

Effect of the COVID-19 Pandemic on the Training of Surgical Resident Doctors at the University College Hospital, Ibadan, Nigeria

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Summary

Background: Studies in many countries have reported that the coronavirus disease 2019 (COVID-19) pandemic disrupted surgical residency training. While a few qualitative studies have been conducted to investigate the effect of this disruption in Nigeria, a country with a small surgical workforce, no known quantitative research has assessed the effect of the pandemic on surgical residency training in the country. We, therefore, conducted this study to evaluate the effects of COVID-19 on the training of resident doctors in surgical specialties at the University College Hospital (UCH), Ibadan, Nigeria, using quantitative indicators. **Methods:** Questionnaires were distributed to surgical resident doctors across different subspecialties at UCH, Ibadan. Data were analyzed with descriptive statistics, chi-squared test, Wilcoxon signed-rank test, and logistic regression. **Results:** A total of 87 surgical trainees (response rate, 89.7%) participated in the survey. Some surgical trainees reported an increase in overall working hours (28.6%) and the frequency of weekend calls (9.5%). Only 22.4% continued to work in their primary subspecialty. In comparison with the pre-pandemic period, there was a significant reduction (% deviation in mean±standard deviation; *p* value) in the time, hours per week, spent in the outpatient clinic (-38 ± 31 ; $p < 0.001$),

on ward rounds (-25 ± 96 ; $p < 0.001$), and in the theater (-35 ± 87 ; $p < 0.001$), and major surgeries performed (-48 ± 55 ; $p < 0.001$) at the height of the pandemic. Senior surgical trainees were half as likely as junior trainees to feel that the pandemic would cause an extension in the normal duration of their training (adjusted odds ratio, 0.64; confidence interval, 0.20–2.01; $p = 0.444$). **Conclusion:** The pandemic caused a reduction in work hours spent performing subspecialty duties and the procedures performed by surgical trainees at UCH, Ibadan. Hospitals should develop strategies to minimize disruptions to surgical residency training programs during pandemics and other healthcare crises.

Keywords: COVID-19, Internship and residency, Pandemics, Surgeons, Personal protective equipment

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Introduction

The novel coronavirus disease 2019 (COVID-19), first discovered in December 2019, in Wuhan, China, was declared a public emergency of international concern by the World Health Organization on January 30, 2020 (1). It is an infection caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which spreads from person to person through droplets or direct contact (2). People with SARS-CoV-2 infection can have severe respiratory symptoms, show non-respiratory symptoms, be carriers, or be asymptomatic (2).

The Federal Ministry of Health in Nigeria confirmed the first COVID-19 case in the country in Lagos State on February 27, 2020. Following international guidelines, the government issued a complete lockdown order on March 30, 2020 (3). The complete lockdown was eased on April 27, 2020, to allow for the minimal essentials, but containment measures, including curfews, restricted work hours, and bans on public gatherings, persisted until September 3, 2020 (4). The third phase, which began on September 4, 2020, was declared after the second phase of the eased lockdown was reviewed (5). The COVID-19 pandemic has had a detrimental influence on individuals, organizations, educational institutions, economies, governments, and the healthcare industry globally. Nigeria experienced this impact, like other nations, in several different areas including the health sector in which surgical training of residents is a component of (5).

Resident doctors and other medical professionals have been under a great deal of stress in the healthcare sector; this was worsened by the pandemic (6). According to studies, treating patients with severe respiratory diseases during pandemics led to greater levels of stress, burnout, and post-traumatic stress disorder in physicians (4). Numerous studies have found that the pandemic also had significant negative impacts on patients and patient care. A negative impact on patient care was caused by the suspension or delay of elective surgeries and outpatient clinics, both of which are typically run with great involvement of resident doctors (3, 7). Patients also frequently shied away from going to hospitals to prevent contracting COVID-19 (4).

