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**Case Report**

# Detection of Cpy-2, Fks and Erg 11 Genes in Fungal Isolates from Sars Cov-2 Individual in Ibadan, Oyo State, Nigeria

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## Abstract

A considerable number of fungal strains have developed resistant to various available antifungal agents due to CPY, FKS and or ERG11 genes complicating coinfection cases of SAR COV-2 virus. Therefore, this study sought to isolate, identify azole and polyene resistant genes in fungal pathogens isolated from confirmed SARS-CoV-2 individual in Oyo State, Nigeria. Nasopharyngeal samples were collected from symptomatic and asymptomatic SARS-CoV-2 infected adult from September, 2020 to April, 2021. Samples were cultured on Sabouraud Dextrose Agar at room and at 37 $^{o}$C temperature for 7days.

Identification of the fungal isolates were performed using MALDITOF MS VITEK. Antifungal Susceptibility Testing (AFST) were performed using Kirby bauer disc diffusion method. The resistant genes in fugal isolates were determined by Polymerase Chain Reaction with specific primers and resistant genes were amplified using agarose gel electrophoresis. Out of 63(15.8%) fungal isolates recorded from 400 samples collected, Asipergillus flavus 11(17.5%), Aspergillus niger 9(14.3%), Candida albicans 7(11.1%), Candida guillermondii 2(3.2%), Candida parapsilosis 2(3.2%), Candida famata 2(3.2%), Candida tropicalis 5(7.9%) and Lodderomyces elongisporus 25(39%) having highest frequency were recorded respectively. Nystatin (84.1%) had highest susceptibility testing and Ketoconazole (39.7%) had the least phenotypically. 10 (52.6%) isolates possessed CPY gene, 8(42.1%) isolates carried FKS gene, 9(47.4%) isolates had ERG11 gene molecularly.

**Keywords:** SARS-CoV-2; Fungal co-infection; MS VITEK MALDITOF; CPY; FKS; ERG 11.


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**Abbreviations:** SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; COVID 19: Novel Corona Virus Disease 2019; BALF: Broncho- alveolar lavage fluid; IgG: Immunoglobulin; DNA: Deoxy-Ribonucleic acid; RNA: Ribonucleic acid; PCR: Polymerase chain reaction; ITS: Internal Transcribed Spacer; MALDITOF: Matrix Assisted Laser Desorption Ionization Time of Flight; MS: Mass Spectrophotometry.

## Introduction

The diagnosis of fungal infection is frequently hampered by the limited accessibility of contaminated material from the affected site. Early intervention is not always possible because to these factors, as well as the slow development of a large number of fungi in commonly used culture media, and the patient's condition, intervention is frequently lost or delayed.

Typically, Gram and Giemsa stains, which have poor sensitivities of about 50 to 80%, are used to diagnose fungal infection [1]. Culture-independent diagnostic procedures are now possible thanks to recent developments in molecular biology techniques. The most popular diagnostic tools are nucleic acid probes and immunological detection and identification using unique metabolites [2-5].

PCR is one such method that has been demonstrated to be effective for the culture-independent diagnosis of a variety of microbial illnesses, including mycoses [6-8].

A small subunit (SSU) 18S rRNA, a large subunit (LSU) 28S rRNA, and a 5.8S rRNA make up the entire rRNA gene. Internal transcribed spacer (ITS) region ITSI and ITSII, which are located between SSU rRNA and 5.8S rRNA and in between 5.8S rRNA and LSU rRNA are more variable than the other ribosomal gene subunits respectively.

In addition, intergenic spacers IGSI and IGSII are located between the completion of the LSU and the beginning of the next SSU sequence [9].

The lanosterol demethylase that is the target of azole antifungals is encoded by the ERG11 gene in Candida albicans. The ability of the azoles to bind to and inhibit ERG11 is altered by mutations in ERG11 that result in an amino acid substitution, leading to resistance.10. The exact contributions of individual ERG11 mutations to azole resistance in C. albicans have not been thoroughly investigated, despite the fact that ERG11 mutations have been found in clinical isolates. Beyond what was provided by any single amino acid replacement, the isolates that were homozygous for many double amino acid substitutions showed decreased azole susceptibilities.

