REPUBLIC OF TÜRKİYE
KIRŞEHİR AHİ EVRAN UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS

DETERMINATION AND COMPARISON OF THE RELATIONSHIP BETWEEN COVID-19 AND BREAST CANCER, TRIPLE NEGATIVE BREAST CANCER AND CLEAR CELL RENAL CELL CARCINOMA BY IN SILICO APPROACHES

AMMAR YASIR AHMED AHMED

MASTER THESIS

KIRŞEHİR
2023

T.C.
KIRŞEHİR AHİ EVRAN ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
MOLEKÜLER BİYOLOJİ VE GENETİK
ANABİLİM DALI

COVID-19 İLE MEME KANSERİ, ÜÇLÜ NEGATİF MEME KANSERİ VE BERRAK HÜCRELİ RENAL HÜCRELİ KARSİNOM ARASINDAKİ İLİŞKİNİN İN SİLİKO YAKLAŞIMLAR İLE BELİRLENMESİ VE KARŞILAŞTIRILMASI

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KIRŞEHİR
2023

KIRŞEHİR AHİ EVRAN UNIVERSITY INSTITUTE OF NATURAL AND APPLIED SCIENCES

MASTER'S THESIS

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Student

Ammar Yasir AHMED AHMED

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ACKNOWLEDGMENTS

At the outset, praise and thanks be to Allah, who facilitated my affairs and enabled me to complete my message, and also sincere thanks with all my heart to the respected Assistance Prof. Dr. Sevinc Akcay, who supported me and taught me the meaning of patience and strength and did not abandon me with his kindness and supported advice in my most difficult situations And also a huge thanks to my father and mother who taught me everything I know today and believed in them and gave me all the support to help me complete my master's degree. I also sincerely thank my dear brother Ahmed and my sisters Naba and Saba, my source of strength for their love and support for me and for providing me with the spirit I need to overcome difficulties and succeed. Finally, From the depths of my soul, I appreciate your unending kindness and generosity. Without you all, I would not have dreamed of achieving success.

July, 2023 Ammar Yasir AHMED AHMED

ABSTRACT

MASTER'S THESIS

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The COVID-19 epidemic has become a major health concern around the world, resulting in a staggering death toll of nearly 15 million individuals worldwide. Individuals afflicted with persistent diseases exhibit more severe symptoms of COVID-19 in comparison to the broader population. More research suggest that COVID-19 poses a greater threat to individuals with breast cancer, triple-negative breast cancer (TNBC) and clear cell renal cell carcinoma (ccRCC). However, further research is needed to explain the fundamental processes. Our study aimed to use computational methods to identify molecular pathways shared in the pathogenesis of COVID-19, breast cancer, TNBC and ccRCC. The present study conducted a differential expression analysis (DEG) by using public Gene Expression Omnibus (GEO) datasets. Identified DEGs were subjected to further analysis to identify common DEGs, pathways, hub genes, transcription factors (TFs), and microRNAs (miRNAs). This investigation has identified commonly expressed hub genes, miRNAs, and TFs in mild and severe COVID-19 and TNBC, breast cancer and ccRCC. Additionally, shared mechanisms have been identified in these patient groups. There were discernible dissimilarities in potential biomarkers and mechanisms between COVID-19 and individuals with TNBC, breast cancer and ccRCC with mild and severe disease. This study represents the inaugural investigation into the potential commonalities in mechanisms and biomarkers between COVID-19 patients and those with three cancer types. Taking into mind the severity of the COVID-19, the results of our research may provide light on the best ways to care for TNBC, breast cancer or ccRCC patient who are also infected with the virus.

Keywords: COVID-19, Triple negative breast cancer, Breast cancer, Clear cell renal cell carcinoma, Bioinformatics

ÖZET

YÜKSEK LİSANS TEZİ

COVID-19 İLE MEME KANSERİ, ÜÇLÜ NEGATİF MEME KANSERİ VE BERRAK HÜCRELİ RENAL HÜCRELİ KARSİNOM ARASINDAKİ İLİŞKİNİN İN SİLİKO YAKLAŞIMLAR İLE BELİRLENMESİ VE KARŞILAŞTIRILMASI

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KIRŞEHİR AHİ EVRAN ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
MOLEKÜLER BİYOLOJİ VE GENETİK ANABİLİM DALI

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COVID-19 salgını dünya çapında önemli bir sağlık sorunu haline gelmiş ve dünya çapında yaklaşık 15 milyon kişinin şaşırtıcı bir şekilde hayatını kaybetmesine neden olmuştur. Kalıcı hastalıklardan etkilenen bireyler, daha geniş popülasyona kıyasla daha şiddetli COVID-19 semptomları sergilemektedir. Daha fazla araştırma, COVID-19'un meme kanseri, üçlü negatif meme kanseri (TNBC) ve berrak hücreli renal hücreli karsinom (ccRCC) olan bireyler için daha büyük bir tehdit oluşturduğunu göstermektedir. Ancak, temel süreçleri açıklamak için daha fazla araştırmaya ihtiyaç vardır. Çalışmamız COVID-19, meme kanseri, TNBC ve ccRCC patogenezinde paylaşılan moleküler yolakları belirlemek için hesaplamalı yöntemler kullanmayı amaçlamıştır. Bu çalışmada, halka açık Gen Expression Omnibus (GEO) veri kümeleri kullanılarak bir diferansiyel ekspresyon analizi (DEG) gerçekleştirilmiştir. Belirlenen DEG'ler, ortak DEG'leri, yolakları, merkez genleri, transkripsiyon faktörlerini (TF'ler) ve mikroRNA'ları (miRNA'lar) tanımlamak için ileri analize tabi tutulmuştur. Bu araştırma, hafif ve şiddetli COVID-19 ve TNBC, meme kanseri ve ccRCC'de yaygın olarak ifade edilen merkez genleri, miRNA'ları ve TF'leri tanımlamıştır. Ayrıca, bu hasta gruplarında ortak mekanizmalar tanımlanmıştır. COVID-19 ile hafif ve şiddetli hastalığı olan TNBC, meme kanseri ve ccRCC'li bireyler arasında potansiyel biyobelirteçler ve mekanizmalar açısından fark edilebilir farklılıklar vardı. Bu çalışma, COVID-19 hastaları ile üç kanser türüne sahip olanlar arasındaki mekanizmalar ve biyobelirteçlerdeki potansiyel ortaklıklara ilişkin ilk araştırmayı temsil etmektedir. COVID-19'un ciddiyeti göz önünde bulundurulduğunda, araştırmamızın sonuçları virüsle enfekte olan TNBC, meme kanseri veya ccRCC hastalarına bakım vermenin en iyi yollarına ışık tutabilir.

Anahtar Kelimeler: COVID-19, Üçlü negatif meme kanseri, meme kanseri, Berrak hücreli renal hücreli karsinom, Biyoinformatik

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INDEX OF SYMBOLS AND ABBREVIATIONS

Symbols		Description
>	:	Bigger
≤	:	Small Equals
≥	:	Great Equals
<	:	Small
%	:	Percentage

Abbreviations		Description
adj p	:	Adjusted p-value
BC	:	Breast Cancer
ccRCC	:	Clear Cell Renal Cell Carcinoma
TNBC	:	Triple Negative Breast Cancer
COVID-19	:	Coronavirus disease 2019
DEG	:	Differentially Expressed Genes
GEO2R	:	Gene Expression Omnibus 2R
GO	:	Gene Ontology
KEGG	:	Kyoto Encyclopedia of Genes and Genomes
PPI	:	Protein-protein interaction
miRNA	:	MicroRNA
WHO	:	World Health Organization
***p*-value**	:	Probability value
BP	:	Biological processes
MF	:	Molecular functions
CC	:	Cellular components
mirDIP	:	microRNA Data Integration Portal
TFs	:	Transcription factors
STRING	:	Search Tool for the Retrieval of Interacting Genes/Proteins
ACE2	:	Angiotensin-converting enzyme 2

1. INTRODUCTION

The novel coronavirus SARS_CoV_2 in China, Wuhan was discovered, Hubei province, in 2019 (Yang et al., 2020). The SARS CoV_2 designation was given to the newly discovered virus by the Viral Genome Sequencing Project (ICTV) due to the fact that it shares 85% of its genome sequence with a virus (SARS-CoV) (Bchetnia et al., 2020). The Covid-19 virus, a member of the beta-coronavirus family, is the breeder agent of the COVID-19 respiratory disease (Abebe et al., 2020). The human coronavirus, sometimes known as HCoV, was found for the first time in the 1960s (Sharma., 2021). The six human coronaviruses that have been found up to this point are MERS-CoV, SARS-CoV, alpha and beta-coronaviruses (HCoVs-NL63 and HCoVs-229E), beta-coronaviruses (HCoVs-OC43 and HCoVs-HK-U1), and SARS-CoV and beta-coronaviruses (Nimesh et al., 2021). Even though SARS-CoV-2 and SARS-CoV share many virological, epidemiological, and clinical characteristics, there is a paucity of experimental evidence about SARS-CoV-2 (Bchetnia et al., 2020).

The genome of the SARS-CoV-2 virus is around 30,000 nucleotides in length (Sreeramulu et al., 2021). Its genomic RNA, which is known as gRNA, has 14 open reading frames (ORFs) (Huang et al., 2000). Both ORF1a and ORF1b are translated into the proteins Polyprotein 1a (PP1a) and Polyprotein-1ab (PP1b), respectively, and together they make up two-thirds of the genome (Prajapat et al., 2020). These poly-proteins are translated into Non--Structural Proteins (NSPs), numbered Nsp1-Nsp16, by viral proteases (Kandwal & Fayne., 2023). Inside double-membrane vesicles, some NSPs, in conjunction with a number of host components, produce what is known as a Replication Transcription Complex (RTC) (DMVs) (Angelini et al., 2013). RTCs are the center of the process through which the viral genome is copied and reproduced (Brant et al., 2021). ORFs that code for the four main structural proteins are present in the final third of the genome (Satarker & Nampoothiri., 2020). The ORFs are the production of four structural proteins and certain auxiliary proteins falls under the responsibility of the aforementioned entity (Gonzalez et al., 2003). These components comprise proteins such as Nucleocapsid(N), Membrane (M), Speke (S), and Envilope (E), along with a few auxiliary proteins ORF6, ORF3a, ORF7b, ORF7a, ORF8, ORF9 and ORF10 (Ayra et al., 2021).

Coronaviruses have an essential structural protein called nucleocapsid protein. It contains several coronaviruses and is highly immunogenic (Ayra et al., 2021). The N proteins transport the virus inside the cell which host the virus, connect to the virus' RNA base, and form the

nucleoprotein core of the virus (RNP) (Liu et al., 2020). SARS-CoV-2 N protein and SARS-CoV N protein have a high degree of similarity, with 90% sequence identity between the two (Grifoni et al., 2020). The N protein is a crucial antigen for coronaviruses that is involved in RNA packaging and viral particle release. The N protein is extensively employed in vaccine formulation and serological analysis (Zeng et al., 2020). A Serine-Arginine (SR)-rich domain, center-binding region (LKR), an RNA binding domain inside the a C−Terminal Domain and N−Terminal Domain (NTD), make up the SARS-CoV-2 N protien (CTD) (Lu et al., 2021).