According to a study conducted in Nigeria, 83.8% of respondents reported that the number of outpatients seen by surgical residents decreased, and 90.8% stated that their units performed fewer elective surgeries in the COVID-19 era (3). Another study among surgical residents in a tertiary care facility in Karachi, Pakistan, found a 39% decrease in emergency surgeries and a 56% decrease in elective surgeries since the pandemic (8). Similarly, a study conducted in the United Kingdom among cardiothoracic surgery trainees found a 44% decline in the number of patients seen in the outpatient clinic and a 78% decrease in the number of surgeries performed (9).

Due to the COVID-19 pandemic, many modifications to surgical resident training were necessary. In addition to surgical residency programs, the COVID-19 pandemic has had a substantial impact on healthcare systems worldwide. Research to determine how the pandemic impacted healthcare in general, surgical residency programs, as well as surgical residents' educational, clinical, and personal lives is imperative. The purpose of this study is to examine how the COVID-19 pandemic had affected surgical residency training at the University College Hospital (UCH), Ibadan, Nigeria, in terms of trainees' personal health, clinical practice, training, and career progression (education and research). Notably, all previous studies conducted in Nigeria on the topic adopted a qualitative approach. As far as we know, this study will be the first to quantitatively evaluate how surgical residency training was affected by the COVID-19 pandemic using indicators such as hours spent in clinics, hours spent on ward rounds, hours spent in the operating theaters, the number of patients seen in clinics, and the number of surgical procedures done.

Materials and Methods

Study design

This was a cross-sectional study conducted after the height of the COVID-19 pandemic and lockdown phase in Nigeria. The 20-item questionnaire was adapted from the validated questionnaire used in the national survey on the impact of COVID-19 on the training and well-being of cardiothoracic surgery trainees in the United

Kingdom (9) and modified to fit our local setting—an online pilot study was conducted among six surgical trainees at UCH, Ibadan, Nigeria.

Setting and participants

This study was conducted at UCH, Ibadan, the largest teaching hospital in Nigeria.

The questionnaire was printed and physically served (as advised by our colleagues who work at UCH and respondents from the pilot test, citing the poor response rate when questionnaires are distributed online to the study population) during clinics and departmental meetings to all the trainees in the following departments of the UCH: Anaesthesiology, Cardiothoracic Surgery, General Surgery, Neurosurgery, Obstetrics and Gynaecology, Ophthalmology, Orthopaedic Surgery, Otorhinolaryngology, Paediatric Surgery, Plastic Surgery, and Urological Surgery. Reminders were sent at random intervals. We collaborated with the chief resident doctor in each department to ease questionnaire distribution, for sending reminders, and for questionnaire retrieval. Data collection lasted 6 months, from June 28, 2022, to December 23, 2022. COVID-19 safety measures (use of face mask and physical distancing) were adhered to at all times during the data collection phase.

All surgical trainees in the UCH departments listed were invited to participate and only those whose departments met the inclusion criteria (mentioned below) were included in the final analysis. There were no other selection or exclusion criteria for respondents. Departments with less than six trainees or with less than six respondents indicating the departments as their primary specialties were excluded from the final analysis. Thus, only the following departments were included in the final analysis: Anaesthesiology, General Surgery, Neurosurgery, Obstetrics and Gynaecology, Ophthalmology, Orthopaedic Surgery, and Plastic Surgery.

Variables

Categorical variables to assess the training background of participants were collected. These include gender, primary specialty, specialty of work during the height of

the pandemic, and year of training. The effect of the COVID-19 pandemic on the trainees' health, safety, clinical practice, training, and progression was evaluated by asking them about their personal COVID-19 diagnosis, immediate access to COVID-19 testing when indicated, availability of face masks, and number of hours per week spent doing subspecialty duties both before and during the pandemic, among others.

Data sources and bias

This study made use of self-reported data by the surgical resident doctors at UCH, Ibadan. To supply these data, participants, for the most part, had to recall details of their day-to-day work both before and during the COVID-19 pandemic. As such, it is prone to recall bias.

Study size

This is a total population survey with a study population of <10,000. The Cochran formula for estimating sample size for cross-sectional studies is useful when the total population is large. In our case, the total population is small (n=130), as such, a modification of the Cochran formula useful in smaller populations was used (10). This gave us an estimated sample size of 97.

