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# The Challenge of COVID-19: The Biological Characteristics and Outcomes in a Series of 130 Breast Cancer Patients Operated on During the Pandemic

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## Rezumat

***Provocarea COVID-19: caracteristicile și rezultatele biologice a 130 de paciente cu cancer mamar operate în timpul pandemiei***

*Context:* Noul coronavirus (COVID-19) care a izbucnit la nivel mondial a apărut prima oară în Wuhan, China, aproape de sfârşitul anului 2019. Analizăm caracteristicile clinice şi rezultatele managementului unui grup mic de paciente care au fost tratate în perioada în care COVID-19 era în stadiu incipient, şi discutăm despre impactul pandemiei asupra serviciului furnizat pacienților cu cancer mamar.
*Material şi metode:* Am analizat o cohortă de 130 de paciente cu cancer mamar, care au fost supuse procedurilor chirurgicale elective la începutul pandemiei COVID-19. Pacientele au fost operate în perioada 16 martie 2020 - 18 mai 2020.
*Rezultate:* Pacientele s-au situat în intervalul de vârstă 33-88 de ani, cu o vârstă medie de 57,6 ani. Majoritatea cazurilor au avut internare de zi pentru intervenția chirurgicală, după un screening preoperator care a avut loc treptat. Pacientele au fost contactate telefonic după intervenția chirurgicală pentru a ne asigura că nu au avut simptome şi au fost consultate după două săptămâni de la intervenție, când rezultatul histopatologic a fost

disponibil. Doar o pacientă a dezvoltat simptome COVID-19 după intervenție şi s-a însănătoşit. *Concluzii:* Implementarea timpurie şi atentă a politicilor de practică adaptate situațiilor de pandemii virale va reduce riscul apariției complicațiilor perioperatorii, a transmiterii bolii de la pacient la personal şi invers, şi va minimiza impactul negativ al COVID-19 asupra gestionării cancerului mamar.

Cuvinte cheie: COVID-19, SARS-CoV, MERS-CoV, SARS-CoV2, ECA2, cancer mamar

**Abstract**

*Background:* The worldwide outbreak of the 2019 novel coronavirus disease (COVID-19) emerged in Wuhan, China close to the end of 2019. We analyse the clinical characteristics and management outcomes of a small group of patients who have been treated in the early stage of the COVID-19 disease, and discuss the impact of the pandemic on the service delivered to breast cancer patients.
*Material & methods:* We analysed a cohort of 130 breast cancer patients who underwent elective surgical procedures during the early period of COVID-19. The patients were operated on in the period from March 16th, 2020 to May 18th, 2020.
*Results:* All the patients were female, with an age range of 33-88 years, with a median age of 57.6 years. Most of the cases were admitted as a day case surgery after passing through a preoperative screening pathway, which was developed gradually. Patients were contacted by phone after their surgery to ensure that they have had no symptoms and were reviewed in person two weeks after the procedure with histology results. Only one patient developed COVID-19 symptoms after surgery and recovered.
*Conclusions:* Early and careful implementation of modified practice policies during emerging situation of viral pandemics will reduce the risk of perioperative complications, reduce the risk of patient to staff to patient transmission and minimize the negative impact of COVID-19 on breast cancer management.

Key words: COVID-19, SARS-CoV, MERS-CoV, SARS-CoV2, ACE2, breast cancer

## Introduction

The outbreak of the 2019 novel coronavirus disease (COVID-19) emerged in Wuhan, China close to the end of 2019, caused by the SARS-CoV2 virus (Severe Acute Respiratory Syndrome type 2). With a high rate of virus transmissibility, it was quickly confirmed that the disease had spread worldwide. Usually it presents with dry cough, fever, dyspnoea, fatigue, and imaging signs of pneumonia (1,2). The infection may results in hypoxic respiratory failure which is associated with increased case fatality rate in the at risk groups such as the older age group, as well as hypertensive and diabetic patients. The increased demand for hospital admissions put tremendous pressures on health care service resources including time, space and manpower; even anaesthetists had to be released from the operating theatres to support COVID care units. The other priority was to protect patients and healthcare professionals from the infection though certain measures such as social distancing, self-isolation, wider use of PPE (Personal Protection Equipment), as well as restriction of using high risk healthcare interferences such as reconstructive surgery and low benefit chemotherapy (3). As breast cancer remains the most common malignancy in women worldwide, and surgery remains the main modality in management of early breast cancer, we briefly discuss key points

related to the COVID-19 pandemic and the impact on the service delivered to breast cancer patients. We analyse the clinical and bio-molecular characteristics as well as management outcome of a small group of patients who have been treated at the early stage of the COVID-19 pandemic.