These results show that azole-resistant clinical isolates frequently carry ERG11 mutations, and that the majority of these mutations significantly alter FLC and VRC susceptibilities. Studies in yeast have revealed several molecular mechanisms of azole resistance [10-15] :(1) The affinity of azoles for the target enzyme CYP51A1 is decreased by point mutations in the ERG11 gene, (2) upregulates the expression of ERG11 to increase the copy number of CYP51A1, (3) metabolic adjustment, and (4) reduced intracellular azole buildup via drug sequestration or activation of multidrug transporters. It has been demonstrated that mutations in the fks1 gene that affect the amino acids in the protein were both essential and sufficient to induce decreased susceptibility in laboratory mutants as well as in some clinical isolates to caspofungin [16,17]. These alterations, which are


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connected to decreased sensitivity to caspofungin, have only been discovered to exist in two "hot spot" (HS) regions of the Fks protein, which are found in Candida albicans at amino acid positions 640 to 650 and 1345 to 1365 [18,19]. Numerous clinical investigations have demonstrated that the most significant independent risk factor for predicting echinocandin treatment responses in patients with IC (Invasive Candidiasis) is the presence of an FKS mutation [20,21]. Additionally, it was discovered that the existence of an FKS mutation was more accurate at predicting clinical outcomes than MIC (Minimum Inhibitory Concentration) values, particularly when testing with caspofungin (CAS).

Carboxypeptidase Y (CPY) has been used as a maker enzyme for investigation on intracellular transport of vacuolar protein and on vacuolar biogenesis in Saccharomyces cerevisiae. The CPY gene homologous encoding from filamentous fungi has been cloned and described; the gene has one intron and encodes a 552 amino acid protein with a potential signal region and pro-sequence. Recently synthesized CPY is transported from the endoplasmic reticulum (ER) to the vacuole where it undergoes post-translational modification and proteolytic digestion [22,23].

**Limitation of the Study**

The study was limited within its scope and the limitation therefore include among others:

- Non-compliance of individuals to readily release their samples because of traditional beliefs about any human body fluid; therefore, informed consent was sought for.
- The field work was stressful in filling of questionnaires to get actual facts from the subjects.

| Primers | Sequence (5' to3') | Size | References |
|---|---|---|---|
| ITS1 | F: TCCGTAGGTGAACCTGCGG | 500-600 | [24] |
| ITS4 | R: TCCTCCGCTTATTGATATGC | | |

**Table1:** Primer used for ITS1 and ITS4 Amplification in Taxonomy of Fungi Isolates.

| Primers | Sequence (5' – 3') | Size | References |
|---|---|---|---|
| FKS2HS1 | F: GCTTCTCAGACTTTCACCG | 600 | [25] |
| FKS2HS2 | R: CAGAATAGTGTGGAGTCAAGACG | | |

**Table2:** Primer used for FKS 1 & 2 Resistance Gene in Fungi to Echinocandins and Polyenes Antifungal Agents.


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| Primer | Sequence (5' – 3') | Sizes | References |
|---|---|---|---|
| ERG11 | F: CCGAGTACAAGGAGGCCTTC | 1300 | [26] |
| | R: CCGATAGAGGTCATAACGTGG | | |

**Table 3:** Primer used for ERG11 Resistance Gene in Candida to Azole Antifungal Agents.

| Primers | Sequence (5' to3') | Size | References |
|---|---|---|---|
| CPY | F: TACACCTATTCCGATCACACCA | 100 | [27] |
| CPY | R: GTCTCTCATTCGTCCTTGTCCT | | |

**Table 4:** Primers used for CPY Resistance Gene in *Aspergillus* Species to Azoles Antifungal Agents.

## Result

| Variable | Frequency (n=63) | Percentage |
|---|---|---|
| **Name of Fungi (n=63)** | | |
| *Aspergillus flavus* | **11** | **17.5** |
| *Aspergillus niger* | **9** | **14.3** |
| *Candida albicans* | **7** | **11.1** |
| *Candida guillermondii* | **2** | **3.2** |
| *Candida parapsiloxis* | **2** | **3.2** |
| *Candida famata* | **2** | **3.2** |
| *Candida tropicalis* | **5** | **7.9** |
| *Lodderomyces elongisporus* | **25** | **39.7** |
| **Total** | **63** | **100** |

**Table 5:** VITEK MS Identification of all Fungal Isolates from samples of COVID-19 Respondents. Source: Author's Laboratory Analysis (2022).