Ethics

Ethical approval for this study was obtained from the University of Ibadan/University College Hospital (UI/UCH) Ethics Committee with the assigned number UI/EC/20/0364.

Statistical analysis

Statistical analysis was done using International Business Machines Statistical Product and Service Solutions (IBM SPSS) version 25 (IBM, Chicago, IL, USA).

Partially completed forms were accepted and included in the final analysis. For missing data, where its value can be reasonably assumed by looking at answers provided for related questions, this was done. Otherwise, missing data were excluded from variable analysis and valid percentages were computed using only the responses provided. Therefore, the total number of

responses got for each item analyzed is stated at every instant in the Results section.

“Early-stage” trainees or registrars were defined as resident doctors in their first 3 years of training, while “late-stage” trainees or senior registrars were defined as those in their fourth or later years of training.

Results for continuous variables are expressed as means and standard deviations (SD) and those for categorical variables as counts and percentages. An intergroup comparison for continuous variables was performed using Student’s *t*-test (independent-samples *t*-test). The association between categorical variables was examined using the chi-square test of independence. The Wilcoxon signed-rank test was used to check for differences in clinical activities before the COVID-19 pandemic and at the height of the pandemic. Logistic regression was used to understand whether certain variables (such as being redeployed to another specialty during the height of the pandemic) could be predicted by the stage of training.

Results

Figure 1 shows the numbers and percentages of surgical trainees (n=87; response rate, 89.7%) in each primary specialty who participated in the survey. Resident doctors in Anaesthesiology constituted 16.1% of the respondents, the second largest group after those in General Surgery, who accounted for 26.4%. The number of respondents from Neurosurgery (n=7) and Ophthalmology (n=8) was the smallest.

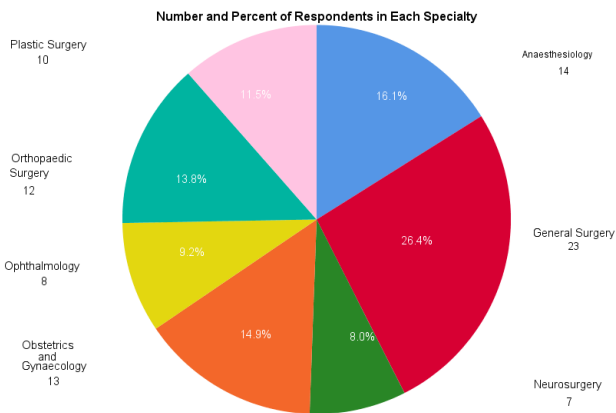


Figure 1. Number and percentage of respondents in each specialty.

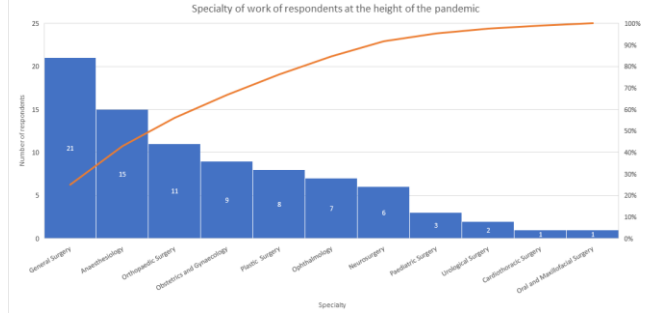


Figure 2. Specialty of work of respondents at the height of the pandemic.

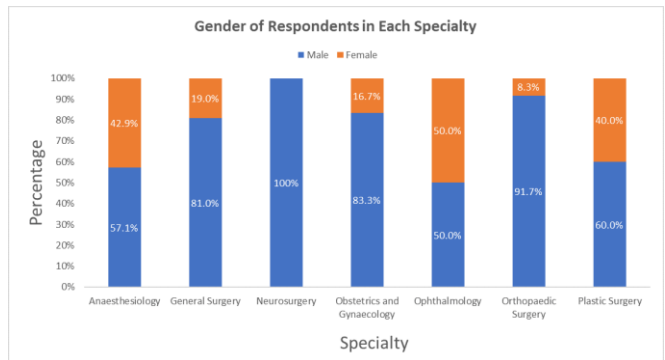


Figure 3. Gender of the respondents in each specialty.

