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REVIEW ARTICLE

Cross Talk between COVID-19 and Breast Cancer

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Abstract: Cancer patients are more susceptible to COVID-19; however, the prevalence of COVID-19 in different types of cancer is still inconsistent and inconclusive. Here, we delineate the intricate relationship between breast cancer and COVID-19. Breast cancer and COVID-19 share the involvement of common comorbidities, hormonal signalling pathways, gender differences, renn-in-angiotensin system (RAS), angiotensin-converting enzyme-2 (ACE-2), transmembrane protease serine 2 (TMPRSS2) and dipeptidyl peptidase-IV (DPP-IV). We also shed light on the possible effects of therapeutic modalities of COVID-19 on breast cancer outcomes. Briefly, we conclude that breast cancer patients are more susceptible to COVID-19 in comparison with their normal counterparts. Women are more resistant to the occurrence and severity of COVID-19. Increased expressions of ACE2 and TMPRSS2 are correlated with occurrence and severity of COVID-19, but higher expression of ACE2 and lower expression of TMPRSS2 are prognostic markers for overall disease free survival in breast cancer. The ACE2 inhibitors and ibuprofen therapies for COVID-19 treatment may aggravate the clinical condition of breast cancer patients through chemo-resistance and metastasis. Most of the available therapeutic modalities for COVID-19 were also found to exert positive effects on breast cancer outcomes. Besides drugs in clinical trend, TMPRSS2 inhibitors, estrogen supplementation, androgen deprivation and DPP-IV inhibitors may also be used to treat breast cancer patients infected with SARS-CoV-2. However, drug-drug interactions suggest that some of the drugs used for the treatment of COVID-19 may modulate the drug metabolism of anticancer therapies which may lead to adverse drug reaction events.

Keywords: Cytokine storm, ACE-2 receptors, diabetes, breast cancer, TMPRSS2, DPP-IV.

1. INTRODUCTION

A cluster of coronavirus disease (COVID-19) cases were first reported in Wuhan, Hubei Province, China in late 2019 [1]. Soon, within a few months, this infectious disease became a pandemic. As on November 19, 2020, the total number of COVID-19 confirmed cases were 55,659,785 with mortality of 1,338,769 [2]. Clinical studies revealed that the severity and mortality of COVID-19 patients were higher in case of comorbidities such as obesity, diabetes, metabolic syndrome, and hypertension [3-5]. Interestingly, women are less susceptible to COVID-19 and exhibited a significantly lower mortality rate, compared to the males [6-8]. Hence, estrogen was thought to be a major factor that inversely regulates the severity of COVID-19 among women [6]. Several studies reported that angiotensin-converting enzyme 2 (ACE2) receptors, dipeptidyl peptidase-IV (DPPP4) and transmembrane protease serine 2 (TMPRSS2) played a crucial role in the molecular pathogenesis of COVID-19 and their inhibitors were effective with varying efficiency for the treatment of COVID-19 [9-12].

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It is noteworthy that the association of COVID-19 with age, sex, hormones and metabolic comorbidities directly links this pathology with breast cancer. Understanding cross-talk between COVID-19 and breast cancer is quite important to make clinical decisions related to treatment modalities for breast cancer patients infected with SARS-CoV-2.

Breast cancer is the most common malignancy among women and the second leading cause of cancer-related mortality [13]. Breast cancer progression and severity are associated with the same comorbidities that are known to affect the clinical outcome and severity of COVID-19, which include obesity, diabetes and metabolic syndrome [13]. In molecular pathogenesis of breast cancer and COVID-19, expression levels of androgen, estrogen, ACE2, DPP-IV and TMPRSS2 play a critical role that resultantly decides the severity of disease and clinical outcomes [9-12, 14-19].

Therefore, in the present review, we shed light on the intricate relationship of COVID-19 and breast cancer pathogenesis in which we discuss the common comorbidities, gender differences, the role of sex hormones, therapeutic modalities of COVID-19 and their possible influence on breast cancer outcomes, clinical management strategies for breast cancer patients during COVID-19, transcriptomics and functional genomics studies of breast cancer in context to molecular players of COVID-19.

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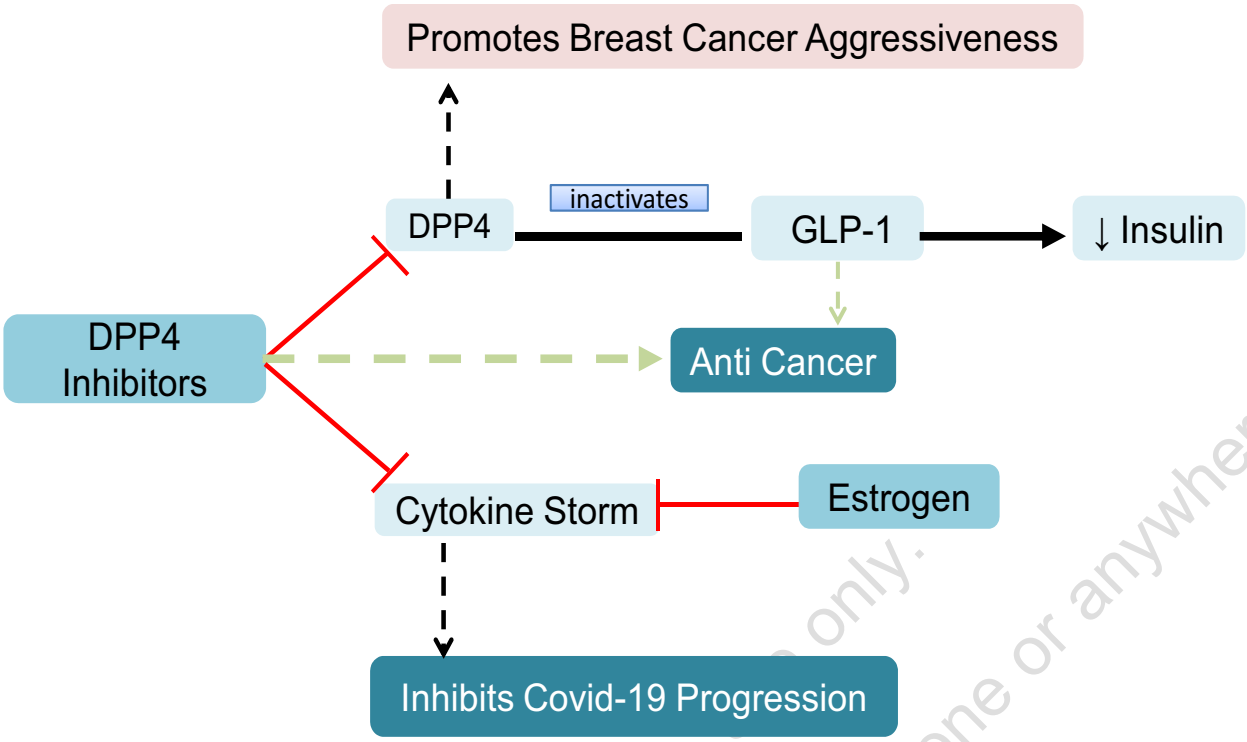

Fig. (1). Role of DPP-IV in the pathogenesis of diabetes, breast cancer and COVID-19. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. ROLE OF ACE2, DPP-IV AND TMPRSS2 IN COVID-19 PATHOGENESIS

Cellular entry of SARS-CoV-2 depends upon the binding of viral spike protein (S) to the cellular receptors. The SARS-CoV-2 binds with membrane-bound angiotensin-converting enzyme-2 (ACE2) receptors [10]. During this process, the priming of the S protein is performed by the host cell protease, *i.e.* transmembrane protease serine 2 (TMPRSS2) [10, 20]. The target cells for SARS-CoV-2 co-express the ACE2 receptor and TMPRSS2, which suggests that mutations in these two proteins may affect the clinical outcomes of COVID-19 [9]. As ACE2 and TMPRSS2 contribute to the SARS-CoV-2 entry and pathogenesis of COVID-19, high levels of ACE2 and TMPRSS2 may worsen the clinical outcome of COVID-19 patients. Recently it has also been suggested that besides ACE2 and TMPRSS2, SARS-CoV-2 also uses DPP-IV as a co-receptor [11]. It is pertinent that besides COVID-19, ACE2, TMPRSS2 and DPP-IV are also known to be associated with the prognosis and clinical outcomes of breast cancer patients (Fig. **1**).

3. DIFFERENTIAL EXPRESSION OF ACE2 AND TMPRSS2: RELATION WITH COVID-19 AND BREAST CANCER

Cancer patients are more vulnerable to acquire infection of SARS-CoV-2 and have a higher risk of severity [21]. However, the prevalence of different types of cancer in patients with COVID-19 is still inconsistent and inconclusive [22-24]. Some interesting comparative studies have deduced the influence of COVID-19 on various cancer types.

One recent meta-analysis and bioinformatics analysis based study was conducted by Wang and Huang (2020) [25] to explore the prevalence of different types of cancer in patients with COVID-19. In this study, they have also evaluated the gene expression levels of ACE2 and TMPRSS2 in normal and seven commonly occurring tumour samples by using Gene expression profiling interactive analysis (GEPIA). A meta-analysis of 205 patients from 6 retrospective studies revealed that the highest prevalence was observed in lung cancer patients; among them 24.5% of patients were infected with SARS-CoV-2, followed by colorectal cancer patients with 20.5% prevalence. This study observed a 13% prevalence of breast cancer patients who acquired SARS-CoV-2 infection. Results of ACE2 and TMPRSS2 expression from GEPIA database showed that the mRNA expressions of these genes were higher in lung and colorectal cancer followed by breast cancer. Here it is noteworthy that in normal tissues, ACE2 expression and distribution is organ-specific; higher expression was observed in the kidneys, testis, female breast, and cardiovascular and gastrointestinal systems. Thus, it may increase the likelihood of COVID-19 in breast cancer patients. Moreover, high expression of ACE2 correlates with increased survival and good prognosis in breast, renal and liver cancers [18, 19, 26].

Another study conducted by Dai *et al.*, (2020) [27] explored the gene expression of three key genes involved in the pathogenesis of COVID-19, out of which ACE2 and TM-

PRSS2 expression were positively correlated with the infection, whereas interferon-inducible transmembrane protein 3 (IFITM3) showed antiviral activity. Low expression of IFITM3 in immune cells suggested that SARS-CoV-2 might attack lymphocytes and induce cytokine release syndrome (CRS). It is worth noticing that lungs express very low levels of ACE2 as compared to the other organs, but still, lungs are the most affected organs, which might be due to the low expression of the protective gene IFITM3. This study also revealed the susceptibility of COVID-19 among 14 different types of tumour based on the difference in the expression of ACE2, TMPRSS2 and IFITM3. By using the cancer genome atlas dataset (TCGA) and Genotype tissue expression (GTEx) dataset, they revealed that invasive breast carcinoma (BRCA) expresses ACE2, TMPRSS2 and IFITM3 differentially in comparison to the normal cells. However, this data showed increased expression of TMPRSS2, IFITM3 and low expression of ACE2 in invasive breast carcinoma, as compared to the normal cells. The provided data suggested that the susceptibility for COVID-19 is greater in case of a higher expression of TMPRSS2 if associated with lower expression of IFITM3. In the case of BRCA, there was a high expression of both TMPRSS2 and IMITM3 along with the low expression of ACE2, which suggested low susceptibility to SARS-CoV-2 infection and severity. However, more aggressive breast cancer subtypes express low levels of ACE2, which is associated with poor prognosis. This study suggests that in comparison with the other cancer types, breast cancer patients are less susceptible to the infection of SARS-CoV--2, which may be further consolidated with the fact that women are more resistant to the infection and severity of COVID-19 as compared to men (breast cancer is prevalent among women).