The RNA virus's genome is highly susceptible to change as the virus replicates and spreads. In addition, in comparison to other RNA viruses, coronaviruses have significantly higher rates of mutation (Teng et al., 2021). It is believed that mutations which exsist in SARS-CoV 2 have major implications on the riskiness of COVID-19 isease, on the propagation of the virus, and on the virus's stability (Mohammadi et al., 2021). In order to evaluate links to pathogenesis, immunological evasion, and viral drug resistance pathways, the biological characterization of viral mutations gives valuable information (Pachetti et al., 2020). The most difficult challenge that has to be met in order to successfully develop new drugs and vaccines is the persistent appearance of new mutations in SARS-CoV-2 (Chowdhury et al., 2020). Because the N protein is involved in a number of significant steps in the virus's life cycle, it could be used as a treatment and preventative target for COVID-19 (Zeng et al., 2020). The rising tide of sequenced whole genome data of SARS-CoV-2 has enabled the detection of changes in the virus's genetic code, and the investigation of the results of these mutations on the structure of proteins and the prediction of how a point mutation alters the stability of the protein is guiding pharmaceutical drug and vaccine design initiatives. Conducting wet laboratory studies with physical proteins is prohibitive due to the amount of time and financial resources that are required (Dehghanpoor et al., 2018). The opposite is true for missense mutations, which may be readily quantified by bioinformatic studies that that expect the impact of a mutation on protein structure (Teng et al., 2021).

COVID-19 can cause symptoms that range from being completely symptom-free to a life-threatening case of ARDS and multi-organ failure (Tsai et al., 2021). Inflammation of the lungs is caused by COVID-19 due to the hyperactivation of immune cells (Erol., 2020). Frequent clinical manifestations consist of fever, cough, sore throat, headache, weariness, muscle discomfort, and dyspnea (Robba et al., 2020). It is more likely for elderly persons and those who already have many medical conditions to have poor outcomes and die as a result of the disease. Between four and

eleven percent of adult inpatients end up passing away every year. It is generally believed that the death rate for cases falls anywhere between 2% and 3% (Coronavirus., 2020).

A number of pieces of evidence point to a connection between the SARS-CoV-2 virus's biology and cancer, which has been shown to exist, According to the data, cancer patients have a greater contracting risk of SARS-CoV-2, ultimately developing severe COVID-19 illness, and ultimately passing away (Bakouny et al., 2020). Age, ACE2, cytokine storms, and coagulopathy are some of the factors that have been shown to have a significant relationship between COVID-19 and cancer (Jyotsana., 2021).

In recent times, cancer has emerged as a significant threat to human well-being and has assumed the position of the primary cause of human mortality (Horrigan et al., 2002). It is generated by a mix of external factors and internal genetic changes, culminating in the phenotypic metamorphosis of healthy cells into cancerous ones is the defining characteristic of cancer (Parsa., 2012). The malignant cells will then begin to grow beyond the confines of the healthy tissue, which will eventually lead to metastasis throughout the body (Si et al., 2019). An essential characteristic (metastasis) of malignant tumors is their propensity to spread to neighbouring tissues and distant places, resulting in secondary malignancies (Fares et al., 2020). Around ninety percent of cancer-related fatalities are attributable to metastatic tumours (Fouad and Aanei., 2017).

Cancer is a biological disorder characterized by carcinogenesis, a complex interaction of hereditary and environmental elements (Demaria et al., 2010). One of the most deadly illnesses to impact the entire world's population is this one (Zhang et al., 2007). Disruptions in normal cellular activities are a distinguishing characteristic of cancer, a disease that is characterised by these disruptions (Jaalouk & Lammerding., 2009). The pathways that control a cell's most fundamental functions are known to become dysregulated as a result of mutagenic events that change a cell's genetic makeup (Patel., 2012). The development of malignant conditions is specifically caused by the accumulation of multiple genetic defects that result in the dysregulation of signalling pathways that regulate cell proliferation, cell death, and DNA repair (Huang & Zhou., 2020).

Uncontrolled growth and division of aberrant cells, which may infiltrate and kill healthy tissues, describe a group of disorders known collectively as cancer (Fares et al., 2020). The majority of the time, it requires a combination of treatments, which may include chemo, radio, immuno, hormone, stem cell transplant, and cellular therapy, to combat cancer (Miller et al., 2016). The immune system is weakened by cancer and the chemotherapy or radiation treatment used to treat

it, weakening the immune system's ability to fend against diseases, especially viral ones. Consequently, those receiving or having just finished cancer treatment with chemotherapy or radiation are at increased risk for infection, particularly viral infections (Jyotsana., 2020).

Studies in recent few years have shown that COVID-19 promotes the production of substances that help to revive dormant breast cancer cells. Therefore, these cells and a pro-inflammatory environment may activate breast cancer, increasing the likelihood of metastasis to the lungs (Ali et al., 2021). To determine whether or if COVID-19 is linked to cancer relapse. Additional research is required. However, if COVID-19-positive breast cancer patients are informed of potential hazards, it may be possible to devise therapeutic methods that avoid metastatic recurrence (Francescangeli et al., 2020).

Breast cancer is characterized by a bump growth or tumor in the breast, which is most often the result of the transformation and abnormal, uncontrolled growth of breast tissue (Pediconi & Galati., 2022). Statistics on breast cancer mortality is second only to that from cardiovascular disease among all cancers (Jemal et al., 2011). Furthermore, breast cancer is the fifth most frequent illness in women globally (Al-Hashimi., 2021).

The most prevalent kind of cancer to be diagnosed in females is breast cancer (Mellemkjær et al., 2006). Imaging methods such as X-rays, magnetic resonance imaging and ultrasound, are widely used in clinical diagnostics for breast cancer (Bozzini et al., 2020). These three procedures are used to diagnose breast cancer in routine medical check-ups or in people without symptoms. Compared with medical biopsy, these three procedures are painless and often used in clinical diagnosis. However, X-ray mammography is painful due to breast compression (Ekici & Jawzal., 2020). In addition, the high dose of ionising radiation used is dangerous for patients and can cause cancer in healthy tissues. It is difficult to detect deep-lying or solid malignant tissue with ultra-sound equipment (Bozzini et al., 2020).

The term "triple-negative breast cancer" (TNBC) refers to a specific breast cancer subtype (Ismail-Khan & Bui., 2010). The deprivation of the estrogin receptor, the progestirone receptor, and the HER2/neu protein receptor distinguishes TNBC from other subtypes of breast cancer. While these receptors are essential for healthy breast cell growth and division, they can actually promote tumour development and metastasis in breast cancer cells (Lehmann & Pietenpol., 2011). The absence of these receptors in TNBC means that hormone therapy and targeted therapies that work by blocking these receptors, such as tamoxifen and trastuzumab, do not work on this

particular form of breast cancer. Instead, TNBC is typically treated with chemotherapy, which kills rapidly dividing cancer cells throughout the body (Yao et al., 2017).

TNBC makes up ranging a percent 10 to17 of all breast cancers (Carey et al., 2007). Patients diagnosed with TNBC often have tumours of a higher grade and a smaller size than individuals identified as having breast cancer (Lee et al., 2011). Particularly within 3 years of diagnosis, TNBC is linked to a greater risk of distant recurrence and death (Lin et al., 2008). Systemic treatment with cytotoxic chemotherapy is the only choice for patients diagnosed with TNBC who do not respond to hormone therapy or medicines that target HER2 (Yao et al., 2017).

Due to the rising corpus of studies demonstrating the presence of microRNAs in circulating blood plasma and serum, there is a larger probability of utilising them as efficient biomarkers for cancer and other disorders (Weiland et al., 2012). Several miRNA genes, including miR-21, miR-155, and miR-10b, have been found to have abnormally changed expression levels in breast cancer, (Köberle et al., 2013; Ng et al., 2013). The value of microRNA as a biomarker in the blood of people with breast cancer, Yet, these people are shown to have reduced levels of three microRNAs: miR-221, miR-125b, and miR-145 (Xie et al., 2013).

Women under the age of 40, those of African origin, and those with a mutant BRCA1 gene are at increased risk for developing TNBC (Lee et al., 2011). In addition to this, the risk increases especially for women with a past in their family of either breast or ovarian cancer (Roett & Evans., 2009). TNBC is generally considered more aggressive than Many Other Breast Cancers, meaning that it tends to develop and become more widespread It also has an increased likelihood of occurrence, particularly within the First Three Year Period of diagnosis, However, some women with TNBC respond well to treatment and achieve long-term survival (Tutt et al., 2018). Research into TNBC is ongoing, and scientists are exploring new targeted therapies and immunotherapies that may be effective against this breast cancer of a certain type In the meantime, early detection and timely treatment are both essential factors in improving outcomes for women diagnosed with TNBC (Rakha & Chan., 2011).

The prevailing form of renal cell carcinoma (RCC) affecting the kidneys is characterized by clear cells and is commonly referred to as clear cell renal cell carcinoma (CCRCC) (Van den Berg., 2013). The area of the kidney known as the proximal tubule is where clear cell renal cell carcinoma, also known as CCRCC, first develops (Najar., 2018). It is the type of kidney cancer that occurs most frequently as well as accounts for 85 percent of all diagnoses of kidney cancer.

The seventh most prevalent kind of cancer in men is ccRCC. Researchers have been able to locate novel target molecules among the essential molecules responsible for this process as a result of their discovery of the function that angiogenesis plays in the development and progression of kidney cancer (Alonso-Gordoa et al., 2019). Tyrosine kinase inhibitors, which target VEGFR and PDGFR, are used with chemotherapy to slow disease progression (Shen et al., 2018). Genetic and acquired causes may lead to ccRCC. Acquired causes include hypertension, long-term dialysis use, smoking, obesity, and diabetes. The two most common genetic causes are defects in the von HippelLindau (VHL) and protein polybromo-1 (PBRM-1) genes (Padala & Kallam., 2021).

COVID-19 may affect breast cancer outcomes, according to some research. One study in Breast Cancer Research and Therapy indicated that COVID-19-positive breast cancer patients had a greater risk of serious complications and mortality, This study had a tiny sample size, thus more research is needed to corroborate these findings (Lee et al., 2020). A study in the Journal of Medical Virology COVID-19 in Breast Cancer Tissue found no COVID-19 RNA in breast cancer tissue, suggesting that the virus may not directly target the disease (Wang & Zhang., 2020). While there may be some indirect links between breast cancer and COVID-19, additional research is needed to completely understand the association. Breast cancer patients must continue to prioritise their health by adhering to COVID-19 prevention guidelines and scheduling regular exams and treatments (Spencer et al., 2021). It is essential to point out that research into the link between COVID-19 and breast cancer is still ongoing, and additional investigation must be attained if one wants to have a complete comprehension of the possible links that exist between the two (Andrews et al., 2022).

TNBC, like other breast cancer subtypes, may be affected in a variety of ways by the COVID-19 pandemic (Garassino., 2020). There has only been a limited amount of study done on the precise link between TNBC and COVID-19. However, other studies suggest that individuals with TNBC may have a higher risk of serious illness or mortality from COVID-19 because cancer treatments tend to weaken the immune systems of patients (Lee et al., 2020).

The link between COVID-19 and various subtypes of breast cancer, including TNBC, was the subject of research that was published in the journal Cancer Discovery, The study's results indicate that individuals diagnosed with triple-negative breast cancer (TNBC) exhibit a heightened susceptibility to severe illness and mortality in the event of a positive COVID-19 diagnosis, relative to patients diagnosed with other subtypes of breast cancer (Givi et al., 2020). TNBC patients who

got chemotherapy during the COVID-19 pandemic had a higher chance of having serious consequences from COVID-19 than TNBC patients who did not get chemotherapy during the pandemic, according to the findings of another study that appeared in Cancer Research (Zhang et al., 2020).