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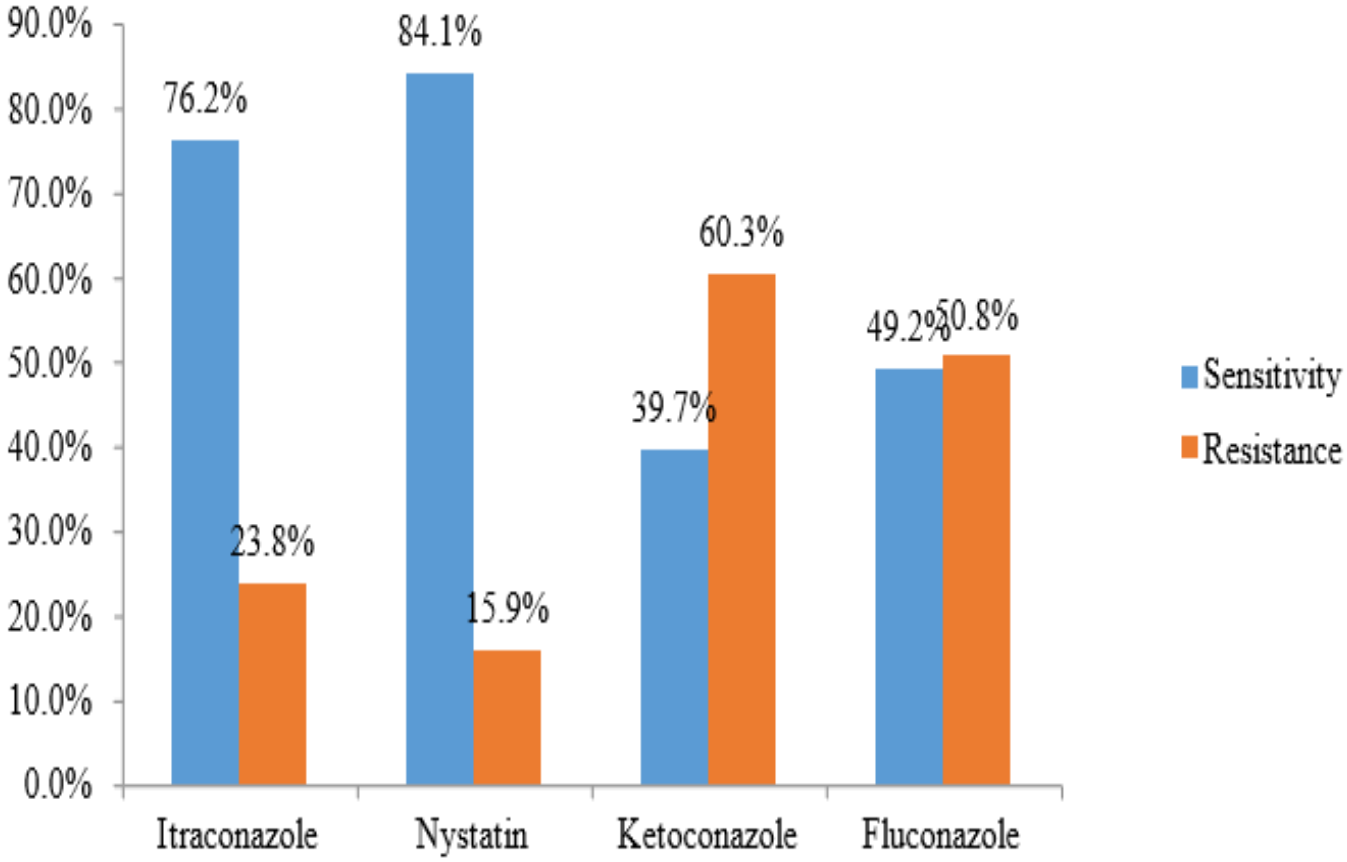