## Material and Methods

The clinical data of 130 early breast cancer patients who underwent elective surgical procedures during the early period of COVID-19 was analysed retrospectively, from the period of March 16th to May 18th, 2020. The data included clinical records, nursing input, laboratory results, and chest (CT) scans where available for all 130 patients. The surgical priority category for all the cases belonged to priority level 2 of the NHS Clinical guide to surgical prioritisation during the coronavirus pandemic (*Tables 1, 2*). This group has to offered elective planned surgery within 4 weeks' time with expectation of being curative (3,4,5).

## Results

The age range of the cohort was between 33 and 88 years, with a median age of 57.6 years. All of the patients were female. The patients are under the care of the Breast units at Basildon University Hospital, Southend University Hospital and Mid Essex Hospital (Chelmsford), all these three trusts are part of the new Mid and South Essex NHS Foundation Trust .However with National Health Service taking over Independent Sector facilities to cope with increased demand, a cancer hub was opened at The

**Table 1.** Prioritization category for surgical procedures (3, 4, 5)

| P (Priority) Category | Time frame | Type of surgery | Aim of surgery | Examples |
|---|---|---|---|---|
| P1a | 0-24 hours | Emergency | Life saving | Post operative bleeding or infection |
| P1B | Within 72 hours | Urgent | | |
| P2 | 4 weeks | Elective | Curative | Post UFCTH.<br>TNBC<br>ER-VE/Her2+ve.<br>Pre-menopausal ER+ve with adverse biology |
| P3 | 5-12 weeks | Elective | Curative | Premenopausal ER+ without adverse biology<br>DCIS |
| P4 | > 12 weeks | Elective | Curative, not linked directly to the primary cancer | Breast reconstruction<br>Risk reducing surgery<br>Benign breast lumps |

UFCTH: Upfront chemotherapy; TNBC: Triple negative breast cancer; DCIS: Ductal carcinoma in-situ

**Table 2.** Detailed surgical Priority 2 and Priority 3 Categories for breast cancer patients

| P2 in order of priority | P3 in order of priority |
|---|---|
| Surgery for local control | T1N0 ER +/Her2 -ve breast cancer** |
| Triple negative breast cancer * | Screen detected ER +ve HG DCIS** |
| Her2 positive breast cancer* | Re- excision of cavity margins |
| N1 ER +ve breast cancer | Completion axillary clearance |
| T2 /T3 ER +ve breast cancer** | Intermediate grade DCIS |
| High risk DCIS : ER -ve /extensive /palpable/ <50yrs | Low grade DCIS |
| Diagnostic surgery for discordant assessment | Surgery for atypia/Benign conditions |

*Upfront chemotherapy should be discussed, and risks/ co-morbidities taken into account

** Neoadjuvant hormonal manipulation therapy can be considered

Adapted from a virtual lecture by Miss Fiona MacNeill, Consultant Breast Surgeon @ Royal Marsden Hospital, London-UK, March 2020 (3)