Figure 2 shows the distribution of respondents based on the specialty of work at the height of the pandemic. Figure 3 shows the percentages of males and females in each specialty who completed the survey. Overall, 24.4% (n=20/82) of all respondents were females, ranging from a low 0% in Neurosurgery to a high 50% in Ophthalmology. Most of the respondents (68.6%, n=59/86) were in their later stage of training (senior registrars).

Health and personal protection

Almost all resident doctors reported being somewhat concerned about their physical health (96.8%, n=61/63). In total, 49.2% (n=31/63) responded that they would not have immediate access to COVID-19 testing for themselves or members of their household when it was indicated.

Some 65.6% (n=40/61) of all the respondents were excused from work due to COVID-19-related issues, with a median time off work of 14 days (range, 2–28 days). Some 9.5% (n=6/63) self-isolated due to having a suspected or confirmed case at home, 4.8% (n=3/63)

were excused from duty due to stress or anxiety, another 4.8% (n=3/63) were excused from work because of a positive result for COVID-19 even though they were asymptomatic, 3.2% (n=2/63) were excused from duty because they were vulnerable or at high risk, and 55.5% (n=35/63) reported having COVID-19 symptoms. Of those who were symptomatic, 15.8% (n=10/63) were never tested, 15.9% (n=10/63) tested negative, and 23.8% (n=15/63) tested positive.

More than 3 in 10 (31.3%, n=20/64) of these doctors felt that they were not adequately trained on how to protect

themselves when caring for patients with COVID-19, and 58.7% (n=37/63) reported not getting suitable face masks. Many of the trainees (76.3%, n=45/59) were concerned about the availability of suitable personal protective equipment (PPE) in the hospital. Notwithstanding, these resident doctors had contact with COVID-19-suspected or -positive patients during ward rounds or at the clinic (73.4%, n=47/64), or in the operating theater (17.2%, n=11/64), but only 4.8% (3/62) wore adequate PPE at those times.

Table 1. Impact of early (registrars) versus late (senior registrars) stage of training on the likelihood of being redeployed to another specialty, reporting valuable learning in current role during COVID-19 era, and the possibility of requiring an extension to planned training time, all specialties combined

	Early stage	Late stage	Adjusted odds ratio (95% CI)	p value
Redeployed ^a	7 (28.0%)	17 (28.8%)	1.04 (0.37–2.94)	0.940
Concerned about impact on training and progression ^b	23 (92.0%)	50 (84.7%)	0.48 (0.10–2.42)	0.376
Valuable learning in current role ^c	18 (72.0%)	49 (84.5%)	2.12 (0.69–6.53)	0.192
May require extended training time ^d	18 (75.0%)	47 (82.5%)	0.64 (0.20–2.01)	0.444

CI, confidence interval; COVID-19, coronavirus disease 2019; n, total number of people who responded to the question.

^an=25 for early stage and n=59 for late stage.

^bn=25 for early stage and n=59 for late stage.

^cn=25 for early stage and n=58 for late stage.

^dn=24 for early stage and n=57 for late stage.

Clinical practice

Some of the respondents (36.2%, n=21/58) reported a change in their working hours, with an increase in antisocial (such as evening or night shift) hours (52.4%, n=11/21) being the most commonly reported, followed by an increase in overall working hours (28.6%, n=6/21), and lastly by a switch to a full on-site working pattern (9.5%, n=2/21) and an increased frequency of weekend call (9.5%, n=2/21).