The COVID-19 pandemic may have several effects on ccRCC. Research on the specific relationship between ccRCC and COVID-19 is limited, just like research on other cancers However, some studies suggest that ccRCC patients may be more likely to get sick or die from COVID-19 because their immune systems are weaker from cancer treatments or cancer itself (Makhov et al., 2018). Research in European Urology Oncology examined the effects of COVID-19 on urological cancer patients, including ccRCC. The study indicated that COVID-19-positive urological cancer patients were more likely to die than those without cancer (Manso et al., 2020). Those with advanced ccRCC who contracted COVID-19 had poorer clinical outcomes, including longer hospital admissions and a higher rate of problems, Unlike Patients with less advanced ccRCC, according to the findings of a different study that was published in the Journal of Urology (López-Fernández et al., 2022). COVID-19's effects on advanced kidney cancer patients, including ccRCC, were examined in a Journal of Clinical Medicine study. COVID-19 infection was linked to greater fatality rates in advanced kidney cancer patients. Advanced kidney cancer patients frequently have weaker immune systems owing to cancer or immunotherapy, leaving them more susceptible to infections like COVID-19, according to the study (Yau et al., 2020). Another European Journal of Cancer study examined how the COVID-19 pandemic affected kidney cancer management in Europe. The pandemic forced many hospitals to postpone or cancel cancer procedures and other treatments, delaying kidney cancer treatment, the study showed. To reduce patient outcomes during pandemics like COVID-19, healthcare systems should establish techniques to manage cancer care (Fakhri et al., 2021).

The primary objective of this thesis is to employ an integrative bioinformatics approach to ascertain potential mechanisms, key biomarkers, transcription factors (TFs), and microRNAs (miRNAs) that are common to COVID-19, triple negative breast cancer, breast cancer, and clear cell renal carcinoma. Hence, this study aims to examine whether there exist any variations in potential mechanisms and biomarkers shared between COVID-19- trìple negative breast cancer, breast cancer, and clear cell renal carcinoma patients, based on the severity of COVID-19.

The second goal of this work is to investigate the existence of biomarkers that are common to COVID-19 across different tumour types. This will be accomplished by conducting a comparative analysis of metastatic and normal, primary tumour and normal, and metastatic and primary tumour datasets, separately for negative triple breast cancer and clear cell renal cell carcinoma.

The third objective of the thesis is to ascertain shared biomarkers and pathways across three distinct cancer types. The present study aims to facilitate the identification of shared biomarkers across various breast cancer subtypes, as well as to identify potential common candidate markers and biological pathways between breast cancer and clear cell renal cell carcinoma.

This study aims to explore the potential shared mechanisms, biomarkers, transcription factors (TFs), and microRNAs (miRNAs) among patients with COVID-19 and breast cancer, COVID-19 and triple negative breast cancer, and COVID-19 and clear cell renal cell carcinoma. It is anticipated that this research will be the first of its kind to investigate these relationships. The current study aims to discern and contrast the correlation between COVID-19 and three distinct forms of cancer. The investigation of potential variations in mechanisms and biomarkers shared among diverse cancer types based on the severity of COVID-19 can facilitate the identification of personalised treatment alternatives for each cancer type. Despite the current state of COVID-19 no longer being classified as a pandemic, the identification of shared biological pathways among various types of cancer may facilitate the elucidation of the correlation between COVID-19 and diverse cancer types. The investigation of potential mechanisms and biomarkers It could help discover new personalized treatment interventions for different types of cancer.

This current study also aims to establish the correlation between COVID-19 and various cancer types. It is anticipated that this research will be the pioneering investigation in this field.

2. LITERATURE REVIEW

2.1. Coronaviruses

The term "novel coronavirus" refers to a novel virus strain in no way before identified in human beings (Atzrodt et al., 2020). Once doctors precisely identify the coronavirus, they assign it a name (Schwab & Malleret., 2020). The term "coronavirus" alludes to how the virus appears under a microscope (Liu et al., 2020). A genetic material core is encased in a spiking protein envelope, which surrounds the core of the virus (Tizaoui., 2020). Because of this, it looks somewhat like a crown (Kaushik & Guleria., 2020). The word "crown" comes from the Latin word "corona" (Bhatt et al., 2021). Diseases caused by coronaviruses are zoonotic, meaning they may be spread from animals to humans (Haider et al., 2020). It has been demonstrated that dromedary camels and civet cats, respectively, has the capability to spread SARS-CoV and MERS-CoV to humans (Al-Salihi et al., 2021). Despite the fact that SARS-COV-2 (Covid -19) virus has yet to be traced back to its point of origin, research is currently being conducted to determine the zoonotic agent that is causing the epidemic (Khan et al., 2020).

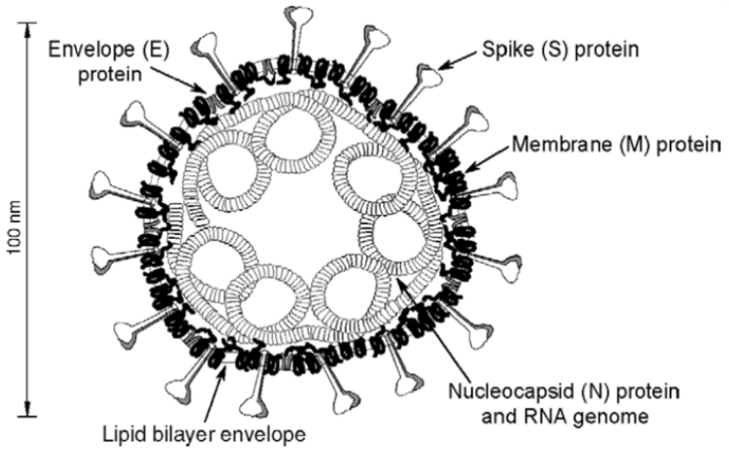

Figure 2.1. Coronavirus virion with few structural proteins (Masters., 2006).

The morphology of the virus was analyzed by the electron micrograph method, and it was found to resemble a spherical structure similar to the sun (Bruce et al., 2010). Coronaviruses are ssRNA, they have a diameter of 60–140 nm and 9–12 nm-long spikes., these spikes earned them the moniker coronaviruses (Adeyinka et al., 2021).

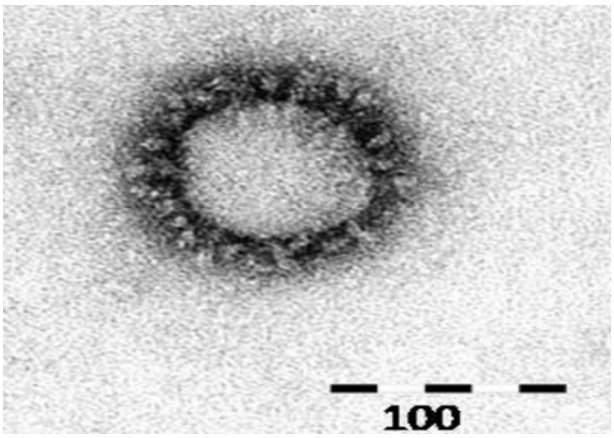

Figure 2.2. The SARS-CoV-2 virus under a microscope (https://www.nicd.ac.za).

The proteins found in coronaviruses are denoted by the letters S, E, M, and N, and they came accompanied through a dimer of haemagglutinin esterase. The genetic material is located inside the virion, but it is known that the N protein is bound to the genetic material. The S, E, M, and HE proteins can be detected on the virus's surface. The total length of the genome is between 26,000 and 32,000 bases, and it contains +ssRNA (Ayra et al., 2021).

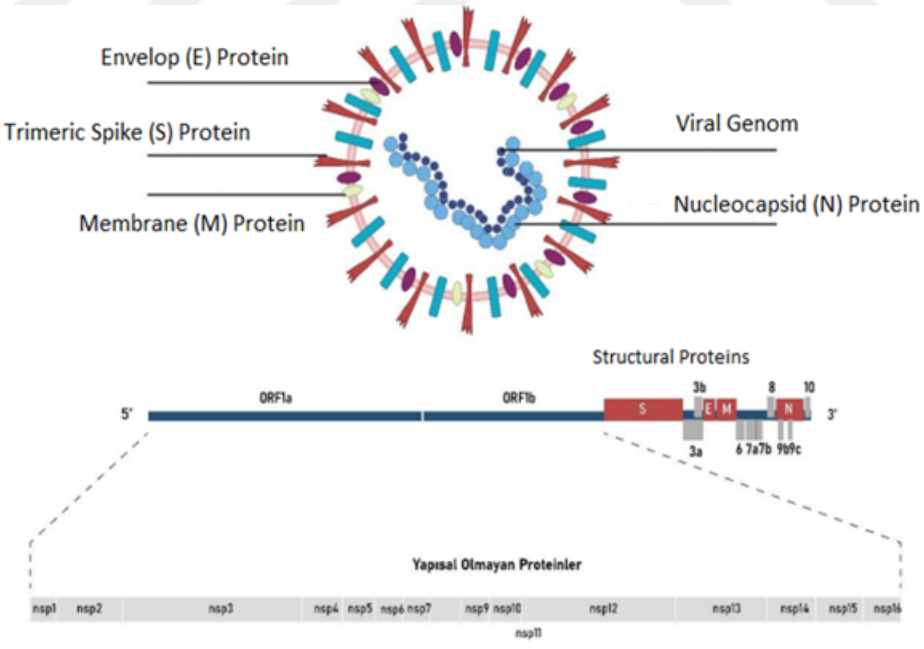

Figure 2.3. Structural details of Coronavirus (Prajapat et al., 2020).

In the 5' to 3' orientation, SARS-RNA CoV-2's genome comprises Six genes: ORF1a, ORF1b, E, S, and M and N (Yadav et al., 2021). ORF1a and ORF1b are reported to be in charge of the synthesis of two viral replicase proteins known as PP1a and PP1b. These two genes take up

two-thirds of the RNA genome. When bound to (ACE2) human angiotensin-converting enzyme (Prajapat et al., 2020). The S protein helps the SARS-CoV-2 genetic material enter the host cell either through endosomes or directly through the process of the viral envelope fusion to the host membrane (Gadanec et al., 2021). After entering the host cell, uncoated viral RNA is released to the cytoplasm of host cells, where the host cell's ribosomes interpret it (Tu et al., 2020). Viral proteases break polyproteins PP1a and PP1ab into Nsp1-16 (Kandwal & Fayne., 2023). After copying the RNA (+) strand to the RNA (-) attached to it, the negative strand is employed to replicate the (+) strand for virion production or to transcribe sub-genomic messenger RNA (mRNA) (Ghosh., 2020). These sub-genomic mRNAs produce structural (S, M, E, N) and auxiliary proteins such as (ORF3a- ORF6- ORF7a- ORF7b- ORF8- ORF9- and ORF10) (Zandi et al., 2022). So that proteins S, M, and E are translocated into the (ER) endoplasmic reticulum, while the N protein engages in the formation of a nucleoprotein complex with the genomic RNA (+) strand (Liu et al., 2020). To spread the disease, the ER-Golgi Intermediate Compartment (ERGIC) is the destination of the nucleoprotein complex and structural proteins, where the virion gathers, matures, and buds out from the Golgi as tiny vesicles, which are then exocytosed by the host cell membrane into the extracellular space (Arya et al., 2021).

