Breast Cancer: Targets and Therapy

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REVIEW

Breast Cancer Management in the Era of Covid-19; Key Issues, Contemporary Strategies, and Future Implications

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Abstract: During the COVID-19 pandemic, several priority diseases were not getting sufficient attention. Whilst breast cancer is a fatal disease affecting millions worldwide, identification and management of these patients did not initially attract critical attention to minimize the impact of lockdown, post-lockdown, and other measures. Breast cancer patients' conditions may not remain stable without proper care, worsening their prognosis. Proper care includes the timely instigation of surgery, systemic therapy, and psychological support. This includes low-and middle-income countries where there are already concerns with available personnel and medicines to adequately identify and treat these patients. Consequently, there was a need to summarize the current scenario regarding managing breast cancer care during COVID-19 across all countries, including any guidelines developed. We systematically searched three scientific databases and found 76 eligible articles covering the medical strategies of high-income countries versus LMICs. Typically, diagnostic facilities in hospitals were affected at the beginning of the pandemic following the lockdown and other measures. This resulted in more advanced-stage cancers being detected at initial presentation across countries, negatively impacting patient outcomes. Other than increased telemedicine, instigating neo-adjuvant endocrine therapy more often, reducing non-essential visits, and increasing the application of neo-adjuvant chemotherapy to meet the challenges, encouragingly, there was no other significant difference among patients in high-income versus LMICs. Numerous guidelines regarding patient management evolved during the pandemic to address the challenges posed by lockdowns and other measures, which were subsequently adopted by various high-income countries and LMICs to improve patient care. The psychological impact of COVID-19 and associated lockdown measures, especially during the peak of COVID-19 waves, and the subsequent effect on the patient's mental health must also be considered in this high-priority group. We will continue to monitor the situation to provide direction in future pandemics.

Keywords: COVID-19, breast cancer, healthcare system, healthcare management, treatment, surgery, guidelines, unintended consequences

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 or COVID-19, was identified in Wuhan, China, in December 2019. It was responsible for pneumonia-like syndrome, acute respiratory

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distress syndrome, and death.[1] Covid-19 has been responsible for over 581 million cases and over 6.4 million deaths globally by the middle of August 2022.[2] Preventative measures, including early diagnosis, social distancing, isolation, and lockdown activities, were introduced across countries to control the virus's spread in the absence of effective treatments and vaccines.[3–6] There was though considerable variation in the timing of lockdown and other measures across countries and their enforcement, which impacted subsequent morbidity and mortality rates.[7–9]

In the early stages of the pandemic, COVID-19 patient management resulted in an appreciable burden on healthcare systems, including Healthcare workers, across countries. The lockdown measures introduced to try and slow the spread of the virus, including the cancellation of elective surgery and hospital clinics as well as disruption in transport services, affected patients already suffering from non-communicable diseases (NCDs) and health systems' ability to provide NCD-related care.[10,11] This appreciably impacted achieving agreed-on sustainable development goals, including reducing current morbidity and mortality from NCDs.[12–14] There have also been concerns that lockdown and other measures increased delays in the diagnosis and management of patients with cancer, increasing future mortality alongside the psychological, social, and economic costs associated with these delays.[15–18] Within cancers, the optimal management of breast cancer is essential, with more than 1.8 million new cases detected annually worldwide and prevalence rates for breast cancer continuing to rise.[19,20] Breast cancer is also the most common cause of mortality among women with cancer, with early detection and active management helping to reduce subsequent morbidity and mortality.[21,22]

Consequently, breast cancer should be well managed, including enhancing early detection. However, limited hospital resources during the COVID-19 pandemic, travel restrictions among patients, and fear of catching COVID-19 when visiting hospitals for diagnosis and potentially early management hampered care provision across countries, including breast cancer patients.[22–24] This is a concern as delays in treating patients with breast cancer increase their morbidity and mortality, with a two-month delay in surgery potentially increasing the risk of mortality by 26% in early-stage invasive breast cancer.[18]

Different studies have been conducted across countries reporting on changes in diagnosis strategies, including delays, treatment approaches, including those brought about by delays in surgery, as well as patients presenting in the late stages of breast cancer brought about by the measures to limit the spread of COVID-19, all adversely impacting on the morbidity and mortality of these patients.[15,18,22] This also includes the psychological impact brought about by delays in the diagnosis and management of breast cancer due to lockdown and other measures.[25,26] Several studies also provided essential guidelines for managing breast cancer patients as safely and efficiently as possible during the pandemic.[27,28] However, we are unaware of any study that has been undertaken to summarize key findings, reports, and recommendations across countries to provide future guidance on ways to improve all aspects of care for patients with breast cancer during the current and future pandemics. Consequently, we sought to address this. This review summarises available literature regarding all aspects of care of patients with breast cancer during the current pandemic, with the aim of documenting key aspects regarding diagnosis and treatment strategies, including the psychological impact of lockdown and other measures, as a basis for improving the care of these patients during current and future pandemics.

Methodology

Three different online databases (ie, Google Scholar, PubMed, and ScienceDirect) were searched for this literature review using specific keywords, which included "COVID-19", "SARS-CoV-2", "breast cancer", "surgery" and "surgical", and following the PRISMA method.[29] The search was restricted from January 2020 to April 25, 2022, and relevant articles were extracted. The inclusion criteria included full-length papers discussing all aspects of managing breast cancer during the COVID-19 pandemic, including diagnosis and management, incorporating systemic treatments and surgery. In addition, articles discuss the management of breast cancer patients with COVID-19 and the psychological impact of COVID-19. Finally, any guidelines on the suggested management of breast cancer patients during the pandemic. Exclusion criteria included articles which were not relevant to our study interest or did not cover the topic of our inclusion criteria, ie, were not full-length research articles such as correspondence, letters to the editor, short communications or reviews, or those found outside our fixed search dates or not written in the English language. Duplicates of the same article found in multiple databases were also excluded (Figure 1).

Three co-authors (AHMSUP, DZI, and SSK) independently assessed each identified study. Any confusion or concern with identified papers was thoroughly discussed, and a consensus was reached among the three authors before proceeding.

A simplified PRISMA diagram of methodology (Figure 1). Nine hundred eighty-six articles were identified through this search strategy. Eight hundred and eighty-four articles were excluded due to ineligibility. Of the remaining 102 articles, 11 were excluded as they did not match the study criteria of full-length research articles on managing breast cancer and the COVID-19 pandemic. After excluding the duplicate articles (n=15), 76 articles were included in this review.

The study findings were broken down into the key aspects of management, including diagnosis and treatment, as well as those from low- and middle-income countries (LMICs) versus high-income countries and worldwide. This is because there are considerable differences in the funding of cancer care between LMICs and high-income countries, with concerns about funding even older biological medicines, such as trastuzumab, in LMICs without significant discounts or donor support.[30–32] Consequently, there may be differences between LMICs and high-income countries in managing

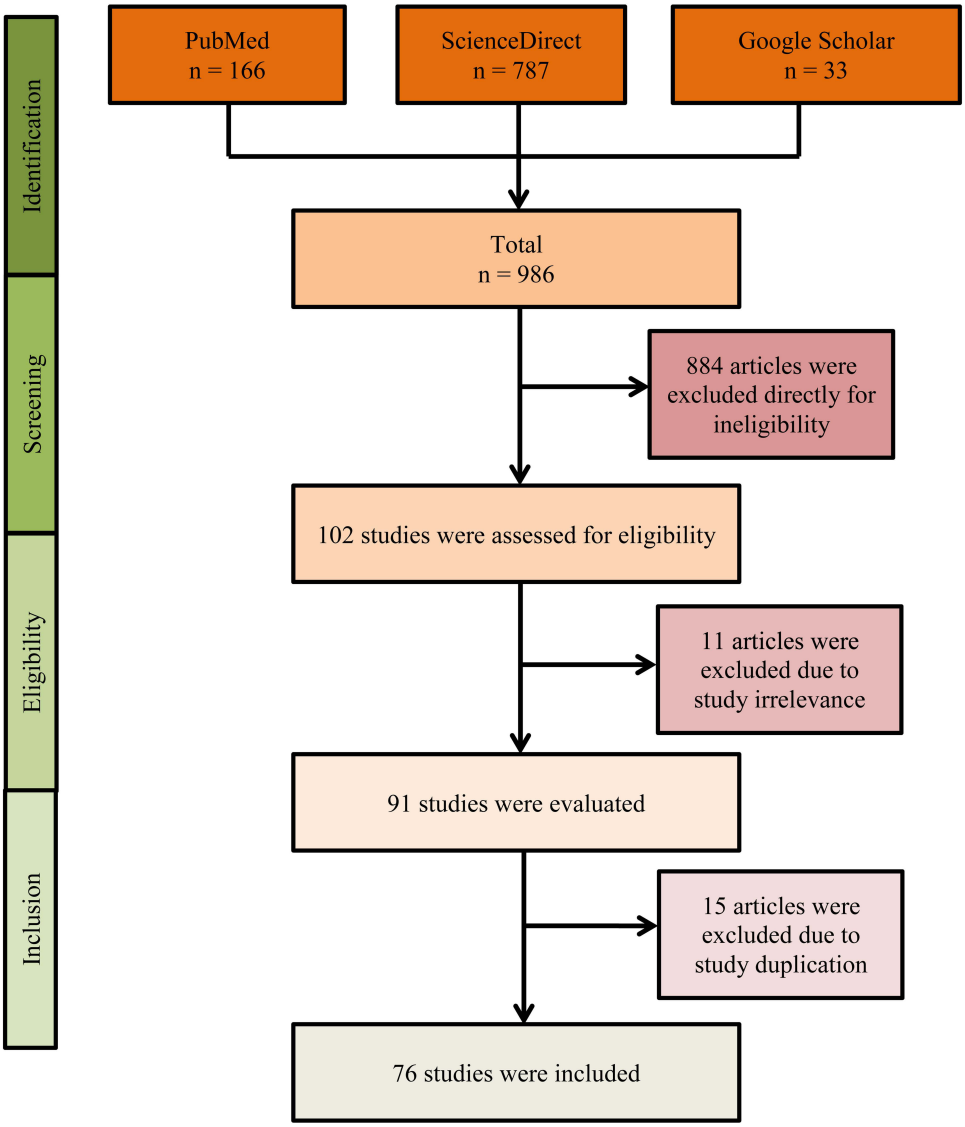

Figure 1 Illustrating literature search strategy.

breast cancer patients during any pandemic, with LMICs struggling with the financial impact of COVID-19 without donor support.[7,8]

In addition, each aspect of care was further broken down into the studied country, type of study, study period, number of participants and their age (if available), key measurements, study results, and comments/ suggestions contained in the published papers. Key areas included the impact of COVID-19 on diagnosis, including delayed diagnosis and presentation of patients with breast cancer, systemic therapy prescribed and the overall management of breast cancer patients during the pandemic, surgery strategies, management of breast cancer patients with COVID-19, and the mental health of patients with breast cancer during the pandemic. Finally, the Publication of specific guidelines for diagnosing and managing patients with breast cancer can provide future direction.

Results

The influence of COVID-19 on the stage of presentation and diagnosis, including any delays in diagnosis due to the pandemic in patients with breast cancer, will be discussed first, along with the implications for future management during further pandemics. Subsequently, the typical presentation of patients for treatment and the implications for different surgical approaches will be discussed. Finally, the impact of COVID-19 on managing patients with both COVID-19 and breast cancer, as well as the pandemic's implications on patients' mental health, will also be discussed.

Diagnosis, Presentation, and the Implications

Twenty-five studies were identified for the comprehensive literature review involving 7 LMICs (Brazil, China, Lithuania, Lebanon, Pakistan, Romania, and Turkey) and ten high-income countries (Canada, France, Italy, Japan, Netherlands, Singapore, South Korea, Taiwan, UK, and the USA) (Table 1) alongside additional studies that did not fulfil the inclusion criteria; however, they also reported on the impact of lockdown and other measures on diagnosis patterns for patients with breast cancer. There was a considerable reduction in the identification of new breast cancer patients, especially among LMICs, due to lockdown and other measures (Table 1). Among the LMICs, Li et al in China demonstrated a significant reduction in the number of new cases detected immediately post-quarantine in Hubei Province compared to pre-pandemic levels. However, variations were seen among the different provinces in China. In addition, lockdown and other measures adversely impacted subsequent patient management, including surgery and chemotherapy initiation delays.[33] In Lebanon, quarantine measures also appreciably affected the presentation of patients with breast cancer. For instance, diagnostic activity was appreciably reduced in Lebanon during the first three months of lockdown measures (73%), with all but one out of 20 new cases in one hospital found to be invasive carcinoma.[34] There was also an appreciable reduction in breast cancer screening activities in Brazil and Lithuania during the initial stages of the pandemic.[35,36] However, there were variable findings in Turkey. Kiziltan et al demonstrated an appreciable reduction in the number of new breast cancer patients being identified in the early stages of the pandemic as well as those attending out-patients, with Koca et al showing similar findings, especially regarding out-patient visits.[37,38] This contrasted with the findings of Güler et al, who found little impact of lockdown measures on delays in diagnosis and management of patients with breast cancer.[39] Crisan et al in Romania also found an appreciable reduction in out-patient visits and mammograms during the early months of the pandemic.[40] Advanced-stage breast cancer cases, along with breast cancer patients presenting later in the disease process, were also reported during the early stages of the pandemic in other LMICs, including Pakistan (Table 1).[33,41]

There were also similar findings in several high-income countries (Table 1). There was an appreciable reduction in the number of mammograms undertaken in Canada during the early stages of the pandemic; however, this was reversed by December 2020.[42] In France, due to lockdown measures, patients presented with more aggressive tumours at diagnosis, which arose from the suspension of screening programs and postponement of biopsies and consultations, with an appreciable reduction in the number of surgeries performed.[43] There were similar concerns and issues in Japan, the Netherlands, Singapore, and Taiwan.[44–47] The pandemic seemingly had a more limited impact in South Korea, with only a 9.9% reduction in the number of newly diagnosed cases in the initial period of the pandemic; however, there was a reduction in breast cancer screening activities similar to other high-income countries.[48]

Table 1 Impact of COVID-19 on Diagnosis and Presentation of Breast Cancer Patients Across Countries

Studied Country	Type of Study	Study Period	Number of Participants (Mean/ Average/ Median Age)	Key Measurements	Key Findings	Comments/ Suggestions
Diagnosis						
Low- and Middle-income countries						
Ribeiro et al, Brazil[35]	Descriptive study	2019–2020	NR	Short-term outcomes of COVID-19 pandemic on breast cancer screening and diagnosis.	Screening mammograms decreased by 42.6%, percentage of breast cancer screening among patients aged 50–69 years reduced slightly (64.8% vs 64.4%) during the pandemic period in 2020 compared to the percentage of the pre-pandemic period in 2019 time interval between various breast cancer screening episodes and diagnosis, ie, diagnostic mammography, screening mammography, breast histopathology palpable lesion and breast histopathology imaging detection did not vary significantly during the pandemic period.	Breast cancer control actions and management were hampered during the COVID-19 pandemic leading to decreased breast cancer screening and diagnosis. Effective measures and strategies are necessary to alleviate the situation and reduce screening and diagnostic procedure delays.
Li et al, China[33]	A retrospective multicentre cohort study	1 Apr 2020–15 May 2020	8397 (50 years)	Impact of COVID-19 on breast cancer diagnosis	Only 5.2% of breast cancer diagnoses happened in Hubei compared to 15.3% in other provinces. Significantly*** more extended diagnosis to the treatment period, significantly**** more aggressive subtypes and histological grades of tumours were detected in Hubei compared to other provinces.	The early breast cancer diagnosis was significantly affected, with more advanced stage tumours being diagnosed during COVID-19, especially in Hubei.
Dabkeviciene et al, Lithuania[36]	Observational study	1 Feb 2019–31 Dec 2020	NR	Impact of COVID-19 on breast cancer screening and diagnosis	62% reduction in breast cancer screening by mammography during the pandemic, and the number of newly diagnosed breast cancer patients decreased by 8%.	Continuous providing of cancer services, shifting centralized cancer service centres to COVID accessible areas, and proper strategies for efficient cancer screening services were required to alleviate the negative effect of the pandemic

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Table 1 (Continued).

