:128751	Indel	c. 171insC	p.Asp57Asn	90
	IDA	Chr8:129189	Indel	c. 609insG	p.Ala203Thr	90
	IDA	Chr8:128809	Transversion	c. 229T>A	p.Cys77Ser	90
	FA	Chr8:129043	Silent	c. 463C>G	p.Leu155Leu	40
	IDA	Chr8:129169	Transition	c. 589G>A	p.Ala197Thr	90
	IDA	Chr8:129313	Transition	c. 733G>A	p.Ala245Thr	90

Abbreviations: FA: Fibroadenoma; IDA: Invasive ductal adenocarcinoma; Indel: Insertion/deletion; VAF: Variant allele frequency.

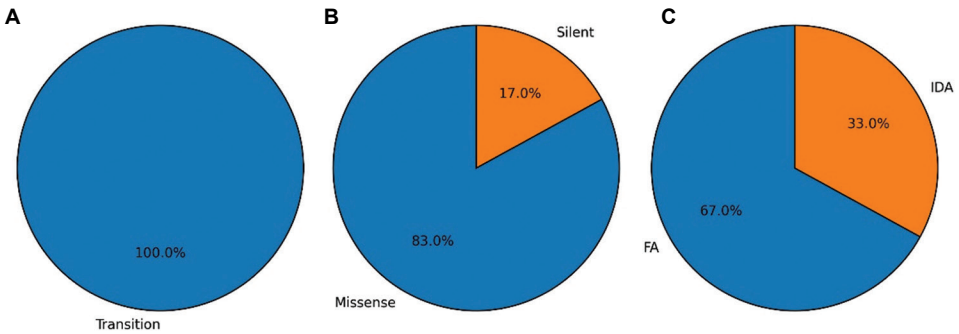

Figure 1. Pie charts of *APC* mutations. (A) *APC* single-nucleotide polymorphisms (SNPs) in fibroadenoma (FA) and invasive ductal adenocarcinoma (IDA) were 100% transitions. (B) Silent and missense mutations accounted for 17% and 83% of the functional mutations, respectively. (C) *APC* mutation frequencies were 33% in IDA and 67% in FA, respectively.

whereas Figure 2 shows the frequencies of *MYC* SNPs, functional mutations, and *MYC* mutation frequencies in fibroadenoma and IDA.

4. Discussion

The *APC* and *MYC* variant profiles differed between fibroadenoma and IDA, highlighting alterations that may be relevant to tumor biology.[13]

4.1. *APC* and *MYC* mutation patterns in invasive ductal adenocarcinoma and fibroadenoma

The results revealed an intricate profile of *APC* gene mutations in IDA specimens, characterized predominantly by transition mutations, which was similar to the study by Ghatak.[20] Notably, A transitions at codon 162 leading to the substitution of asparagine with serine, and G transitions at codon 573 causing alanine to threonine changes,

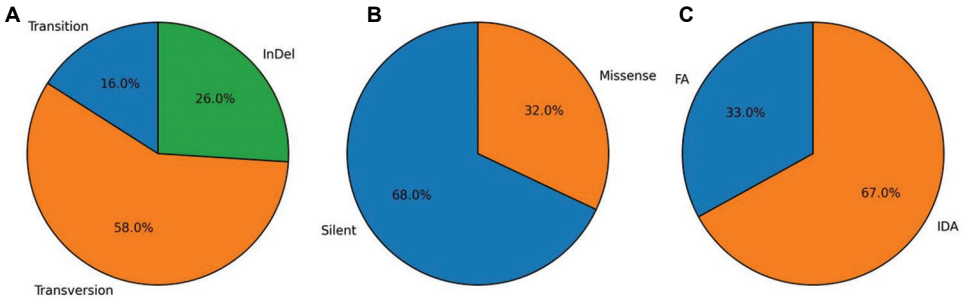

Figure 2. Pie charts of *MYC* mutations. (A) MYC single-nucleotide polymorphisms (SNPs) in fibroadenoma (FA) and invasive ductal adenocarcinoma (IDA) were 16% transitions, 26% insertions/deletions, and 58% transversions. (B) Silent and missense mutations accounted for 68% and 32% of the functional mutations, respectively. (C) *MYC* mutation frequencies were 33% in FA and 67% in IDA, respectively.