Nuffield Hospital (Brentwood) and Springfield Hospital (Chelmsford). The screening initially was through the clinical preoperative assessment unit to ensure that the patients did not have any history of recent travel from COVID pandemic countries and or did not have any COVID symptoms. In addition, there was a clinical questionnaire on the day of admission and monitoring of patients' temperature. As time progressed, the screening pathway was continuously developed such that the patients were tested for COVID-19 infection 72 hours prior to surgery. The various surgical procedures performed are shown below (*Table 3*). Breast conservation surgery was performed in 51.5% (67) of the cohort, compared to mastectomy in 41% (53). Regarding the axillary surgery, 62% (80) had sentinel lymph node biopsy and 31% (40) underwent axillary node clearance. The tumour subtypes in the invasive disease were grade 3 in 44% (57), grade 2 in 41.8% (54) and grade 1 in 11.6% (15). The biology characteristics revealed, (ER/PR +ve, Her2 –ve) in 56.6% (73), (ER/PR+ve, Her2-ve) in 28%(36), triple negative in 19% (24) and Her-2 enriched tumour seen only in 7.7% (10). Postoperatively, the patients were reviewed 2-3 weeks after surgery, only one patients has developed signs of COVID-19 infection during the postoperative period, and has fully recovered from the infection at the time of finalising the paper.

**Table 3.** The surgical procedures performed for the cohort of 130 patients

| The surgical procedure | Number |
|---|---|
| Wide local excision +SLNB* | 53 |
| Wide local excision + ANC** | 8 |
| Mastectomy+ SLNB (4 bilateral) | 24 |
| Mastectomy+ ANC | 24 |
| Bilateral mastectomy +SLNB | 3 |
| Cavity margin re-excision | 3 |
| Wide local excision | 5 |
| Mastectomy | 2 |
| Completion axillary node clearance | 8 |

*SLNB: Sentinel lymph node biopsy; **ANC: Axillary node clearance

## Discussion

Close to the end of 2019, a new disease causing severe and fatal respiratory failure called coronavirus disease 2019 (COVID-19) appeared in Wuhan, China, caused by SARS-COV2 (severe acute respiratory syndrome type 2). It was given name coronavirus for the crown-like spikes on their enveloped surface, originating from Latin (corona = crown). SARS-CoV2 is a single stranded RNA enveloped virus and belongs to the Coronaviridae family and the order Nidovirales (6). Although much is known about the mortality of the clinical disease, much less is known about its pathobiology (7). Coronavirus infectivity depends on its four major proteins: spike protein (S), membrane protein (M), envelope protein (E) and the nucleocapsid protein (N), (*Fig. 1*). The spike protein (S) type I membrane glycoprotein mediates membrane receptor binding and facilitates virus entry into the host cells through endocytosis, with help of ACE2 receptors (8,9). SARS-CoV2 genome is a positive-sense, single-strand RNA (+ssRNA) and is known as the second largest of all RNA virus genomes (10). The SARS-CoV2 virus belongs to the same family as severe acute respiratory syndrome virus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). They were related to previous coronavirus epidemics, all are zoonotic. The severe acute respiratory syndrome virus (SARS-CoV), has caused widespread infection in China, in November 2002. (11). Its overall mortality was about 10% (10,12). In 2012, was the outbreak of he Middle-East respiratory syndrome (MERS), with an average mortality of 35.5% (10,13)(*Table 3*).

The SARS-CoV2 (COVID-19) virus' intermediate host is believed to be the Malayan pangolins (Manis javanica) which are ant-eating, long-snouted, mammals smuggled illegally to China for use in traditional medicine (16,17). The researchers urge that the Malayan pangolins sold in Wuhan' seafood market were the animal source of COVID-19 outbreak. It is thought to be transmitted through respiratory droplets and contact routes, and can be transmitted from asymptomatic individuals. Its