Similarly, Huang *et al.*, (2020) [28] also compared ACE2 expression between cancers and matched normal tissues using GEPIA for a variety of cancers and found similar data as observed by Wang and Huang (2020) [25]. This study also revealed the higher expression of ACE2 in invasive breast carcinoma (BRCA), which was correlated with the high overall survival (OS) and disease-free survival (DFS). Further, gene set enrichment analysis (GSEA) on the related signalling pathways was conducted, which triggered various metabolic and immunologic pathways, including allograft rejection, autoimmune thyroid disease, sphingolipid biosynthesis ganglio series, graft versus host disease, NOD-like receptor signalling pathways, and primary immunodeficiency. Immune infiltration using tumour immune estimation resource (TIMER) and GEPIA deduced that ACE2 was positively and significantly associated with the infiltration of immune cells in invasive breast carcinoma. It is remarkable that tumour-infiltrating lymphocytes (TILs) can influence prognosis and response to therapy in breast cancer subtype--dependent manner [29].

Infiltration of the lymphocytes including, both T and B lymphocytes in breast cancer, was positively correlated with a good prognosis, disease-free survival and overall survival. It has been suggested that the infiltration of lymphocytes was the result of the immunologic resistance developed against the tumour antigens [30]. We believe that in patients with breast cancer showing higher levels of ACE2 in tumours may invoke antitumor immunity and improve the clinical outcome through internal resistance; hence, COVID-19 infection to the breast cancer patients showing higher expression of ACE2 may increase the anti-viral response besides more likelihood of viral entry in these subjects.

Immunologic resistance against a variety of tumours is a concern and neoantigen plays an important role. Neoantigens or tumour specific antigens (TSA) are derived from various mutations occurring in the process of carcinogenesis and these changes make them truly foreign proteins. This repertoire of the peptides is displayed on the tumour surface and could be specifically recognized by neoantigen-specific T cell receptors (TCRs) and displayed by major histocompatibility complexes (MHCs) molecules. These neoantigens influence the clinical outcomes through various ways including, but not limited to: (i) the occurrence of antitumor immune response *via* T cell recognition of neoantigens, (ii) the relationship between tumour mutation/ neoantigen burden and clinical outcomes to immune checkpoint blockade (iii) and the induction of the antitumor effects through therapeutic vaccines or adoptive T cell transfer based on neoantigens [31].

We want to pose an interesting question that whether SARS-CoV-2 infection to the breast cancer patients may serve as a neoantigen to trigger cell-mediated anti-tumour response to the cancer patients? Because, in virus-associated tumours such as human papillomavirus (HPV), oropharyngeal cancer, Merkel cell polyomavirus (MCPyV) and Epstein-Barr virus (EBV) related head and neck cancers; epitopes derived from the open reading frame (ORFs) of the viral genome contribute as a potential source of neoantigens and the underlying anti-tumour immunologic response [32-34]. However, it is equally important to understand whether it may also promote the cytokine storm.

Emerging reports also speculate that SARS-Cov-2 may use DPP-IV/ CD26 as a co-receptor, as also reported for MERS-CoV [11]. A wide distribution of DPP-IV/CD26 on various cell types, including epithelial cells, systemic endothelial cells, lung, kidney, small intestine and heart, supports the possibility of DPP-IV to serve as a co-receptor for SARS-CoV-2 viral entry [12]. The presence of this receptor on human respiratory tract and lung tissue cells may facilitate the entry of SARS-CoV-2 into the airway itself and may contribute to the immunopathology of the COVID-19, such as cytokine storm. DPP-IV inhibitors are also reported for their beneficial effects on the pathogenesis of MERS-CoV [35], making DPP-IV inhibitors (such as gliptins) a potential therapy to treat COVID-19 [11, 36].

Interestingly, DPP-IV expression was associated with aggressive breast cancer and metastasis to the lungs [16, 17, 37]. DPP-IV inhibitors and GLP-1 agonists were found to be effective against breast cancer progression [38-40].

4. THE CANONICAL AND NON-CANONICAL REN-IN-ANGIOTENSIN SYSTEM (RAS) IN NORMAL PHY-SIOLOGY

The understanding of the molecular pathogenesis of COVID-19 revealed that the SARS-CoV-2 entry is mediated by the binding of S (spike) protein with angiotensin-converting enzyme-2 receptors (ACE2) [10]. Here it is important to understand the intricate role of the rennin-angiotensin system (RAS) in breast cancer, inflammation, infection of SARS-CoV-2 and cytokine storm for the development of an appropriate therapeutic regimen of COVID-19 in breast cancer patients.

In classical RAS, when renal blood flow decreases in juxtaglomerular cells of the kidney, blood precursor protein prorenin gets converted into renin by enzyme convertase. Then rennin converts angiotensinogen (released from the liver) into angiotensin I. Now, angiotensin I is converted into angiotensin II by angiotensin-converting enzyme (ACE). This angiotensin participates in increasing vasoconstriction and a resultant increase in blood pressure (BP). Angiotensin II also promotes secretion of aldosterone from the adrenal cortex, which increases sodium and water reabsorption from renal tissue, whereas excretion of the potassium increases the extracellular fluid volume and blood pressure [41, 42]. To exert underlying effects, angiotensin II binds to the type I angiotensin II receptor (AT1R) and AT2R3 [42]. Angiotensin II is involved in the activation of sympathetic nervous system tone, cardiac hypertrophy, fibrosis, inflammation, vascular smooth muscle dedifferentiation and production of reactive oxygen species (ROS). Besides, angiotensin II decreases parasympathetic nervous system tone, baroreflex sensitivity, nitric oxide (NO) production, and natriuresis [43-55].

In the non-canonical pathway, angiotensin II can be further processed into angiotensin 1-7 by angiotensin-converting enzyme -2 (ACE-2), which then metabolizes into alamandine. Angiotensin II can also be cleaved by aspartate decarboxylase (AD) to form angiotensin A, which is also metabolized into alamandine by ACE2. Aminopeptidase A can also process angiotensin II and converts it into angiotensin III, which acts through AT1R. Angiotensin III can be cleaved by alanyl aminopeptidase N (APN) to generate angiotensin IV, which binds to AT4R.

Angiotensin I can be processed by ACE2, which converts it into angiotensin 1-9. Angiotensin I can also be processed by neprilysin (NEP) to produce angiotensin 1–7.

Angiotensin IV, in contrast to the canonical RAS, exerts opposite effects after binding with AT4R, which includes an increase in NO production [56], reducing vasoconstriction [57], VSMC dedifferentiation [58], anti-inflammatory [59] and cardioprotective effects [59]. Similarly, angiotensin 1-9 can activate AT2R and exert similar effects as shown by angiotensin IV including natriuresis [60], increased NO production, vasodilation and reduced blood pressure, cardioprotection, anti-inflammatory, attenuation of cardiac hypertrophy and fibrosis [61]. Angiotensin 1-7 exerts its functions through binding with the proto-oncogene Mas receptor (Mas R) and reduces both blood pressure [62] and noradrenaline release in the hypertensive rodent model [61]. Activation of Mas R leads to the generation of NO, natriuresis, vasodilation, parasympathetic nervous tone and baroreflex sensitivity [63-66]. Alamandine binds with Mas-related G protein-coupled receptor member D (MRDG) and produces the same effects as observed for angiotensin 1-7, except natriuresis [67-69].

5. ROLE OF THE RENNIN-ANGIOTENSIN SYSTEM (RAS) IN COVID-19 AND BREAST CANCER: IMPLI-CATIONS IN THERAPEUTIC DECISION MAKING

Some reports suggest the likelihood of severe COVID-19 in ER+ breast cancer patients who are on tamoxifen estrogen inhibitor therapy [70]. It may be because estrogen plays a protective role against COVID-19, whereas estrogen inhibition by tamoxifen increases the risk of COVID-19 in breast cancer patients. This mechanism is based on the RAS. During the pathogenesis of COVID-1 9, the virus blocks ACE2 and resultantly decreases the production of angiotensin 1-7, which is anti-proliferative, anti-cancer, anti-inflammatory and anti-oxidant in nature [70]. At the same time, there will be an increase in the ACE, which is associated with some breast cancer types [71]. Hence, ACE will convert angiotensin I into angiotensin II, which activates AT1R, thus promoting proliferation, angiogenesis and tamoxifen resistance in breast cancer [71]. Angiotensin II will be further converted into angiotensin III by another enzyme, aminopeptidase, which further enhances the angiogenesis, tumorigenesis and chemo-resistance. Importantly, ACE2 helps in the viral entry, but premenopausal women have higher ACE2 expression than postmenopausal women and men, which makes the infection of SARS-CoV-2 more severe in men and postmenopausal women. Presumably, estrogen reinforces the effects of angiotensin 1-7 and angiotensin 1-7 exerts protective effects against ischemic cardiac damage, acute respiratory distress syndrome and vasodilating effects. Besides, estrogen-mediated up-regulation of ER-α in T lymphocytes also increases the release of interferon I and III that alleviates COVID-19. Another important reason of the severity of COVID-19 in patients on tamoxifen therapy is that tamoxifen promotes apoptosis of lung cells through mutations and loss of ER-α receptors on lung cells and also *via* P-glycoprotein inhibitory effects which result in the suppression of T cell functions and interferon release [70]. Thus, exogenous estrogen therapy may be useful to alleviate the severity of COVID-19 (Fig. **2**).

Another therapeutic option for COVID-19 may be a specific and selective inhibitor of APA, *i.e.* RB150/fibristat; the first prodrug which was shown to be clinically and biologically well tolerated even at higher doses in phase I clinical trial phase on healthy human subjects and with lowered BP [72].