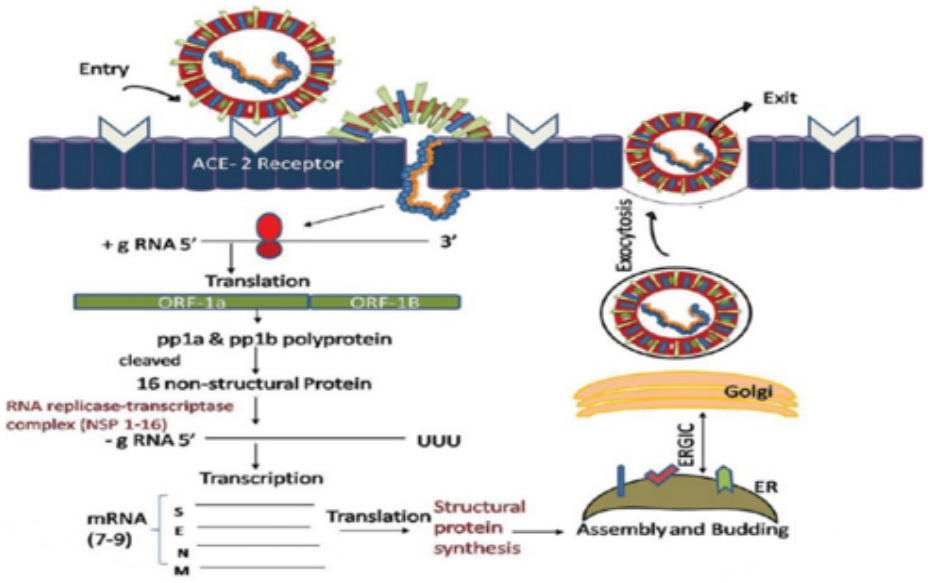

Figure 2.4. The SARS-CoV-2 virus's contribution to disease (Prajapat et al., 2020).

Real-time PCR is one of the procedures used to diagnose COVID-19 disease (Jawerth., 2020). The RT-PCR technique was designed specifically purpose of detecting gRNA since it is

rapid, accurate, and yields result in just a few hours (Behera et al., 2021). Samples for RT-PCR can be collected from a wide variety of infected sites, including the nasopharynx, oropharynx, Lavage of the bronchi and trachea, as well as aspiration of the upper and lower airways, and sputum, and have been available since January 2020 (Gualano et al., 2020). Thirty percent of RT-PCR technique results, especially in early cases, can be interpreted as false negatives. Both the immunoglobulins M (IgM) and g (IgG) tests and the antigen test are utilized in determining COVID-19 illness (Asselah et al., 2021).

2.1.1. History of COVID-19

Over the past 1000 years, coronaviruses have undergone several evolutionary changes (Forni., 2017). After the discovery of animal diseases, coronaviruses were first discovered, the virus that causes infectious bronchitis (IBV) was then isolated from poultry in 1937 (Beaudette., 1937). Throughout the 1960s, respiratory tract infections were the source of the discovery of the first human coronaviruses (Al-Khannaq et al., 2016). The first two viruses discovered were called B814 and 229E (Estola., 1970). Since then, two additional coronavirus strains known as OC16 and OC43 have been isolated from individuals who have used tissue culture (Myint., 1995). Between 2002 and 2003, SARS-CoV infected 29 countries, mostly China and Hong Kong. The sickness was eradicated after 8096 reported cases, 774 of which died, a 9.6% death rate (World Health Organization., 2003). Based on its genome sequence, SARS-CoV may have originated from a virus from Himalayan palm civets (Al-Salihi et al., 2021). MERS-CoV first surfaced in Middle Eastern countries ten years later, and dromedary camels continued to be the primary source of human infection in these countries (Ramadan & Shaib., 2019). More than 99% of the differences (substitutions) between human-camel MERS-CoV strains are found in the S, ORF3, and ORF4b genes (Chu et al., 2018). MERS-CoV penetrates cells via DPP4 receptors on the human side (Bassendine et al., 2020). Viruses with a high degree of similarity to MERS were recently discovered in Chinese bats, and their spike proteins interact with the MERS-CoV receptor (Chu et al., 2018). SARS-CoV-2 first showed up in China, Wuhan City 2019, resulting in respiratory disease and fatalities (Yang et al., 2020). Evidence from early research linking it to bats is based on the virus's high degree of similarity (96.3% identity) to the bat coronavirus RaTG13 (Helmy et al., 2020).

2.1.2. Aetiology of Covid-19

Huanan Wholesale Market for Seafood may have transferred SARS-CoV-2 from animals to humans, as early instances of Covid-19 were strongly associated with it (Li et al., 2020). The virus may have propagated from one individual to another in the past, but genomic research has demonstrated that it was brought into the market from another, as-of-yet-unknown source, and spread more quickly there (Yu et al., 2020). Evidence of P2P transmission has been shown beyond a reasonable doubt by outbreaks involving clusters of affected family members and healthcare personnel (Chan et al., 2020). When infected individual coughs or sneezes, respiratory droplets spread the disease to close contacts (Robba et al., 2020). By the beginning of the year 2020, fewer than ten percent of patients would have experienced market exposure, while over seventy percent of patients would not (Chan et al., 2020). Since SARS-CoV and other coronaviruses may persist for up to 14 days, faeces may be one of the most important transmission channels (Wang et al., 2022).

2.1.3. Classification of Coronavirus

Coronaviruses are found in the Nidovirales order, Coronaviridae family and Orthocoronavirinae subfamily (Malik., 2020). Orthococonavirinae subfamily includes 4 genera of viruses; Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus (Keskin & Keskin., 2021). SARS-CoV-2 is a beta coronavirus subgenus (Abebe et al., 2020). HCV-229E and HCV-OC43 were first thought to induce the common cold (Sizun et al., 2000). SARS-CoV and MERS-CoV epidemics broke out in 2002 and also 2012, respectively (Lee & Hsueh., 2020). On December 31, 2019, cases of pneumonia with no known cause were reported to WHO from Wuhan, Hubei Province, China (Yang et al., 2020). These cases were linked to a novel coronavirus on January 7, 2020 (holshue et al., 2020). On February 11, 2020, WHO announced the new coronavirus discovery that causes pneumonia; the International Virus Classification System dubbed SARS-CoV-2 (Malik., 2020). The CoV-2 - SARS virus's genome is 85% similar to that of the SARS virus (Bchetnia et al., 2020). Prior to the discovery of SARS-CoV-2, it was known that six different coronaviruses, including MERS-CoV and CoV - SARS, could in humans cause disease (Nimesh et al., 2021).

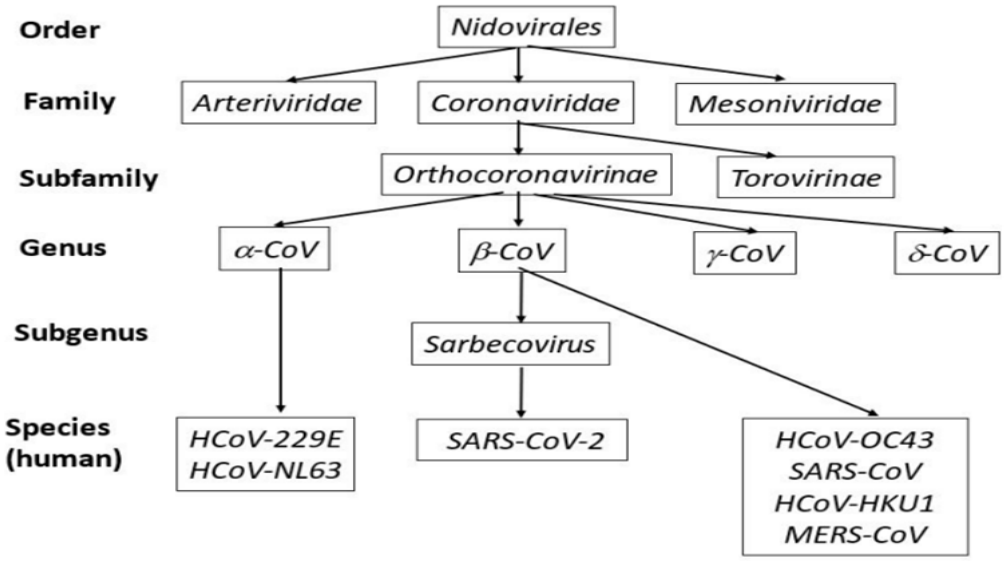

Figure 2.5. Classification of Human Coronaviruses (Malik., 2020).

2.1.4. The Structure of a Coronavirus

The coronavirus (CoV) is a ribonucleic acid (RNA) virus (ssRNA) (Xu et al., 2020). This virus, whose genome measures between 26 and 32 kb, has been proposed as it is believed to be a covert entrapping virus that is the biggest RNA virus to date., positive-sense, nonsegmented virus (Ayra et al., 2021). The 3' end of the SARS-CoV-2 virus are to blame for encoding proteins with structural roles, such (S) the spike, (M) film, and (E) envelope proteins, in addition to the nucleocapsid (N) proteins, Not only do viruses include genes for structural proteins, but they also have genomic regions that code for replication-specific proteins. Several non-structural proteins, including (PLpro) the papain-like protease and (3CLpro) the coronavirus's main protease that are encoded by these areas as well (Cui et al., 2019).

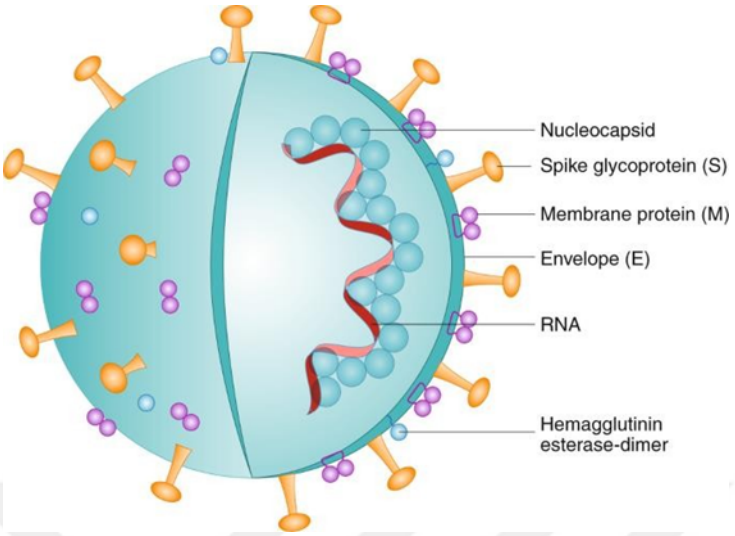

Figure 2.6. A representation in schematic form of the SARS-CoV-2 structure (Ziebuhr et al., 2000).

The SARS-CoV-2 surface is covered in glycosylated S protein units, which bind to the cellular ACE2 receptor for angiotensin-converting enzyme., initiating viral cell invasion (Gadanec et al., 2021). Viruses are able to enter host cells thanks to TM protease serine2, also known as TMPRSS2, which is located in the adenosine cyclase2 receptor on the host cell membrane and activates the viral S protein (Shulla et al., 2011). As the infection reaches the confines of the cell, Host cells replicate viral RNA and package major proteins to carry viral particles; the RNA is supplied, polyproteins are translated from the RNA genome, together with RNA genome replication and transcription are triggered by protein cleavage and the replica-transcriptase complex. Viruses cannot survive without these proteins (Huang et al., 2020).

2.1.5. Biochemical Characteristics

On the outside of numerous types of cells, including kidney tubular cells, intestinal enterocytes, and additional cells, one can find the zinc-containing metalloenzyme angiotensin-converting enzyme-2 (Akbari Aghababa & Nadi., 2021). N-terminal peptidase M2 and renal amino acid transporter collection domains make up ACE-2 (Khin et al., 2020). Hence, (ACE2), a membrane protein is a type I with a single transmembrane passage, It contains a domain of enzymatic activity on the surface of tissue cells such as the intestines (Chekol Abebe et al., 2021). When the extracellular and transmembrane domains of ACE2 are hydrolyzed by sheddase, the

resulting soluble protein is absorbed by the circulation and eventually expelled in the urine (Hikmet et al., 2020).