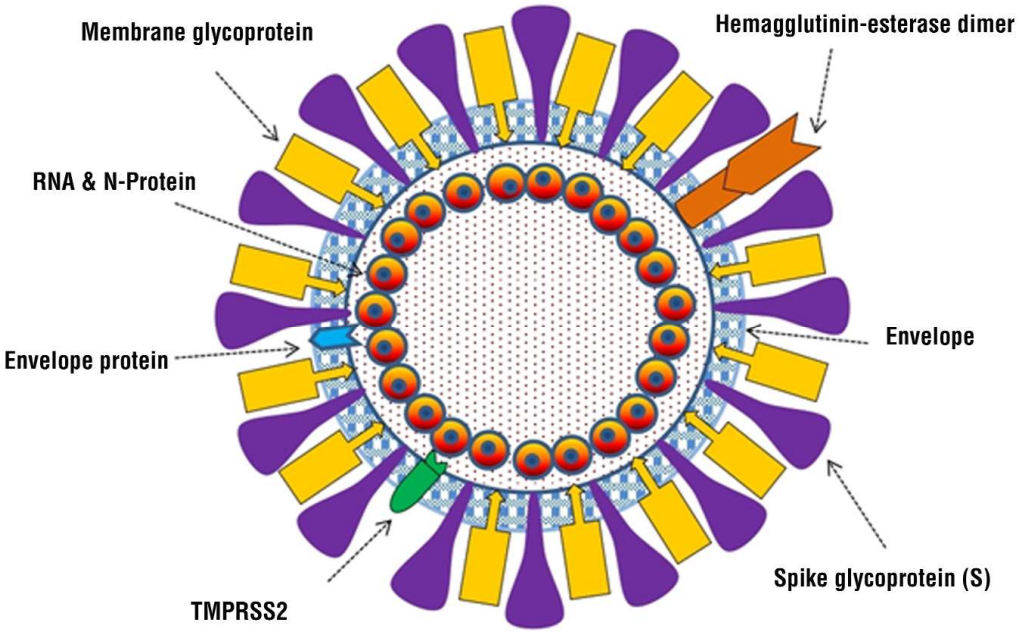



**Figure 1.** The structure of COVID-19 , the main viral surface proteins, membrane, spike, envelop, in addition to hemagglutinin-esterase dimers and Type II transmembrane serine protease (TMPRSS2) are embedded in a bilayered lipid membrane. The single-stranded positive-sense viral RNA is linked with the nucleocapsid protein (14,15)

reported incubation period is 1-15 days with estimated mean incubation periods between 5-8 days with 20 days of shedding phase (1,18-21). One of the key differences between COVID-19 and previous coronaviruses such as SARS-CoV and MERS-CoV is that various infected persons do not show obvious symptoms but are capable to spread the disease with high contagiousness and pass the virus to others during the incubation period of 14 days or longer (1,21).

When the SARS-CoV2 virus enters the airway, it binds to the angiotensin-converting enzyme 2 (ACE2) receptor, mainly in the ciliated bronchial epithelial cells and also targeting type II pneumocytes (22). Patients may deteriorate and develop severe ARDS (Acute Respiratory Distress Syndrome) and will require ICU admission for oxygen therapy and mechanical ventilation support (21). The virus may attack other organs and lead to hepatic injury, acute renal failure, coagulation abnormalities as well as cardiac injury, resulting in multiple organ failure. The organs severe damage resulting from the infection was seen in an autopsy as significant haemorrhagic necrosis of the lung (1,21).

Yan et al in recent detailed autopsy description in a Hispanic woman who died from SARS CoV-2 infection noted that the lungs were found were remarkable for extensive severe acute lung injury consistent with viral pneumonia, characterized by severe pulmonary oedema, alveolar damage, pulmonary infarction, desquamation of pneumocytes with intra-alveolar aggregation, and alterations consistent with viral cytopathic effect. However electron microscopic (EM) examination revealed the presence of intravascular ultrastructural fibrin aggregates s, suggesting an increased propensity toward clot formation. (23). Histopathological assessment of the tissue specimens carry with it the risk of infection of the pathologist and the Royal College of Pathologist have given advice on how best to handle or deal with frozen section requests, Fine needle aspiration cytology procedure, opening or dissection of unfixed or poorly fixed specimens and handling of glass slides and request forms during the pandemic (24-26).

**Table 4.** Worldwide infectious diseases outbreaks in the last 25 years (10,27,28, 29,30, 31,32)

| Disease | Year | First cluster | Pathogen | CFR: Case Fatality Rate |
|---|---|---|---|---|
| vCJD* | 1996 | UK | Prions | 1.46% |
| SARS | 2002 | Foshan, China | SARS-CoV | 11% |
| Mumps | 2009 | Nova Scotia, Canada | Mumps virus | - |
| H1N1 Flu Pandemic | 2009 | Veracruz, Mexico | Pandemic H1N1/09 Virus | 0.02% |
| MERS | 2012 | Saudi Arabia | MERS-CoV | 35.5% |
| EVD** | 2013 | Guinea | Ebola virus | 50% |
| Zika virus | 2015 | Brazil | Zika virus | 8.3% |
| COVID-19 | 2019 | Wuhan, China | SARS-CoV2 | ? |