The SARS-CoV-2 viral entry also depends on the serine protease TMPRSS2 secreted by the host cells and this protease performs priming of the S protein to facilitate its bind-

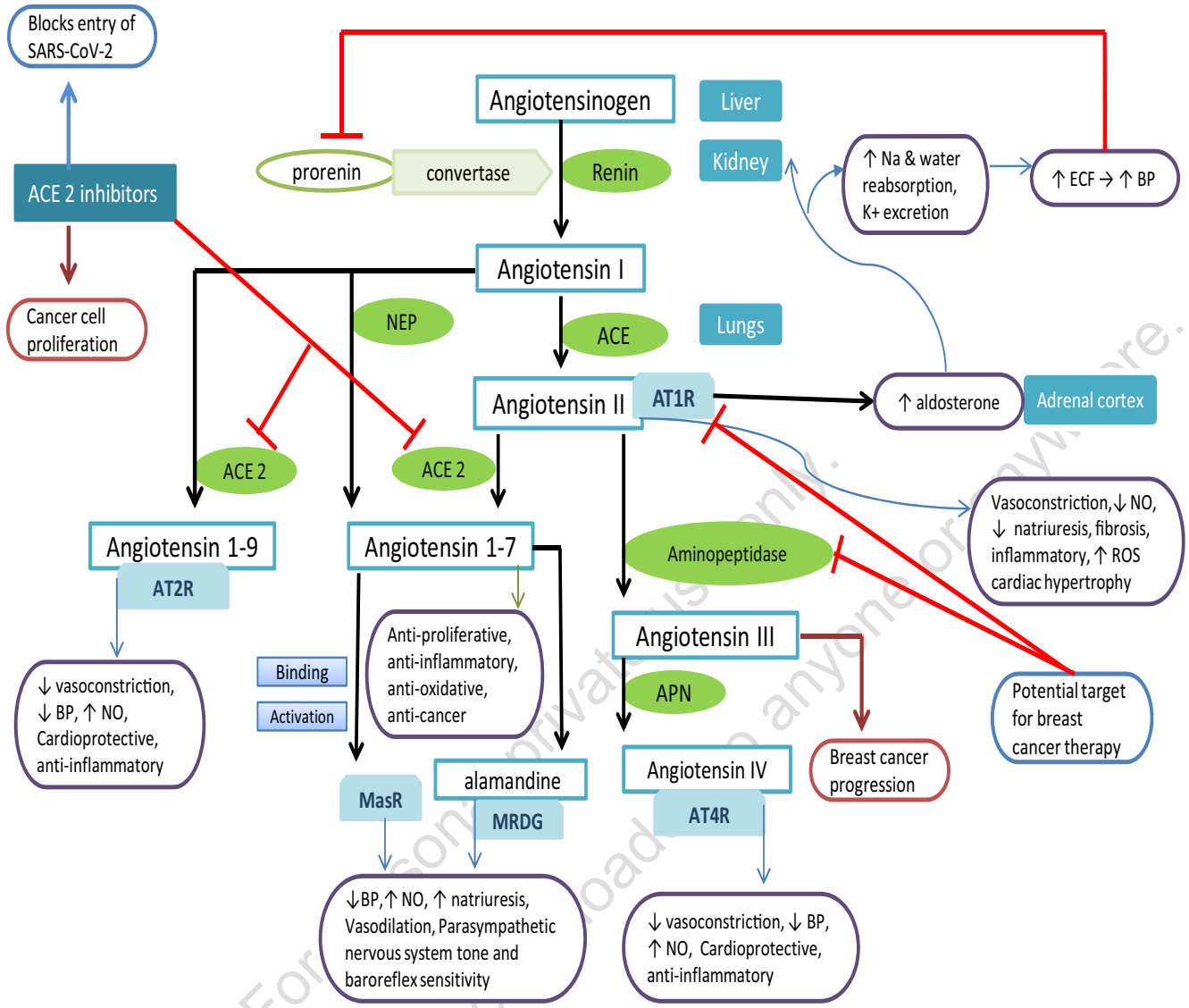

Fig. (2). Role of renin-angiotensin system in pathogenesis of COVID-19 and breast cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ing with ACE2 and subsequently its entry into the host cell [10]. COVID-19 pathogenesis may promote the migratory potential as well as the metastatic phenotype of breast cancer, as an increase in TMPRSS2 secretion increases the migratory potential of MCF-7 and MDA-MB-231 cancer cell lines along with the degradation of extracellular matrix (ECM) [73].

Chi *et al.*, 2020 [73] demonstrated that the treatment of highly selective α2-adrenergic receptor agonist dexmedetomidine (DEX) increases the malignancy of breast cancer cells *in vitro* and stimulates the tumour growth in mice. This pathway is dependent on the STAT3 activation followed by the secretion of TMPRSS2 by Rab11 positive exosomes, which resultantly cleaved ECM, as observed by a decrease in fibronectin, collagen IV, matrix metallopeptidase 16 (MMP16) and tenascin C. Therefore, TMPRSS2 inhibitors may provide better clinical efficacy against COVID-19 and breast cancer [9, 10, 74].

A clinical study of 1779 women breast cancer patients on ACE inhibitors (ACEi) shows that ACEi exposure is associated with breast cancer recurrence but not cause-specific or overall mortality [75]. Similarly, ACE2 inhibits the angiogenesis and patients with higher ACE2 expression had longer relapse-free survival, whereas, lower expression was accompanied by the poor prognosis of the patients. ACE2 also inhibits breast cancer cell migration and proliferation. These protective effects of ACE2 expression may be through the inactivation of VEGFR2 phosphorylation, MEK1/2 and

ERK1/2 signalling [19]. Another report suggests that low ACE2 protein levels were associated with the increased metastatic potential of breast cancer cells [18]. In this report, authors have shown that ACE-2 mediated angiotensin 1-7 and its binding with the Mas receptor (ACE2/angiotensin1-7/-Mas axis) exert anti-proliferative and anti-metastatic effects on breast cancer cells *in vitro* and *in vivo via* inhibition of store-operated calcium entry (SOCE) and PAN/NF-kB/Snail pathways and induce E-cadherin expression. Based on these study outcomes, we hypothesize that ACE2 inhibitors/antagonists for COVID-19 protection may worsen the clinical condition of breast cancer patients with poor prognosis.

6. INFLUENCE OF COVID-19 DRUG REPURPOSING ON BREAST CANCER

6.1. Antiviral Agents

6.1.1. Remdesivir

It is a broad-spectrum antiviral agent, which is a phosphoramidite prodrug. After metabolizing, remdesivir is converted into its active form GS-441524. This drug obscure viral RNA polymerase (RNA dependent RNA polymerase; RdRp) and evades proofreading by viral exonuclease, thus causing a decrease in RNA production and subsequently the viral load. Till date, there is no evidence of its influence on breast cancer and drug-drug interaction with anti-cancer therapies [76, 77].

7. HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (CQ)

These drugs are used to treat lupus erythematosus, rheumatoid arthritis and malaria. These drugs are known to accumulate in lysosomes and change the pH, which lead to changes in the activity of lysosomal proteases through which it affects the degradation of proteins and glycosamine glycans. Compared with chloroquine, hydroxychloroquine has a hydroxyl group, which makes it less toxic, but maintaining a similar activity. These drugs interfere with the glycosylation of ACE2 receptor and their binding with spike protein of SARS-CoV-2. They also possess anti-inflammatory effects on Th17 related cytokines (IL-6, IL-17 and IL-22), thus also known to inhibit cytokine storm.

Zinc is also known to inhibit the activity of viral RdRp, thus blocks the replication of viruses *in vitro*. There is evidence that zinc enhances the intracellular uptake of chloroquine.

Many reports have suggested anti-cancer activity of HCQ and CQ on breast cancer through stimulation of p300/CBP- associated factors and histone acetyltransferase activity [78]. HCQ and CQ are also known to inhibit autophagy in cancers, which may stimulate radio and chemosensitivity to the cancers. Phase I / II clinical trials of HCQ, in combination with hormonal therapies for metastatic ER+ breast cancer, are also in progress [79]. HCQ and CQ also promote differentiation in breast cancer cell lines [80].

7.1. Lopinavir-Ritonavir

Lopinavir is a protease inhibitor, which is administered in co-formulation with ritonavir due to the poor bioavailability and biotransformation of lopinavir. It is a specific HIV-1 protease inhibitor. It is a peptidomimetic molecule containing a hydroxy ethylene scaffold that mimics the peptide linkage which is targeted by HIV-1 protease. Lopinavir was found to be effective against COVID-19 by significantly decreasing the viral titres [81]. This anti-viral drug is known to inhibit breast cancer resistance protein efflux transporter that results in the increased exposure of rosuvastatin [82]. It seems that this drug may be useful to overcome chemo-resistance in breast cancer. This drug showed anti-cancer properties for bladder cancer by increasing the ER stress through which an increase in the AMP-activated kinase suppressed the mammalian target of rapamycin pathways. It also increased the expression of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors and thereby sensitized the cancer cells for TRAIL [83].

7.2. Umifenovir (Arbidol)

Umifenovir is an indole carboxylic acid derivative, used for treating prophylaxis and infections associated with influenza A and B and other arboviruses. It is also used to treat Ebola virus, human herpesvirus 8 and hepatitis C virus. Umifenovir inhibits virus-cell and virus-endosome fusion through incorporation into cell membranes which interfere with the hydrogen bonding network of phospholipids [84]. Viral inhibitory potential of umifenovir on SARS-CoV and SARS-CoV-2 was reported *in vitro* [85]. A clinical study revealed that it was more effective with the combination of lopinavir-ritonavir demonstrating a negative conversion rate of SARS-CoV-2 and improved chest CT scan data [86]. However, currently, no data is available on the interaction of umifenovir with breast cancer clinical and therapeutic outcomes.

7.3. Favipiravir (Avigan)

It is a guanine analogue with a pyrazine carboxamide structure. First, the prodrug favipiravir enters into the infected cells through endocytosis and then, it is converted into the active drug- favipiravir ribofuranosyl phosphate through phosphoribosylation and phosphorylation. It selectively targets the conservative catalytic domain of the RNA-dependent RNA polymerase (RdRp), which interrupts the nucleotide incorporation process during viral replication. The dysregulation of viral RNA replication results in an increased number and frequency of mutations, which ultimately lead to destructive mutagenesis in viruses. It is effective against SARS-CoV-2 [87]. It inhibits aldehyde oxidase; thus, it should be cautiously used with tamoxifen therapy. However, no report is available for its influence on breast cancer.

7.4. Oseltamivir (Tamiflu)

It is a drug approved for the treatment of influenza A and B. It targets the neuraminidase which is distributed to

the surface of the influenza virus and thus inhibits the spread of the virus in the human body. Oseltamivir proved to be effective against SARS-CoV-2 in combination with other drugs repurposed for the treatment of COVID-19 [88]. Interestingly, oseltamivir phosphate in combination with metformin and acetylsalicylic acid has been shown to exert anticancer effects on triple-negative breast cancer cell line MDA-MB 231 in which reversal of chemo-resistance, decrease in viability and promotion of apoptosis were observed [89]. Similarly, *in vivo* results were also observed in response to the administration of oseltamivir alone [90].