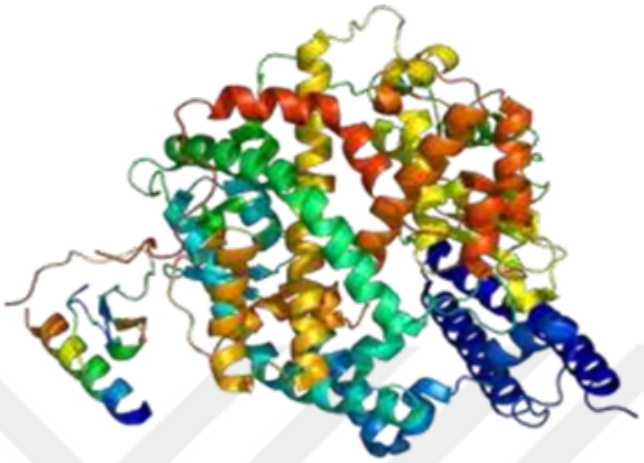

Figure 2.7. Structures that are available for ACE-2 (Ahmad et al., 2021).

2.1.6. COVID-19 and Cancer

Individuals who have comorbidities, such as cancer, are more susceptible to experiencing unfavourable clinical outcomes when infected with COVID-19. This has been noticed in previous severe acute respiratory epidemics, such as MERS-CoV and SARS-CoV (Alqahtani et al., 2018). Unknown is whether SARS-CoV2 affects cancer pathobiology directly or indirectly. However, it is obvious that patients receiving cancer-related treatments, such as radiation, chemotherapy therapy, or CAR-T cell therapy, are more likely to deteriorate after contracting COVID-19 (Liang et al., 2020). Based on the results of a recent study carried out in China, involving 1,590 individuals who tested positive for COVID-19, it has been determined that cancer is a notable comorbidity that increases contracting risk COVID-19 (Guan et al., 2020). Thus, it is imperative that cancer patients undergoing anti-tumour therapy be carefully assessed for COVID-19 infection, since this may necessitate modifying the course and/or intensity of their immunosuppressive treatment (Zhang et al., 2020). Some patients must wait until the antiviral course of therapy is complete before starting chemotherapy, while others cannot receive viral infection therapy while receiving cancer treatment (Borchardt & Torres., 2014). Cancer patients experience a wide range of symptoms from COVID-19; however, the majority is shared with the general population (Kalinsky et al., 2020). However, drugs used to treat cancer, such as steroids, may help alleviate the fever associated with COVID-19 and a conclusion of how to aid in the cure of cancer who favourable results for the COVID-19

mutation depends on cancer type, treatment level, and severity of the mutation and It is possible that immune dysregulation and chronic inflammation in cancer patients who test positive for COVID-19 will have devastating effects on their health (Nash et al., 2021). Hence, a deeper comprehension of the molecular connection between the two will aid in the prevention of infection-related deleterious consequences and also make it possible to build novel therapeutics that simultaneously target COVID-19 and cancer (Jyotsana & King., 2020).

2.1.7. The Cancer

Cancer refers to a category of disorders that are defined by the uncontrolled proliferation of cell tissue (Pediconi & Galati., 2022). Ninety percent of cancer-related deaths result from tumor metastasis, which if allowed to develop and continue, could turn fatal (Jain., 2013). Cancer is a complex illness that involves multiple genes and multiple stages, and it all starts with a single aberrant cell (Pediconi & Galati., 2022). The accumulation of mutations triggers abnormal cell growth, which ultimately results in tumours; these mutations often arise in protein-coding genes that control cell division. More than a hundred distinct forms of cancer have been identified because some tumour cells undergo additional mutational cycles that produce cancerous cells capable of spreading disease (metastasis) (Hejmadi., 2014). Cancer cells are distinguished by their capacity to produce one's own growth signals, resistance to signals that restrict development, and resistance to apoptosis, their seemingly endless capacity for proliferation, their ability to generate new blood vessels (angiogenesis), and their capacity to control and metastasize normal tissues (Hanahan & Weinberg., 2000). Formerly listed factors that lead to cancer proliferation have been broadened to include deregulation of cellular energetics, avoidance of immune response, inflammation that promotes tumour growth, as well as mutation and genomic instability (Hejmadi., 2014).

However, tumours can either be benign or malignant, depending on the type of cancer they contain (Russo & Russo., 2000). Benign tumours are not malignant, can usually be surgically removed, and in the great majority of cases, benign tumour cells do not metastasize (Anad et al., 2008). Despite the presence of cancerous cells in malignant tumours, these cells It may be spread to other body parts by invading adjacent tissues, a process known as metastasis., Examples of cancers that do not cause tumours to form include those that affect the blood and bone marrow, such as leukaemia (American Cancer Society., 2012). Cancer originates from DNA mutations and genomic instability and there are two cancer-causing variables (Kreeger & Lauffenburger., 2010).

Inherited features cause 5-10% of malignancies, while environmental variables or a combination of the two cause 90-95% (Anand et al., 2008).

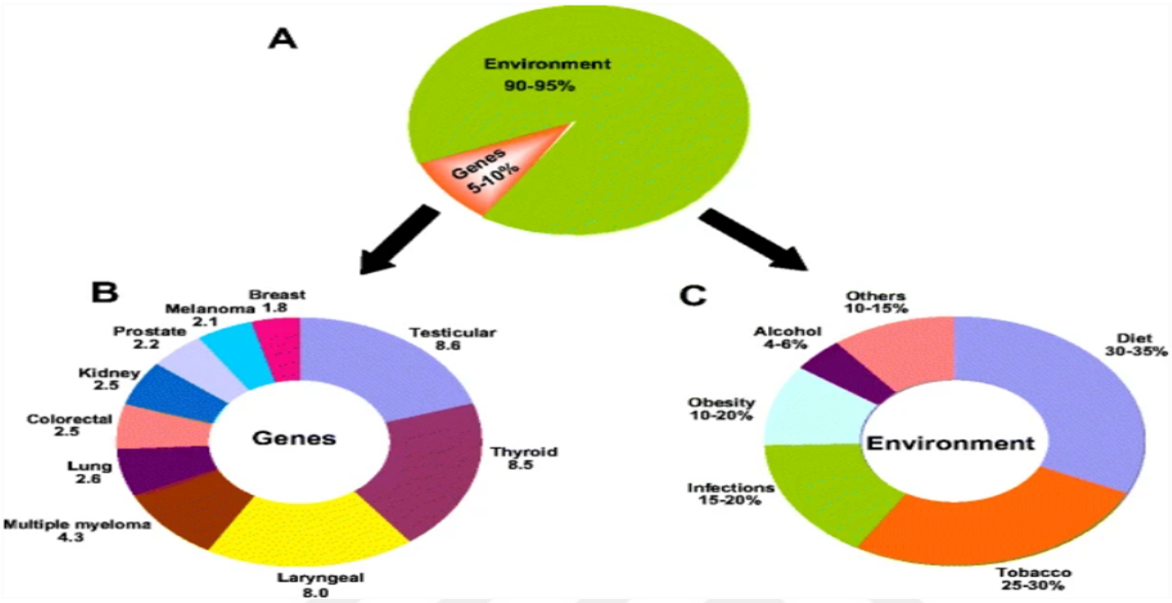

Figure 2.8. Cancer development and genes/environment and the top graphic displays hereditary and environmental cancer contributions (Anand et al., 2008).

Genome instability and genetic mutations create tumours, but environmental variables that affect cell genome instability, transcription, translation, and posttranslational processes, and gene-coding protein that regulate cell division also cause tumours or other cell phenotypes (Kreeger & Lauffenburger., 2010).

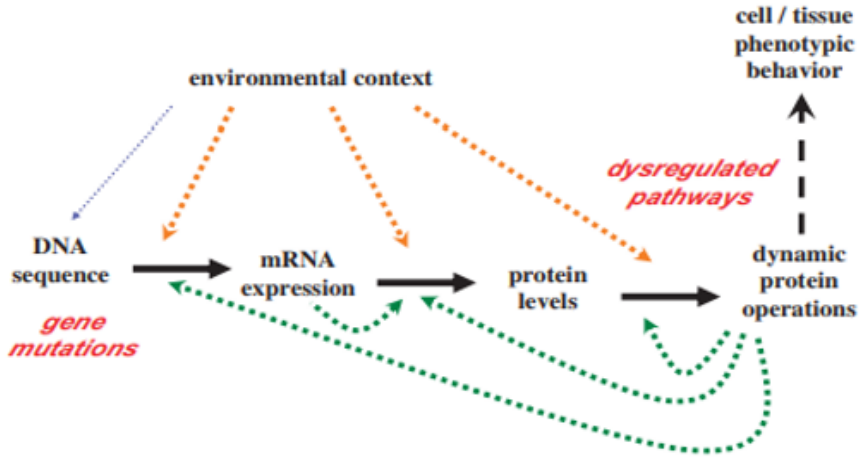

Figure 2.9. Central dogma (Kreeger & Lauffenburger., 2010).

2.1.8. MicroRNA and Cancer

Early research on the significance of miRNA in cancer has shown how these molecules regulate cell growth and apoptosis in the fruit fly Drosophila and the nematode C. elegans, respectively (Brennecke et al., 2003).

Calin et al., (2005) carried out preliminary research regarding microRNA expression in human malignancy, while looking into a recurrent deletion on chromosome 13q14, tumour suppressor genes connected to chronic lymphatic leukaemia were sought out (CLL). According to the research, this region of the chromosome is responsible in order to encoding two of microRNAs: miR-16-1 and miR-15a.

Unearthed in 2004 that human cancer genes often amplified or deleted contain miRNA genes in vulnerable regions. The study suggests that all miRNAs in the genome may contribute to cancer and lists the miRNA genes that may do so (Calin et al., 2004).

Many cancers, as well as other clinical disorders and biological processes, involve miRNA. Several studies have found that aberrant expressions in miRNA levels are associated with cancer type, tumour stage, and therapy response. These findings validate miRNAs as a promising new biomarker for cancer detection, staging, and treatment (Bartels & Tsongalis., 2009).

Carcinogenesis and its association with malignant cellular phenotype, sometimes known as cancer have led researchers to identify miRNA-196 and miRNA-10a as members of homebox clusters (Chen & Sukmar., 2003).

A single miRNA may target several genes, resulting in modifications to cellular function that may eventually lead to cancer development (Ryan et al., 2010). MicroRNAs may act as oncomiRs or tumour suppressors, as shown by tumor-associated microRNA expression up- and down-regulation (Dhar et al., 2011).

Oncogenes are often localised to chromosomal areas that are amplified or overexpressed in cancer, while tumour suppressor microRNAs are frequently localised to chromosomal regions that are deleted or underexpressed in cancer (Miska., 2005). It has been demonstrated that microRNA can operate as oncogenes by causing unregulated proliferation, a reduction in apoptotic activity, encouragement of angiogenesis and invasion, the development of tumours (Gramantieri et al., 2008).

All tumors had elevated levels of miR-21, supporting the evidence for this miR's function in malignancies and its oncomiR activity and this oncomiR targeted huge amounts of genetic

material known to inhibit the growth of tumours, one of which was called Phosphatase and TENsin (PTEN) (Lou et al., 2010).

MicroRNA-143 has been studied for its possible significance in colon and bladder cancer in humans, and it was discovered a considerable decrease in tumours than in healthy tissues, This difference was found to be significant (Lin et al., 2009). This microRNA's ability to prevent cell growth supports the idea that it functions as a tumor suppressor.