Only 22.4% (n=19/85) continued to work exclusively in their primary subspecialty, while 24.8% (n=21/85) spent less than half of their time on duty treating patients in their primary subspecialty. Logistic regression analysis was done to find out if the likelihood of respondents

being redeployed to another specialty, their report of valuable learning in current role during the COVID-19 era, and their perception of the pandemic causing an extension in their training time could be predicted using their stage of training. The adjusted odds ratios (AORs) of our findings are presented in Table 1. For senior surgical trainees, the odds (AOR, confidence interval [CI]) of being redeployed was the same (AOR, 1.04; CI, 0.37–2.94), of being concerned about the impact of the pandemic on their training was half (AOR, 0.48; CI, 0.10–2.42), of reporting valuable learning in current role was twice (AOR, 2.12; CI, 0.69–6.53), and of feeling the disruption would cause an extension to their normal training duration was half (AOR, 0.64; CI, 0.20–2.01),

in comparison to junior surgical trainees. However, these odds ratios were not statistically significant.

Among those who were redeployed, 25.0% (n=6/24) covered more units than they should in their primary subspecialty, 37.5% (n=9/24) covered other surgical subspecialties, 4.2% (n=1/24) worked in the intensive care unit, 25.0% (n=6/24) covered COVID-19 medical

wards, and 8.3% (n=2/24) were redeployed to cover acute medical or emergency admissions. Only 9.6% (n=8/83) of the trainees reported not feeling confident in performing their roles.

Table 2 summarizes the percentage change in weekly activity across a variety of clinical activities done by the resident doctors.

Table 2. Percentage change in weekly activity between the pre-COVID-19 and COVID-19 period for all specialties combined

Activity	Percent deviation, mean±SD
Hours in the outpatient clinic (n=67)	-38±31
Hours on ward round (n=69)	-25±96
Hours in the operating theater (n=72)	-35±87
Hours at grand round (n=62)	-23±53
Hours doing research or audit (n=48)	+56±193
Hours on structured learning (n=63)	+34±80
Free or flexible hours at work per week (n=48)	+93±117
Follow-up patients seen in clinic (n=56)	-40±47
New patients seen in clinic (n=56)	-40±70
Cases assisted in the theater (n=53)	-50±37
Minor cases performed in the theater (n=52)	-37±90
Major cases performed in the theater (n=45)	-48±55

A negative (-) deviation implies less time spent on that activity during the COVID-19 pandemic. COVID-19, coronavirus disease 2019; SD, standard deviation.

There were significant deviations in the number of hours per week spent in the outpatient clinic ($p = 0.000$), on ward rounds ($p = 0.000$), in the operating theater ($p = 0.000$), at grand rounds ($p = 0.001$), in structured learning sessions ($p = 0.001$), and free/flexible time at work ($p = 0.000$) for all specialties combined. There was no significant difference in the time spent on research and audit ($p = 0.587$).

Training and progression

Most of the respondents reported being somewhat (34.1%, n=29/85) or very concerned (52.9%, n=45/85) about the effect of the pandemic on their career progression. There was no significant association between declared concern and the stage of training (Table 1).

Almost 2 in 10 of the trainees (19.0%, n=16/84) reported that their current responsibility offered little to no

chance to learn and that this deterred their professional development, but most (81.0%, n=68/84) had a comparable or above-average learning experience.

There was a significant decline in weekly clinical exposure in the outpatient clinic, for both new ($p = 0.000$) and follow-up patients ($p = 0.000$), as well as a significant decrease in the number of surgical procedures they were involved in, both as an assistant ($p = 0.000$) and a primary surgeon ($p = 0.000$) (Table 2). It is to be noted that even though there was a reduction in the number of surgeries they did, there was no disproportionate decline in entrustment as trainees reported performing 86±85% of all cases (major and minor) before the pandemic which is comparable to the 86±129% of total cases they performed during the pandemic. Although respondents spent more time weekly conducting research or audit during the height of the pandemic compared with the pre-pandemic period

(mean±SD, 56±193%), this was not statistically significant ($p = 0.587$). Nevertheless, there was a significant increase (mean±SD, 34±80%) in the average time spent on structured, self-directed learning weekly during the pandemic compared to before its onset ($p = 0.001$).