8. SUPPORTING AGENTS

8.1. Azithromycin and Doxycycline

Azithromycin is an antibiotic used to treat various bacterial infections, which is also known to inhibit Zika and Ebola viruses and prevent severe respiratory tract infections. Azithromycin binds with the 50S ribosome subunit, through which it inhibits protein synthesis. Azithromycin in combination with HCQ has been found to be effective against SARS-CoV-2 [91]. Similarly, doxycycline is another antibiotic that is highly lipophilic in nature and known to chelate the zinc component of matrix metalloproteases (MMPs). It is imperative to mention that coronaviruses heavily rely on MMPs for survival, cell infiltration, and replication; thus it inhibits their survival. It also has an anti-inflammatory effect through which it might be effective against cytokine storms during COVID-19 [92].

Both azithromycin and doxycycline, along with vitamin C, were found to inhibit the formation of cancer stem cells in breast cancer model system. Azithromycin and doxycycline inhibited large and small mitochondrial ribosome, respectively. Vitamin C acts as a mild prooxidant (at 250 uM) which produces free radicals and as a consequence, and induces mitochondrial biogenesis that ultimately leads to eradicate cancer stem cells [93].

8.2. Vitamin C (Ascorbic Acid)

Vitamin C was reported as an anti-viral agent against the influenza virus. A high dose of Vitamin C positively influences the development and maturation of T lymphocytes and NK cells, thus modulating the immune response. Vitamin C, through its antioxidative effects, re-modulates the cytokine network of the systemic inflammatory syndrome [94, 95]. Based on these reports, clinical trials of vitamin C were conducted and it was found effective against COVID-19. It is also important here to discuss the role of vitamin C as a potent anticancer agent in breast cancer. Several emerging reports suggest that vitamin C promotes apoptosis through an increase in the expression of TRAIL [96], cancer cell membrane remodelling and changes in the EGFR and MAPK signalling [97], inhibition of invasion and metastasis *via* inhibiting the epithelial-mesenchymal transition (EMT) [98]. Vitamin C also inhibits the TNBC metastasis through upregulation of synaptopodin 2 (SYNPO2) and downregulation of the transcription coactivator YAP1; genes from the Hippo pathway. It was revealed that the treatment of vitamin C inhibited F-actin assembly and lamellipodia formation, which correlates with SYNPO2 and YAP1 expression [99].

8.3. Corticosteroids

Corticosteroid drugs such as methylprednisolone and dexamethasone are known to be anti-inflammatory and anti-fibrotic drugs. At low doses, methylprednisolone prevents extended cytokine response and sepsis, along with an accelerated resolution of pulmonary and systemic inflammation of COVID-19 associated pneumonia [100]. Importantly, corticosteroids are immunosuppressive in nature and thus, steroid therapy may further worsen the clinical outcomes in breast cancer patients who are COVID-19 positive. No report is available on the role of corticosteroids treatment in breast cancer patients, but the role of steroidal receptors in breast cancer is well established and blocking of steroidal receptor function is one of the therapeutic modalities for breast cancer. Thus, one should be cautious before prescribing the corticosteroid to breast cancer patients [101]. Cancer patients, especially on chemotherapy, are immune-compromised which may further increase their chances to acquire other infections as well.

8.4. Nitric Oxide and Epoprostenol

Nitric oxide (NO) and epoprostenol (a naturally occurring prostaglandin) are pulmonary vasodilating agents. These inhaled vasodilator drugs have been used in hypoxemia patients who are refractory to conventional drugs. *In vitro* studies on SARS-CoV also revealed their anti-viral activity, which may apply to the SARS-CoV-2 due to genetic similarities [102, 103]. Interestingly, depending on the concentration and site of administration, NO can function both positively and negatively act as a pro and anti-cancer agent. NO donors are known for their hypoxic cell radiosensitizers and radioprotective effects in a variety of tumours. Increased NO plays a role in metastasis and tumour growth promotion including breast, pancreatic, gynaecologic and head and neck tumours [104-107]. Presently, no report is available on the role of inhaled vasodilators in cancer patients infected with COVID-19. Therefore, such agents should be used cautiously in cancer patients.

8.5. Sirolimus (Rapamycin)

It is an immunosuppressant that is used to prevent organ transplant rejection. It is well known that the mTORC1 protein complex, formed by mTOR plays a key role in viral replication and has been found to inhibit MERS-CoV activity *in vitro* [108]. Several clinical trials are going on to evaluate its effects on respiratory improvements and on pro-inflammatory cytokines in COVID-19 patients. The beneficial role of sirolimus along with other immunosuppressant drugs has been evaluated on breast cancer. It is effective against chemo-resistance through the inhibition of resistance protein ABCG2 [109]. Similarly, a reversal of trastuzumab resistance was also observed in response to the administration of sirolimus in HER2 positive breast cancers. The inhibition of mTOR was suggested as an underlying mechanism [110].

8.6. Tocilizumab

Tocilizumab is a humanized mAb developed for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis. In a clinical trial, 21 critical patients of COVID-19 treated with antibody and all of them were recovered. Based on these results, another large and multicenter clinical trial is underway [111]. Recently, it has been reported that tocilizumab potentiated the cytotoxicity of cisplatin, inhibited IL6 pro-invasive/ metastatic marker, along with the inhibition of breast cancer stem cells in TNBC. The suggested underlying mechanisms are *via* the inhibition of IL-6/STAT3 signalling that inhibits the positive feedback loop *via* suppressing cancer/ inflammatory IL-6/ STAT3/ NF-kB. Besides, tocilizumab also has shown inhibition of EMT through suppression of the Wnt/ β-catenin pathway, thereby inhibiting cancer stem cell formation [112].

8.7. Sarilumab

Sarilumab is a humanized mAb against IL6-R developed by Regeneron Pharmaceuticals and Sanofi for the treatment of RA. Recently, clinical trials phase 2/3 is underway to evaluate its effects on C-protein levels and time is taken for clinical improvement in patients. It is based on a 7 point scale system that includes death, time of hospitalization of the patients showing serum IL6 levels above than the set threshold (NCT04315298). Based on the role of IL-6 in breast cancer progression, sarilumab may be explored in breast cancer treatments [113].

8.8. Ibuprofen

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are also ACE2 receptor activators and their use may increase the risk of contracting COVID-19 similar to the use of ACE inhibitors. However, no harmful effects of ibuprofen were observed in COVID-19 patients and FDA considered ibuprofen as a potentially promising drug against COVID-19 [114]. In context to breast cancer, long-term use of ibuprofen is associated with the increased risk of various breast cancer subtypes [115].

8.9. Thiazolidinediones

Drugs of this category are prescribed for type 2 diabetes. However, few reports revealed their anti-viral efficacies against the respiratory syncytial virus (RSV) or H1N1 influenza virus [116, 117]. Importantly, thiazolidinediones may up-regulate ACE2 receptor expression, which may facilitate the entry of SARS-CoV-2 [118]. However, they exert anti-cancer effects, including breast cancer [119].

8.10. Indomethacin

Indomethacin is an NSAID cyclooxygenase (COX) inhibitor. Recently, it was demonstrated as a potential antiviral agent against SARS-CoV and canine coronavirus (CCoV). It inhibited viral RNA synthesis in dogs infected with CCoV [120]. Indomethacin has been extensively evaluated on breast cancer and it is known to exert anti-metastatic, invasion inhibition and positive influence on metabolism in breast cancer cells [121, 122].

8.11. Colchicine

It is an anti-inflammatory drug, commonly prescribed in gout. It inhibits neutrophils' migration to the site of inflammation through which blocking the inflammasome complex in both neutrophils and monocytes. This ultimately leads to a reduction of IL-1beta activation. Besides, colchicines also exert inhibitory effects on macrophages *via* inhibiting the NACHT-LRRPYD-containing-protein 3 (NALP3) inflammasome and pore formation activated by purinergic receptors P2X7 and P2X2. Colchicine is also known to exert anti- cancer effects on breast cancer [123]. Clinical trials are going on for the potential therapeutic benefits against COVID-19 [124, 125].

8.12. Niclosamide and Ivermectin

Niclosamide and ivermectin are anthelmintic drugs. Niclosamide demonstrated the inhibition of SARS-CoV replication [126]. It is effective against MERS-CoV replication *via* reduction of SKP2 regulated BECN1 ubiquitination and enhancement of autophagic flux [127]. Ivermectin also inhibits the interaction of HIV-1 viral integrase with its nuclear transport receptor importin α/β [128]. Besides, ivermectin also exhibited broad-spectrum anti-viral effects on dengue, flavivirus and influenza. Recently, ivermectin has shown inhibition of SARS-CoV-2 up to 5000 fold at 48 h *in vitrovia* inhibition of IMP α/ β1 mediated nuclear import of viral proteins [129]. Here it is imperative that niclosamide also exerts anti-cancer effects on breast cancer through promotion of apoptosis, inhibition of metastasis, a reversal of radio-resistance, reduction of immunosuppressive cells and inhibition of cancer stem cell formation through the involvement of various underlying molecular pathways [130-133]. Additionally, ivermectin also demonstrated anti-breast cancer effects *via* blocking the PAK1/ Akt axis, inhibition of cancer stem cells, induction of cell death *via* modulating the P2X4/P2X7/Pannexin-1 sensitivity to extracellular ATP [134-136].

8.13. Nitazoxanide and Tizoxanide

These anti-microbial drugs have been shown to exert broad anti-viral response on MERS-CoV, murine coronavirus, hepatitis virus strain (MHV-A59), bovine coronavirus and human enteric coronavirus 4408 (HECoV-4408) *via* suppression of viral N protein [137]. Nitazoxanide also suppresses pro-inflammatory cytokines, including IL-6. Thus, it seems to be useful to treat cytokines storm in COVID-19 [138]. Nitazoxanide is also known to exert anti-cancer effects on a variety of cancers, including breast cancer, *via* inhibition of c-Myc oncogene [139, 140].

8.14. Anticoagulants

Disseminated intravascular coagulation and elevated D-dimer levels were identified as a predictor of poor clinical outcome in COVID-19 [141]. Besides, heparin, low molecular weight heparins have also shown to inhibit viral attachment through conformational changes and anti-inflammatory properties through IL-6 inhibition [142, 143]. Heparin

Table 1. Effects of COVID-19 therapies on breast cancer and drug-drug interactions with chemotherapies.