As well as influencing cancer, miRNAs are involved in a variety of contexts other disorders, among them are diabetes and obesity, heart failure, infections, and inflammatory and autoimmune conditions like liver disease and autoimmune disease (Erson & Petty., 2008). These findings emphasise the importance of microRNA in the several illnesses development (Kumarswamy et al., 2011).

2.2. Breast Cancer

Breast cancer regards the second common type in the world and the most common cancer in women (Fidler et al., 2018). The World Health Organisation has released its 2018 statistics, which reveals that (Ferlay et al., 2019).

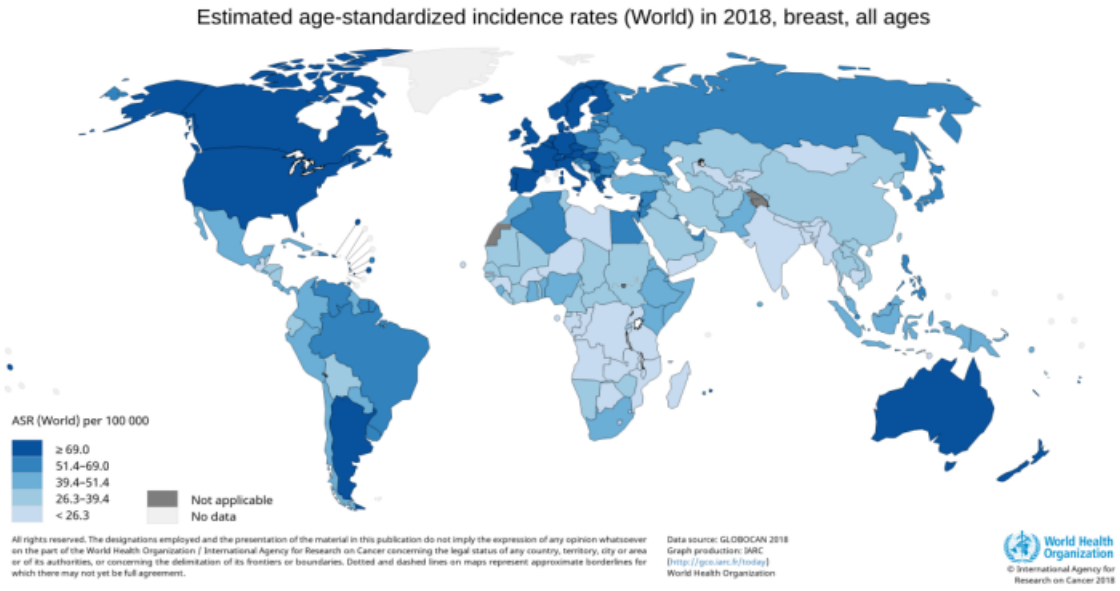

Figure 2.10. Breast Cancer in the World Incidence Rate, According to World Health Organisation Data (http://gco.iarc.fr/).

There are two types of malignant tumours: those of epithelial origin and those of mesenchymal origin (sarcoma) (carcinoma). Many breast cancer instances are carcinomas. Breast cancer in situ, which is discovered where it first appeared, does not spread, in contrast to invasive breast cancer, which does. The five subtypes of breast cancer that occur most frequently are invasive breast carcinoma, cancers of the invasive ducts, lobes, and in situ ductal and lobular carcinomas (Feng et al., 2018). 80% of breast cancers are of the ductal carcinoma subtype, making it the most common form of the illness. Breast ductal carcinomas begin in the milk duct, invade the surrounding duct wall, and eventually spread to the breast's fatty tissue. It does occur in men, albeit much less often (Angeles., 2018).

Specifically, the existence of BRCA2 and BRCA1 gene mutations, along with anomalies in several other genes, heightens the likelihood of breast cancer incidence in women (Konishi et al., 2011). Most scientists categorize breast cancer into one of four main molecular subtypes: Triple negative/basal-like, Luminal B, Luminal A, and HER2 type. In some cases, in situ of ductal carcinoma, these subtypes may also be present (DCIS) (Howlader et al., 2014). Hormone therapy is used to treat ER-positive Luminal A tumours, of which 30–70% are 1%, Luminal A tumours are ER-positive and HER2-negative, Luminal A tumours are associated with the greatest survival rates for breast cancer (Matikas et al., 2019).

2.2.1 Historical View of Breast Cancer

Breast problems have been investigated since before Christ since the breast is a marker of fertility. Breast cancer was first referenced in the Edwin Smith operative papyri (3000–2500 BC) as an incurable sickness (Breasted., 1930). Egyptian papyri from 1500 BC also mention breast problems (Kwok et al., 2015). Hippocrates (460–375 BC), a medical pioneer, knew about breast diseases. Hippocrates reported his postmenopausal breast cancer therapy in Corpus Hippocraticum (Beenken., 2005). The Egyptian surgeon Leonides, one of the first to recommend breast cancer surgery, advised against surgery for tumours that had spread to surrounding tissues (Retief & Cilliers., 2011). After breast surgery began, Galen (A.D. 131–203), who created the name "cancer," described the disease's development in both directions to a crab's legs. Over the years, many physicians attempted breast cancer therapies, but the disease's aggressive course could not be reversed (Lichtman., 2018). Breast cancer therapy did not develop until the Renaissance because medicine stalled throughout the Middle Ages. During the Renaissance, cadaver studies improved breast anatomy. Because anaesthesia and antisepsis were not yet established, surgical applications

and results were unsatisfactory (Loudon., 1997). Moore's 1867 advocacy of complete tumour excision and axillary lymph node ectomy was a major surgical development. Radical mastectomy surgery expanded worldwide after Halsted described it in the late 19th century. X-rays enabled modified radical mastectomy (Sanders-Goebel., 1991).

2.2.2. Breast Cancer Classification

Breast cancer contains several tumour entities, each with its own histological patterns, molecular features, and clinical behaviour. Histological appearances were used to classify breast cancer, although there is no unanimity across the classification methods (Weigelt & Reis-Filho., 2009). In its 4th edition, the WHO categorises invasive breast cancer into more than 21 subgroups (Lakhani., 2014). However, histological classifications are arbitrary and do not impact treatment choices (Nicholson et al., 2020). Clinicopathological factors include lymph node metastases, histological grade, and lymphovascular invasion determine breast cancer subtypes. Therapeutically helpful prognostic indicators include PR, ER, and HER2 expression (Weigelt et al., 2010). Malignant epithelial cells cause most breast cancers, which may be separated into invasive and non-invasive subtypes based on tissue histology (Lyng et al., 2007). Carcinoma in situ of the ducts or lobes of the breast is a kind of invasive breast cancer (Pravettoni et al., 2016). These include invasive lobular, medullary, papillary, tubal, adenoid cystic, secretory, apocrine, metaplastic, hypersecretory, and cribriform carcinomas (Makki., 2015). Malignant Cystosarcoma Phyllodes is an uncommon breast cancer kind (Franceschini et al., 2005). In-situ lobular carcinoma increases breast cancer risk, although it is not precancerous (Clark et al., 2009). Younger women and those from cancer-prone families are at higher risk (Easton., 2002). Surgery is uncommon for bilateral, multifocal in-situ lobular cancer. High-risk women may like it. In-situ ductal carcinoma. Stage 0. Poor treatment may reoccur. Mastectomy is suggested if extensive. Most invasive breast tumours are infiltrative ductal and lobular (Lopez-Garcia et al., 2010).

2.2.3. Breast Cancer Types

2.2.3.1. Non-invasive Breast Cancer

This kind of breast cancer, known as ductal carcinoma in situ, does not spread beyond the lobule or duct in which it is located (Mohamed et al., 2007). The abnormal cells that lead to ductal carcinoma in situ are contained inside the milk ducts where they first formed and atypical cells will grow into invasive breast cancer since they don't travel beyond the lobules or ducts. Each scientific

unit's background and biological meaning are presented. After selection, sequential follow-up is indicated as carcinoma lobular in situ is a minimally dangerous indication that precedes aggressive malignancy. This conservative therapy has clear effective and least invasive option When treating ductal carcinoma in situ (Posner & Wolmark., 1992).

2.2.3.2. Lobular Cancer in Situ

A specific subtype of breast cancer has its origin in the lobular structures of the mammary gland (Makki., 2015). Breast tissue lobules have not been affected by the breast cancer that has disseminated. Lobular cancer in situ is the name that most usually refers to non-invasive breast cancer (Chuba et al., 2005).

2.2.3.3. Ductal Cancer in Situ

Around 20% of breast cancers identified by mammography are now DCIS, a noninvasive breast cancer type that has grown dramatically in prevalence over the last several decades, DCIS has been shown to be a harbinger of an invasive cancer in both laboratory and patient studies (Leonard & Swain., 2004).

2.2.3.4. Invasive Breast Cancer

Invasive breast cancer is more common in females, It happens when aberrant lobule or milk duct cells touch breast tissue and Immune or systemic circulation brings cancer cells to the breast and can spread, as it grows rapidly, the tumour can relocate (Ziperstein et al., 2003).

2.2.3.5. Lobular Carcinoma Infiltration (LCI)

The term "infiltrating lobular carcinoma" refers to a subtype of "invasive lobular carcinoma and " although the disease can extend to other areas of the body, LCI begins in the lobules of the mammary glands (Arpino et al., 2004).

2.2.3.6. Ductal Carcinoma Infiltrating

Invasive ductal carcinoma (DCI) is a form cancer of breast that originates in the milk ducts and progresses to infiltrate the ductal wall, potentially leading to infiltration of the adipose breast tissue and metastasis to other body regions (Somiari et al., 2003).

2.2.3.7. Mucinous Cancer

Mucinous carcinoma (MC) accounts for about 4% of all invasive breast malignancies (Anderson et al., 2004). and as a consequence, it is more prevalent in women who are in the perimenopausal and postmenopausal stages of life, when compared to other forms of breast cancer, such as ductal or lobular forms, its prognosis is much more favourable (Li et al., 2010).

2.2.3.8. Inflammatory Breast Cancer

Breast enlargement with dimples and/or large protrusions is a symptom of inflammatory breast cancer, that occurs when cancer cells obstruct lymphatic vessels arteries, or ducts (Baker et al., 2010). 1nflammatory breast cancer is the rarest, most inflammatory, and develops quickly. There must be careful coordination between the various treatment modalities used, including as Neoadjuvant chemotherapy, radiation therapy, chemotherapy, imaging, and finally surgery has improved overall survival and regional therapies like radiation and surgery since the initial investigations on this issue (Cariati et al., 2005).

2.2.4. Breast Cancer Stages

2.2.4.1. Phase 0

At this point in the development of a tumour, both malignant and noncancerous cells exist inside the breast, but there is no sign of invasion (Kim et al., 2011). Cancers such as ductal cell carcinoma in situ can first appear in the tissues immediately around the affected area (DCIS) (Mardekian et al., 2016).

2.2.4.2. Stage 1

This stage identifies invasive breast cancer and implies that there is a high probability of microscopic invasion occurring (Allred et al., 2010). As per the medical taxonomy, Stage 1A denotes a neoplasm that exhibits a diameter of up to 2 centimeters and has not disseminated to any lymph nodes. Conversely, Stage 1B is distinguished by the identification of malignant cells that exceed 0.2 millimeters in dimension within a lymph node (Hanrahan et al., 2006).

2.2.4.3. Stage 2

In addition, 2A and 2B refer to two distinct variants, A tumour of at least 2 centimeters in diameter and no more than 5 centimeters in length is at axillary lymph node or sentinel lymph node of breast cancer stage (Solá et al., 2013). The tumour can be greater than 5 centimeters in diameter,

but it must not have spread to the nodes of axillary lymph, as stated in Step 2B (Neuman et al., 2010).