Many of the resident doctors (39.0%, $n=32/82$) felt that the disruption to their training occasioned by the COVID-19 pandemic would cause an extension of the normal duration of their residency training, while 26.8% ($n=22/82$) and 14.6% ($n=12/82$) felt this would only be the case if the disruption lasted for more than 6 and 12 months, respectively. This was not significantly different between registrars and senior registrars ($p = 0.444$).

Discussion

The COVID-19 pandemic has had significant effects on the healthcare systems globally, including on the surgical residency training programs. This study aims to investigate the effect of the COVID-19 pandemic on the training of surgical resident doctors at UCH, Ibadan, Nigeria.

Effect on health and personal protection

The vast majority (96.8%, $n=61/63$) of resident doctors reported varying degrees of concern about their physical health during the COVID-19 pandemic, and about half of them expressed concerns about the unavailability of COVID-19 testing for themselves and their household when it was indicated. This finding is consistent with previous studies (9, 11) that reported high anxiety and fear levels among surgical trainees and other healthcare workers during the pandemic.

While the risk of infection is inherent in clinical practice, healthcare workers should be empowered by the provision of adequate PPE. It is therefore disappointing that despite a majority of them having missed work due to COVID-19-related issues and voicing concerns about the availability of and training on the appropriate use of PPE in the hospital, only a small percentage of surgical residents (4.8%, $n=3/62$) reported wearing adequate PPE. This is despite the fact that 9 out of 10 of them had contact with COVID-19-suspected or -positive patients

during ward rounds, clinic visits, or surgical procedures. This is a significant concern as inadequate PPE use can increase the risk of exposure and transmission of the virus, leading to severe consequences for both the resident doctors and the patients.

Similar results were reported in a study amongst cardiothoracic surgery trainees in the United Kingdom by Caruana et al. (9) who discovered that despite efforts to provide PPE, many resident doctors expressed concerns about inadequate PPE, with 86% of them having been exposed to suspected or confirmed cases of COVID-19. It is interesting to note that these concerns exist despite a higher percentage of them (55%, $n=36/65$) wearing appropriate PPE at the time of exposure. Another study by Rosenbaum (12) in Italy showed similar poor rates of PPE coverage and highlighted the generalizability of the trend globally, a truly concerning reality.

These highlight the need for healthcare institutions to ensure that resident doctors have access to appropriate PPE and adequate training on infection prevention and control measures to minimize the risk of infection.

Effect on clinical practice

The COVID-19 pandemic has also significantly impacted clinical practice, resulting in reported changes in working hours, including an increase in overall working hours and antisocial hours. Furthermore, many trainees were redeployed to cover other surgical subspecialties, COVID-19 medical wards, or acute medical or emergency admissions, reducing their exposure to their primary subspecialty, which could negatively impact their training and progression. These findings are consistent with a cross-sectional study on surgical residents of a tertiary care hospital in Pakistan by Osama et al. (8), which also reported comparable adjustments to work schedules and the redeployment of surgery residents during the pandemic.

Another consequence of the pandemic is the significant reduction in the number of hours spent on clinical activities such as outpatient clinics and the operating room, which can have adverse effects on the training and progression of residents. This reduction in clinical exposure was also observed by Al-Jabir et al. (13) in a

study assessing the influence of the pandemic on surgical prioritization across multiple healthcare institutions in the United States and United Kingdom. This study found that the pandemic had affected surgical training significantly, with a reduction in the number of cases performed by resident doctors, delays in carrying out surgical procedures, and an increased consideration of non-surgical management options where possible.

Single-center studies conducted in North-Central Nigeria among surgical resident doctors across multiple specialties (14) and in Southern Nigeria among plastic surgery trainees (15) support our findings of a reduction in the number of cases seen in the outpatient clinics and the operating theater. This is also in keeping with the findings from a multicenter study conducted among surgical resident doctors in Nigeria (4). While these studies only qualitatively reported a decline in clinical activities during the pandemic compared to the pre-pandemic period, our study objectively assessed and quantified how much these clinical activities were reduced.