COVID-19 Therapy	Effect on Breast Cancer	Interaction with Breast Cancer Treatment
Chloroquine and hydroxychloroquine	Anti-cancer activity on breast cancer through stimulation of p300/CBP-associated factors and histone acetyltransferase activity. Inhibit autophagy in cancers, which may stimulate radio and chemosensitivity Also promote differentiation in breast cancer cell lines.	CQ ↓ levels of tamoxifen by CYP2D6 inhibition effect.
Protease inhibitors like ritonavir, lopinavir, atazanavir	Inhibit breast cancer resistance protein efflux transporter.	Strong inhibitors of CYP450 isoform CYP3A, thus ↑ concentration of CYP substrate drugs and may cause cardiac toxicity by QT prolongation.
Favipiravir (Pyrazine analog)	No report is available for its influence on breast cancer.	Inhibit aldehyde oxidase thus cautiously used with tamoxifen.
Ivermectin	Anti-breast cancer effects *via* blocking PAK1/ Akt axis, inhibition of cancer stem cells, induction of cell death *via* modulating the P2X4/P2X7/Pannexin-1 sensitivity to extracellular ATP.	Caution with drugs metabolized by CPY34A and p-glycoprotein inducers/inhibitors.
Tocilizumab (IL-6 blocker)	Inhibit breast cancer stem cells in TNBC *via* inhibition of IL-6/STAT3 signalling and inhibition of EMT through suppression of Wnt/ β-catenin pathway.	TCZ reverse the reduced activity of CYPA50, thus should be used cautiously with agents that are metabolized by CYP450
Remdesivir	No evidence for effect on breast cancer.	No data available for drug interactions
Umifenovir	No evidence for effect on breast cancer.	No data available for drug interactions
Oseltamivir	Anticancer effects on triple-negative breast cancer MDA-MB 231.	No data available for drug interactions
Vitamin C	Potent anticancer agent in breast cancer.	-
Azithromycin and Doxycycline	Both azithromycin and doxycycline, along with vitamin C, inhibit the formation of cancer stem cells in breast cancer model system.	No data available for drug interactions
Sirolimus	Currently no evidence of its influence on breast cancer.	Reverse trastuzumab resistance in HER2 positive breast cancers by mTOR inhibition.
Ibuprofen	Long term use of ibuprofen is associated with the increased risk of breast cancer of various subtypes.	No data available for drug interactions
Sarilumab	May exhibit anticancer activity on breast cancer.	No data available for drug interactions
Thiazolidinediones	Exert anti-cancer effects in breast cancer.	No data available for drug interactions
Indomethacin	Anti-metastatic, invasion inhibition and positive influence on metabolism in breast cancer cells.	No data available for drug interactions
Colchicine	Anti-cancer effects on breast cancer.	No data available for drug interactions
Niclosamide	Anti-cancer effects on breast cancer through promotion of apoptosis, inhibition of metastasis, a reversal of radio resistance, reduction of immunosuppressive cells and inhibition of cancer stem cell formation.	No data available for drug interactions
Nitazoxanide and Tizoxanide	Anti-cancer effects *via* inhibition of c-Myc oncogene.	No data available for drug interactions
Heparin	Anti-metastatic role on breast cancer cells.	No data available for drug interactions
Bromhexine	Inhibits cancer metastasis.	No data available for drug interactions
Nitric oxide and Epoprostenol	NO can function both positively and negatively as a pro and anti-cancer agent, depending upon concentration and site of administration.	No data available for drug interactions
ACE2 inhibitors	May increase chemo-resistance and metastasis of breast cancer.	May increase drug resistance
TMPRSS2 inhibitors	Positive influence on breast cancer	No data available for drug interactions
DPP4 inhibitors	Positive influence on breast cancer	No data available for drug interactions

and low molecular weight heparins exert an anti-metastatic role on breast cancer cells. CXCR4 expressing breast cancer cells migrate towards the metastatic target sites, which constitutively express CXCL12 and heparin bind with the CXCL12, resultantly decreasing tumour size and reducing lung metastases [144].

8.15. Bromhexine

Bromhexine has been used for decades as a mucolytic agent and expectorant. It is a potent inhibitor of TMPRSS2 protease [145]. The expression of TMPRSS2 is associated with poor prognostic factor in TNBC [146] and the severity of COVID-19 is associated with an increased level of TMPRSS2. Bromhexine also inhibits metastasis in a variety of cancers, including breast cancer [147] (Table **1**).

9. DRUG-DRUG INTERACTIONS AND POSSIBLE ADVERSE EVENTS: COVID-19 AND BREAST CANCER

Cancer patients are at more risk of adverse events because of possible drug-drug interactions during multiple drug regimes. Currently, there are limited data about the drug-drug interactions for COVID-19 and breast cancer therapies.

Hydroxychloroquine and chloroquine being weak inhibitors of CYP2D6 drug-metabolizing enzyme, result in de-

creased bioavailability of tamoxifen. Similarly, protease inhibitor drugs lopinavir-ritonavir, when administered with tamoxifen, anthracyclines, tyrosine kinase inhibitors (TKIs) such as lapatinib, increase the exposure time of these anticancer drugs. This may correlate with the prolongation of QT interval and may result in cardiotoxicity [76, 148]. Ivermectin should be used cautiously with drugs metabolized by CYP34A and P-glycoprotein modulating drugs, as the drug exposure time may be varied [76]. The pyrazine drug favipiravir can increase the effect of tamoxifen, as both are aldehyde oxidase inhibitors (AO). It may also interfere with CYP2C8 isoenzyme substrates such as paclitaxel [76]. Knowledge about drug interactions is crucial for better management of cancer patients (Table **1**).

10. MANAGEMENT OF BREAST CANCER CHEMOTHERAPY, RADIOTHERAPY AND SURGERY DURING COVID-19

COVID-19 pandemic severely affected the management of cancer patients worldwide. It impacts early diagnosis, surgical treatments of cancer patients and proper follow-up due to travel restrictions. Indirect impacts through delays in recruitments and financial losses further worsen the situation for the patients with advanced cancers accompanied by the reduced possibility of survival and optimal care [149, 150]. However, the protection of cancer patients and health caregivers remains a high priority, as COVID-19 infection may impact overall mortality of the cancer patients which may breakdown the healthcare system along with the associated economic losses [151].

One recent retrospective multicentric study by Li *et al.*, (2020) [152] demonstrated that breast cancer management suffered severely due to lack of diagnosis and surgical treatments. Data of 8397 breast cancer patients showed that Hubei province in China recorded the lowest incidence of early breast cancer (5.3%) in comparison to the other provinces (15.3%). Similarly, surgical procedures decreased from 16.4% (December 2019) to 2.6% (February 2020), while there was also a delay in timelines from surgery to adjuvant therapy.

In the Lombardy region of Italy, which was worst affected by COVID-19 during March 2020, most of the hospitals and healthcare units were converted into intensive care units and in most of the cases, breast cancer patients were classified as non-urgent [153, 154]. Instead of Lombardy, European Institute of Oncology, in Milan was recognized as a major centre for breast cancer treatment. However, there was an 87% decrease in cancer surgery and also 84% reduction in the extra-regional patients, including 42% reduction in patients from Lombardy [155]. Interestingly, there was 20% increase in the number of patients from Lombardy when compared to the same period of 2019 because these patients were already scheduled for surgery and other health services, but transferred to Milan centre from Lombardy. It is noteworthy that the management of breast cancer patients is essential to change the state of illness into a state of health by the medical care system which directly affects the cancer survivorship. Inline to this concept, an international group of clinical experts described the recommendations for early breast cancer management during this pandemic of COVID-19 [156]. It seems that when this COVID-19 pandemic will fade away, cancer patients will be a new health emergency before the medical health care systems.

Al-Jabir *et al.*, (2020) [157] reviewed the surgical prioritization and their guidelines for cancer patients. The review describes surgical procedures for breast cancer patients during COVID-19 pandemic. According to these guidelines, the grades of tumours from the Breast Imaging –Reporting and Data System (BI-RADS) score may be considered for decision making. Patients with score <3 are suitable for 3 months deferral, patients with grading ≥4 should have a biopsy which should be reviewed in 4-8 weeks and then reassessed. Patients with grade ≥4 are highly suspected for malignancy and thus, a core needle biopsy or fine needle aspirate should be performed urgently. In cancer hospitals in phase 2 or 3, neoadjuvant therapy should be given priority over surgical interventions and should be administered within a day to avoid unnecessary admissions. They also recommended postponing the follow-up adjuvant therapy to the patients who recently underwent surgery for early breast cancer. For the patients at higher risk (elderly or immunosuppressed) and those having a low tumour burden should be administered a reduced dose (≥85% of the standard dose). It was also recommended that wherever possible, adjuvant radiotherapy should be delayed by 1-2 months.

For patients with stable remission, reviews should be conducted after every semester instead of the trimester. Besides, phase 1 surgical priorities should be given to the patients who completed neoadjuvant therapy, clinical stage T2 or N1 ER+/PR+/HER- tumours, triple-negative or HER2+ tumours, malignant incongruous biopsy cases and recurrent tumours. The patients with incision and drainage of breast abscess, evacuation of haematoma, revision of ischemic mastectomy flap and revascularization of an autologous tissue flap should be given phases 2 and 3 surgical priorities. For deferred cases of surgery in phase 1 are the patients with tumours responding to neoadjuvant therapy, clinical Stage T1N0 ER+/PR+/HER2- tumours, inflammatory and locally advanced breast cancer, incongruous biopsy cases likely to be benign, prophylactic surgery, delayed sentinel lymph node biopsy (SNB) for cancer identified on excisional biopsy, re-excision surgery, duct excisions, excision of benign lesions, high-risk lesions and autologous reconstruction. For phase 2 and 3, all the other breast procedures must be deferred [156, 158].

Similarly, based on the risk/ benefit ratio and shared decision making of oncologist and patients, guidelines have been framed for radiotherapy (RT) to the breast cancer patients during COVID-19 pandemic [159, 160]. The recommendations of these guidelines are as follows:

- Radiotherapy for patients ≥ 65 years or younger with relevant co-morbidities having invasive breast cancer (up to 30 mm) with clear margins, grade 1-2, ER+/HER2- and node-negative who are planned for treatment with endocrine therapy.

- Deliver RT in 5 fractions only, for the patients with node-negative and do not require a boost. Options include 28-30Gy in once weekly fractions over 5 weeks or 26Gy in daily fractions over 1 week, as per the FAST and FAST Forward trials, respectively.
- Boost RT should be omitted to reduce fractions and/or complexity in the vast majority of patients unless they are ≥ 40 years old and or under 40 years with significant risk factors for local relapse.
- Nodal RT can be omitted in post-menopausal women requiring whole breast RT following SNB and primary surgery for T1, ER+, HER2-, G1-2 tumours with 1-2 macrometastases.
- Moderate hypo fractionation should be used for all breast/chest wall and nodal RT, *e.g.* 40Gy in 15 fractions over 3 weeks.

Another study based on the data collected from Research electronic data capture (REDCap) hosted at the University of Illinois, Chicago, USA, revealed that 44% of the breast cancer participants reported delays in all aspects of cancer care and treatment during COVID-19.

COVID-19 Pandemic Breast Cancer Consortium (USA) proposed a detailed guideline, mainly developed from the algorithms based on tumour biology and extent of disease that guide breast cancer management decisions during the pandemic [161]. The management of breast cancer patients depends upon the grade, stage and clinical conditions of cancer. These guidelines provided insight into the decision making on the therapeutic options, hospital visits, radiotherapy treatments and surgical procedures.