*vCJD: Variant Creutzfeldt–Jakob disease; **EVD: Ebola virus disease

The first report revealing outbreak of COVID-19 infection in Wuhan, Hubei province-China was on 31st December 2019, the first confirmed cases of coronavirus in the UK were on January 29th 2020 (*Table 5*). It was only on 11th March 2020 WHO made the assessment that COVID-19 can be characterized as a pandemic.

The most frequent symptoms are fever (90%), dry cough (80%), fatigue 70% and dyspnoea (40%). Laboratory diagnosis is based on real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) assay (33) and the current testing sensitivity may be as low as 70% (1). It was reported that replication of SARS-CoV-2 most likely takes place in the lower part of the respiratory tract rather than the throat. This hypothesis may explain the reason for the false negative results from throat swab epithelial cell specimens sent for RT-PCR assays to detect SARS-CoV2 infection, however false positive rates also seen to be low (1,34). Blood test may reveal leucopenia and lymphpenia; high transaminases; elevated troponin, D-dimer, creatinine kinase, ferritin, LDH (Lactate dehydrogenase), CRP (C-reactive protein),. HRCT (High resolution CT scan) of the chest will show bilateral multifocal ground-glass changes in the lungs (35,36). Currently, no specific treatment is available for the SARS-CoV-2 infection, and the supportive medical interventions remain the mainstay modality to treat COVID-19 infection. Clinical data related to 44,672 infected Chinese patients infected with COVID-19 revealed that infected older age group cases are associated with a higher CFR (Case Fatality Rate), this also the

**Table 5.** The first reported COVID-19 cases by country

| Country | Date of confirmed first case |
|---|---|
| China | 17th November 2020 |
| USA | 21st January 2020 |
| UK | 29th January 2020 |
| Italy | 31st January 2020 |
| Romania | 26th February 2020 |
| Poland | 04th March 2020 |
| Libya | March 2020 |

case in patients with underlying conditions as cardiovascular disease, diabetes mellitus, chronic obstructive airway diseases, hypertension, and malignancy (29,37,38).

Lei et al in March 2020 presented a small cohort of 34 patients who were unintentionally scheduled for elective surgical procedures during the early stage of COVID-19 pandemic. Despite preoperative assessment not revealing COVID-19 infection, the post-operative infection rate was 100%. In addition, there was an ICU admission rate of 44% and mortality rate of 20.5%. Around 38% of the patients had level-3 technical difficulty in the surgical procedures; this includes various operations associated with intermediate risks, and technically moderate or difficult complex procedures (2). Reviewing Lei et al paper, performing elective complex procedures during viral pandemics may expose the patient to prolonged operation time, as well as need for postoperative ITU admission, which we believe may be the risk factors for getting COVID-19 infection and increased mortality (2,39). Zhang L et el, reported Chinese data related to a cohort group of 28 cancer patients infected with COVID-19, about 30% developed the infection while having their anti-cancer treatment in the hospital and 70% encountered the infection in the community, CFR among this group was 28.6% (35,37). This may increase up to 48.5% if $\geq$ 3 other chronic conditions such as diabetes, hypertension, and cardiovascular disease coexist (40). The apparently healthy breast cancer patients belong to the high infection risk group especially if they belong to the older age group (30% of breast cancer patients are $\geq$70 years at time of diagnosis) (3,37,41). Additionally, if they had upfront chemotherapy, their immunity will be compromised. As the pandemic was progressing, scalable recommendations had been suggested by the related professional bodies worldwide to provide a framework to aid clinicians in categorising essential breast cancer care, especially as breast cancer remains the most frequently diagnosed female cancer globally and is the lead cause of cancer mortality among females (42). Advisory groups from the Royal College of Surgeons of England, Association of UK Breast Surgeons, Association of Breast Surgeons of Ireland and the American Society of Breast Surgeons recommended guidelines for breast cancer management during the COVID-19 pandemic (7,43,44,45). The recommendations suggested the need for breast cancer surgery to be categorised and prioritised according to availability and desirability of other self-administered safe primary cancer treatments such as hormonal manipulation. As 80% of breast cancers are oestrogen receptor positive, neoadjuvant hormonal blockade therapy could be recommended for the suitable group for whom surgery could be deferred as low-grade tumours with hormone positive disease (3,7, 43-45). Also, risk reducing surgery and reconstruction is not advisable as this may prolong the procedure duration, increase chance of high dependency unit admissions and risk more complications and possible return to the theatre. One of the important recommendations is to limit the use of high risk healthcare interventions such as low benefit upfront chemotherapy as it will increase the risk of COVID-19 infection, also the use of intra-operative radiotherapy (TARGIT-IORT) may be considered where available and appropriate (3,43,44).