Studied Country	Type of Study	Study Period	Number of Participants (Mean/ Average/ Median Age)	Key Measurements	Key Findings	Comments/ Suggestions
Salem et al, Lebanon[34]	Retrospective study	9 Mar 2020–11 May 2020	205 (50.3 years)	Radiology Department activity during COVID-19	Activity reduced by 73%. Mammograms were mainly used (41.5%) for breast screening. 41% of biopsies were found positive.	The activity of the radiology department dropped during the lockdown.
Crisan et al, Romania[40]	Observational study	Mar 2020 – Oct 2020	NR	Number of mammograms and outpatient visits during COVID-19	27% reduction in outpatient visits and 19% reduction in mammograms.	N/A
Güler et al, Turkey[39]	Survey	11 Mar 2020–31 May 2020	93 (NR)	Radio- and pathological diagnoses during COVID-19	No delay was found except for less multidisciplinary breast councils.	The breast cancer diagnosis was not affected.
Kiziltan et al, Turkey[37]	The single-centre retrospective observational cohort study	11 Mar 2020–1 Jun 2020	396 (NR)	Impact of COVID-19 pandemic on breast cancer diagnosis	The number of patients having a new breast cancer diagnosis decreased significantly (146 during pandemic vs 250 during pre-pandemic)) during the pandemic, the number of patients applying for outpatient clinics also reduced compared to the pre-pandemic period.	N/A
Koca et al, Turkey[38]	Retrospective cohort study	11 Mar 2019–11 Mar 2021	148 (51.2 years)	Impact of COVID-19 on number of outpatient visits, breast screening, and diagnosis	26.3% visit reduction breast outpatient clinics, a 79.8% reduction in screening mammography, and a 47.7% decrease of patients diagnosed with surgeries in the first year of the pandemic compared to the year before.	Effective measures should be taken to reinitiate the screening programs to reduce delays in breast cancer diagnosis. Patients with breast cancers should be made aware of the necessity of regular breast screening. Continuation of proper breast cancer diagnosis and screening should be guaranteed.

High-income countries						
Decker et al, Canada[42]	Observational study	16 Mar 2020–31 Aug 2021	(50–74 years)	Number of screening mammograms during COVID-19	In June 2020, a 54% reduction was observed between the predicted and expected values. However, by December 2020, the values had no significant difference.	Screening plans taken quickly to the COVID-19 pandemic.
Dorri et al, France[43]	Observational study	Jan 2020–Jul 2020	581 (NR)	Diagnosed tumour types during COVID-19	Significantly higher rate of large (cT2-4) tumours**, SBR3 tumours*, and ER^{-} tumours* and significantly lower luminal A-like ((ER+, HER2-, SBR1-2) tumours** were diagnosed from March 17 to May 11, 2020, compared to the same period of 2019.	More aggressive types of breast cancer are being detected during the COVID-19 pandemic.
Losurdo et al, Italy[49]	An observational monocentric retrospective study	Mar 2019–Apr2021	549 (64 years)	Impact of COVID-19 on breast cancer screening and diagnosis	17.1% reduction in breast cancer screening during the COVID period, a significant decrease in diagnosing advanced stage (III and IV) breast cancers.	Good backup plans and procedures are required to ensure rapid screening and diagnosis of breast cancers in cases of new emergencies.
Vanni et al, Italy[51]	Multicentric retrospective study	11 Mar 2020–30 May 2020	223 (62 years)	Diagnosed tumour types during COVID-19	A significantly* higher number of patients were diagnosed with lymph node involvement and G2-3 graded cancer in lockdown than before.	The waiting time can be a significant predictive factor in lymph node involvement. Diagnosis delay can lead poorer prognosis of tumours.
Toss et al, Italy[50]	Retrospective monocentric study	May 2020–Jul 2020	177 (NR)	Impact of a 2-month mammographic stop on breast cancer stage	A significant rise in the number of patients diagnosed via mammographic follow-up ****, cT4 tumours**, cN+ tumours **, and stage III breast cancer****. A significant decrease was found in in-situ diagnosis**, stage 0 (in situ) breast cancer**, and stage IIA breast cancer**.	An increase in node-positive and stage III tumours indicates immediate screening program restoration.
Saeki et al, Japan[44]	Survey study	Jan 2019–Mar 2021	991 (NR)	Influence of COVID-19 pandemic on breast cancer screening and diagnosis	Breast cancer detection rate by screening reduced significantly during the pandemic period; in terms of breast cancer stage classification, the average percentage of stage-0 decreased substantially in the pandemic period compared to the pre-pandemic period.	The breast cancer screening rate probably decreased due to refraining the COVID-19 susceptible people from receiving screening and the restrictions of some local governments during the pandemic period.

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Table 1 (Continued).

Studied Country	Type of Study	Study Period	Number of Participants (Mean/ Average/ Median Age)	Key Measurements	Key Findings	Comments/ Suggestions
Eijkelboom et al, Netherlands[45]	Observational study	Jan 2020–Apr 2020	4769 (NR)	Effect of COVID-19 on breast cancer diagnosis	Diagnosed breast cancer significantly reduced during COVID-19 across all tumour stages and age groups, especially for DCIS and stage I. Around 1150 breast cancer cases were missed.	National screening programs should be resumed. Patients should visit general practitioners more.
Mok et al, Singapore[46]	Observational study	Feb 2020–May 2020	NR	Effect of COVID-19 on breast cancer diagnosis	The screening was suspended, but patients with abnormalities detected on mammograms continued to be reviewed by the physicians. Diagnosed new cancer cases reduced due to COVID-19.	Hospital visits should be minimized based on priority, and screening can be deferred for 6–12 months. However, delay in diagnosis can degrade breast cancer conditions.
Kang et al, South Korea[48]	The multi-institutional retrospective cohort study	1 Feb 2019–31 Jul 2020	2398 (53 years)	Impact of COVID-19 pandemic on breast cancer screening and diagnosis	9.9% reduction in newly diagnosed breast cancer during the pandemic period in 2020 compared to 2019, and the number of breast cancer screenings decreased by 27.4% during 2020. Several breast mammograms and breast ultrasonography also reduced during the pandemic period, and stage IIB and IV diagnosis rates increased during the COVID-19 pandemic.	Fear of nosocomial transmission of SARS-CoV-2 resulted in declining breast cancer screening and diagnosis.
Shen et al, Taiwan[47]	Observational study	Jan 2020–Apr 2020	NR	Number of mammograms during COVID-19	Hospital screening was reduced by 41.43%, and an average of 23.99% decreased outreach screening.	Outreach services were preferred with mobile mammography during the pandemic.
MacInnes et al, UK[52]	Multicentre observational study	16 Mar 2020–24 Apr 2020	202 (57 years)	Number of new cancer diagnoses during COVID-19	Did not reduce much relative to 2019.	N/A
Romics et al, UK[53]	Cohort study	31 Jul 2019–7 May 2020	179 (54 years)	Effect of COVID-19 on breast cancer diagnosis	Significant increase in symptomatic service***, patients having ER-*** and HER2+** disease, patients with cT3-4*** and pT2-4** undergoing surgery during the lockdown.	N/A
Gheorghe et al, UK[54]	Population-based modeling study	Up to 6 Oct 2020	32,583 (60.5 years)	Excess death, QALY loss, and economic loss due to COVID-19	There were three hundred forty-four additional deaths and 4100 QALY losses due to diagnostic delays for COVID-19. The estimated productivity loss was 23.2 million pounds.	Significant economic loss may occur due to excess deaths and QALY losses because of diagnostic delay of breast cancer during COVID-19.

Kennard et al, USA[65]	Cohort study	1 Mar 2020–15 Jun 2020	73 (60.6 years)	Diagnosed tumour types during COVID-19	44% of patients experienced a treatment change during COVID-19. Significantly*** more HER2 positivity and TNity and significantly*** less hormone receptor positivity was seen in the no-change group.	N/A
Sprague et al, USA[55]	Observational study	Mar 2020 – Sep 2020	NR	Effect of COVID-19 on breast imaging facilities	97% of facilities were closed or operated at limited capacity. Diagnostic breast imaging was prioritized in 92.8% of facilities over screening. During re-opening of the imaging services, rescheduled cancelled appointments, patients who contacted facilities and wanted to visit, patient's characteristics and risk factors, suspicious malignancy on imaging, and the time since last imaging were considered mainly for prioritizing screening, diagnostic, and biopsy.	COVID-19 greatly impacted breast imaging services, and multiple factors were considered for prioritizing the services during the reopening of the facilities.
Wilke et al, USA[66]	Review report	1 Mar 2020–15 Mar 2021	2791 (62.7 years)	Impact of COVID-19 pandemic on breast cancer testing and diagnosis	The surgeons stopped the mammographic screening at some points during the initial period of the pandemic; 51.5% of patients underwent genomic testing, 20.7% of patients received genomic analysis on core biopsy specimens during COVID-19, whereas 21.8% of patients performed core biopsy specimen genomic testing as per usual practice.	N/A
Yin et al, USA[56]	Multicentre observational study	2 Feb 2020–11 Apr 2020	NR	Breast imaging and genetic consultation	Significant*** reduction compared to pre-COVID situations.	The decline in breast screening can increase breast cancer risk and pressure healthcare facilities.

Note: ****p≤0.0001, ***p≤0.001, **p≤0.01, *p≤0.05.

Abbreviations: ERAS, Enhanced Recovery after Surgery; ECOG, Eastern Cooperative Oncology Group; NR, not reported; NAF, nipple aspirate fluid; BR, breast reconstruction; IBR, immediate breast reconstruction; GAD-2, Generalized Anxiety Disorder two-item questionnaire; IORT, intraoperative radiation therapy; DCIS, ductal carcinoma in-situ; BCS, breast conservation surgery; ER, the estrogen receptor; HER, human epidermal growth factor receptor; PgR, progesterone receptor; HR, hormone receptor; ST, systematic therapy; TN, triple-negative; NAC, neo-adjuvant chemotherapy; CDK, cyclin-dependent kinase; ET, endocrine therapy; N/A, not available.

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In Italy, there was also an appreciable upsurge in the number of patients presenting with node-positive and late-stage tumours following a reduction in screening activities due to lockdown measures, which resulted in recommendations to restore screening programs despite these measures immediately.[49–51] There were though variable findings in the UK. MacInnes et al documented a partial lockdown effect on the number of new cases diagnosed, although referral rates were down.[52] This contrasted with the findings of Romics et al, who found that the tumour size of patients with breast cancer undergoing surgery during the pandemic was significantly larger than before, with a higher number of estrogen receptor (ER) negative cases impacted by lockdown measures and a reduction in screening activities.[53] Gheorghe et al calculated an additional 344 deaths due to diagnostic and management delays following lockdown measures, resulting in a loss of 4100 quality-adjusted life years and an estimated productivity loss of GB£ 23.2 million.[54] There were also variable findings in the USA. Sprague et al and Yin et al reported appreciable reductions in diagnostic services following the pandemic.[55,56] However, Boyd et al reported a lower reduction in mammogram activities (11%) initially coupled with a quick return to normal and even an increase (15%) in patients presenting between October to December 2020 versus pre-pandemic levels.[57] Cairns et al also documented a significant decrease in the number of screening mammograms (44% reduction) and diagnostic mammograms (21% reduction) following lockdown measures in 2020 versus a similar period in 2019. However, they found no significant difference in the number of operations for new breast cancer patients in 2020 versus 2019.[58]

Self-screening breast cancer can be a possible alternative strategy given the limited diagnostic facilities available due to COVID-19 and the potential impact of late diagnosis. Jiwa et al, in their study in the UK, ascertained that undertaking NAF (nipple aspirate fluid -NAF) at home for early-stage detection of breast cancer during any pandemic was possible.[59–61] As hospital visits are minimized during the COVID-19 pandemic, the usage of NAF can be a potential screening tool for early-stage breast cancer detection and reducing breast cancer risk. However, they found that 83.4% of women did not know about NAF, and 89.4% did not know that NAF can be expressed in 90% of women. Promisingly, 89.8% of women in their study were eager to learn about their future breast cancer risk, and 92% were keen to experience home testing, especially during pandemics. The authors suggested that public awareness should be increased regarding breast screening protocols like NAF testing to reduce the risk of breast cancer.[61] There were similar findings across high-income countries and LMICs (Table 1).