were recurrent findings. These missense mutations are critical as they result in non-synonymous substitutions that can alter the conformation and functionality of the APC protein. Such alterations may compromise its tumor-suppressive capabilities, promoting β-catenin accumulation and subsequent transcriptional activation of oncogenic pathways, as suggested by studies on aberrant Wnt signaling in cancer.[21] The mutation at codon 765, leading to a glutamate-to-glycine substitution, further supports the potential disruption in APC's interaction with other cellular proteins, such as axin and glycogen synthase kinase 3 beta, which are crucial for β-catenin degradation. This molecular impairment can lead to unchecked cellular proliferation, facilitating malignant transformation in IDA, which aligns with research showing that missense mutations in tumor suppressor genes are strongly associated with invasive cancer phenotypes.[22]

In fibroadenoma lesions, the mutation profile in *APC* was predominantly silent, exemplified by the T transition at codon 625. This finding is in agreement with a 2021 report by Ghadamyari *et al.*[23] in a clinical laboratory analysis, which demonstrated the nature and effect of *APC* gene mutation in familial adenomatous polyposis tumorigenesis. The silent nature of these mutations suggests a lower pathogenic potential, consistent with the benign histological classification of fibroadenoma. However, the presence of these silent mutations suggests potential genomic instability, which could predispose the tissue to further mutations under stress or during cellular aging.[24,25] The sporadic missense mutations observed, such as the C transition at codon 902 leading to a proline-to-serine substitution, suggest that although these may not drive tumorigenesis, they might be an early indicator of genomic alteration preceding malignancy.

The *MYC* gene analysis in IDA samples revealed various mutation types, including indels and transversions. Indels, such as insertions at codon 609 (resulting in the insertion of alanine) and deletions at codon 231 (resulting in the deletion of cysteine), highlight the dynamic genomic instability observed in invasive carcinomas. Indels, such as those observed in inflammatory breast cancer, can disrupt the reading frame or introduce aberrant amino acids, resulting in truncated or non-functional MYC proteins, which in turn disrupt its downstream transcriptional programs and promote oncogenesis.[26] Moreover, mutations that affect the MYC–myc-associated factor X interaction interface, such as those targeted by recently developed inhibitors, demonstrate that structural disruption of MYC–myc-associated factor X dimerization reduces binding affinity and impairs oncogenic transcriptional activation, underscoring the functional significance of such mutations in contributing to malignancy.[27] These findings align with the literature that describes the role of *MYC* mutations in enhancing transcriptional activity, promoting oncogenic transformation, and contributing to poor prognosis in invasive breast cancer.[28] The fibroadenoma sample exhibited a mutation profile in *MYC* skewed toward silent mutations (68%), indicating mutations that do not alter the protein's coding potential. The predominant silent transversions, such as the G change at codon 463, reflect a lower likelihood of contributing to oncogenesis, which agrees with the report by Xu-Monette *et al.*[29]. However, the presence of missense mutations, such as the G transition at codon 733, demonstrates that benign tumors can possess genetic alterations that may serve as early molecular precursors to more aggressive alterations under oncogenic stimuli.[30] A comparison between fibroadenoma and IDA revealed that the mutation frequency was higher in fibroadenoma (67%) than in IDA (33%). This counterintuitive finding may reflect a broader range of non-functional mutations in fibroadenoma, whereas IDA harbors fewer but more impactful, pathogenic mutations. This observation aligns with current literature, which shows that benign lesions can harbor diverse somatic mutations that do not necessarily drive malignancy but reflect underlying genomic vulnerability.[31] In contrast, *MYC* alterations were more frequent in IDA, consistent

with its role as a potent oncogenic driver that contributes to genetic instability and tumor adaptation.[32]

A functional breakdown of the mutations revealed that 83% of the mutations in IDA were missense, in contrast to 17% silent mutations, reinforcing the concept that missense mutations in *APC* contribute significantly to the malignancy's invasive nature. Missense mutations impact the protein's structural integrity, likely leading to the disruption of the tumor suppressor role of *APC*. This is supported by studies indicating that the loss of *APC* function promotes the stabilization and nuclear translocation of β-catenin, a key player in oncogenic transcriptional programs.[22] In IDA, missense mutations accounted for 32% of *MYC* mutations, indicating a direct role in modifying protein function. The presence of mutations causing substitutions, such as alanine to threonine at codon 589, can impact the protein's interaction with transcriptional co-factors and DNA binding, enhancing its oncogenic potential.[33] Silent mutations, although deemed non-pathogenic, could still influence splicing or mRNA stability, contributing to *MYC* overexpression, a common occurrence in breast cancer linked to aggressive behavior.