**Figure 1:** Antibiogram Susceptibility pattern of fungi isolates using Kirby Bauer disc diffusion methods. Source: Author's Laboratory Analysis (2022).

| Variable | ITS1&4 Positive(%) | CPY2 Positive(%) | FKS1&2 Positive(%) | ERG11 Positive(%) |
|---|---|---|---|---|
| *Aspergillus niger* | 6(30.0) | 4(20.0) | 4(20.0) | 1(5.0) |
| *Aspergillus flavus* | 6(30.0) | 3(15.0) | 2(10.0) | 1(5.0) |
| *Lodderomyces elongisporusis* | 6(30.0) | 2(10.0) | 0(0) | 6(30.0) |
| *Candida tropicalis* | 0(0) | 0 | 0(0) | 0 |
| *Candida famata* | 1(5.0) | 1(5.0) | 1(5.0) | 1(5.0) |
| **Total** | 19(95) | 10(50) | 7(35) | 9(45) |

**Table 6:** Antifungal resistant genes with specific primers among fungal isolates. Source: Author's Laboratory Analysis.


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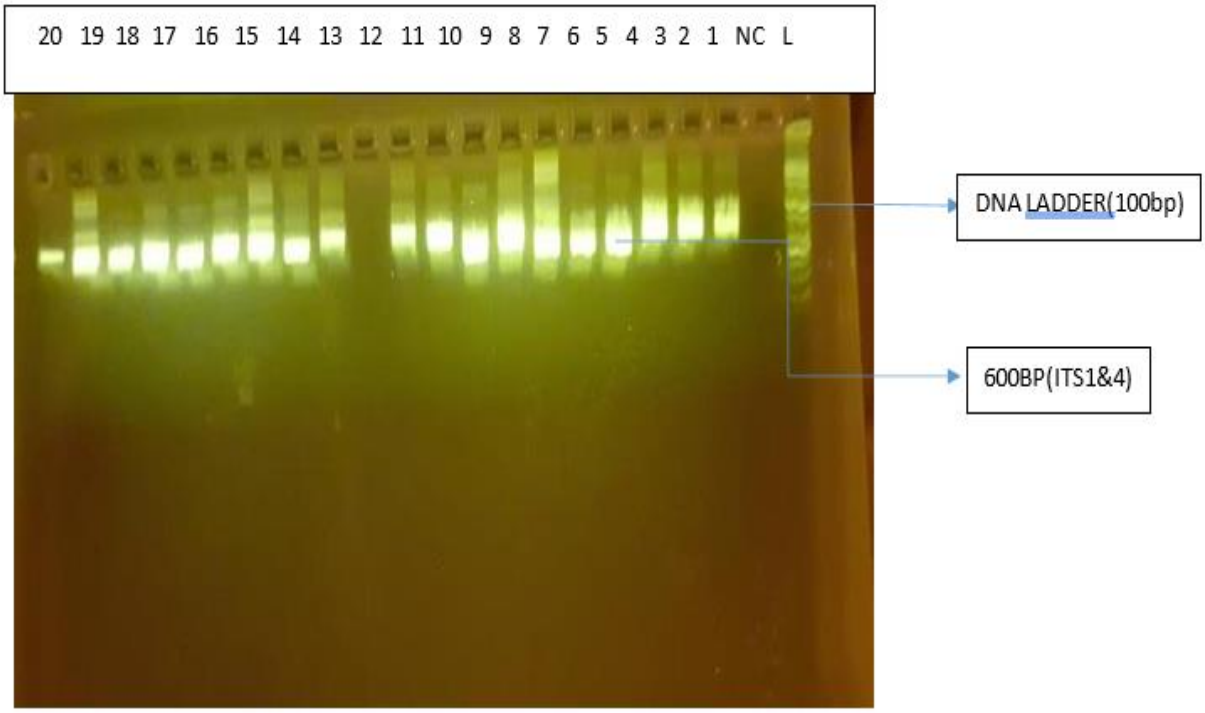


**Figure 2:** Agarose Gel Electrophoresis of ITS1 and ITS4 gene. Key: Lane 1=Ladder (100bp), Lane 2=Negative Control, Lane 3-20=Fungi isolates. Source: Author's Laboratory Analysis.