Overall, a number of protocols and guidelines regarding screening the patient population for COVID-19 infection were proposed and followed in different high-income countries to maintain a balance between COVID-19 safety protocols and breast cancer diagnosis. In Italy, Maio et al proposed a protocol of screening patients for COVID-19 infections through a telephone-based questionnaire and classifying patients into one of four groups: Non-COVID-19 patients, confirmed COVID-19 in an asymptomatic screening patient, suspected COVID-19 in symptomatic or confirmed breast cancer and confirmed COVID-19 in symptomatic or confirmed breast cancer.[62] Tari et al also proposed a tele-questionnaire-based screening protocol to separate the patients into distinct clinical scenarios: non-COVID-19 patients, suspected COVID-19 patients and confirmed COVID-19 patients before each diagnosis or a nasopharyngeal swab test before recovery. If not urgent, the COVID-19-confirmed or suspected patients were rescheduled.[63] Seely et al in Canada proposed guidelines for pre-screening patients for any symptoms of COVID-19 at the time of scheduling and immediately before their imaging visit. The author added that any patient with recent travel history, close contact with a COVID-19 patient, or even mild symptoms should be rescheduled to 2 weeks after symptoms have resolved.[64]

Systemic Therapy and Patient Management

Twenty-five eligible studies were identified that fulfilled the inclusion criteria. These included 6 LMICs (Brazil, China, Egypt, Lithuania, Pakistan, and Turkey), 11 high-income countries (Canada, France, Netherlands, New Zealand, Portugal, Saudi Arabia, Singapore, Spain, UAE, UK, and the USA), as well as world-wide studies (Table 2). Typically, strategies and approaches of systematic therapies were compared, including prescribing neo-adjuvant chemotherapy (NEC) or neo-adjuvant endocrine therapy (NET) for breast cancer patients during the COVID-19 pandemic with pre-pandemic era following delays with surgery as a result of lockdown and other measures.

Concerning LMICs, the menopausal and genomic status of patients played an appreciable role in choosing NET. In Brazil, NET was recommended for post-menopausal patients with HR+ tumours, with nuclear protein Ki-67<20% and

Table 2 Summary of Systematic Therapy and Management of Patients with COVID-19 During the Pandemic

Systematic therapy and patient management						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Participants (Mean/ Average/ Median Age)**	**Key Measurements**	**Key Findings**	**Comments/Suggestions**
Cavalcante et al, Brazil[67]	Questionnaire survey	30 Apr 2020–11 May 2020	503 (NR)	Change in breast cancer management during COVID-19	Significantly*** more respondents changed their management strategies when the outbreak progressed than at the beginning. For HR+ tumours with Ki-67<20% and Ki-67>30%, 47.9% and 34% of specialists recommended NET for postmenopausal women. Menopausal status played a significant***** role in choosing NET. For ≥1.0 cm tumours, 42.9% and 39.6% recommended NET for TN and HER2+ tumours. 63.4% recommended IBR. 84.9% denied prophylactic mastectomy.	The recommendations from the specialists can help manage patients with breast cancer during COVID-19.
Li et al, China[33]	The retrospective multicentre cohort study	1 Apr 2020–15 May 2020	8397 (50 years)	Changes in therapy due to COVID-19	Significantly*** more extended diagnosis to the treatment period, **** more adjuvant therapy, and significantly**** less neoadjuvant treatment were detected in Hubei compared to other provinces.	The therapeutic strategy for early breast cancer was significantly changed during Covid-19 in Hubei province, especially
Zhang et al, China[68]	Cross-sectional study	21 Feb 2020–29 Feb 2020	31 (NR)	Changes in treatment due to COVID-19	90.3% of patients shifted from intravenous to oral therapy, and 77.4% reported taking complementary and alternative medicine during COVID-19.	Patients remained relatively stable during COVID-19.
Dabkeviciene et al, Lithuania[36]	Observational study	1 Feb 2019–31 Dec 2020	3262 (NR)	Impact of COVID-19 on breast cancer therapy	The number of patients receiving systemic anticancer therapy (SACT) and radiotherapy increased by 38% and 3%, respectively, during the pandemic in 2020 compared to the pre-pandemic period in 2019.	N/A
Mooghal et al, Pakistan[41]	The single-centre retrospective cohort study	1 Jan 2020–30 Jun 2021	69 (53 years)	Effect of COVID-19 pandemic on breast cancer patient management	60 out of 69 patients presented advanced-stage breast cancer (stage 2b or above), and 21 of 60 patients with advanced-stage breast cancer underwent upstaging of disease due to lockdown and delayed presentation.	The delayed presentation was mainly caused due to the unawareness of the disease

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Table 2 (Continued).

Systematic therapy and patient management						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Participants (Mean/ Average/ Median Age)**	**Key Measurements**	**Key Findings**	**Comments/Suggestions**
Sattar et al, Pakistan[69]	Method report	18 Mar 2020–12 May 2020	NR	Guidelines to triage breast cancer patients during COVID-19	Patients were divided into 3 groups based on the priority of treatment. Hospital management was done to reduce COVID-19 exposure.	The institutional approaches can act as guidelines for treating breast cancer patients during COVID-19.
İlgün et al, Turkey[70]	Observational study	Mar 2019–Mar 2021	382 (48 years)	Effects of COVID-19 pandemic on breast cancer patients in the breast cancer centre	Breast cancer patients' admission to breast centres was reduced by almost 15% in the pandemic period compared to the pre-pandemic period, patient-related delay time (PRDT) significantly increased during the pandemic (57.7% vs 45%), rate of pre-menopausal patients significantly rose, bigger tumour size and excessive metastatic lymph nodes were reported among the patients admitted during COVID-19, de novo stage IV breast cancer cases were increased considerably during the pandemic period.	Fear of SARS-CoV-2 transmission and lockdown due to the COVID-19 pandemic significantly decreased breast cancer patient admission and increased patient-related delay time.
Kiziltan et al, Turkey[37]	The single-centre retrospective observational cohort study	11 Mar 2020–1 Jun 2020	52 (NR)	Impact of COVID-19 pandemic on breast cancer intervention	The number of patients receiving neoadjuvant treatment decreased significantly during the pandemic compared to the pre-pandemic period (18 during the pandemic vs 34 during the pre-pandemic).	N/A
Sezer et al, Turkey[71]	Questionnaire survey	25 Mar 2020–7 Apr 2020	51 (NR)	Guidelines to manage breast cancer during COVID-19	Neoadjuvant systemic therapy for patients with HER2+, small-size TN, node-negative, and luminal A-like tumours. Systemic treatment for patients with luminal B-like and HER2+ tumours had a complete clinical response after neoadjuvant therapy.	The guidelines based on the consensus of experienced health professionals can be helpful during the surgical delay of breast cancer patients during COVID-19.
High-Income Countries						
Di Lena et al, Canada[72]	Multi-institutional matched historical cohort study	1 Dec 2019–1 May 2020	76 (65 years)	Effects of NET on early-stage ER+ breast cancer patients during COVID-19 pandemic	Early-stage ER+ breast cancer patients taking NET did not experience upstaging of breast cancer during the pandemic in 2020 despite having 2.5 times longer delay due to the pandemic.	NET can be applied to early-stage ER+ breast cancer patients in cases of surgical delays.

Elsamany et al, Egypt, Saudi Arabia and UAE[73]	Survey	10 Jul 2020–30 Jul 2020	82 (NR)	Changes in therapy due to COVID-19	74% and 58% of the oncologists preferred NET and AC, respectively, in HR- and HER2- patients. 43% chose CDK 4 and 6 inhibitors with ET in HR+ patients. 80% preferred ET with the dual anti-HER2 blockade in metastatic HER2+ and HR+ breast cancer patients. 67% preferred adjuvant trastuzumab for 6 months in HER2+ patients.	NET in HR+ /HER2- patients, 6 months of The oncologists preferred adjuvant trastuzumab in HER2+ patients and ET with the dual anti-HER2 blockade in metastatic HR+ or HER2+ patients.
Dorri et al, France[43]	Observational study	Jan 2020–Jul 2020	581 (NR)	Chemotherapy during the COVID-19 period	A higher NAC, absence of chemotherapy, and a significantly lower** rate of adjuvant chemotherapy were seen from March 17 to May 11, 2020, compared to 2019.	N/A
Eijkelboom et al, Netherlands[45]	Observational study	Jan 2020–Apr 2020	4769 (NR)	Changes in treatment due to COVID-19	DCIS was less treated primarily. Initially, invasive tumours were less likely by IR after mastectomy or BCS. Chemotherapy was given less originally but was given more later. Primary hormonal treatment was more common. Females diagnosed in the first two months of 2020 faced treatment delays only.	Initial treatments changed from surgical processes to primary hormonal treatments during COVID-19.
Gurney et al, New Zealand[74]	Observational study	2018–30 Oct 2020	NR	Impact of COVID-19 on breast cancer management	40% decline in cancer registrations and a sharp decline in endoscopies during the national shutdown restoring to normal in later months. Surgery, medical oncology, and radiation therapy were minimally affected.	New Zealand's COVID-19 elimination pursuit helped minimize COVID-19 impact on breast cancer management.
Alpuim Costa et al, Portugal[75]	Cross-sectional survey-based study	Dec 2020–Feb 2021	129 (NR)	Impact of COVID-19 on clinical practices of oncologists for breast cancer patients.	71.3% of subjects reported reduced visits for new breast cancer cases, an increase in the tendency for telemedicine use, in cases of most aggressive indications such as HER2-positive, triple-negative, visceral crisis, clinical decision-making procedures remained unaffected, use of neoadjuvant therapy increased, but dose-dense regimens decreased, for less aggressive cases application of cycline-dependent kinase 4/6 inhibitor decreased, treatment with oral formulations and metronomic chemotherapy improved. In contrast, clinical trial participation was reduced during the COVID-19 pandemic period.	Although the Portuguese oncologists' changes in breast cancer management and clinical practices were reasonable after the responses to the healthcare crisis during the pandemic, the actual effects on breast cancer patients remained unknown.

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Table 2 (Continued).

Systematic therapy and patient management						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Participants (Mean/ Average/ Median Age)**	**Key Measurements**	**Key Findings**	**Comments/Suggestions**
Mok et al, Singapore[46]	Observational study	Feb 2020–May 2020	NR	Changes in therapy and management strategies due to COVID-19	Non-essential patient visits were deferred, and essential visits were accepted. ST and radiation therapy were continued. All non-essential hospital programs were postponed to minimize infection risk	Patient prioritization, the quick adaptation of undervalued resources, risk reduction, and multidisciplinary team efforts are crucial for patient management during COVID-19.
Brenes Sánchez et al, Spain[77]	Retrospective observational study	15 Mar 2020–21 Apr 2020	36 (NR)	Management of patients receiving therapies	Patients received ST and were given telemedicine to reduce hospital visits. No unexpected incidents occurred during the study.	Patients receiving therapies can be managed successfully during COVID-19
MacInnes et al, UK[52]	Multi-centre observational study	16 Mar 2020–24 Apr 2020	202 (57 years)	Use of NAC	Considerably more patients received it during COVID-19 than before.	N/A
Romics et al, UK[53]	Cohort study	31 Jul 2019–7 May 2020	179 (54 years)	Use of NAC and overall patient management	Significantly*** more patients received NAC during COVID-19 than before. Therapy and surgery were affected in 43.6% of patients due to COVID-19.	N/A
Kennard et al, USA[65]	Cohort study	1 Mar 2020–15 Jun 2020	73 (60.6 years)	Changes in therapy and management strategies due to COVID-19	Significantly*** less NET was given to the no-change group than to the change group. 65.6% were given NET in the change group. Telemedicine was given to 90% of change group patients.	NET was given to the change group more to reduce the adverse effects of surgical delay.
Wilke et al, USA[66]	Review report	1 Mar 2020–15 Mar 2021	2791 (62.7 years)	Impact of COVID-19 pandemic on breast cancer therapy	For ER+/HER2- patients, NET was used for an additional 31% (542) patients due to the COVID-19 pandemic, 24.3% (560) patients with invasive disease, and 30.8% (149) patients with DCIS received NET due to COVID-19.	N/A

Worldwide						
Brown et al, Worldwide[87]	Observational study	19 Jul 2020–8 Oct 2020	48 (NR)	Adjuvant bisphosphonate use during COVID-19	72% of clinicians reported that their centre used adjuvant bisphosphonate to prevent bone metastasis in breast cancer. Among them, 66% said their service was hampered because of COVID-19.	Modified guidelines of ASCO can be followed to adapt to COVID-19 conditions.
Curigliano et al, Worldwide[85]	Guidelines	NR	NR	Guidelines to manage breast cancer during COVID-19	Routine breast screening should be suspended. Patients should be treated on an outpatient basis as much as possible. Patients should be appointed by telemedicine as much as possible. Hospital visits should be minimized. International guidelines should be followed, and the multidisciplinary tumour board should take all the decisions.	N/A
Dowsett et al, Worldwide[84]	Guidelines	NR	NR	Guidelines to triage post-menopausal breast cancer patients during COVID-19	Patients were divided into 3 groups. Allred ER≤6 and PgR<6 patients should undergo surgery. ER=7/8 and PgR<6 or ER=6/7 and PgR≥6 patients whose Ki67>10% after NET should follow surgery. ER=8 and PgR≥6 or Ki67≤10% of patients should follow NET.	The guidelines can effectively manage early ER+ HER2− breast cancer patients during and after COVID-19 conditions.
Gasparri et al, Worldwide[81]	Questionnaire survey	18 Apr 2020–28 Apr 2020	377 (NR)	Change in breast cancer management during COVID-19	The workload was reduced by 50% at 34.2% of centres. The time between diagnosis and treatment significantly**** increased. 67% of responders considered chemotherapy as a risk factor for COVID-19 complications. Modification of primary ST was done in 56% of centres. Significantly **** more centres provided primary ST to <10% of patients. For T1cN0 TN and ER^{-} HER2+ pT1c breast cancers, significantly* fewer patients received chemotherapy, and more patients have undergone surgery. Chemotherapy protocols were changed at 51% of centres, and 68% of responders adopted initial endocrine treatment in Luminal A disease to defer surgery. Radiation therapy was not modified in 51.9% of centres and was delayed at 22.6% for low-risk patients. Genomic profiling was done only in 18.8% of centres.	COVID-19 pandemic made considerable modifications to breast cancer management

Notes: ****p≤0.0001, ***p≤0.001, **p≤0.01, *p≤0.05.

Abbreviations: ERAS, Enhanced Recovery after Surgery; ECOG, Eastern Cooperative Oncology Group; NR, not reported; BC, breast cancer; NAF, nipple aspirate fluid; BR, breast reconstruction; IBR, immediate breast reconstruction; GAD-2, Generalized Anxiety Disorder two-item questionnaire; DCIS, ductal carcinoma in-situ; IORT, intraoperative radiation therapy; BCS, breast conservation surgery; ER, the estrogen receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor; ST, systematic therapy; HR, hormone receptor; TN, triple-negative; NAC, neo-adjuvant chemotherapy; CDK, cyclin-dependent kinase; ET, endocrine therapy; N/A, not available.