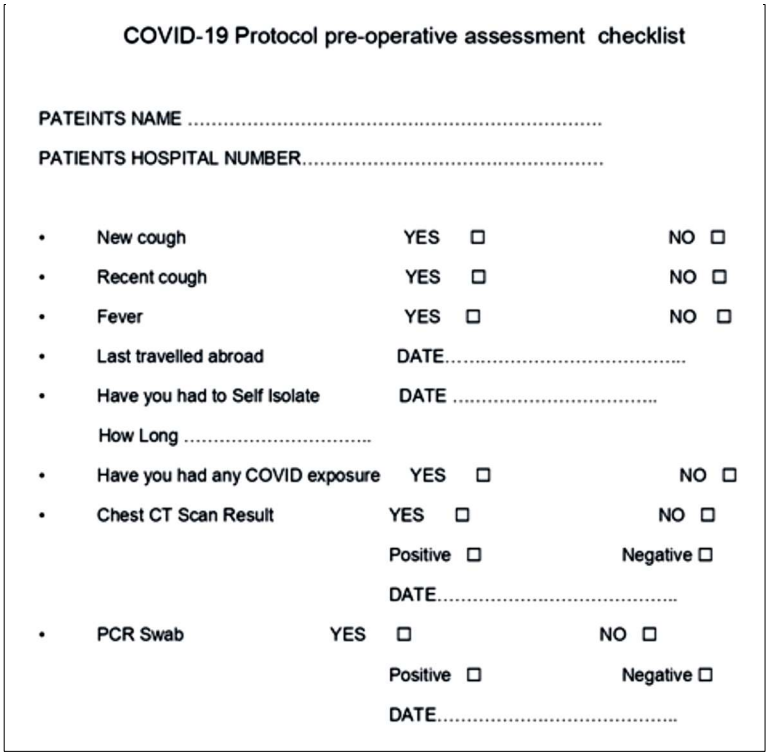
Patient age, physiological reserve, tumour biological characteristics and disease stage are helpful to categorize the patient for whom surgery is time-critical and those who can have surgical treatment delayed safely. Inevitably, if surgery is not performed, cancer progression has to be monitored. Lei et al in his recent report cautioned that performing a surgical procedure may accelerate and expedite COVID-19 disease progression during the pandemic (2), however only one patient belongs to our cohort has developed COVID-19 infection after surgery however recovered. Newly diagnosed patients should be appropriately well informed that advanced age and the coexistence of underlying comorbidities such as hypertension, COPD and diabetes could expose them to significant death risk if they get COVID-19 infection, also

the risk of COVID-19 infection should be added to the consent (3,37). The COVID personal protective equipment should be available to deliver care to COVID-19 free patients including cancer surgery since it is imperative to consider every patient as potential COVID risk during the Pandemic. At the regional level, one of the policies adopted during the crisis is that the services were divided into a COVID-19 positive hub (usually the main public hospitals) and COVID-19 protected units (independent hospitals and adapted units located separate from COVID-19 hubs). Coordination between all the regional healthcare sites is necessary and is fundamental. Implementation of new agreed local protocols and policies will ensure safe service delivery and best use of resources.