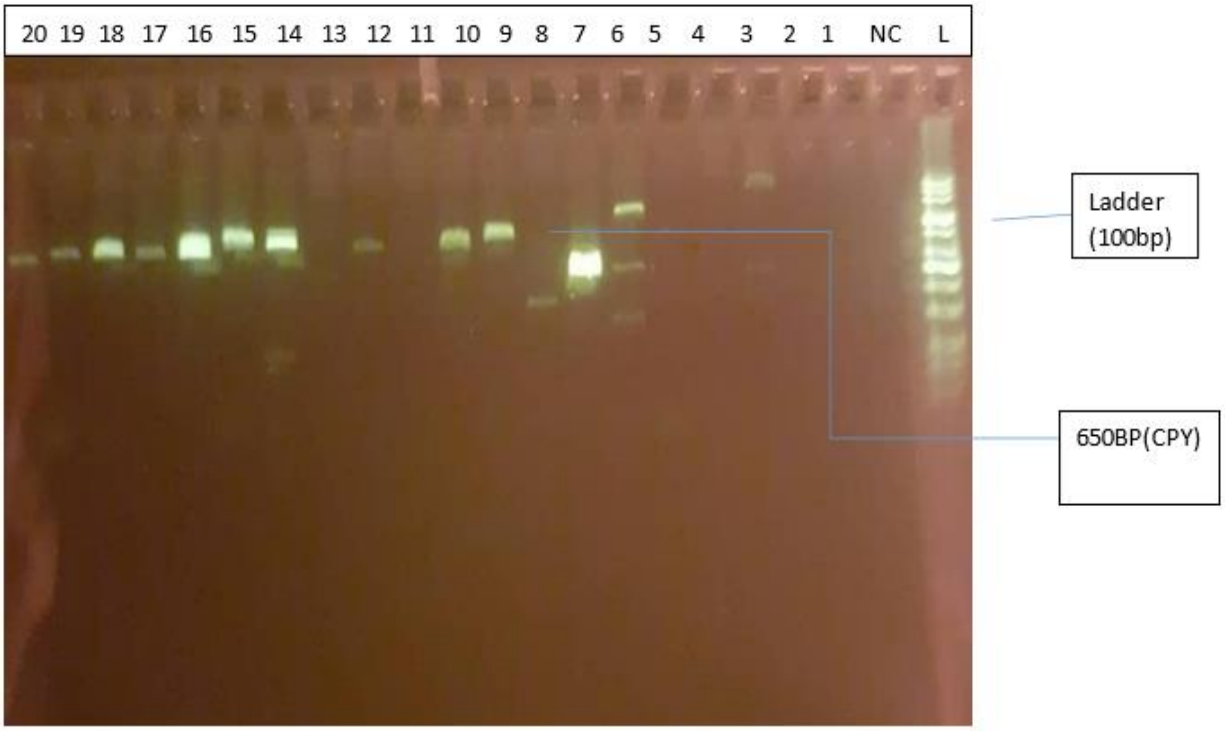


**Figure 3:** Agarose Gel Electrophoresis of CPY gene. Key: Lane 1=Ladder (100bp), Lane 2=Negative Control, Lane 3-20=Fungi isolates. Source: Author's Laboratory Analysis.