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Ki-67>30%, and for ≥1.0 cm tumours whilst waiting for surgery. 42.9% and 39.6% of the specialists, respectively, in Brazil recommended NET for TN and HER2+ tumours.[67] In a study in China, 90.3% of patients were shifted from intravenous to oral therapy where appropriate in view of lockdown measures, including the closure of clinics and the need for immunocompromised patients to avoid being in contact with potentially affected personnel.[68] 77.4% of surveyed patients in China also took complementary and alternative medicines to help improve their physical and general wellbeing as they were concerned with the potentially reduced effectiveness of oral therapies versus intravenous therapies. During the pandemic, concerns with the switch to oral therapy also enhanced anxiety and depression levels among patients with more advanced tumours in China.[69] This needs to be avoided going forward through effective educational activities among patients. There was also an increase in adjuvant therapy, typically endocrine therapy with low infection potential, among patients with breast cancer in Hubei Province in China, but a decrease in neoadjuvant therapy during the recent pandemic.[33] In Lithuania, whilst there was an appreciable reduction in diagnostic services at the start of the pandemic, including mammograms for patients with possible breast cancer (−62%), there was also a reduction (−8% versus a similar period in 2019) in systemic anti-cancer treatment (−8% versus a similar period in 2019). However, systemic anti-cancer treatment services recovered and even increased in Lithuania in the last four months of 2020 versus pre-pandemic levels (Table 2).[36]

In Pakistan, guidelines were rapidly produced to sort patients based on the urgency of their care during the pandemic, with patients divided into three groups based on their perceived priority for treatment. The highest priority was for breast cancer patients whose condition was viewed as immediately life-threatening or urgently requiring treatment, with the next priority for breast cancer patients whose condition did not require immediate treatment, ie, could be altered or delayed by four to eight weeks before the pandemic was seen as under control, but still required treatment.[69] Centres in Pakistan also saw patients presenting with more advanced tumours as an aftereffect of lockdown and other measures (Table 2).[41]

In Turkey, Ilgun et al found there was an increase in patients presenting with larger tumour size and more metastatic lymph nodes, along with de-novo stage IV breast cancer cases, during the pandemic.[70] Alongside this, the admission of breast cancer patients was reduced by almost 15% during the pandemic, with delays in patients seeking care enhanced by the fear of catching COVID-19 whilst attending hospital. This was similar to other studies in Turkey, with patient-related time delays in seeking care increasing the number of de novo patients presenting with Stage IV breast cancer in Turkey.[37,70] Of concern is that Kiziltan et al reported a decrease in neoadjuvant therapy during the early stages of the pandemic despite systematic neoadjuvant therapy being suggested in the Turkish guidelines to manage patients' breast cancer during COVID-19, especially for human epidermal growth factor receptor-positive patients (HER+), small size triple-negative (TN), node-negative and luminal breast cancer patients (Table 2).[37,71]

A similar situation has been seen among high-income countries (Table 2). In Canada, Di Lena et al documented an increase in NET among patients with early-stage ER+ breast cancer cases where surgery was delayed due to the pandemic. Encouragingly, breast cancer patients with early-stage ER+ who were taking NET did not experience pathological upstaging of their cancer despite having a longer delay for their surgery.[72] Similarly, 74% of oncologists surveyed in Egypt, Saudi Arabia, and the UAE preferred NET for hormone receptor-positive (HR+) and HER2 negative patients during COVID-19 with delays to surgery and concerns regarding the immune system following traditional chemotherapy. However, 58% of those surveyed still preferred 6 to 8 cycles of neoadjuvant chemotherapy to treat breast cancer patients where delays in surgery. 67% also preferred adjuvant trastuzumab if patients were HER2 positive before delayed surgery.[73] In France, there was a rise in the number of patients presenting with large tumours during the early stages of the pandemic, those with SBR Grade 3 ER-ve tumours, and those with ER-ve tumours, resulting in increased use of NAC with reduced surgery.[43] In the Netherlands, patients diagnosed in the first two months of 2020 also faced treatment delays, with treatments changed from surgical approaches to primarily hormonal therapy where possible to minimize the impact of delayed surgery.[45]

There was also a 40% decline in cancer reporting in New Zealand at the start of the pandemic and a sharp decrease in endoscopies following lockdown measures. Radiation therapy was also affected due to COVID-19 in New Zealand, with a move to deliver the same dose in a shorter time frame. However, activities had bounced back by August 2020.[74] In Portugal, medical choice-making procedures remained unchanged in the most aggressive breast cancer cases. However,

similar to other countries, the prescribing of neoadjuvant therapy increased when there were difficulties with undertaking surgery due to lockdown measures. Where possible, prescribing oral formulations was also proposed to limit attendance at hospitals with associated concerns with catching COVID-19 alongside increasing home delivery of medicines where possible.[75] The prescribing of metronomic chemotherapy, ie, frequent low doses of chemotherapy versus maximum dosing, may also be beneficial during a pandemic to limit the impact of chemotherapy on the immune system and patient recovery times (Table 2).[75,76]

There were similar changes in Singapore to managing patients with breast cancer at the start of the pandemic with the postponement of care where possible. However, out-patient visits should not be postponed for newly diagnosed breast cancer, those with recent onset of symptoms, and those who recently initiated treatment and needed follow-up.[46] In Spain, patients also received adjuvant treatment whilst waiting for surgery assisted by telemedicine support during COVID-19 to reduce hospital visits and the risk of COVID-19 transmission.[77] Patients also presented for surgery with larger tumours during the lockdown in the UK, with NAC interrupted in one study.[53] In another study in the UK, a number of patients still underwent surgery either because they had completed their NAC or because there were concerns with immunocompromising patients if NAC was continued. Alongside this, a number of suitable patients were prescribed endocrine therapy with surgery planned once the pandemic subsided.[52] Increased prescribing of NET was also seen in the British B-MaP-C study, with theatre capacity reduced following the pandemic.[78] In the USA, NET was again appreciable prescribing to reduce the impact of surgical delays during COVID-19, building on the findings of Goldbach et al[65,79] Wilke et al also reported the increased use of NET for ER+/HER+ patients, patients with invasive disease, and those with ductal carcinoma in situ (DCIS) due to COVID-19.[66] Similarly, Murphy et al reported successful selective de-escalation of axillary surgery in breast cancer patients treated with NET.[80]

Across Europe, there was a significant reduction in the workload at breast cancer centres among surveyed institutions at the start of the pandemic, with responders reporting a reduction in their overall workload of 50% or more at the beginning of the pandemic (Table 2). There was also increased time between diagnosis and treatment, increased use of NET with delays in surgery, modification of primary systemic therapy and chemotherapy protocols due to the fear of COVID-19 complications, which included switching to oral therapies where possible or prolonging the interval between cycles.[81] Coles et al suggested an international guideline regarding radiation therapy to modify and limit its use where possible, for example, in patients prescribed NET; however, in the Pan-European survey of Gasparri et al, over 50% of surveyed responders had not altered their radiation therapy schedules during the pandemic.[81,82] Ramdas et al suggested that in LMICs, TARGIT– intraoperative radiation therapy (IORT) could gain more acceptance to improve radiation efficiency and reduce hospital workloads with low complication rates.[83] Dowsett et al also developed international guidelines for breast cancer patients with primary ER+ HER2− tumours. The authors also recommended that breast cancer patients with insufficient endocrine tumours should be managed with NEC or early surgery.[84] Curigliano et al also developed international guidelines to manage patients with breast cancer during COVID-19. Their guidelines included suggested measures regarding triaging and prioritizing patients as well as treating patients on an out-patient basis as much as possible, minimizing hospital visits, and increasing the use of telemedicine. In addition, the place of NEC as well as the place of trastuzumab in HER2+ patients.[85] In their multi-country review and a web-based poll, Rocco et al described the impact of COVID-19 on breast cancer surgical management. They reported that primary systemic treatment was widely accepted by surgeons as an alternative when surgery was postponed. For patients with T2N1 HR+/HER2- tumours, suspicious malignant biopsies, and malignant recurrence excision, more than 50% of surgeons surveyed prioritized NAC over surgery.[86]

Brown et al reported that in several countries, the use of adjuvant bisphosphonates to prevent bone metastasis during COVID-19 had been substantially compromised with delays in CT and bone scans and delays in palliative care radiotherapy for bone pain. These issues, including adequate pain relief for patients with breast cancer, need to be considered in future pandemics to minimize their impact on the morbidity and mortality of patients with breast cancer (Table 2).[87]

Surgical Approaches to Manage Breast Cancer Patients During the Pandemic

As seen in 3.2 (Table 2), the COVID-19 pandemic and associated lockdown measures significantly decreased breast cancer surgical volumes across countries, although the reduction was less in some countries. Among the LMICs, Li et al in China reported an appreciable reduction in the proportion of patients with breast cancer undergoing surgery (16.4% to 2.6%) during the initial pandemic period.[33] In Iran, Sadri et al reported on the successful application of low specific activity of Tc-99m elutes to help with diagnosis and treatment approaches, including surgery with generator shortages.[88] There was also a 35.5% reduction in breast cancer surgeries in Pakistan during the early stages of the pandemic.[89] Breast cancer patients were typically divided in Pakistan into those that require urgent surgery, those where surgery can be altered or delayed for 4–8 weeks, and those where surgery can be postponed until the end of the pandemic combined with other management approaches.[69,90] Sattar et al also documented that surgical patients in Pakistan were prioritized into 3 groups, with surgical procedures divided into elective, semi-elective, orange emergency, and red emergency groups depending on their priority and whether surgery can wait replaced by other treatment approaches.[69] In Turkey, several studies also documented a decline in the number of breast cancer surgeries during the early stages of the COVID-19 pandemic; however, the number of surgeries increased soon after the initial reduction, with Kara et al documenting an increase during the inter-pandemic period (Jun 2020- Sep 2020) to pre-pandemic levels.[37–39,91]

In high-income countries, Illmann et al in Canada reported a 78% reduction in breast reconstruction cases with a complete cessation in breast reconstructive services among 27.4% of responders during the first wave of COVID-19, with less impact in successive waves, with patients prioritized based on their identified need.[92] In France, there was a variable impact, with Dorri et al reporting an 18.05% decrease in surgeries during the first wave, whilst Murris et al reported a variable impact with 50% of participating centres actually increasing their surgical activities, with 33% reducing the number of surgeries during the pandemic, with 17% showing no change, with all centres looking to reduce post-operative stay to reduce the chances of patients catching COVID-19 during hospitalization.[43,93] In Italy, there was a limited reduction in the number of breast cancer surgeries performed during the first wave (8.5%); however, a significant reduction in breast reconstructive surgery was seen during the first wave of the pandemic.[49,94] A significant reduction in breast cancer surgeries was also seen in Japan in the early stages of the pandemic, with similar findings, especially in T1-T2 and N0 tumours, in the Netherlands.[44,95] In South Korea, Kang et al also reported a decline in every type of breast cancer surgery during the pandemic, ie, lumpectomy, mastectomy, lymph node surgeries, sentinel biopsies, axillary lymph node dissections, and breast reconstruction, with appreciable reductions in surgical procedures also seen in the UK in the first wave.[48,52,53] In their survey of surgeons in the USA, Wilke et al reported a partial cessation and modification in elective surgery schedules during the first months of the pandemic and even cessation of all surgeries initially in some hospitals.[66] Yin et al in the USA also documented a weekly decline of 20.5% in surgical procedures versus pre-pandemic levels, with Boyd et al documenting breast cancer surgeries declining by 6.8% in the first wave with the level of breast reconstruction surgery also declining.[57,66] However, Cairns et al in the USA reported no statistically significant difference in the number of breast cancer operations for new patients during the first wave of the pandemic versus pre-pandemic levels.[58]

Alongside these changes, there were also typical changes in surgical approaches due to the pandemic (Table 3). For instance, Vanni et al in Italy reported an increase in axillary lymph node dissection in the first wave, with awake breast conservative surgery being the most frequent surgical procedure during the pandemic.[51,96] Pellini et al in Italy believed re-engineering approaches could optimize pre-operative and post-operative times during pandemics benefitting all.[97] The use of dilutional local anaesthetic (DLA) was seen as a safe and effective alternative approach in the UK to general anaesthesia when performing breast cancer surgeries to help minimize the patient time in the hospital, with Sud et al documenting that even modest delays in surgery in the UK without suitable alternatives would have a significant impact on survival.[98,99] Joseph et al in the USA reported that 39% of surgeons in their study still followed the original plan for breast reconstruction/mastectomy during the pandemic, with chemotherapy or hormonal therapy also used when there were delays in surgery, with Kennard et al reporting that 44% of patients with breast cancer faced treatment changes during the pandemic mainly due to surgical prioritization, with diagnosis to surgery times significantly higher during the pandemic.[65,100]

Curigliano et al (2020), in their multi-country guidelines, suggested that patients should be grouped into urgent, high, intermediate, and low-priority categories based on surgical urgency during the pandemic, with all non-urgent surgeries deferred with systemic therapies and out-patient surgeries adopted were possible.[95] Isaac et al developed

Table 3 Surgery Strategies Across Countries

Surgery Strategies						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/Median Age)**	**Key measurements**	**Key Findings**	**Comments/Suggestions**
Li et al, China[33]	The retrospective multicentre cohort study	1 Apr 2020–15 May 2020	8397 (50 years)	Breast cancer surgeries during COVID-19	The proportion of surgery dropped from 16.4% to 2.6% in Hubei. Despite that, significantly**** more surgery was detected in Hubei compared to other provinces.	Surgeries of early breast cancer were significantly altered due to COVID-19, especially in Hubei.
Sadri et al, Iran[88]	Observational study	7 Mar 2019–18 Apr 2020	35 (48 years)	Application of Tc-99m elute during Mo99-Tc-99m generator shortage	SLNB can be done with excellent results using Tc-99m pertechnetate elute during Mo99-Tc-99m generator shortage.	Using special personal protection, nuclear medicine Departments can perform lymphatic mapping and biopsy.
Sattar et al, Pakistan[69]	Method report	18 Mar 2020–12 May 2020	30 (NR)	Prioritizing surgical patients and proposed workflow	Surgical patients were prioritized into 3 groups. The proposed workflow divided surgical procedures into elective, semi-elective, orange emergency, and red emergency groups.	The institutional workflow can act as a guideline for triaging surgical patients.
Vohra et al, Pakistan[89]	The retrospective comparative cohort study	1 Mar 2019–31 Mar 2021	380 (51 years)	Impact of COVID-19 pandemic on breast cancer surgery	35.5% reduction in breast cancer surgeries during the pandemic compared to the pre-pandemic period.	The decline in breast cancer surgeries is probably caused due to the fear of nosocomial SARS-CoV-2 infection, which lead to decreased breast cancer screening and diagnosis.
Vohra et al, Pakistan[90]	Retrospective observational study	15 Mar 2020–31 Dec 2020	206 (NR)	Surgical prioritization during COVID-19	Surgical procedures were prioritized into 3 groups: urgent, can be delayed for 4–8 weeks, and can be suspended until the pandemic ends. The mean hospital stay was 24 hours. No post-operative complication was recorded.	Implementation of surgical guidelines and multidisciplinary management made successful surgical completions.
Ramdas et al, South Africa[83]	Retrospective study	Nov 2017–May 2020	107 (60.8 years)	Viability and acceptance of TARGIT–IORT	TARGIT–IORT had low complication and recurrence rates which confirms its viability.	TARGIT–IORT can gain more patient acceptance and reduce hospital patient load during the pandemic.
Güler et al, Turkey[39]	Survey	11 Mar 2020–31 May 2020	93 (NR)	Effect of COVID-19 on the number of breast cancer surgeries	Though the number of breast cancer surgeries reduced initially, it soon increased.	Breast cancer surgeries were not affected.
Kara et al, Turkey[91]	Retrospective study	Dec 2019–Nov 2020	332 (NR)	Impact of COVID-19 pandemic on the surgical volume of breast cancer	The number of breast cancer surgeries decreased by 50–60% during the first wave (Apr 2020-May 2020) of the pandemic than in the pre-pandemic period (Dec 2019-Mar 2020), The number of breast cancer surgeries increased during the inter-pandemic period (Jun 2020-Sep 2020) and rose to a similar level during the pre-pandemic period.	The Covid-19 pandemic affected the surgical volume of breast cancer significantly. Allotting some hospitals for breast cancer surgeries could overcome the breast cancer surgical overload due to undone operations during the pandemic.