2.2.4.4. Stage 3

Three distinct subcategories were established, namely 3A, 3B, and 3C (Cohen et al., 2000). A breast tumour is not present in stage 3A, however in stage 3B, the disease has progressed to 4–9 sentinel lymph nodes or axillary lymph nodes., a tumour of any size causes edoema or ulceration (Koh & Kim., 2019). Stage 3B inflammatory breast cancer is characterised by redness, warmth, and swelling of the breast surface and up to 9 axillary lymph nodes or sentinel lymph nodes (Robertson et al., 2010). In stage 3C of the disease, the neoplasm has metastasized to a minimum of ten axillary lymph nodes, so that, lymph nodes located superior and inferior to the clavicle (Hoang et al., 2013).

2.2.4.5. Stage 4

Metastatic illness is characterized by the spread of cancer to various organs, including but not limited to the lungs, bones, brain, and liver, indicating an illness in its last stages (Neuman et al., 2010).

2.2.5. Epidemiology of Breast Cancer

When it comes to cancer-related death, breast cancer comes in second, following only lung cancer (Jemal et al., 2011). However, it constitutes 33% of all female malignancies (Lacey et al., 2002). Cancer of the breast is a common condition form of malignancy that is often associated with a familial history of the disease and exposure to hormone treatment (Key et al., 2001). However, the death rate has been falling since 1990. Age, gender, ethnicity, obesity, family history, cancer, and reproductive and hormonal variables are risk factors (Novak., 2007):

2.2.5.1. Age

The probability of acquiring breast cancer more than triples after the age of 30, and less than 1% of breast cancer diagnoses are made in girls under the age of 25., according to recent research, we can state with certainty that in common older women have a close risk of breast cancer developing, with one exception being the plateau that occurs between the ages of 45 and 50 (Novak et al., 2007).

2.2.5.2. Diet, Obesity, Alcohol

There are specific dietary variables linked with an increased breast cancer risk incidence discrepancies and having a healthy, balanced diet has been demonstrated to lower the chance of developing breast cancer, according to meta-analysis research, it has been suggested that drinking a lot of wine raises the risk, even though a definitive link between overall alcohol intake and breast cancer has not been identified (Brennan et al., 2010).

2.2.5.3. Variables Related to Reproduction and Hormones

The longer a woman lives past her reproductive years, the greater her risk of her breast cancer spreading (Lacey Jr et al., 2002). The risk of developing breast cancer is much high for women who have their first menstruation at a younger age, whereas the reverse is true for those who experience their first menopause at a younger age (Berkey et al., 1999). Compared to natural early menopause, the protective benefit given by surgical menopause induced by oophorectomy is greater (Lobo., 2007). Even though breastfeeding is not linked to a higher chance of getting breast cancer, the incidence of the disease is greater in women who have never given birth compared to those who have had more than one child (Lipworth et al., 2000). It has been reported that using oral contraceptives does not work, regardless of the family history, duration of use, or presence of benign breast disease; however, there are studies that show that using Oral contraceptives raise the chance of cancer a little bit in comparison to people who do not use them. It has been observed that combined estrogen and progesterone hormone treatment administered for the chance of developing cancer increases dramatically during a very little time span (Novak., 2007).

2.2.5.4. Cancer History

Breast cancer-stricken ladies in the past has a fifty percent chance of developing cancerous cells in the other breast as well, whereas the incidence of cancer in clinical settings is somewhere between twenty and twenty-five per cent (Vachon et al., 2000). Even if a woman tests negative for the BRCA2 and BRCA1 genes, her risk of having breast cancer is still elevated by her family history of the illness, especially if it includes endometrial, ovarian, or colon cancer, Bilateral lobular carcinoma is more prevalent than ductal carcinoma (Sifri et al., 2004).

2.2.5.5. Family History

Approximately 20% to 30% of women who receive a breast cancer diagnosis have a familial disease history (Novak., 2007). While the presence of a first-degree relative diagnosed with postmenopausal breast cancer may increase one's risk to some extent, the risk does not appear to

be significantly elevated in the case of a second-degree relative or a more distant relative (Singletary., 2003). The likelihood of a female developing unilateral premenopausal breast cancer is increased if either her mother or sister suffered from the illness. When it nears 30%, the lifetime risk in bilateral instances is between 40% and 50% (Kash et al., 1995). There is some evidence to suggest that oncogene genes are to blame for this increase; between 5 and 10 percent of breast cancers have a genetic component, with BRCA1 and BRCA2 gene deletions being the most common (Novak., 2007). People with three or more family members who have had breast or ovarian cancer, provided one is diagnosed before 50, should undergo genetic counselling for BRCA testing. Prophylactic surgery in chosen individuals requires genetic counselling, which greatly impacts patient survival (Singletary., 2003).

2.2.5.6. Genetics

Around 33% of breast cancers exhibit familial traits, Nonetheless, a lesser fraction of these cases can be attributed to mutations in genes that are responsible for breast cancer susceptibility (Hedenfalk et al., 2003). A correlation has been noticed between certain genetic disorders and an increased susceptibility to breast cancer (Stratton & Rahman., 2008). Hereditary Breast-Over Cancer caused by BRCA gene mutations; Li-Fraumeni syndrome associated with p53 gene mutation which may include sarcoma, leukaemia, melanoma, pancreas, lung and cervix cancers; Cowden syndrome associated with PTEN gene mutation; Peutz-Jegher Syndrome associated with LKB1 gene mutation which may include breast, bowel, endometrium, cervix, lung and ovarian cancers (Rajaneesh., 2021).

2.2.5.7. Pregnancy

The age at which a woman experiences her initial pregnancy is a component of her reproductive history that is related with her ability to breast cancer developing (Kobayashi et al., 2012). The risk of breast cancer development is less high for women who begin or postpone having children at an earlier age, respectively (Gorman et al., 2011).

2.2.5.8. Other Factors

Numerous studies examined the possibility that having a left hand increased the risk of breast cancer developing, and one from 2007 found that the risk rose by a factor of 2.59 (Roychoudhuri et al., 2006).

2.2.6. Molecular Heterogeneity in Breast Cancer

Perou et al. released a key article showing that complementary DNA (cDNA) microarray research shows that breast cancers have phenotypic variety and molecular heterogeneity in gene expression patterns. In the current investigation, they examined the gene expression patterns in 65 breast tissue samples from 42 people. At least four kinds of breast cancer were discovered, and the study confirmed the presence of 8,102 unique human genes. Gene expression profiles were used to define the biological consequences of the subtypes (Perou et al., 2000). Researchers have found that breast cancers have different versions of the estrogen receptor- (ER-) gene and the 2nd tyrosine kinase of the erb-b2 receptor (ERBB2) gene, which are linked to the ER and HER2 proteins (Muthukaruppan et al., 2017). The ER positive group of tumours exhibited elevated expression levels of genes that are typically expressed by luminal cells in the breast, while ER-negative tumours demonstrated gene expression patterns that is typical of breast basal cells (Weigelt et al., 2010). Immunohistochemistry (IHC) revealed that the presence of ER protein in tumours is proportional to the quantity of ER mRNA, Positive immunohistochemistry staining for basal cell markers was also seen in tumours whose gene expression was indicative of basal epithelial cells (Muthukaruppan et al., 2017). In order to create a distinctive "molecular portrait" of each tumor and divide breast cancer into four separate "intrinsic" subtypes, Perou and colleagues used gene expression profiling. Breast cancer have four main different molecular subtypes: basal-like, ER-positive/luminal-like, ERBB2 or HER2-positive, and normal breast (Perou et al., 2000).

In 2001, a study was conducted wherein 85 breast samples from 84 distinct patients were analyzed, the study supported the categorization of self-identified subtypes made by Perou et al, The subtypes were classified into lumen A, lumen B, basal-like, ERBB2, and each category was found to be linked with a distinct clinical outcome (Sørlie et al., 2001).

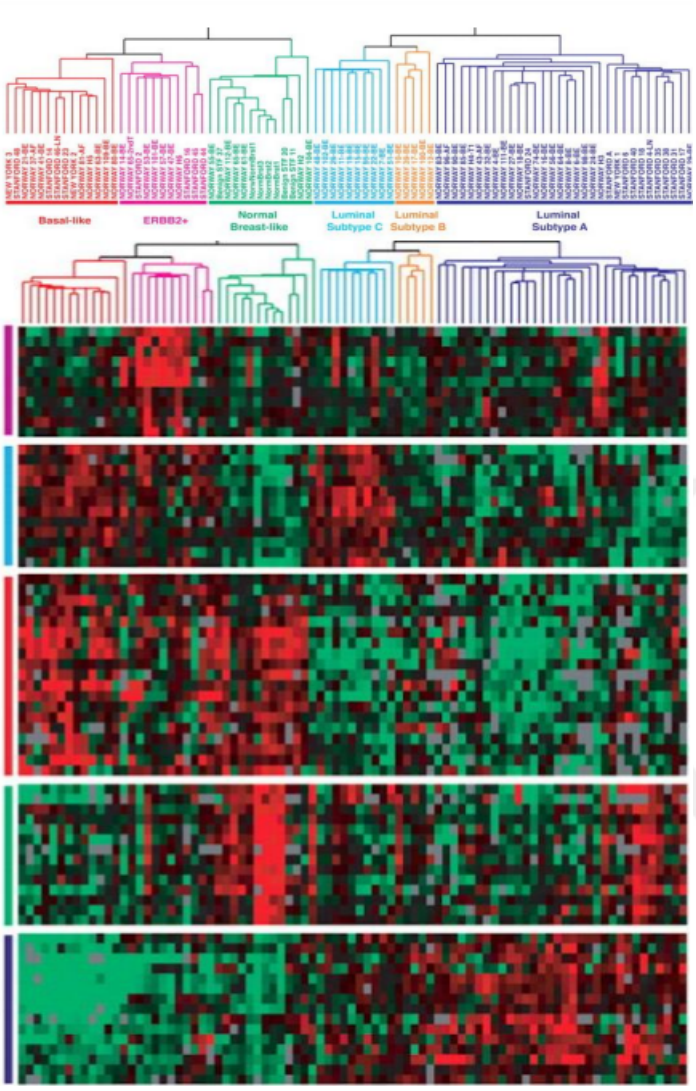

Figure 2.11. A heat map illustrating the subtypes of breast cancer (Sørlie et al., 2001).

Several studies subsequent confirmed the intrinsic subtypes' predictive power and Rouzier et al.' study explore that ERBB2 and the basal-like positive subgroups had the highest pathologic complete response, compared to the luminal subgroup's 6% and the authors found that molecular class alone may be sufficient to predict pCR (Rouzier et al., 2005). Parker et al. developed the PAM50 test. This test determined intrinsic subtypes using a 50-gene signature and This showed that intrinsic breast cancer subtypes can be recreated at the population level and that the PAM50 test can predict recurrence and NACT response across all intrinsic subtypes (Parker et al., 2009).

Additional genetic profiling was carried out, and certain results coincided with the clinical traits of several illness types. Researchers found a genetic signature that may provide useful insights into the efficacy of adjuvant chemotherapy, aiding in treatment decision-making. The

study used a set of 70 genes and showed that analyzing the patterns of gene expression at primary breast cancers can yield accurate predictive data (Van't Veer et al., 2002). A genetic by using reverse reaction of chain of transcriptase polymerase (RT-PCR) was the result of more research, and it was used to predict therapy effectiveness and the likelihood of cancer recurrence. In therapeutic contexts, the 21-gene test, often known as "Oncotype Dx," is routinely used (Paik et al., 2004). Empirical evidence has demonstrated that each of the distinct gene assays exhibits a high degree of reproducibility and concordance with the prognostic data provided by the intrinsic subtypes (Fan et al., 2006).