Brazil is one of the worst affected countries with COVID-19 that severely derailed early breast cancer treatment and management. A study from Cavalcante *et al.*, (2020) [162] reported a survey from the members of the Brazilian Society of Breast Cancer Specialists. Data suggested that 69.8% of oncologists changed their breast cancer management approaches. For receptor-positive tumours with the best prognosis (Ki-67< 20%), 47.9% and 17.7% of specialists recommended neoadjuvant endocrine therapy for postmenopausal and premenopausal women, respectively. For tumours with poor prognosis (Ki-67 > 30%), 34% and 10.9% recommended neoadjuvant endocrine therapy for postmenopausal and premenopausal women, respectively. For tumours ≥1.0 cm, 42.9% of respondents recommended neoadjuvant systemic therapy for triple-negative tumours and 39.6% for HER2+ tumours. Overall, 63.4% recommended breast surgery for immediate total breast reconstruction, while 4.3% recommended partial breast reconstruction; however, 54.1% would contradict mammoplasty.

Nevertheless, 84.9% of respondents did not recommend prophylactic mastectomy in cases of BRCA mutation. This survey further highlighted the necessity of breast cancer management with the changing need of time during COVID-19 pandemic in almost all areas of Brazil.

Poggio *et al.*, (2020) [163] reported another interesting survey-based study on the impact of COVID-19 outbreak on the attitudes and practice of Italian oncologists toward breast cancer care and research activities. The questions broadly focused on the neo-adjuvant setting, metastatic setting and research activities, it was found that in the neo-adjuvant setting, there was a decrease in the weekly paclitaxel (pre 68.5% v during 93.9% pandemic) and dose-dense schedule for anthracycline-based chemotherapy (pre 43% v during 58.8% pandemic). In the metastatic setting, compared with pre-emergency, a lower number of oncologists adopted first line weekly paclitaxel for HER2+ disease (41.8% v 53.9%) or CDK4/6 inhibitors for luminal tumours with less aggressive features (55.8% v 80.0%) during COVID-19. A significant delay was also observed in monitoring the therapy, assessing the treatment response by imaging tests and flushing the central venous devices. Clinical research and scientific activities also reduced by 80.3% and 80.1%, respectively among the respondents previously involved in these activities.

Hence, overall these guidelines for breast cancer management during COVID-19 are to overcome the impact of COVID-19 pandemic on cancer care, as a gap in disaster preparedness left cancer survivors at risk of poor outcomes [164].

11. COMMON COMORBIDITIES IN COVID-19 AND BREAST CANCER

Diabetes, obesity and metabolic syndrome are the comorbidities found to be associated with the severity and poor prognosis of both COVID-19 and breast cancer. A cross-sectional analysis of hospitalized adults in Chicago exhibited that the younger patients (age <50 years) with COVID-19 were having higher BMI than the older patients, suggesting an association of obesity with COVID-19 [3]. Another pilot study based on 25,593 hospitalized patients of COVID-19 concluded that the patients of obesity, diabetes and hypertension were having higher odds of developing severe COVID-19 [165]. The study showed that obese, diabetic and hypertension patients had 1.43, 1.87 and 1.77 folds higher odds of the severity of COVID-19, respectively [165]. Similarly, many other clinical reports have also shown a correlation between obesity and metabolic syndrome with the increased risk, severity and mortality of COVID-19 [4, 5, 166].

The prevalence of the different types of cancers in patients with COVID-19 is still inconsistent and inconclusive [22-24]. Therefore, it is important to delineate the relation between COVID-19 and breast cancer pathogenesis. Breast cancer is the most prevalent cancer among women and the second leading cause of cancer–related mortality among women [13]. Diabetes mellitus is one of the most chronic diseases worldwide, which is known to be associated with the higher incidence, accelerated progression, increased aggressiveness, relapse and poor prognosis of breast cancers [13]. Several studies have reinforced a link between increased breast cancer risk and type 2 diabetes [167, 168]. Various clinical studies estimated that women with diabetes have 20-28% increased risk of having breast cancer along with

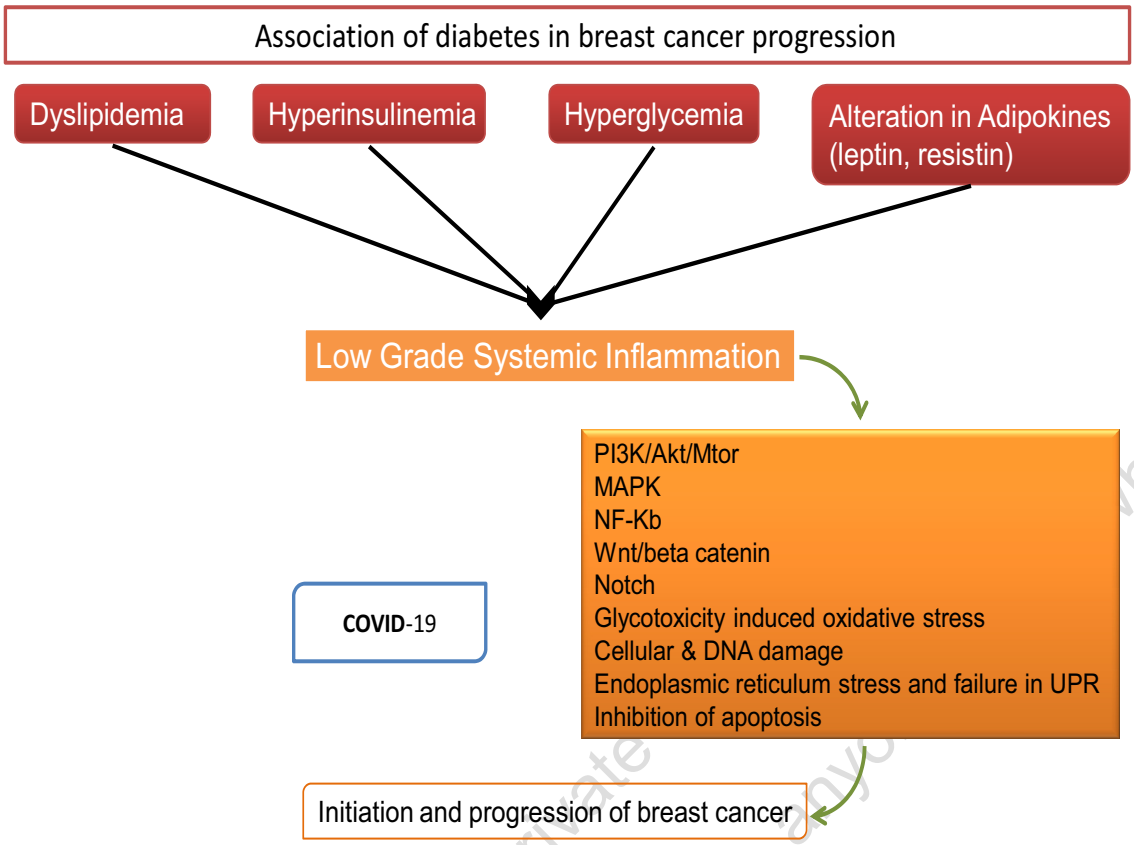

Fig. (3). Association of diabetes in breast cancer progression. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

overall poor survival and disease-free survival [13, 168-171].

Increase in the prevalence of diabetes and obesity-related metabolic alterations including insulin resistance (IR), elevated insulin-like growth factors (IGFs), hyperglycemia, dyslipidemia, alterations in adipokines level and inflammatory cytokines pose an increased risk of breast cancer [13, 172-176].

12. HIGHLIGHTS OF THE SIGNALLING PATHWAYS LINKING DIABETES, OBESITY AND BREAST CANCER

As we have briefly described above that the metabolic alterations including diabetes, obesity and hyperglycemia increased the likelihood of breast cancers along with the poor prognosis and worse clinical outcomes [177, 178]. Here, we briefly discuss the molecular cross-talk of diabetes, obesity and breast cancer.

Type2 diabetes usually initiates through an increase in the insulin resistance along with glucose intolerance accompanied by higher than the normal serum glucose levels, which is known as the pre-diabetes condition. Four metabolic alterations develop during diabetes progression, *viz*. i) dyslipidemia/ hyperlipidemia (elevated levels of triglycerides, fatty acids and cholesterol accompanied with the decrease in HDL), ii) hyperinsulinemia, iii) hyperglycemia and iv) alterations in adipokines (leptin, adiponectin, resistin); that develop a condition of low-grade systemic inflammation [179, 180]. All these conditions trigger alterations in various signalling pathways that ultimately lead to the progression of breast cancer in diabetic patients. These pathways include PI3K/Akt/mTOR [181, 182] MAPK [181], notch [183], NF-kB [184], Wnt/ β-catenin [185], glucotoxicity induced oxidative stress [186], cellular and DNA damage [185, 186] endoplasmic reticulum stress and failure in unfolded protein response (UPR) [187, 188], inhibition of apoptosis [189], and initiation and progression of breast cancer [186, 190] (Fig. **3**).

13. GENDER DIFFERENCES IN SEVERITY AND MORTALITY FROM COVID-19

Global data report on mortality and severity of COVID-19 suggest that compared to women, men have severe clinical outcomes and higher mortality [8, 191-193]. As per the data available at Global Health 5050, which is an organization that promotes gender equality in the health care system and publishes total and partial publicly available sex-disaggregated data from government sources, showed that till November 16, 2020, the overall COVID-19 fatality ratio in men is higher than in women [192]. Data from more than 50 countries indicated that the proportional male to female ratio in COVID-19 confirmed cases was higher in men than

in women. The highest male to female ratio was seen in Myanmar, Thailand, Albania, Wales and Peru, which is 3.84, 2.52, 2.2, 2.12 and 1.91, respectively. It is important to note that this disproportionate death ratio in men, may at least in part can be explained by their relatively higher contribution to pre-existing diseases including cardiovascular diseases (CVDs), hypertension, diabetes and chronic lung disease; higher risk behaviour such as smoking and alcohol use [191, 192]. Some other social and behavioural attributes that favour women are their better hand hygiene practices [175] and preventive care [194].

During the early pandemic of COVID-19, studies from Wuhan, China also reported that death rates were higher in patients with comorbidities such as 10.5% for CVD, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension and 5.6% for various cancers [195]. Some other clinical studies also have drawn clear observations on the higher mortality among men than women infected with COVID-19. Report from Italy on the mortality of 3200 patients by COVID-19 revealed that women accounted for only 29.4% of total deaths across all age groups [196]. In this report, overall women dying from COVID-19 were older than the men and among the 9 deaths of patients younger than 40 years, 8 were men and the overall mortality among all the age groups was less in women than men. Similar to the Chinese trend, in Italy also the comorbidities diagnosed before COVID-19 were hypertension (73.8%), diabetes (33.9%), ischemic heart disease (30%) and atrial fibrillation (20%) [196]. It is noteworthy that SARS-CoV and MERS-CoV also infected more men than women [197].