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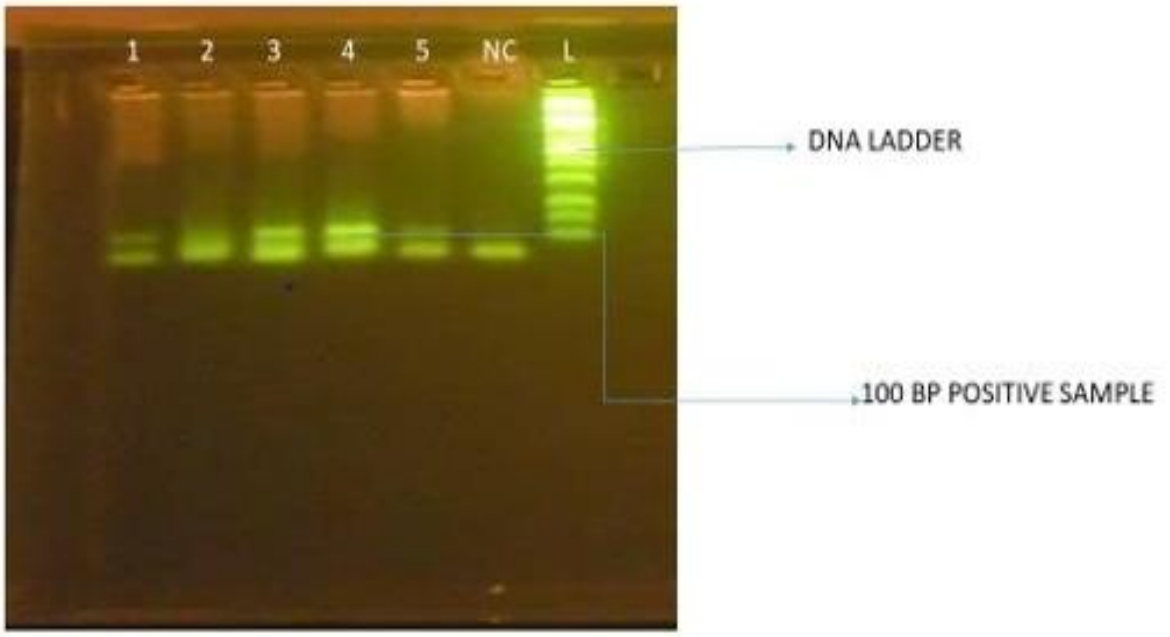


**Figure 4:** Agarose Gel Electrophoresis of FKS 1 and FKS 2. Key: Lane 1=Ladder (100bp), Lane 2=Negative Control, Lane 3-5=Fungi isolates. Source: Author's Laboratory Analysis.