The Chinese ophthalmologist Dr. Li Wenliang, who worked at Wuhan Central Hospital warned the authorities and the public about SARS-CoV2 risk on 30 December 2019 (later was detained for doing so), died from SARS-CoV2 infection on February 7th, 2020 at age of 33. Charles Kwame Tanor, who worked as a mental health worker at Eden Place Mental Health Nursing Home in Leamington Spa, was the first UK health care worker who died after contracting COVID-19, on March 11th, 2020. Dr Adil El Tayar, a surgeon working at West Middlesex University Hospital, was the first working UK NHS surgeon to die from coronavirus in Britain, he died on March 25th, 2020. Mr Thomas Harvey who worked as a mental health nurse in the North East London region, passed away on Sunday March 29th, 2020 after contracting Covid-19 from a hospital patient. By the time of finalizing this paper, there are more than 300 UK NHS workers and more than 3000 health workers globally who have lost their lives trying to save others. Use of the PPE (Personal Protection Equipment) such as (PPF masks, N95 masks, goggles, face shields, aprons and protective gowns) in the clinical areas is essential to protect patients and workforce, and is crucial to lower the nosocomial infections risk, in particular Patient-to-Staff-to-Patient transmission. At the team level, to minimise healthcare interactions, the specialist teams were advised to follow the social distancing policy and use digital MDT (3,9,46). At early stages, the asymptomatic patients were not being routinely tested for COVID-19 infection as the test wasn't available; however every asymptomatic surgical patient was considered as possible COVID-19 positive candidate. A screening protocol was built gradually as the pandemic progressed. Patients scheduled for surgery had been advised to adhere to the 14 days self-isolation policy and use phone call or digital pathway consultation when appropriate. It has been reported that even asymptomatic carriers are able to spread COVID-19 with high contagiousness, so after testing kits were available, the patients are screened by COVID-19 testing 5-7 days before surgery date (*Table 6*) in addition to high resolution chest CT scan when

**Table 6.** The Suggested Pre-operative assessment and screening protocol for planned care during COVID-19 Period

| **P1 (Priority 1)** | | **P2 ≥ (Priority 2 and above)** |
|---|---|---|
| HRCT Chest (high-resolution computerised tomography) | | 1) MDT or specialty specific decision to provide planned operative care.<br>2) Patient advised self-isolation from 14 days preoperatively. |
| +ve for COVID-19 | -ve for COVID-19 | 3) Patient swabbed for (COVID-19) 5-7 days preoperatively (estimated result turnaround time – 48 hours) |
| Proceed to three Consultant decision making about need for surgery | Proceed to surgery | a) If swab positive operation postponed and patient re-swabbed in 21 days. If second swab negative then proceed to surgery. If second swab positive, then proceed to surgery in amber or blue site if surgery cannot be postponed – 3 consultant decision making<br>b) If swab negative then proceed to CT protocol (given below) if indicated. |



COVID-19 Protocol pre-operative assessment checklist

PATEINTS NAME .....

PATIENTS HOSPITAL NUMBER.....

- New cough YES ☐ NO ☐
- Recent cough YES ☐ NO ☐
- Fever YES ☐ NO ☐
- Last travelled abroad DATE.....
- Have you had to Self Isolate DATE .....

  How Long .....
- Have you had any COVID exposure YES ☐ NO ☐
- Chest CT Scan Result YES ☐ NO ☐

  Positive ☐ Negative ☐

  DATE.....
- PCR Swab YES ☐ NO ☐

  Positive ☐ Negative ☐

  DATE.....

**Figure 2.** COVID-19 protocol pre-operative assessment checklist

indicated (47). On the day of admission, a questionnaire is used after temperature measurements are taken to screen for recent symptoms (*Fig. 2*).

## Conclusion

COVID-19 is a real worldwide health threat; we are learning from this crisis how we can adapt our practice and deliver optimum care in a highly dynamic situation. Health care units' coordination is crucial to ensure better utilization of available resources and reduce the risk of exposure. Implementation of evidence based agreed protocols by the relative professional bodies will boost the system with a safer framework to aid clinicians to deliver safer intervention.

### *Conflict of Interest*

The authors declare no conflicts of interests.

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