Effect on training and career progression

Most of the resident doctors raised concerns about the impact of the pandemic on their education and career progression. Some reported a lack of relevant learning opportunities in their current roles, and others opined that it would cause an extension to the duration of their training, which could impede their professional development. These findings are consistent with those of previous studies (8, 9, 13, 16) reporting a perceived negative impact on the quality of surgical training during pandemics. This is a significant concern as surgical residency programs require extensive training and exposure to a wide range of clinical activities to ensure that the resident doctors acquire the necessary skills and knowledge to become competent surgeons.

The findings highlight the need for healthcare institutions to develop strategies that will ensure continuity of care and minimize disruptions to surgical residency training programs during pandemics and other healthcare crises (17). Previous studies have recommended strategies such as telemedicine and simulation training to provide surgical resident doctors

with relevant learning opportunities despite the pandemic restrictions (13, 18, 19). This approach, while still largely uncommon in Nigeria (14), could help address the concerns of the resident doctors and ensure that they receive the necessary training and experience to progress in their careers.

Limitations

There are some limitations to this study that must be considered when interpreting the results. First, the study relied on self-reported data, which may be subject to recall bias. Second, the sample size was relatively small and may not be representative of all surgical resident doctors. Third, the study was conducted at a single institution, and therefore, the results may not be generalizable to other surgical residency programs. However, it is noteworthy that our findings are consistent with those of similar studies conducted in other institutions and countries, such as Al-Jabir et al. in the United Kingdom and United States, Caruana et al. in the United Kingdom, Osama et al. in Pakistan, and Rosenbaum in Italy. These studies suggest that the impact of the pandemic on surgical residency programs is a global concern. Therefore, our study contributes to the growing body of literature on this topic, offers the perspective of the surgical residency program of the largest teaching hospital in Nigeria, and highlights the need for further research to identify effective strategies to mitigate the negative effects of pandemics on surgical education and training.

Conclusion

The COVID-19 pandemic has significantly impacted the trainees of surgical residency programs. Our findings should be interpreted with the study limitations in mind. This study sheds light on the challenges faced by resident doctors in Ibadan, Nigeria, during the pandemic, including concerns about their health, inadequate protective measures, and concerns about the quality of their training and careers. However, despite these difficulties, the majority of them reported a comparable or even better experience compared to the pre-pandemic period, reflecting the resilience of surgical residency programs and the commitment of the resident

doctors to their profession. The findings of this study have significant implications for surgical residency programs, highlighting the need to develop strategies to mitigate the impact of future pandemics and other healthcare crises on surgical education and residency training.

What is already known on this topic?

- There are some data on the extent to which regular hospital services and residency training were affected due to COVID-19 in some countries such as the United Kingdom, Italy, and Pakistan.
- Regular healthcare services provided in hospitals such as elective surgeries and clinic follow-ups were seriously disrupted by the COVID-19 pandemic.

What this study adds

- This study tells us quantitatively how surgical residency training at UCH, Ibadan, Nigeria, was affected by the COVID-19 pandemic using indicators such as hours spent in clinics, hours spent on ward rounds, hours spent in the operating theaters, the number of patients seen in clinics, and the number of surgical procedures done.
- It provides information on COVID-19 exposure, illness, and access to PPE by surgical resident doctors at UCH, Ibadan, Nigeria, during the pandemic.
- It reveals that the learning experience of surgical resident doctors during the pandemic was the same despite the stage of training.

Authors' Contributions

BIA: Study conception, study design, administration of questionnaires, data analysis, preparation of the manuscript, and manuscript revision. AVA: Study design and preparation of the manuscript. OSA: Study design, administration of questionnaires, and manuscript preparation. ATA: Study design, administration of questionnaires, and manuscript revision. GZI: Study design, administration of questionnaires, and formatting

of the manuscript according to the journal requirements. TO: Study design and data entry. ISE: Study design and manuscript revision. AOA: Study design and manuscript revision. All authors read and approved the final version of the manuscript.

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