Differential immune regulation in men and women depends upon immune response genes located on X-chromosomes and women might have higher ACE2 (specifically soluble ACE2) levels which protect against more severe disease phenotype, compared to the men [17]. Sex-specific disease outcomes are attributed to the virus infection-induced production of steroids, the difference in copy number of immune response X-linked genes, as well as the presence of disease susceptibility genes in males and females [198, 199]. Among women, high density of X-linked immune response genes mount stronger innate and adaptive immune responses than men, resultantly the faster clearance of pathogens and greater vaccine efficacy, but the same reason increases the susceptibility of inflammatory and autoimmune diseases among women [200].

Clinical observations on 118 pregnant women with COVID-19 in China revealed that there was no increased risk of COVID-19 infection in pregnant women. No mortality was found even among women with severe or critical COVID-19 [7]. Another reason may be differences in the density, types and location of ACE2 receptors which is required for the entry of SARS-CoV-2 in COVID-19 pathogenesis. ACE2 receptors are present on higher levels at diversified cell types including lungs, myocardium, kidneys, gastrointestinal system and reproductive systems [187, 201] with higher ACE2 levels in testes than ovaries [201]. Higher ACE2 levels are associated with facilitating the entry of SARS-CoV-2, but on the other hand, ACE2 plays an anti-inflammatory role which protects against lung injury. Here soluble forms must be responsible for anti-inflammatory effects underlying the protective effects against lung injury, whereas membrane-bound ACE2 is responsible for the viral entry [202].

Another reason for the differences in the clinical outcome of male and female patients of COVID-19 may be due to the differences in the expression of membrane-bound TMPRSS2. Some recent reports suggest that TMPRSS2 may be circulating and possibly act upon the cells without membrane expression. Prostate cancer cells secrete TMPRSS2 *in vitro* and *in vivo* [203], suggesting that the differences in the soluble TMPRSS2 levels among men and women may be linked with the more severe clinical outcomes among men [204]. However, further research is required to study whether soluble TMPRSS2 may cause SARS-CoV-2 infection [205] (Fig. **4**).

13.1. Role of Sex Hormones in COVID-19

Various *in vivo* studies target towards understanding the roles of sex hormones in male and female differences related to COVID-19. These studies reveal that estrogen plays a crucial role in lethal infection of SARS-CoV-2 [206]. A study on mice infected with SARS-CoV demonstrated that the male mice were more susceptible to infection and gonadectomy did not affect the disease outcome in male mice [206]. Interestingly, in the same study, female mice underwent oophorectomy or treated with estrogen receptor antagonist showed increased mortality, which is consistently suggesting the protective role of estrogen signalling for protection against lethal infection.

Epidemiological studies consistently reveal that SARS-CoV, MERS-CoV and SARS-CoV-2 are more severe in men than the women, suggesting that sex hormones play an important role in these viral pathologies [9, 197, 207].

Two studies from COVID-19 hospital care on male patients reported decreased testosterone levels and altered gonadal functions [208, 209]. Similar observations of androgen imbalance and disease complications in male COVID-19 patients were reported from the UK Biobank and Yale-New Haven Hospital [210].

Androgenic alopecia (AGA) is a condition among men in which pattern hair loss occurs in males and accompanied by the higher levels of androgens and androgen receptors. So, to understand the sex-dependent effects of COVID-19 pathogenesis, it has been proposed to correlate the clinical outcomes of COVID-19 among AGA patients [211]. In a preliminary observational study in Spain, 71% of men diagnosed with COVID-19 related bilateral pneumonia were also diagnosed with AGA [45]. In a follow-up study of 175 patients of COVID-19, it was found that 122 (69%) were men having AGA [212]. These observations indicate that androgens may increase the likelihood of occurrence and severity of pathogenesis of COVID-19.

Interesting observations related to androgen were also made by Montopoli *et al.*, 2020 [213] on COVID-19 patie-

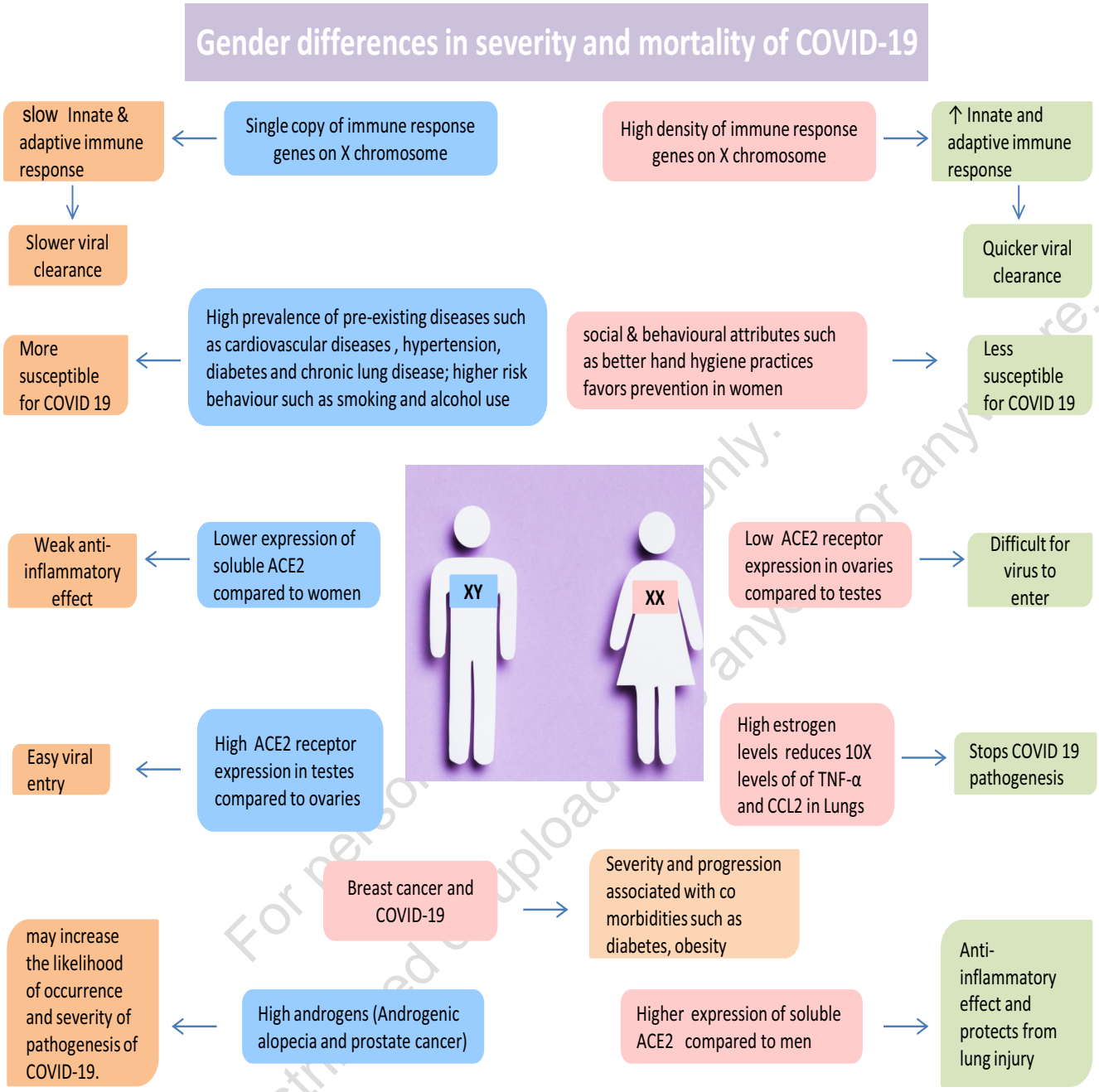

Fig. (4). Gender differences in severity and mortality of COVID-19. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

nts and some of them were also on androgen deprivation therapy (ADT) which is used to block or inhibit testosterone in prostate cancer patients. The study on 4532 male COVID-19 patients from the Veneto region of Italy showed that 9.5% (430) patients had cancer out of which 28% (116) had prostate cancer, suggesting that men with cancers have worse disease representation than men without cancer. Prostate cancer patients on ADT appeared partially protected from COVID-19. From the same region, out of 5273 prostate cancer patients on ADT, only 4 were found positive for SARS-CoV-2. Authors concluded that ADT may reduce the chances of SARS-CoV-2 infection as well as exert protective effects among men positive for SARS-CoV-2 infection. This preliminary study raised the possibility that ADT may be a good therapeutic option for male patients.

Estrogen may play a key role for gender differences in the pathogenesis of COVID-19, as postmenopausal women