In addition, the counterintuitive result in fibroadenoma and IDC can be due to technical factors, including a small sample size, biological explanations, such as fibroadenoma harboring a broader range of low-impact or "passenger" mutations that accumulate during benign proliferation but do not confer selective growth advantages, and the absence of matched normal controls sample to help distinguish somatic mutations from rare germline polymorphisms.

4.2. Functional implications of *APC* and *MYC* mutations

The functional breakdown of mutations revealed that 83% of *APC* mutations in IDA were missense, compared to only 17% silent mutations. This strongly reinforces the concept that missense mutations in *APC* contribute significantly to the malignancy's invasive nature. This is supported by more recent work showing that truncating *APC* mutations disrupts the β-catenin destruction complex (by interfering with axin-mediated condensate formation), thereby inhibiting β-catenin phosphorylation and degradation, leading to its stabilization and nuclear accumulation.[22] Similarly, in IDA, 32% of *MYC* mutations were missense, suggesting direct disruption of *MYC*'s transcriptional control mechanisms. Notably, amino acid substitutions such as alanine to threonine at codon 589 may enhance *MYC*'s interaction with transcriptional co-factors, promoting tumor progression.[33] While silent mutations were more common in fibroadenoma, they may still influence mRNA stability or splicing, indirectly contributing to *MYC* overexpression, a known driver of aggressive breast cancer behavior.

4.3. Limitations

This study is a small, pilot investigation (n = 10) and was therefore underpowered to detect low-frequency variants or provide robust estimates of mutation prevalence. The small sample size increases the risk of sampling bias and limits the generalizability of the results. Consequently, our findings are hypothesis-generating and require validation in larger cohorts with prospectively collected specimens and matched normal controls.

Moreover, protein validation was not performed. Matched normal tissue controls were unavailable in this pilot study, and variant filtering relied on population frequency data. Furthermore, information on hormone receptor status, human epidermal growth factor receptor 2 expression, and tumor grade was not available, limiting clinicopathological correlation.

4.4. Recommendations

Future studies should include larger cohorts with detailed clinicopathological information, including hormone receptor status, to facilitate the translation of genetic findings into clinical practice. Protein-level validation is also essential, and the use of immunohistochemistry and proteomics, alongside *in silico* functional analyses such as PolyPhen-2 and SIFT, would help link genotype to phenotype in a larger cohort. In addition, the inclusion of matched normal tissue samples will be critical for robust variant validation.

5. Conclusion

The observed mutations in the *APC* and *MYC* genes across fibroadenoma and IDA highlight crucial insights into their roles in breast tissue tumorigenesis. *APC*'s involvement in IDA underscores the loss of tumor suppressive functions through missense mutations, which likely promote cellular pathways that lead to invasion and metastasis. In contrast, MYC mutations, particularly in IDA, align with its role in enhancing oncogenic pathways through complex alterations that disrupt normal cellular control and drive malignancy. The contrasting mutation frequencies between fibroadenoma and IDA for both genes may indicate that while benign tumors harbor a variety of mutations, invasive tumors possess targeted genetic changes with higher pathogenic potential. The mutational spectrum of *APC* and *MYC* in fibroadenoma and IDA reveals critical differences in genetic alterations that contribute to tumor behavior. Overall, IDA exhibited a higher proportion of variants with predicted functional

impact, whereas fibroadenoma predominantly harbored variants with lower predicted pathogenicity. These findings underscore the importance of further genomic and proteomic studies to elucidate the roles of these mutations in breast cancer progression, potentially guiding targeted therapeutic strategies to support precision management of breast cancer.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors
Methodology: All authors
Writing–original draft: Kehinde Adedapo Olajide
Writing–review & editing: Kehinde Adedapo Olajide

Ethics approval and consent to participate

Ethical approval was obtained from the ethics committee at Federal Teaching Hospital, Ido (protocol number: ERC/2023/04/26/958B). Informed consent was obtained from the patients by the hospital management before sample collection.

Consent for publication

Not applicable.

Availability of data

Data will be made available upon request to the corresponding author.

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