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Table 3 (Continued).

Surgery Strategies						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/Median Age)**	**Key measurements**	**Key Findings**	**Comments/Suggestions**
Kiziltan et al, Turkey[37]	The single-centre retrospective observational cohort study	11 Mar 2020–1 Jun 2020	350 (51 years)	Impact of COVID-19 pandemic on breast cancer surgery	The number of patients treated with breast cancer surgery reduced significantly during the pandemic (121 vs 229 during the pre-pandemic period).	Hospitals having no SARS-CoV-2 infected patients can be helpful places for escaping surgical delays.
Koca et al, Turkey[38]	Retrospective cohort study	11 Mar 2019–11 Mar 2021	148 (51.2 years)	Impact of COVID-19 on breast cancer surgery	47.7% reduction in the number of patients who underwent breast surgery during the first year of the pandemic, the total number of BCS + sentinel lymph node biopsy (SLNB) decreased, while the number of mastectomies and modified radical mastectomy (MRM) increased during the first year of the pandemic (11 Mar 2020–11 Mar 2021) compared to the year before the pandemic (11 Mar 2019–11 Mar 2020).	The reduction in breast cancer screening and diagnosis during the pandemic resulted in a decline in the total number of surgeries. Regular breast cancer screening should be ensured to restore surgical procedures and reduce the decline in the number of breast cancer surgeries.
High-income countries						
Cadili et al, Canada[107]	Questionnaire survey	13 Oct 2020–31 Dec 2020	123 (54 years)	Patients' perception of telemedicine	Among the operated patients, 85% enjoyed telemedicine consultation, 93% found there was enough time to talk, and 66% wanted to retake the service.	The patients were delighted with telemedicine.
Isaac et al, Canada[101]	Expert opinion	Apr 2021–Jun 2021	NR	Guidelines for BR during COVID-19	During resource shortages, multidisciplinary teams are strategically used for patient sorting using coordinated alternative treatment methods. Patient-centred shifting and consolidation of resources are made easier with collaborative decision-making. Perioperative administration strategies and surgical care plans are applied to expand the provision of BR treatments.	These strategies can ensure optimized patient care.
Illmann et al, Canada[92]	Questionnaire-based cross-sectional survey	Mar 2020–May 2021	49 (NR)	Impact of COVID-19 on breast reconstructive services	First wave of COVID-19: 78% reduction in breast reconstruction cases were reported by the responders, a complete cessation in breast reconstructive services was reported by 27.4% of responders, and all responders reported at least a 5% reduction in breast reconstruction services. The second wave of COVID-19: 31% reduction in breast reconstructive services, complete reconstruction services provided by 8% of the responders, and no report of complete cessation of services. The third wave of COVID-19: An average of 49% reduction in reconstruction services reported by the responders.	Following the local institutional capacity, proper application of best practice standards, guidelines, and strategies may improve breast reconstruction services.

Dorri et al, France[43]	Observational study	Jan 2020–Jul 2020	581 (NR)	Effect of COVID-19 on the number of breast cancer surgeries	Breast cancer surgeries decreased by 18.05% in 2020 compared to 2019. Ambulatory hospitalization rate decreased significantly* in COVID-19 conditions. The IBR after mastectomy rate was not much affected by COVID-19.	The routine gynecological follow-ups should be restored urgently during the COVID-19 period.
Murris et al, France[93]	Multicentre retrospective study	16 Mar 2020–21 May 2020	NR	Effect of lockdown on surgical management of breast cancer	50% of centres increased their surgical activity, whereas 33% reduced during COVID-19. 81% of centres postponed IBR. 83% of centres did conservative surgeries on an outpatient basis.	A total reorganization of the healthcare system was required during the COVID-19 pandemic.
Fancellu et al, Italy[94]	Retrospective comparative study	1 Mar 2020–30 Apr 2020	42 (62 years)	Breast cancer surgeries during COVID-19	The number of IBR***, the use of regional nerve blocks***, and the length of hospital stay** were significantly reduced.	Breast cancer care level was decreased due to COVID-19.
Lisa et al, Italy[103]	Retrospective observational study	9 Mar 2020–9 Apr 2020	51 (53.4 years)	Guidelines for BR during COVID-19	Patients were double-step screened before surgery, proper anesthesia and pain control protocol was followed, patient and clinician protection was ensured, IBRs adopting implants were performed, patients were discharged quickly, post-operative consultations were lessened, and telemedicine was enforced.	The protocol was safe and effective for immediate implant-based BR after tumour resection.
Fregatti et al, Italy[102]	Observational study	9 Mar 2020–9 Jun 2020b	203 (NR)	Preventive surgery strategies during COVID-19	A patient-tailored program was followed to avoid hospitalization of COVID-19 symptomatic patients and to prioritize surgical procedures. Breast-conserving surgery was mainly preferred. Hospital stay was minimized. Systematic home telemonitoring was introduced after the patient's discharge.	Breast cancer surgeries can be safely and effectively provided during COVID-19 by following preventive strategies.
Losurdo et al, Italy[49]	The observational monocentric retrospective study	Mar 2019–Apr 2021	549 (64)	Impact of COVID-19 on breast cancer surgeries	4.6% reduction in the number of breast cancer surgeries (281 in pre-COVID era vs 268 in Covid period), conservative surgery increased by 8.5% whereas mastectomies decreased by the same percent in Covid era, changes in types of surgeries increased significantly in Covid period than in pre-Covid period.	Maintaining standards of care and proper guidelines is the most crucial strategy for handling diagnostic and operative procedure delays during the pandemic.
Marcasciano et al, Italy[109]	Multicentre collaborative study	Oct 2019–Mar 2020	307 (NR)	Role of online videos in the training of breast surgeons	Trainee and faculty surgeons rely on videos from YouTube and other sources for training and education.	Online videos can be helpful for surgeons if the source is reliable.
Pellini et al, Italy[97]	Case-control study	Jan 2018–Jun 2020	341 (62 years during COVID-19)	Efficacy of interventions by lean thinking	No significant difference was found in lengths of pre-admission and stay between COVID and characteristics-matched pre-COVID groups.	The interventions can optimize preoperative and postoperative times during COVID-19.

(*Continued*)

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Table 3 (Continued).

Surgery Strategies						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/Median Age)**	**Key measurements**	**Key Findings**	**Comments/Suggestions**
Vanni et al, Italy[51]	Multicentric retrospective study	11 Mar 2020–30 May 2020	203 (NR)	Breast cancer surgeries during COVID-19	Significant* increase in sentinel lymph node biopsy and axillary lymph node dissection during lockdown compared to before.	N/A
Vanni et al, Italy[96]	Retrospective monocentric study	30 Jan 2020–30 Mar 2020	86 (64.77 years)	Breast cancer surgeries during COVID-19	Awake breast surgery*** and awake BCS** significantly increased during COVID-19 than before. A significant* decrease in operative room time and length of hospital stay was found	Awake surgery and ERAS protocols can be followed to reduce cross-infection and patient discharge time.
Saeki et al, Japan[44]	Survey study	Jan 2019–Mar 2021	2877 (NR)	Influence of COVID-19 pandemic on breast cancer surgeries	The number of surgeries significantly decreased during the pandemic compared to the pre-pandemic period.	The reduction in breast cancer surgeries during the COVID-19 pandemic was caused due to decreased screening, triage, and postponement of surgeries for stage 0 patients.
Filipe et al, Netherlands[95]	The multicentre retrospective cohort study	9 Mar 2020–17 May 2020	217 (62.2 years)	Effect of COVID-19 on the number of breast cancer surgeries	Breast cancer surgeries were dramatically reduced, especially in T1-T2 and N0 tumours. Having co-morbidities and undergoing mastectomy were significant* risk factors for post-operative complications.	The National breast cancer screening program should be restarted, and patients should visit general practitioners more.
Mok et al, Singapore[46]	Observational study	Feb 2020–May 2020	NR	Surgery strategies during COVID-19	Non-urgent surgeries were deferred. Oncological, therapeutic, intermediate, and diagnostic surgery requiring cases were performed. Oncoplastic and IBR surgeries were also done. The surgical team was subdivided to continue operations if any group was quarantined.	These strategies can help prioritize surgical cases and adapt to evolving COVID-19 situations.
Brenes Sánchez et al, Spain[77]	Retrospective observational study	22 Apr 2020–6 May 2020	28 (57 years)	Surgery strategies and patients' satisfaction after surgery during COVID-19	Patients were categorized into 3 groups based on priority: high, medium, and low. A pre-operative COVID-19 protocol was maintained. Non-urgent surgeries were deferred. After surgery, patients' satisfaction was "very good" and "excellent" as per the EORTC IN-PATSAT32 questionnaire.	The prioritization of patients and following the pre-operative COVID-19 protocol led to successful surgeries and gaining patients' satisfaction.
Kang et al, South Korea[48]	A multi-institutional retrospective cohort study	1 Feb 2019–31 Jul 2020	2398 (53 years)	Impact of COVID-19 pandemic on breast cancer surgery	The number of breast cancer surgeries, ie, lumpectomy, mastectomy, lymph node surgeries, sentinel biopsies, axillary lymph node dissections, and breast reconstruction surgeries, decreased during the pandemic period in 2020 compared to the pre-pandemic period in 2019.	Continuation of routine screenings, COVID vaccination of individuals having risk factors such as the family history of cancer, and immediate medical attention after experiencing breast cancer symptoms are recommended.

Abdalla et al, UK[104]	Cohort study	16 Mar 2020–18 May 2020	130 (57.6 years)	Breast cancer surgeries during COVID-19	Patients were prioritized and screened for COVID-19 before surgery. Mostly held surgical procedures were WLE + SLNB (40.77%), mastectomy + SLNB (18.46%), and mastectomy + axillary node clearance (18.46%). About 86% of tumours were grade 2 or 3, similarly prevalent.	Early implementation of modified surgical policies can reduce patient complications, COVID-19 infectivity, and negative impacts of COVID-19.
Batt et al, UK[98]	Observational study	NR	74 (64 years in the DLA group)	Efficacy of dilutional local anesthetic (DLA)	Postoperative pain did not increase significantly in the DLA group, though the pain score was higher during 30 and 60 minutes than in the control group.	DLA can be a safe and effective alternative approach to performing breast cancer surgeries.
Ho et al, UK[112]	Retrospective study	03 Jun 2020–31 Dec 2020	46 (50.7 years), 29 (51.7 years)	Breast cancer surgeries during COVID-19	During the pandemic, fewer DIEP flaps were done. Flap weight was found significantly increased. The post-operative length was significantly**** less.	Autologous BR was safely conducted throughout the pandemic.
MacInnes et al, UK[52]	Multi-centre observational study	16 Mar 2020–24 Apr 2020	202 (57 years)	Surgery strategies during COVID-19	Strict COVID-19 protocols were followed. Patients were instructed to isolate themselves for 2 weeks before surgery. All clinicians wore full PPEs. The number of operations was minimized by 38% compared to 2019 to reduce infection. The patients were released on the surgery day whenever possible.	No mentionable unexpected event occurred. So, surgeries can be safely delivered during COVID-19 by following safety protocols strictly.
Romics et al, UK[53]	Cohort study	31 Jul 2019–7 May 2020	179 (54 years)	Breast cancer surgeries during COVID-19	Significantly fewer BCS**** and increased level II oncoplastic conservation*** during COVID-19. No IBR was offered during the lockdown. No perioperative COVID-19-related complication arrived.	More oncoplastic breast conservations should be done as IBR was not offered after mastectomy due to COVID-19 risk. Breast cancer surgeries can be safely done in selected patients in a population where 50% have co-morbidities.
Sud et al, UK[99]	Observational study	2013–2020	NR	Effect of surgical delay due to COVID-19	Surgical delay of 3–6 months had minimal impact on the survival of early-stage breast cancer patients.	Alternative breast cancer management strategies should be evaluated to reduce surgical delay-related mortality.
Kennard et al, USA[65]	Cohort study	1 Mar 2020–15 Jun 2020	73 (60.6 years)	Surgery strategies during COVID-19	44% of patients faced treatment change during COVID-19, and it was significantly* linked to surgical prioritization. Diagnosis to surgery time was significantly *** higher in the change group than in the no-change group.	Surgical prioritization leads to deferring surgical time for many patients.
Ludwigson et al, USA[108]	Questionnaire survey and interview	Aug 2020 – Feb 2021	133 (NR)	Patients' perception of telemedicine	Among the patients presenting for surgical consultation, 63% attended telemedicine appointments, and 67% were satisfied with their experience.	The patients were satisfied with telemedicine.
Murphy et al, USA[80]	Observational study	2008–2019	186 (66 years)	Surgical management of axilla following NET	Selective de-escalation of axillary surgery was done effectively in breast cancer patients treated with NET in the same way as the current way of treating first with surgery.	Breast cancer patients receiving NET can be managed safely by adopting the same way as patients with similar tumours treated with a surgery-first approach.

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Table 3 (Continued).