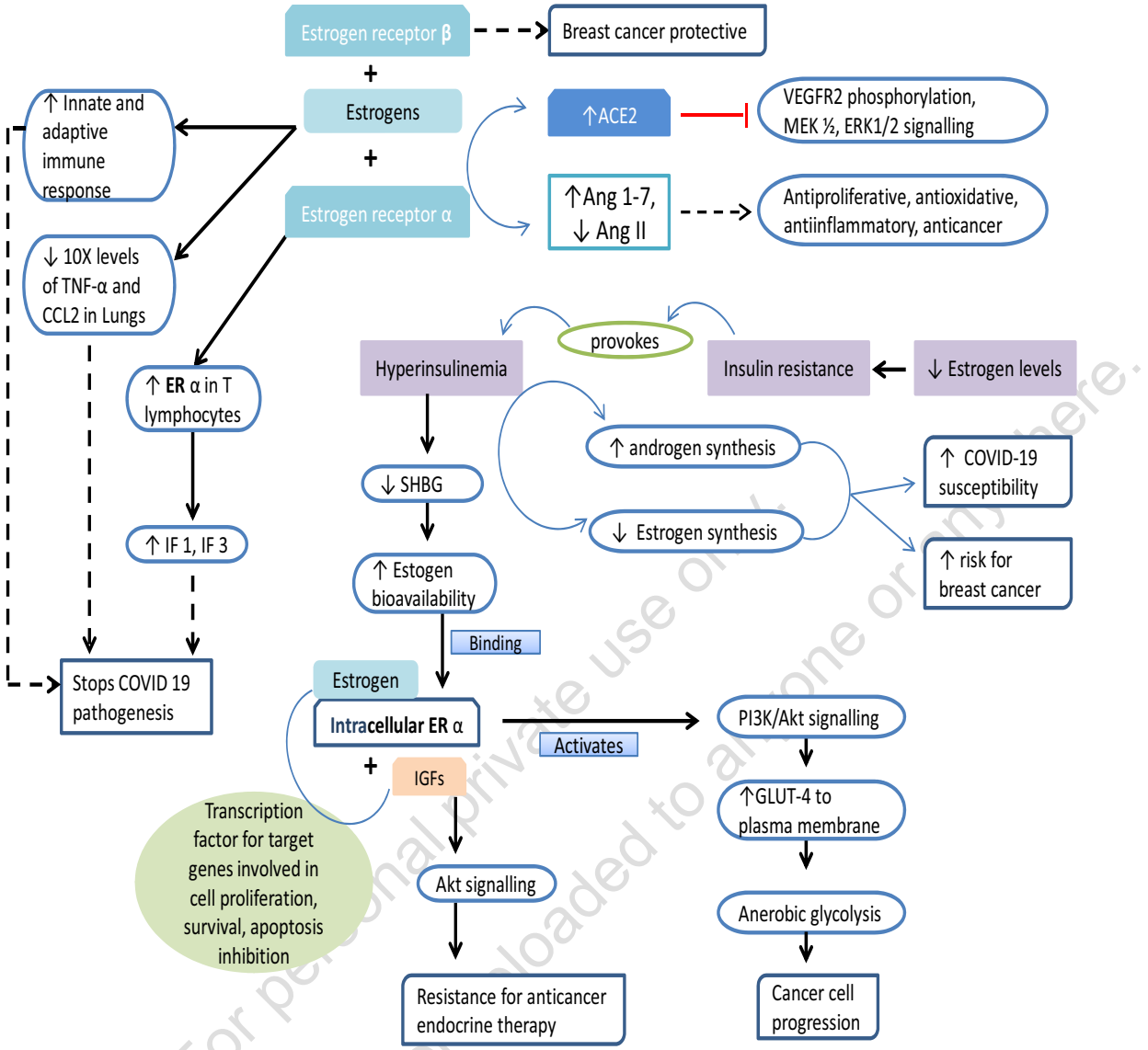

Fig. (5). Role of estrogen signaling in breast cancer and COVID-19. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

are more susceptible than premenopausal women, which may be explained by the anti-inflammatory role of estrogen that protects women COVID-19 patients from a cytokine storm. Experimental studies on H1N1 influenza in female mice, when treated with estrogen, showed 10 times decrease in the levels of pro-inflammatory cytokines-TNF-α and CCL2 in lungs, which is protective against the severity of H1N1 influenza in female mice [198]. Based on the experimental and epidemiological reports, estrogen therapy may be a therapeutic option for COVID-19 [6].

Estrogen is known to heighten the immune response (both innate and adaptive) and enhance immunological markers and response [214] by increasing the T-cell proliferation [214], this is further evident by the fact that females have a greater presence of autoimmune disorders [214]. In contrast, testosterone is shown to be immunosuppressive by down-regulating the natural killer cells and TNF-α [214]. Often, it is observed that females mount a more pronounced immune response, which is effective in quicker infection clearance but also poses a risk of immunopathological problems. Therefore, sex differences directly attribute to the prevalence, severity, and outcomes of viral infections [215, 216] reflected in the epidemiological data of SARS-CoV, MERS-CoV and SARS-CoV-2 with the similar trend of worse clinical outcomes in men [197, 207] (Fig. **5**).

Briefly, till now line of evidences are suggesting that gender is a dominant driver of the risk and mortality to COVID-19 patients, however further research on the molecular pathways related to the hormonal, inflammatory, and immunologic along with an association of comorbidities is further required.

14. ROLE OF ESTROGEN SIGNALLING IN BREAST CANCER PATHOGENESIS

Both deficiency and high levels of estrogen contribute to breast cancer tumorigenesis [13, 172]. Several clinical studies reveal low levels of estrogen in postmenopausal women and a greater risk of breast cancer to diabetic-postmenopausal women when compared to younger-diabetic women [179, 190, 217]. Insulin resistance and deficiency of estrogen are concomitant disorders with mutual interrelationship. Hyperinsulinemia provokes androgen synthesis at the expense of estrogen production and even a slight decrease in the circulating estrogen levels increases the chances of breast, endometrium and ovary cancers, because these organs having high estrogen demand [173]. Remarkably, women with polycystic ovary syndrome (PCOS) have cardinal sign of anovulation, infertility, obesity, insulin resistance along with low levels of estrogen and high testosterone [218].

In a study on the mortality of PCOS patients, breast cancer proved to be the leading cause of death [219]. However, an increase in estrogen levels was also shown to increase the likelihood and aggressiveness of breast cancer. Hyperinsulinemia reduces the sex hormone-binding globulins (SHBG) which resultantly increase the bioavailability of free estrogen and this resultant increase in insulin also leads to the risk of breast cancers [179, 186, 190, 217]. Estrogen binds with the intracellular estrogen receptors, which serve as a transcription factor for the target genes mainly involved in cell proliferation, survival and inhibition of apoptosis [186, 217]. Cross talk of ER and insulin-like growth factors (IGF-s) further aggravate breast cancer progression through Akt activation [218] and cause resistance for anticancer endocrine therapies [220-222]. Another pathway mediated through ER is the activation of PI3K/ Akt signalling, which enhances the recruitment of glucose transporter-4 (GLUT-4) to the plasma membrane. Increased recruitment of GLUT4 participates in high glucose uptake by cancer cells to utilize for aerobic glycolysis and proliferation of the cancer cells (Warburg hypothesis) [223]. Therefore, GLUT4 is one of the promising targets for breast cancer treatment, in fact, lapatinib (HER2 inhibitor) treatment to the ER-ve/ HER+ve breast cancers was shown to inhibit HER2/Akt signalling and subsequently the down regulation of GLUT4 that results in decreased proliferation with enhanced apoptosis of cancer cells [224]. The carcinogenic or anticancer role of estrogen is dependent upon the types of ER receptor activation, as ER-α and ER-β differently regulate the cell cycle. The ER-α promotes cell proliferation and inhibition of apoptosis, whereas ER-β induces inhibitory effects on cell cycle and promotes apoptosis [225]. Nevertheless, many clinical studies supported that the elevated estrogen levels are associated with increased risk of breast, endometrial and ovarian cancers [226-231]. A population-based study of postmenopausal women on hormone replacement therapy (HRT) also supported the incidence of increased risk of cancer [232]. Available data consistently suggest that the use of hormone replacement therapy (HRT) for 5-10 years significantly increases the risk of breast cancer [233]. In fact, the carcinogenic activity of steroidal estrogen has been documented by the International Agency for Research on Cancer (IARC), which classified the evidence for these effects in humans (IARC, 1999) [234].

CONCLUSION

Briefly, we conclude that breast cancer patients are more susceptible to COVID-19 in comparison with their normal counterparts. Women are more resistant to the occurrence and severity of COVID-19. High expression of ACE2 and lower expression of TMPRSS2 are correlated with increased survival and good prognosis in breast cancer. The ACE2 inhibitors for COVID-19 treatment may aggravate the clinical condition of breast cancer patients through chemo-resistance and metastasis. We also suggest that most of the therapeutic modalities used for COVID-19 exert positive effects on breast cancer outcomes, except ACE2 inhibitors and ibuprofen, which may aggravate the clinical condition of breast cancer patients. Besides, TMPRSS2 inhibitors, estrogen supplementation, androgen deprivation and DPP-IV inhibitors may also be used to treat breast cancer patients infected with SARS-CoV-2. However, drug-drug interactions suggest that some of the drugs used for the treatment of COVID-19 may modulate the drug metabolism of anticancer therapies, which may lead to adverse events.

LIST OF ABBREVIATIONS

ACEi	=	ACE Inhibitors
APN	=	Alanyl Aminopeptidase N
APA	=	Aminopeptidase
ADT	=	Androgen Deprivation Therapy
AGA	=	Androgenic Alopecia
ACE-2	=	Angiotensin-Converting Enzyme-2
AD	=	Aspartate Decarboxylase
BP	=	Blood Pressure
BI-RADS	=	Breast Imaging –Reporting and Data System
BRCA	=	Breast Invasive Carcinoma
CCL2	=	Chemokine (C-C Motif) Ligand 2
CXCR4	=	Chemokine Receptor type 4
CQ	=	Chloroquine
CD26	=	Cluster of Differentiation 26
COVID-19	=	CoronaVirus Disease 2019
DEX	=	Dexmedetomidine
DPP-IV	=	Dipeptidyl Peptidase 4
DFS	=	Disease Free Survival
EGFR	=	Epidermal Growth Factor Receptor
EMT	=	Epithelial-Mesenchymal Transition

EBV = Epstein-Barr Virus
ER- α = Estrogen Receptor Alpha
ER-β = Estrogen Receptor Beta
ECM = Extracellular Matrix
ERK1/2 = Extracellular Signal-Regulated Kinase ½
GEPIA = Gene Expression Profiling Interactive Analysis
GSEA = Gene Set Enrichment Analysis
GLP-1 = Glucagon-like Peptide-1
GLUT-4 = Glucose Transporter type 4
HDL = High Density Lipids
HRT = Hormone Replacement Therapy
HER2 = Human Epidermal Growth Factor Receptor 2
HPV = Human Papillomavirus
HCQ = Hydroxychloroquine
IR = Insulin Resistance
IGFs = Insulin-like Growth Factors
IFITM3 = Interferon-inducible Transmembrane Protein 3
MHCs = Major Histocompatibility Complexes
Mas R = Mas Receptor
MRDG = Mas-related G Protein-Coupled Receptor Member D
MMPs = Matrix Metalloproteases
MMP16 = Matrix Metalloproteinase-16
MCPyV = Merkel Cell Polyomavirus
MCF-7 = Michigan Cancer Foundation-7
MERS-CoV = Middle East Respiratory Syndrome-Coronavirus
MAPK = Mitogen-Activated Protein Kinase
NEP = Neprilysin
NO = Nitric Oxide
NF-kB = Nuclear Factor Kappa- Light-Chain-Enhancer of Activated B Cells
ORF = Open Reading Frame
OS = Overall Survival
PI3K/Akt/mTOR = Phosphoinositide 3-Kinase/ Protein Kinase B/ Mammalian Target of Rapamycin
PCOS = Polycystic Ovary Syndrome
ROS = Reactive Oxygen Species
RAS = Renin Angiotensin System
SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2
SHBG = Sex Hormone-Binding Globulins
SNB = Sentinel Lymph Node Biopsy
STAT3 = Signal Transducer And Activator Of Transcription 3
SOCE = Store-Operated Calcium Entry
SYNPO2 = Synaptopodin 2
TCRs = T Cell Receptors
TMPRSS2 = Transmembrane Protease, Serine 2
TNBC = Triple-Negative Breast Cancer
TNF-α = Tumor Necrosis Factor
TIMER = Tumour Immune Estimation Resource
TRAIL = Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand
TSA = Tumour Specific Antigens
TILs = Tumour-Infiltrating Lymphocytes
AT1R = Type I Angiotensin II Receptor
UPR = Unfolded Protein Response
VEGFR2 = Vascular Endothelial Growth Factor Receptor 2
VSMC = Vascular Smooth Muscle Cells
Wnt = Wingless and Int-1

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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