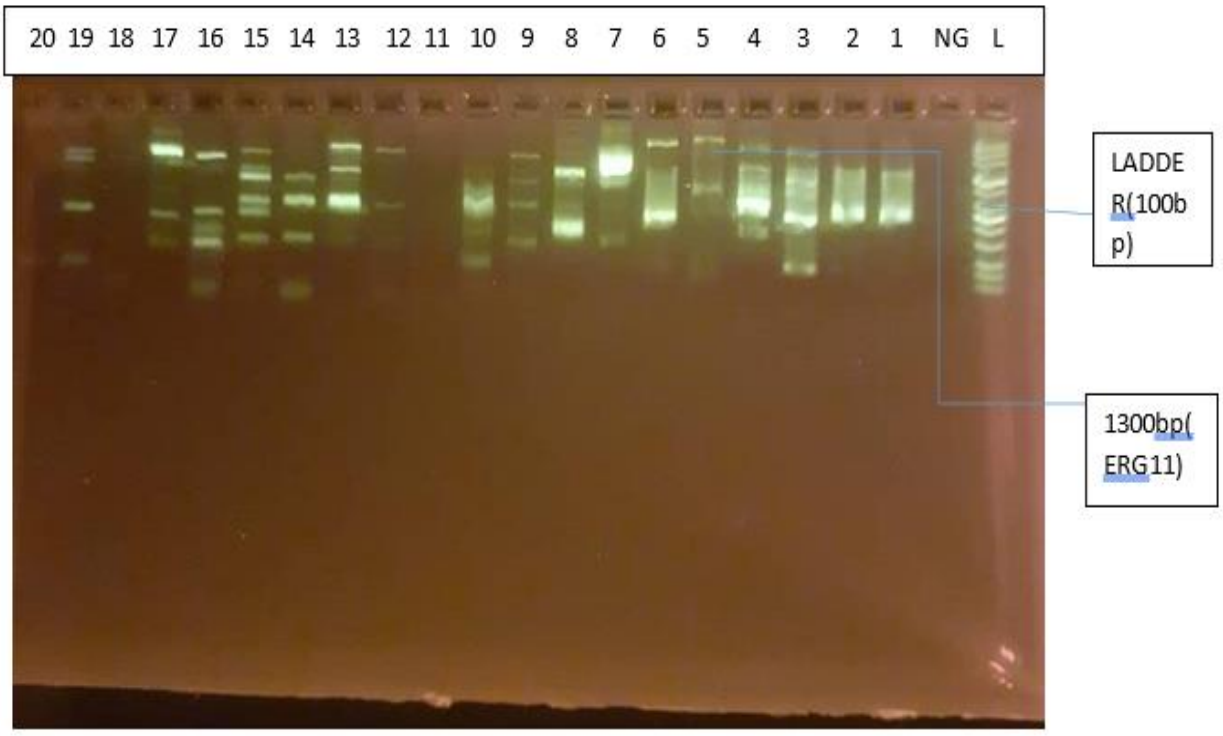


**Figure 5:** Agarose Gel Electrophoresis of ERG11. Key: Lane 1=Ladder (100bp), Lane 2=Negative Control, Lane 3-20=Fungi isolates. Source: Author's Laboratory Analysis.


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## Discussion

There was emerging evidence report of fungal co-infection among the SARS-CoV-2 individuals from this study in agreement with14 and all these incidents serve to emphasize the need for caution regarding the possibility of an opportunistic fungal disease among SARS-CoV-2. All of the classical risk factors for developing fungal infection like candidemia in a critically ill patients are manifested in COVID-19 positive patients like use of mechanical ventilation, parenteral nutrition, broad spectrum anti-bacterial treatment, indwelling central nervous or bladder catheter intervention, older age, comorbidities, lymphopenia corticosteroids etc. that make a possible occurrences of co-fungal infections among COVID-19 positive individuals 15reported fungal co- infection in 29.5% cases with SARS-CoV-2 which is not in concordance with 15.8% of fungal infection recorded in this study. 16,17reported 33.3% of fungal culture among COVID-19 cases in 2 hospitals in Wuhan, China.

Some researchers; [18,19] reported a prevalence index of 20-35% in COVID-19 positive patients, chronic pulmonary aspergillosis is prevalent. in some European countries like France, Germany, Belgium and The Netherland. An observational research from Pakistan also revealed the isolation of 39.1% *Aspergillus* species from COVID-19 positive patients [20]. Some studies from China [21,22] documented significant aspergillosis rates among COVID-19 patients. Due to compromised immune system processes, people with COVID-19 can also get a yeast infection. According to data from a hospital in Spain, invasive candidias are becoming more common in COVID-19 positive patients, and they are 40% more likely to die from them [22]. Similar reports of invasive Candida albicans infection was made in COVID-19 patients needing critical care in UK hospitals23. Invasive aspergillosis caused by *A. funmigatus, A. niger, A. flavus, A. terreus* carries an overall 30-95% mortality rate even if it is early diagnosed and despite antifungal treatment approaches and all this statement are a great concern because of evidence based result recorded from this research work.

## Conclusion

In the ongoing COVID-19 pandemic, the prevalent frequency of coinfection of fungal with SAR-CoV-2 infected individual as well as increasing reports of resistance to some antimicrobial agents is imperative. This work investigated and detected the phenotypes and genotypes of azole and polyenes resistance genes among the pathogenic organisms isolated from nasopharyngeal samples of SARS-CoV-2 infected individual in Oyo-State, Nigeria.

In summary, report from this research study confirms the presence of fungal co-infecting agents among individual with COVID-19 infection in our setting. Meanwhile, the occurrence of these coinfections was high when compared to reports from other researchers in other countries setting.

Also, the predominance and emergence of Candidiasis and Aspergillosis infection having azole and polyene resistant genes are of great alertment and concern.

Additionally, this study demonstrated Lodderomyceses elongisporus as the most frequently identified species from symptomatic COVID-19 patients. Since


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Candida infections are virtually entirely endogenous, identifying the species and corresponding antifungal sensitivity patterns can aid with the best possible therapy of these infections.

As demonstrated in this study, resistance to azole drugs such as fluconazole and ketoconazole, which are the most frequently.

In order to treat invasive candidiasis more effectively, routine fungal culture and in-vitro drug susceptibility testing of fungus may be required in various medical facilities.

This might be indicated by the antifungal that is currently being used in the nation. and invasive *aspergilliosis* among SARS-CoV-2 infected individuals.

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