Surgery Strategies						
Low- and Middle-Income Countries						
Studied Country	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/Median Age)**	**Key measurements**	**Key Findings**	**Comments/Suggestions**
Mo et al, USA[106]	Retrospective, population-based cohort study	1 Mar 2019–1 Dec 2020	2942 (NR)	Follow-up after resection of stage I/II breast cancer during COVID-19 situations	Only 42% of patients attended follow-up during the pandemic. Patients being younger, with lower socio-economic status, and previously taking adjuvant radiotherapy were more likely to participate in the follow-up.	Breast cancer survival rate can decline if in-person follow-up care is not re-established after the pandemic, as telemedicine is not enough.
Specht et al, USA[105]	Clinical trial	Feb 2020–Mar 2020	15 (45.38 years)	Same day mastectomy and BR	A protocol consisted of pre-operative, day of surgery, and post-operative sections. Patients' hospital visits were minimized before and after surgery by emphasizing telehealth services. Surgical oncology and plastic surgery teams operated together. Patients were discharged after a few hours of surgery.	Same-day mastectomy and BR can be successfully performed following the protocol to reduce infection risk and optimize hospital resources during the pandemic.
Worldwide						
Curigliano et al, Worldwide[85]	Guidelines	NR	NR	Guidelines for breast cancer surgeries during COVID-19	Based on surgical urgency, patients were grouped into urgent, high, intermediate, and low-priority categories. All non-urgent surgeries were suggested to be deferred. Outpatient surgeries were recommended to be adopted.	N/A
Rocco et al, Worldwide[86]	Questionnaire survey	4 Apr 2020–14 Apr 2020	112 (NR)	Impact of COVID-19 on breast cancer surgical management	Countries adopted the triage system in Phase 2 or 3 of the pandemic. Patients with progressive disease on NAC completed NAC, small TN, HER2+ BC, T2N0 HR+/HER2- breast cancer not eligible for neo-adjuvant treatment were prioritized. Primary systemic treatment was widely accepted by surgeons as an alternative when surgeries got postponed. For T2N1 HR+/HER2- tumours, suspicious malignant biopsies, and malignant recurrence excision, more than 50% of surgeons prioritized NAC over surgery. The pandemic phase and the surgical restriction level were significantly*** associated. Benign cases, re-excision cases, in-situ HR+ cases, autologous BR surgery, and bilateral procedures were mainly deferred.	The physicians were reluctant to shift from conventional guidelines whenever possible. Alternative strategies were followed if not possible.

Notes: ****p≤0.0001, ***p≤0.001, **p≤0.01, *p≤0.05.

Abbreviations: ERAS, Enhanced Recovery after Surgery; ECOG, Eastern Cooperative Oncology Group; NR, not reported; NAF, nipple aspirate fluid; BR, breast reconstruction; IBR, immediate breast reconstruction; GAD-2, Generalized Anxiety Disorder two-item questionnaire; IORT, intraoperative radiation therapy; BCS, breast conservation surgery; DCIS, ductal carcinoma in-situ; ER, the estrogen receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; PgR, progesterone receptor; ST, systematic therapy; TN, triple-negative; NAC, neo-adjuvant chemotherapy; CDK, cyclin-dependent kinase; ET, endocrine therapy; N/A, not available.

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guidelines for breast reconstruction services during the pandemic in Canada. They suggested that multidisciplinary teams could be strategically used for patient selection and triage, with centralized and collaborative approaches adopted, including surgical approaches.[101] In Italy, Fregatti et al developed a telephone-triaged system to help avoid hospitalization of COVID-19 symptomatic patients. They prioritized agreed surgical procedures, with telemonitoring facilities initiated following discharge. Lisa et al also developed guidelines ensuring patient and clinician protection and discharging patients quickly, which was helped by appropriate pain management telemedicine facilities.[102–104] In Singapore, Mok et al included deferring non-urgent surgeries in their guidelines, performing surgery with the shortest anaesthesia and post-operative period.[46] In Spain, Brenes Sánchez et al introduced similar guidelines with surgery deferred where possible, aided by systemic therapy, and, when performed, designed to minimize complications and post-operative stay.[77]

Abdalla et al in the UK also reported on patient prioritization and screening for COVID-19 before surgery given reduced facilities.[104] Specht et al in the USA reported that same-day mastectomy and breast reconstruction could be successfully performed following an agreed protocol, with surgical oncology and plastic surgery teams operating together and discharging patients after a few hours of surgery to reduce infection risk and optimize hospital resources.[105] Mo et al in the USA evaluated the efficacy of follow-up after resectioning stage I/II breast cancer during COVID-19 situations. They suggested that breast cancer survival rates decline if follow-up care is not fully re-established.[106]

There was an appreciable increase in telemedicine and telecommunication facilities for treatment and training during the pandemic following lockdown and other measures, especially in high-income countries. In Canada, Cadili et al evaluated the patients' perception of telemedicine and reported that among operated patients, 85% enjoyed telemedicine consultations, 93% found there was enough time to talk, and 66% wanted to resume the service, with appreciable satisfaction with telemedicine appointments also seen in the USA.[107,108] Marcasciano et al in Italy reported on the role of online videos in the training of breast surgeons given the closure of medical schools across countries at the start of the pandemic; however, there were concerns about their reliability which need to be addressed going forward.[109–111]

Management of Breast Cancer Patients with COVID-19

There was a variable impact on breast cancer patients infected with COVID-19 (Table 4). In Pakistan, in the study of Vohra et al, 4.9% of asymptomatic patients were subsequently identified pre-operatively to have COVID-19. These patients were later operated on when tests were negative, with no complications post-operatively. 4.6% were identified as having COVID-19 when receiving neoadjuvant or systemic therapy. All patients recovered well, with chemotherapy re-commenced once virus-

Table 4 Management of Breast Cancer Patients with COVID-19

Breast cancer patients with COVID-19						
Low-and Middle-income countries						
Studied Countries	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/ Median Age)**	**Key Measurements**	**Key Findings**	**Comments/ Suggestions**
Wei et al, China[113]	Multi-centre retrospective study	13 Jan 2020–15 Apr 2020	45 (62 years)	COVID-19 severity after chemotherapy in breast cancer patients	COVID-19 symptom onset within 7 days after chemotherapy can increase the risk of severe COVID-19, manifested by neutropenia and augmented CRP, LDH, and procalcitonin levels.	Oral chemotherapy can be administered where possible. If not, intravenous chemotherapy can be helped by taking necessary measures within strict observations.
				Baseline factors increasing severity of COVID-19 in breast cancer patients	Age >75 and lower ECOG score are associated with increased risk of COVID-19 severity in breast cancer patients.	Ideal supportive treatment and preventive care is necessary for these patients.

(*Continued*)

Table 4 (Continued).

Mooghal et al, Pakistan[41]	A single-centre retrospective cohort study	1 Jan 2020–30 Jun 2021	12 (59.75 years)	Effects of the COVID-19 pandemic on the management of the breast cancer patients infected with COVID-19	The majority of the Covid-19-positive breast cancer patients (9 out of 12) had disease upstaging, and half of the Covid-positive patients (6 out of 12) had a late presentation due to the lockdown	A significant correlation was found between breast cancer upstaging and COVID status. Reconsideration of the performed protocols for COVID-positive breast cancer patients is required.
Vohra et al, Pakistan[90]	Retrospective observational study	15 Mar 2020–31 Dec 2020	292 (NR)	Surgery and treatment of breast cancer patients with COVID-19	4.9% of surgical and 4.6% ST receiving patients tested COVID-19 positive. No severe complication was developed in them. Their surgery/treatment continued after remission.	The COVID-19 infection rate and related complications were low in breast cancer patients.
High-income countries						
Fregatti et al, Italy[102]	Observational study	9 Mar 2020–9 Jun 2020b	203 (NR)	The death rate of breast cancer patients with COVID-19	3 out of 207 breast cancer patients were hospitalized after being infected by COVID-19, all of which died.	COVID-19 imposes an increased risk of mortality in breast cancer patients.
Kathuria-Prakash et al, USA[115]	Observational study	1 Jan 2020–31 Dec 2020	132 (60 years)	Hospitalization of breast cancer patients with COVID-19	Older age*, comorbidities**, lobular subtype*, and Hispanic/Latinx ethnicity* were significantly associated with hospitalization. Endocrine therapy might protect from worse conditions.	N/A
Kuderer et al, USA, Canada, Spain[114]	Cohort study	17 Mar 2020–16 Apr 2020	928 (66 years)	Prevalence of breast cancer among cancer patients with COVID-19	Breast cancer was the most prevalent malignancy (21%).	N/A

Notes: **p≤0.01, *p≤0.05.

Abbreviations: ERAS, Enhanced Recovery after Surgery; ECOG, Eastern Cooperative Oncology Group; NR, not reported; NAF, nipple aspirate fluid; BR, breast reconstruction; IBR, immediate breast reconstruction; GAD-2, Generalized Anxiety Disorder two-item questionnaire; IORT, intraoperative radiation therapy; DCIS, ductal carcinoma in-situ; BCS, breast conservation surgery; ER, the estrogen receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; ST, systematic therapy; TN, triple-negative; NAC, neo-adjuvant chemotherapy; CDK, cyclin-dependent kinase; ET, endocrine therapy; N/A, not available.

free.[89] Mooghal et al found that most COVID-19-positive breast cancer patients in their study had disease upstaging due to a lack of awareness of their disease and lockdown measures.[41]

Wei et al in China measured the clinical characteristics of breast cancer patients affected with COVID-19 and the risks related to anti-cancer treatment. They found that 73.3% of breast cancer patients developed non-severe COVID-19, while 26.7% of patients developed severe conditions, and 6.7% died. Those patients aged >75 and lower Eastern Cooperative Oncology Group (ECOG) scores were significantly related to COVID-19 severity. Those who initiated chemotherapy within 7 days before the onset of COVID-19 symptoms also had a significant association with COVID-19 severity, with more pronounced neutropenia compared with other breast cancer patients. As a result, patients receiving IV chemotherapy need to be carefully monitored until at least 7 days after stopping chemotherapy.[113]

Among the high-income countries, Kuderer et al found breast cancer to be most prevalent (21%, 191 out of 928) among cancer patients infected with COVID-19 in the USA, Canada, and Spain, which needs to be carefully handled in view of the immune system being compromised by chemotherapy (Table 4).[114] Fregatti et al in Italy reported that COVID-19 posed an increased risk of mortality in breast cancer patients, with all 3 breast cancer patients (out of 207 studied) hospitalized in their study due to COVID-19 infections subsequently dying.[102] However, Kathuria-Prakash et al in the USA in their study reported that patients who received endocrine therapy were less likely to suffer from adverse conditions with COVID-19 infections. Overall, 30.3% of breast cancer patients with COVID-19 infection had to be

hospitalized in their study, 8.3% needed intensive care, and 6.1% died. Older age, the presence of comorbidities, lobular subtype, and Hispanic/Latinx ethnicity were significantly associated with hospitalization due to COVID-19.[115]

Perspectives and Mental Conditions of Breast Cancer Patients During Covid-19

Eight studies were identified, with the vast majority from high-income countries. Among LMICs, Juanjuan et al reported that poor general condition, aggressive breast cancer, and close contact with patients with COVID-19 enhanced anxiety, depression, and insomnia (Table 5).[116]

Table 5 Mental Health State of Patients with Breast Cancer During the Pandemic

Perspectives and mental conditions of breast cancer patients						
Low- and middle-income countries						
Studied Countries	**Type of Study**	**Study Period**	**Number of Subjects (Mean/ Average/ Median Age)**	**Key Measurements**	**Key Findings**	**Comments/ Suggestions**
Juanjuan et al, China[116]	Cross-sectional survey study	16 Feb 2020–19 Feb, 2020	658 (NR)	Psychological conditions of breast cancer patients during COVID-19	Anxiety, depression, distress, and insomnia are significantly correlated with the general condition by self-identification, treatment discontinuation, clinical stage of breast cancer, Wuhan exposure, close contact with COVID-19 patients, central venous catheter flashing, and diagnosis time of breast cancer, with a few exceptions.	The psychological conditions of breast cancer patients should be addressed more during COVID-19.
High-income countries						
Fregatti et al, Italy[102]	Observational study	9 Mar 2020–9 Jun 2020	203 (NR)	Fear of COVID-19	7.4% of breast cancer patients were more afraid of COVID-19 than their cancer.	N/A
Vanni et al, Italy[119]	Monocentric retrospective study	16 Jan 2020–20 Mar 2020	160 (post-COVID: 59.5 years)	Refusal of procedure and surgery	Significantly* more refusals during COVID-19 than before.	Fear of COVID-19 can be a cause of refusal. Physicians should give patients mental support and warn them about the adverse effects of delay
Kennard et al, USA[65]	Cohort study	1 Mar 2020–15 Jun 2020	73 (60.6 years)	Anxiety and breast care outlook	Treatment change occurred in 44% of patients. Around 30% of the difference and no-change groups showed anxiety positivity in the GAD-2 score. The change group reported that COVID-19 significantly* affected their breast care outlook.	Anxiety levels did not differ between the change and no-change groups.
Ludwigson et al, USA[108]	Questionnaire survey and interview	Aug 2020–Feb 2021	133 (NR)	Fear of COVID-19	Among the patients presenting for surgical consultation, 50% feared the pandemic's impact on their cancer care or recovery, and 66% noted anxiety about getting COVID-19.	Patients inform anxious about infection with COVID-19 and potential care modifications.
Sokas et al, USA[117]	Telephone interview	1 May 2020–7 May 2020	8 (66 years)	Effect of surgical delays	Significant distress was recorded due to breast cancer and COVID-19. Most patients were not surprised and accepted the delays though anxiety persisted. Poorly communicated patients were more distressed.	Delay-related distress should be anticipated early, and surgeons should directly contact patients to reassure them.

(*Continued*)

Table 5 (Continued).

Soriano et al, USA[118]	Cross-sectional study	27 Jun 2020–13 Aug 2020	50 (60.1 years)	The psychological impact of surgical delay due to COVID-19	Fear and psychological distress were low-to-moderate. Fear of cancer progression was significant among 26% of patients. One-third of patients still waiting for surgeries reported lower satisfaction with communication.	Overall psychological difficulties of waiting-for-surgery patients were similar to those who already had surgeries. The psychological states can be managed well.
Wilke et al, USA[66]	Review report	1 Mar 2020–15 Mar 2021	2791 (62.7 years)	Patients' perspectives on receiving breast cancer therapy and diagnosis during the COVID-19 pandemic	Elderly patients were more willing to receive NET during the pandemic; node-positive patients with increasing age were comparatively more likely to receive core biopsy genomic testing, whereas node-negative patients were less inclined to accept such genomic testing.	N/A

Note: *p≤0.05.

Abbreviations: ERAS, Enhanced Recovery after Surgery; ECOG, Eastern Cooperative Oncology Group; NR, not reported; NAF, nipple aspirate fluid; BR, breast reconstruction; IBR, immediate breast reconstruction; GAD-2, Generalized Anxiety Disorder two-item questionnaire; IORT, intraoperative radiation therapy; DCIS, ductal carcinoma in-situ; BCS, breast conservation surgery; ER, the estrogen receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; ST, systematic therapy; TN, triple-negative; NAC, neo-adjuvant chemotherapy; CDK, cyclin-dependent kinase; ET, endocrine therapy; N/A, not available.

Fear and anxiety among breast cancer patients due to COVID-19, and its associated impact on treatment schedules, were also seen in high-income countries. Interestingly, Fregatti et al in Italy found that 7.4% of breast cancer patients were more afraid of COVID-19 than their cancer.[102] Low to moderate fear and psychological distress were also seen among breast cancer patients in the USA.[108,117] Ludwigson et al observed fear among 50% of the patients presenting for surgical consultation about their cancer care and recovery during the pandemic, with 66% being anxious about contracting COVID-19.[108] However, Sokas et al found that most patients were not surprised and accepted their treatment delays; however, there was poor communication with patients, and these patients were more distressed about their treatment during the pandemic.[117] Soriano et al also had concerns with communication between patients and physicians during the pandemic in the USA, exacerbating fear and psychological distress.[118]

Fear of COVID-19 also resulted in more refusals for procedures, including surgery, among breast cancer patients during the pandemic. Providing mental support and warning patients about the adverse effects of treatment delays could minimize the number of refusals and alternative treatment strategies.[119] Interestingly, Kennard et al in the USA found no difference in anxiety levels between patients who had undergone treatment change as a result of the pandemic and those patients who had no change in their cancer treatment regimen, with approximately 30% of the patients in both groups showing anxiety.[65]

Particular attention should be given to the psychological condition of breast cancer patients as part of management strategies, as most breast cancer patients undergo anxiety, depression, and distress exacerbated by lockdowns and other measures (Figure 2).

Guidelines for the Management of Breast Cancer Patients

The various published guidelines (17 identified – 3 from LMICs, 11 from high-income countries, and worldwide) typically prioritized the patients into high, medium, and low-priority groups for management during the pandemic. Their content is summarised in Table 6.

Discussion and Recommendations

As mentioned, at the start of the pandemic, there were no known effective treatments or vaccines for COVID-19 and primarily relied on early diagnosis.[120,121] This impacted the diagnosis and management of breast cancer patients during the pandemic. This included concerns with late diagnosis due to lockdown and other measures, and the subsequent impact on potential neoadjuvant treatment regimes, including NET, as a result of delays in surgery. Potential approaches to surgery were suggested and undertaken, including prioritizing patients based on their needs

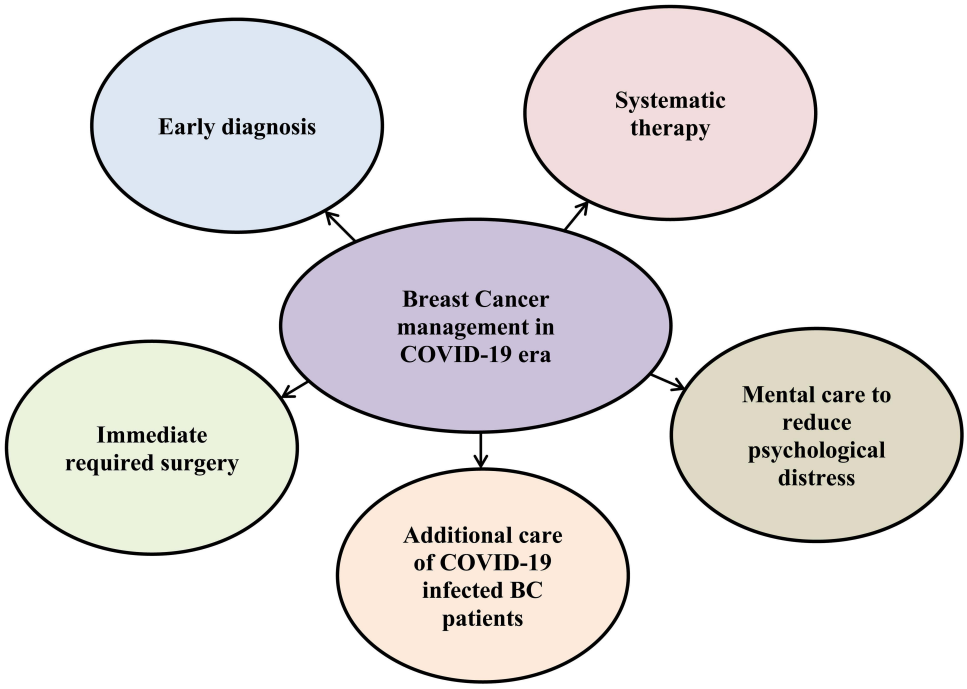

Figure 2 Strategies of Breast Cancer Management During The COVID-19 Pandemic.

given restrictions in available facilities, besides limiting post-operative stay where possible. Radiation changes were also implemented, along with changing IV chemotherapy regimens to oral therapies where possible to limit time spent with out-patients. Alongside, there was also an increase in telemedicine approaches before and after surgery to cut down on hospital visits across countries.

The various findings across countries (summarised in Tables 1–3) resulted in developed guidelines across countries (Table 6). There was little difference in the recommendations between LMICs versus high-income countries, with a key area being the agreed prioritization of patients. Significant reductions in breast cancer screening and diagnosis, reduction in out-patient visits, and extended diagnosis to treatment period were noticed among both LMICs and high-income countries. However, the situations were typically worse among LMICs. However, high-income countries, eg, Italy and Canada, followed different protocols and guidelines to screen and categorize patients based on their COVID-19 status and clinical scenarios to avoid spreading COVID-19. More adjuvant therapy and less neoadjuvant treatment, increased shift from intravenous to oral treatment, more complementary and alternative medicine, increased upstaging of advanced-stage breast cancer, reduced admission, and patient-related delay were more noticeable among the LMICs. In contrast, the high-income countries applied various strategies such as increased telemedicine, referring to NET more, reducing non-essential visits, and expanding the application of NAC to meet the challenges. The proportion of breast cancer surgeries dropped notably among various LMICs and high-income countries during COVID-19, primarily due to lockdowns and restrictions. However, different high-income countries adopted various strategies to address the challenges of lockdown and virus transmission, eg, telemedicine consultation, coordinated alternative treatment methods, proper screening, and dividing the patients into groups based on priority. Numerous guidelines regarding patient management, diagnosis, and surgery, such as prioritizing and classifying patients based on disease conditions, priority and other criteria, and pre-operative, operative, and post-operative strategies, were adopted and followed by various LMICs and high-income countries during COVID-19 to alleviate breast cancer treatment. However, the availability of more resources and preventive measures in high-income countries could lead to better care and management of breast cancer patients during the pandemic. This needs to be explored further going forward. In any event, the published guidelines provide a basis for discussions among all key stakeholder groups managing patients with breast cancer in new waves

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Table 6 Specific Guidelines Used for Different Selective Patients

Studied Country	Published Guidelines, Their Development, and Patient Selection Criteria
	Low-and Middle-income countries
Sattar et al, Pakistan[69]	*Guidelines*: At the Aga Khan University of Pakistan, the Multidisciplinary Breast Program Leadership Committee (BPLC) developed and approved guidelines for breast disease management. The recommendations were to the ethical guidelines developed by the Sindh Institute of Urology and Transplantation (SIUT), Karachi's the Centre of Biomedical Ethics and Culture (CBEC). *Patient selection criteria*: Priority A: Patients with immediately life-threatening or symptomatic conditions will require urgent treatment. Priority B: Patients do not require immediate treatment but started treatment before the pandemic is under control. Treatment of priority B may be delayed for 4–8 weeks. Priority C: patients having conditions that can be safely deferred until after the pandemic is under control. To facilitate decision-making in the respective disciplines, these groupings were defined for each speciality, such as surgery, medical oncology, radiation oncology, breast imaging, genetics, and pathology.
Vohra et al, Pakistan[90]	*Guidelines*: Formal guidelines were designed and approved by a Multidisciplinary Breast Cancer Team at the hospital. *Patient selection criteria*: 1. Urgent care: (a) Breast Abscess – aspiration or I&D should be considered. (b) Ischemic mastectomy flap warranting revision. (c) Hematoma warrants evacuation. (d) T1N0M0 (TN) tumours are of high priority for surgery. NAC may be considered for T1c. (e) Malignant phyllodes tumours. (f) Angiosarcoma. (g) Progressive local disease on systemic therapy. (h) Autologous reconstruction warranting revascularization/ revision (during the pandemic, no reconstruction to be performed). 2. Intervention may be altered or delayed for 4–8 weeks: (a) $ER^-/HER2^+$ invasive tumours. Post-NAC is a high priority for surgery, but surgeries can be deferred by 4–8 weeks until the healthcare facilities tackle the surgical cases. (b) Invasive TN tumours. Post-NAC is a high priority for surgery, but surgeries can be deferred by 4–8 weeks until the healthcare facilities tackle the surgical cases. (c) Discordant core biopsies seem to be malignant on excision. 3. Intervention may be delayed until the pandemic is over: (a) ER- tumours on core biopsy, responsive to NAC; (b) ER+ tumours on core biopsy, responsive to NAC; (c) Non-progressive DCIS (ER^+/ER^-); (d) Sentinel node for invasive tumour identified on the previous excision; (e) Margin re-excision; (f) Duct excision for nipple discharge; (g) Fibro epithelial benign-borderline lesions (phyllodes or fibro adenomas); (h) High-risk lesions (papilloma, atypia); (i) BR; (j) Prophylactic surgery.
Sezer et al, Turkey[71]	*Guidelines*: Guidelines were developed based on a consensus of experienced surgeons and medical oncologists for breast cancer surgical delay management during the COVID-19 outbreak. *Patient selection criteria*: 1. Strong endorsement: For a new patient: (a) With stage T1N0M0, TN tumour (HER2- /HR-), grade 3, receiving NST (4–6 months) with a suitable regimen is preferred. (b) With stage T1N0M0, HER+ tumour, grade 3, receiving NST (4–6 months) with proper treatment (eg anti-HER2 treatment) is preferred. (c) With stage T1N0M0, luminal A-like (HER2- /HR highly+/ Ki67<15%) tumour, grade 1, receiving NET alone (4–6 months) is preferred. (d) With HER2+ /HR+ tumours with a clinical response after NST, receiving combined endocrine treatments (with/without RT) and anti-HER2 is suitable (e) With a luminal B-like (HER2- /HR low+) tumour with a complete clinical response after NST, receiving endocrine treatment only (with/without RT) is prefered. For a new post-menopausal patient: (f) With stage T1-2N1M0, luminal A-like (HER2-/HR-highly +/Ki67<15%) tumour, grade 2, receiving NET alone (4–6 months) is preferred. (g) With HER2+ /HR- tumours with clinical response after NST, anti-HER2 treatment (with/without RT) is suggested. 2. Endorsed: (a) For a new pre-menopausal patient with stage T1-2N1M0, luminal A-like (HER2- /HR highly+/ Ki67<15%) tumour, grade 2, receiving NAC alone (4–6 months) is suggested. (b) For a new patient with stage T1N0M0, luminal B-like (HER2- /HR low+/Ki67>15%) tumour grade 2, receiving combined NAC and endocrine treatment (4–6 months) is suggested. 3. Weak endorsement (only by absolute majority >50% with rejection rate ≥ 25%): For a pre-menopausal patient with HER2+ /HR- tumour who had a complete clinical response after NST, continuing with anti-HER2 treatment alone (with/without RT) is suggested.
	High-income countries
Illmann et al, Canada[92]	*Guidelines*: Guidelines were developed to address concerns with surgery for breast cancer patients during the pandemic, divided into 4 approaches: 1. Triage and patient selection strategies. 2. Clinic shifting and consolidation of operating room resources strategies. 3. Strategies for peri-operative management. 4. Surgical management strategies. *Patient selection criteria*: 1. Patient selection: (a) Ensuring pre-operative testing facilities for all surgical patients, (b) applying neo-adjuvant chemotherapy or endocrine therapy to increase mastectomy to partial mastectomy conversion or lengthen the surgical resection period. 2. Clinic shifting and consolidation of operating room resources: (a) Proper alteration of operating room time allocation among the plastic surgeons and surgical oncologists for IBR cases, (b) shifting of reconstructive services to outpatients' facilities, (c) proper allocation of surgical facilities and resources among the plastic surgeons. 3. Peri-operative and surgical management: (a) Ensuring enhanced recovery after surgeries, (b) limiting the application of autologous breast reconstruction as well as the types of surgical procedures, (c) advancement of oncoplastic reconstructions, and (d) proper staging of the reconstruction with temporary prosthesis insertion.
Isaac et al, Canada[101]	*Guidelines developed covered 6 key areas*: 1. Strategic use of multidisciplinary teams for patient selection and triage. 2. Centralized, coordinated use of alternate treatment plans during times of resource restrictions. 3. Shared decision-making. 4. Patient-centered shifting. 5. Consolidation of resources. 6. Targeted application of perioperative management strategies and surgical treatment plans.

Lisa et al, Italy[103]	*Guidelines developed covered 4 key areas*: 1. Team structure and preoperative assessment: plastic surgery team subdivisions into subgroups; double-step COVID-19 screening of patients before surgery. 2. Anesthesia and pain control: Video laryngoscopy in lieu of classical tracheal intubation; Intercostal and inter-fascial blocks; and TPVBs of the pectoral area for alleviating postoperative pain and ensuring quick release; adequate safety of anaesthesiology team and nurses. 3. Intraoperative recommendations: IBR using implants (breast prosthesis or tissue expanders); contralateral healthy breast symmetrization deferral; suspension of microsurgical flaps or pedicled flaps; proper safety of the operators. 4. Post-operative protocol and telehealth: postoperative consultation abatement; telemedicine consultation to avoid a hospital visit. *Patient selection criteria*: A double-screening protocol to identify possible COVID-19 patients requiring surgery in agreement with rules made by the Lombardy government: 1. 3 days before surgery or less: a low-dose CT scan of the chest (2.5mm thickness) and a pharyngeal swab were done. 2. On the day of surgery: signs of breathing difficulties, cough, pharyngitis, and diarrhea were tested. If body temperature was found to be over 37.7°C for >3 times (at an interval of 30 minutes), the surgical process was postponed.
Pellini et al, Italy[97]	*Guidelines*: Critical interventions based on lean thinking: 1. Consultation with the breast surgeon. 2. If further diagnosis is needed, consult the surgeon again with diagnostic reports. 3. Pre-admission and additional check-ups depending on co-morbidities. 4. If a sentinel lymph node biopsy is needed, Lymphoscintigraphy was done a day before admission. 5. Priority-based admission is made. 6. Surgery, pectoral nerve blocks, and fluorescence-guided surgery are performed. 7. Medications are given before discharge.
Fregatti et al, Italy[102]	*Guidelines covered 2 main areas*: 1. "Patient Screening Flow-chart" to avoid hospitalized COVID-19 symptomatic patients. 2. Prioritization of surgical procedures by "Patient Selection Guidelines" proposed by the American College of Surgeons. *Patient selection criteria*: 1. Treating group patients: (a) aged <50 years and in clinical-stage T1/2 N0, and with $ER^+/PgR^+/HER2^-$ tumours, (b) in clinical-stage T1 N0, and with TN or $HER2^+$ tumours, (c) with cTisN0 lesions (nodular presentation, G3 or extensive micro-calcification area), (d) with biopsies suspected to be malignant, B4, (e) finished neo-adjuvant treatment (any T or N stages), (f) having a recurrence of malignancy excision, (g) uncertain malignant potential Tru-cut biopsy, B3 (h) requiring re-excision surgery. 2. Deferred group patients: (a) having duct excision (in case of suspected intraductal papillomas mostly), (b) with benign lesions (nodules, fibroadenoma), (c) with doubtful biopsies seems to be benign, B3, (d) >50 years old in clinical stage T1/T2 N0 and with $ER^+/PgR^+/HER2^-$ tumours, receiving neoadjuvant hormonal treatment, (e) BRCA1 or BRCA2 positive patients with prophylactic mastectomy, (f) in clinical stage N+ and any T, referred to neoadjuvant therapy, (g) with tumours responding to NAC.
Vanni et al, Italy[96]	*Guidelines covered 2 main areas*: 1. Awake surgery; 2. Enhanced Recovery After Surgery (ERAS) protocols.
Mok et al, Singapore[46]	*The guidelines developed covered 5 key areas*: 1. Outpatient visits: outpatient visits should be minimized and replaced with telehealth services if possible; conditions that would augment the risks of delayed deterioration or relapse should be prioritized. 2. Screening/imaging: hospital visits should be minimized; all screening imaging should be deferred for 6–12 months; conditions that would augment the risks of deterioration or relapse if delayed should be prioritized. 3. Surgery: urgent/life-threatening conditions should be considered for surgery only; oncologic resection should be performed with the shortest anesthesia, minimized hospital stay, most minor morbidity, and fastest recovery; alternative strategies to surgery should be considered in suitable cases. 4. Systemic treatment: systemic treatments imposing minimal immunosuppression risks should be chosen; treatment should be delayed as per current evidence in case of limited resources; treatment duration (dose-dense) should be shorter; visits should be minimized as much as possible. 5. Radiation therapy: should be postponed for 3–6 months in case of limited resources; accelerated partial radiation therapy or shorter fractions should be applied in selected cases. *Patient selection criteria*: 1. Outpatient visits: (a) patients requiring routine follow-up or having benign conditions were deferred. (b) breast abscess, breast imaging-reporting and data system 4 or 5 categories, suspicious mammogram or ultrasound results, suspicious signs and symptoms of breast cancer, and/or newly diagnosed breast cancer cases were accepted. (c) Breast cancer patients on routine follow-up were treated within the last 2 years because the risk of recurrence of breast cancer within the first 2 years of treatment is more significant. 2. Screening/imaging: patients recalled for unusualness identified on screening mammogram under BSS were selected for review. 3. Surgery: (a) non-urgent diagnostic and benign breast surgeries were postponed. (b) Oncological cases, therapeutic surgery, or cases requiring diagnostic surgery for suspicious lesions and indeterminate cases were given priority. 4. Systemic and radiation therapy: were continued for all patients who require these.

(*Continued*)

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Table 6 (Continued).

Studied Country	Published Guidelines, Their Development, and Patient Selection Criteria
Brenes Sánchez et al, Spain[77]	*The guidelines developed covered 2 key areas*: 1. "Traffic light" system to evaluate surgical time. 2. A pre-operative COVID-19 protocol to avoid symptomatic patients' hospitalization. *Patient selection criteria*: 1. High priority (red, surgical process should be done within 2 weeks): Patient who completed NAC and/or additional mono-chemotherapy in progressing breast cancer and ER^- tumours. 2. Medium priority (yellow, surgical process should be done within 4 weeks): Patients taking endocrine therapy without genomic testing. Higher priority was given to younger females taking neoadjuvant endocrine therapy. 3. Low priority (the green surgical process can be done after 4 weeks): Elderly patients receiving endocrine therapy and patients with re-excision surgeries, anti-HER2 monotherapy, and DCIS (ER^+/ER^-). Comorbidities and patients' preferences were also considered to applying the triage. Cosmetic, benign, and risk-reducing surgeries were deferred. Patients were screened for COVID-19 symptoms via telephone before admission for surgery, and the patients with symptoms were deferred to 2 weeks later for further evaluation.
MacInnes et al, UK[52]	*Followed guidelines covered 2 key areas*: 1. Regularly revised local management-guided strategies; 2. Recommendations from the Association of Breast Surgery, NHS England, and The Royal Colleges of Surgeons concerning the use of PPE, pre-operative COVID-19 screening, and case prioritization. *Patient selection criteria*: To increase the time between the movement of patients and maintaining social distancing, the number of surgical patients on a list was reduced by adjustments.
Kennard et al, USA[65]	*Guidelines*: COVID-19 Breast Cancer Consortium recommendations. *Patient selection criteria*: Priority A: Operative drainage and evacuation for breast abscess/hematoma. Priority B1: First, give NAC or $HER2^-$ targeted therapy or proceed to surgery depending on institutional resources for TN and $HER2^+$ tumours. Priority B2: Operate patients receiving neoadjuvant treatment, finishing treatment, or progressing on treatment depending on resources or extend neoadjuvant therapy if possible. Priority B3: consider NET with a delay of surgery in patients in clinical stage T2 or N1 $ER^+/HER2^-$ tumours. Priority C1: (a) Delay surgery of ER^- DCIS unless there is a greater risk of invasive cancer. (b) Give NET and delay surgery in clinical stage T1N0 ER^+/ HER2– tumours. Priority C2: (a) Give NET and delay operation in ER^+ DCIS. (b) Delay surgery in high-risk lesions. Priority C3: (a) Delay operation in benign lesions and discordant biopsies seemingly benign. (b) Delay operation in prophylactic surgery.
Specht et al, USA[105]	*Guidelines covered 3 key areas*: 1. Pre-operative protocols: surgical oncologists and plastic surgery units co-operated in surgical planning, emphasizing the selection of patients; pre- and post-operative medications were sent to patients, patients' were given education, and the visiting nursing association service was set up. 2. Day of surgery protocols: ERAS protocol was adopted to perform blocks; simultaneous operation by surgical oncology and plastic surgery teams; nipple-sparing and pre-pectoral placement was done to minimize pain, operating time, and dissection; intravenous medications were avoided; patients were observed for 4–6 hours; instructions for discharge were written. 3. Post-operative protocols: drains were removed by visiting nurses at weeks 1 and 2; virtual follow-ups were done by both surgical oncology and plastic surgery units, and the surgical oncology team reviewed pathology reports. *Patient selection criteria*: (a) Requiring unilateral or bilateral mastectomy with tissue expanders or direct-to-implant BR. (b) Age <75 years. (c) American Society of Anesthesiology score <4. (d) Reside within a 2-hour distance from the hospital. (e) Has proper support at home. (f) Stage of cancer was not taken into account.

Worldwide	
Brown et al, Worldwide[87]	*Guidelines*: Modified guidelines of the American Society of Clinical Oncology – ASCO to prevent bone metastasis in breast cancer: 1. Advanced breast cancer: intravenous use of zoledronic acid 4 mg every 12 weeks if Denosumab 120 mg cannot be administered subcutaneously every 4 weeks. If it is also not possible, bisphosphonates, ie, Clodronate 1200 mg and Ibandronate 50 mg, should be administered daily. 2. Early breast cancer: Zoledronic acid 5 mg should be considered once a year if intravenous Zoledronic acid 4 mg/6 months or oral Clodronate 1600 mg/day are unavailable. 3. Early breast cancer and prevention of bone loss: WHO FRAX score should be considered if DEXA scans are unavailable to assess bone mineral density.
Curigliano et al, Worldwide[85]	*Guidelines covered several scenarios to guide management* according to the European centre disease control during the pandemic: Scenario 1: Multiple introductions but limited local transmission in the country. Scenario 2: Increasing number of introductions and more widespread reports of localized human-to-human transmission in the country. Scenario 3: Localised outbreaks, which start to merge, becoming indistinct. Scenario 4: Widespread, sustained transmission where healthcare systems are overburdened. Prioritization was categorized into 4 sections: urgent, high priority, medium priority, and low priority, based on the 4 scenarios. The sections are: (a) outpatient, screening and diagnostic visits, (b) surgery, (c) radiotherapy, and (d) systemic treatment (divided into [i] early breast cancer and [ii] metastatic breast cancer). *Patient selection criteria*: diverse, based on the sections, modularity, scenario, and priority.
Dowsett et al, Worldwide[84]	*Guidelines*: Guidelines were developed for managing primary ER^+ $HER2^-$ breast cancer patients deferred from surgery due to COVID-19. *Patient selection criteria*: Group 1: Patients (~5% of all) whose Allred scores are ER≤6 and PgR<6. NET should not be considered for these patients, and surgery is preferred. Group 2: patients (~35% of all) whose Allred ER=7/8 and PgR<6 or ER=6/7 and PgR≥6. NET should be started for them, and a Ki67 diagnosis should be made. If Ki67≤15%, then NET should be considered. If Ki67>15%, a core biopsy should follow after 2–4 weeks. If Ki67≤10% is found, then NET should be continued. If Ki67>10% is found, then surgery should be chosen. Group 3: Allred ER=8 and PgR≥6 patients for whom NET is preferable only.

Abbreviations: ERAS, Enhanced Recovery After Surgery; NAC, neo-adjuvant chemotherapy; ER, the estrogen receptor; NA, not available; HER, human epidermal growth factor receptor; PgR, progesterone receptor; TN, triple-negative; PPE, personal protective equipment; DCIS, ductal carcinoma in-situ; BRCA, breast cancer gene; TPVB, thoracic paravertebral block; IBR, immediate breast reconstruction; BSS, BreastScreen Singapore; BR, breast reconstruction; NET, neo-adjuvant endocrine therapy; HR, hormone receptor; NST, neo-adjuvant systemic treatment; RT, radiation therapy; SLNB, sentinel lymph node biopsy.

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of COVID-19 and future pandemics. The published studies suggest that breast cancer surgeries can be safely and effectively performed during pandemic situations by strictly following safety protocols and surgical management guidelines. All non-urgent surgeries should be deferred and supported by adjuvant therapies, including NET, where applicable. All surgical patients must be tested for COVID-19 negative before surgery, with surgery delayed if needed until patients test negative.

It is also important that healthcare professionals involved in managing patients with breast cancer, including physicians, regularly speak with patients during the pandemic to discuss their situation and potential approaches, including planned changes in treatment. This is vital to help reduce rising levels of anxiety and depression among patients (Table 5). Studies have shown increased anxiety and depression among breast cancer patients if there is limited communication between physicians and patients, which needs to be avoided in the future. In addition, physicians talking with patients can help address their concerns about coming to the hospital for vital procedures rather than delaying surgery and subsequent management where this can be undertaken.[117,118] This is vital to reduce future morbidity and mortality, which can be avoided by the prompt treatment that can be undertaken.

There was a variable impact on breast cancer patients who developed COVID-19. However, the administration of chemotherapy should be carefully monitored among these patients, given concerns about the impact on the immune system of patients and the potential for increased morbidity and mortality if they subsequently develop COVID-19 (Table 4). These concerns have resulted in moves to switch to oral therapies where possible and a re-look at chemotherapy administration regimes, including metronomic chemotherapy.[76]

Conclusion

It was a challenge for healthcare professionals to recommend and adopt ideal strategies to manage patients with breast cancer care during the current pandemic as countries had typically not experienced such events before, including extended lockdown activities. As diagnostic facilities became more limited at the start of the pandemic, advanced-stage cancers began to be detected. This resulted in multiple research activities across countries to ascertain the current situation and its impact to guide potential ways forward to address current challenges. Guidance and activities included developing potentially new diagnostic approaches, including self-screening, given concerns with undertaking clinics. Alongside this, instigating potentially new treatment approaches to alleviate the problems caused by the reduced number of surgical procedures. New strategies included greater use of neo-adjuvant endocrine or chemotherapy alongside changes in surgical strategies. In addition, increasing where possible, the use of telemedicine and oral chemotherapy to limit hospital attendance. These proposals, combined with suggestions for prioritizing breast cancer patients for treatment, including surgery, were contained in numerous guidelines developed across both LMICs and high-income countries to optimize the management of breast cancer patients during pandemics. We will continue to monitor the situation to limit the impact of successive waves of the pandemic on the morbidity and mortality of patients with breast cancer, including their mental health.

Abbreviations

AC, Adjuvant Chemotherapy; BCS, Breast Conservation Surgery; BR, Breast Reconstruction; DCIS, Ductal Carcinoma In-Situ; DLA, Dilutional Local Anesthetic; ER, Estrogen Receptor; ET, Endocrine Therapy; HER, Human Epidermal Growth Factor Receptor; HR, Hormone Receptor; IBR, Immediate Breast Reconstruction; IORT, Intraoperative Radiation Therapy; NAC, Neo-Adjuvant Chemotherapy; NAF, Nipple Aspirate Fluid; NET, Neo-Adjuvant Endocrine Therapy; PPE, Personal Protective Equipment; PR, Progesterone Receptor; SLNB, Sentinel Lymph Node Biopsy; ST, Systematic Therapy; TN, Triple-Negative; WLE, Wide-Local Excision.

Author Contributions

All authors made a significant contribution to the work, whether that is in the conception, study design, acquisition of data, analysis, and interpretation, or in all these areas; took part in writing, revising, or reviewing the article; gave final approval of the final version; have agreed on the journal choice; and agreed to be accountable for all aspects of the work.

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