2.2.7. Breast Cancer Risk Genes Known as BRCA

Biochemical, environmental, and genetic variables all have an impact on breast cancer (Calaf et al., 2020). It is generally established that hereditary abnormalities in genes like p53, BRCA1, and BRCA2 contribute to the risk of developing breast cancer. (Holstege et al., 2009). Previous research on breast cancer concentrated on specific methods such as DNA copy number analysis, mRNA expression profiling, or massively parallel sequencing (Schweiger et al., 2009). However, advancements in high-information-content assays have expanded our understanding of breast cancer by examining DNA methylation, miRNA expression, and protein expression, which were developed in response to recent progress in the field (Brigham et al., 2012). BRCA1 and BRCA2, two closely related breast cancer susceptibility genes (Konishi et al., 2011). Mutations in the BRCA1 and BRCA2 genes are linked to about 20% of family breast cancer cases (Euhus., 2001). Notably, the prevalence of BRCA1 and BRCA2 germline mutations varies significantly among different ethnic groups and geographical regions (Fackenthal & Olopade., 2007). The cloning of the BRCA1 gene occurred in 1994, followed by the discovery of the BRCA2 gene in 1995 (Narod & Foulkes., 2004). Both genes serve as tumor suppressors and protect against breast and ovarian cancers, while mutations at those genes increase the danger of breast cancer and ovarian (Teng et al., 1996). The BRCA1 protein is involved in the repair of DNA damage, whereas BRCA2 is essential for preserving DNA integrity during the repair of double strand breaks and chromosomal damage (Yoshida & Miki., 2004). Inheritance of a faulty copy of the BRCA2 or BRCA1 gene can increase a woman's likelihood of breast cancer developing by up to 85% (Parmigiani et al., 1998). Women with BRCA1 mutations have a higher risk of ovarian cancer, around 55% by the age of 40, whereas those with BRCA2 mutations face an increased risk of approximately 25% (Tapia et al., 2008). Due to disturbances in the cell cycle, division, and DNA

repair, BRCA1 and BRCA2 mutations have the potential to have an adverse effect on reproduction (Smith et al., 2013).

2.2.8. MicroRNA and its Function in Breast Cancer

MiRNA microarrays, quantitative reverse-transcription PCR (Q-PCR), bead-based flow cytometry, and other methods were used to first identify the relationship between miRNA and tumor biology. These techniques exposed miR-15 and miR-16 deletions and downregulation in B-cell chronic lymphocytic leukemia (Blenkiron et al., 2007). MicroRNAs (miRNAs) play a unique role in human cancer, as demonstrated by the fact which high than 50% of miRNA genes are found in diverse chromosomal regions that are altered in these tumors (Peruzzi & Lawler., 2014). miRNAs expression was studied between breast tumors and non-tumor breast tissue in a study by Iorio et al. They uncovered 29 significant miRNAs using microarray profiling, with miR-21 and miR-155 found to be elevated while miR-10b and miR-145 shown to be downregulated. As a result, it is possible for miRNAs to act as both tumor-suppressor genes and oncogenes (Iorio et al., 2005). According to Corcoran, Friel, Duffy, Crown, and O'Driscoll (2011), clinical features analysis contain lymph node status, HER2, PR, and ER status, vascular invasion profile, and proliferative index also revealed a few miRNAs that were differentially expressed. This finding suggests a link amaong the molecular and miRNAs and pathological characteristics of breast cancers. The aberrant expression of miRNAs in breast tumors has been discovered during the past ten years using a variety of miRNA profiling methodologies (Heneghan, Miller, Lowery, Sweeney, & Kerin, 2010). Tumor formation may result from the loss or reduction of tumor suppressor miRNAs and/or the overexpression of oncogenes, miRNAs can function as both tumor suppressors and oncogenes (OncomiRs). Furthermore, increased prometastatic miRNA expression and decreased antimetastatic miRNA expression may promote metastasis (Ferracin et al., 2010).

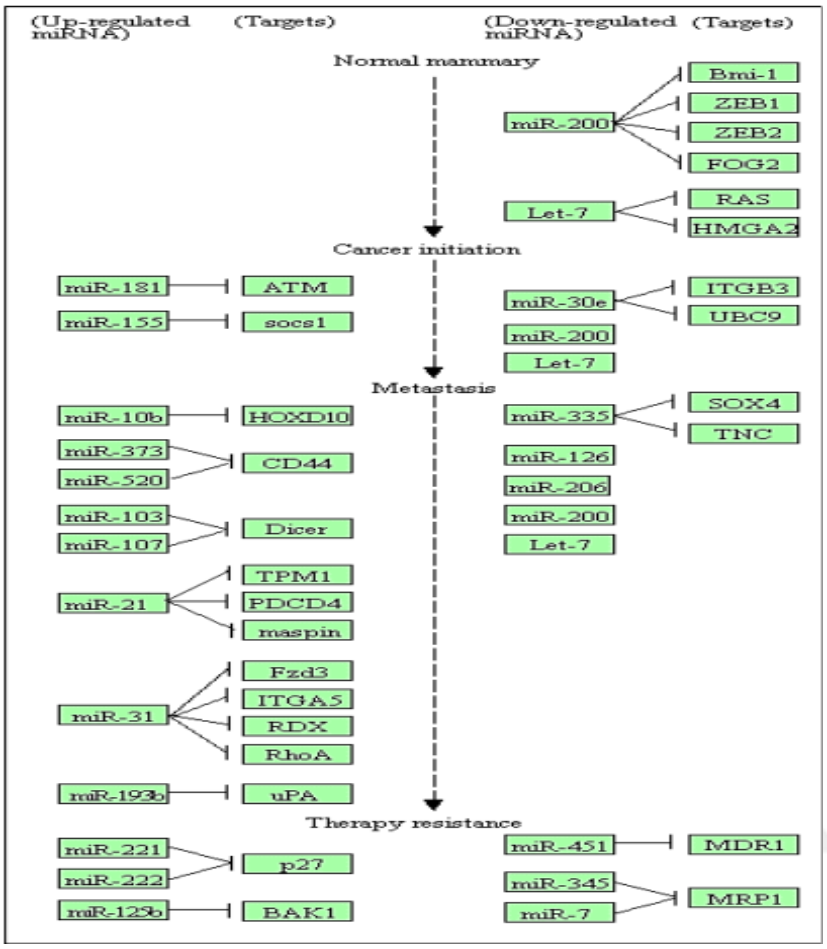

Figure 2.12. miRNAs in breast cancer (Ferracin et al., 2010).

A signature was also discovered to distinguish between normal and cancerous breast tissues (Veeck & Esteller., 2010). alot of studies have demonstrated expression of aberrant miRNA in sporadic breast cancers relative to normal breast tissue. 86 breast cancers and matching normal tissues showed several dysregulated miRNAs in breast cancer. Additional studies using various methodologies have shown deregulation of miRNAs in breast cancer. Some miRNAs, including let-7a, miR-125a, miR-125b, miR-143, miR-145, miR-100, miR-10b, miR-101, miR-205, miR-210, miR-29b, miR-497, miR-99a, and miR-99b regularly exhibit modifications in sporadic breast cancer even though the precise patterns may differ. This amazing consistency has been validated by numerous research. (Farazi et al., 2011).

Numerous miRNAs that exhibit consistent deregulation in breast tissue have been extensively studied to determine their significant biological functions and molecular targets (O'Day

& Lal., 2010). Several microRNAs, including miR-21, miR-155, miR-145, and the let-7 family, exhibit dysregulation in various cancer types, such as colon, lung, and liver cancers (Lujambio & Lowe., 2012).

Table 2.1. Differences between miRNA expression in malignant breast tumours and normal breast tissue.

miRNA		nº of cases		Method	Reference
up-regulated	down-regulated	tumor	normal		
miR-21	**let-7a**	6		Bead-based flow cytometry; Northern blot	Lu et al, Nature, 2005
miR-213, **miR-210**, miR-206, miR-203, miR-202, miR-196, miR-191, **miR-155**, miR-149, miR-136, **miR-128b**, **miR-122a**, miR-34, **miR-21**, miR-9, let-7i	miR-204, **miR-145**, **miR-143**, **miR-125a**, **miR-125b**, **miR-101**, **miR-10b**, **let-7a**, **let-7d**, let-7f	76	10	miRNA microarray; Northern blot	Iorio et al, Cancer Res, 2005
miR-213, **miR-210**, miR-199b, miR-181a, **miR-155**, miR-146, **miR-122a**, mir-31, miR-29a, **miR-29b**, miR-29c, **mir-21**, miR-17-5p	miR-224, **miR-205**, **miR-125b**, **miR-145**, **miR-140**, **miR-130a**, **miR-100**, miR-30c, miR-16, **miR-10b**, **let-7a**	79		miRNA microarray	Volinia et al, PNAS, 2006
miR-21	miR-451, **miR-145**, **miR-205**, **let-7a**	100		miRNA microarray; Northern blot; ISH	Sempere et al, Cancer Res, 2007
miR-26a, miR-26b, miR-499-3p, miR-607, miR-135b, miR-616, miR-769-5p, miR-330-5p, miR-132, miR-149, miR-557, **miR-29b**, miR-657, miR-483-3p, miR-371-3p, miR-593, miR-596	**miR-145**, miR-92a, miR-99b, miR-214, miR-191, miR-454, **miR-10a**, miR-195, **miR-10b**, **miR-130a**, miR-374a, miR-146b-5p, miR-146a, miR-181c, miR-218, let-7g, miR-15b, **miR-125a**, miR-223, **miR-99a**, **miR-140**, **miR-126**, miR-199b, **miR-100**, miR-199a, **miR-125b**	28*		miRNA microarray	Fassan et al, Breast Cancer Res, 2009
miR-196a*, miR-196a, miR-345*, miR-493, miR-301a*, miR-1250, miR-1268, miR-629*, miR-25*, miR-181b, miR-769-3p, miR-181a*, miR-200a, miR-429, miR-182, miR-183*,**miR-21**, **miR-210**	miR-135a, miR-489, **miR-452**, miR-244*, miR-585, miR-1260, miR-27a*, miR-23a*, miR-223, miR-18a, miR-935, miR-1255b, miR-15b*, miR-215, miR-1249, **miR-10b, miR-125b**, **miR-99a**, miR-26a, miR-105, miR-130a, **miR-125a**, **miR-101**, **miR-143**, **miR-100**, **miR-145***, miR-218, miR-584, miR-139-5p, miR-218*, **miR-376a***, miR-378*, miR-1179, miR-335, **miR-145**, **miR-140**, **miR-126**, miR-101*, miR-328, **miR-378**, miR-139-5p, miR-106a, miR-144*, **miR-451**, miR-486-5p, miR-551b	5	5	Massively parallel sequencing	Persson et al, Cancer Res, 2011
miR-21, miR-142-3p, miR-1425p	**miR-22**, **miR-125a**, **miR-99a**, **let-7a**, **miR-451**, miR-144, **miR-145**, **miR-143**, **miR-143***, **miR-320**, **miR-378**, **miR-497**, miR-16	168	11	Massively parallel sequencing	Farazi et al, Cancer Res, 2011
miR-361-5p, **miR-21**, miR-374a, miR-96, miR-183, miR-374b, miR-16, miR-142-5p, miR-429, miR-182, miR-15b, miR-106b, miR-200c, miR-107, miR-32, miR-26b, miR-223, miR-30d, **miR-128**, miR-200b, miR-342, miR-340, miR-155, miR-142-3p, miR-29c, miR-20a, **miR-29b**, miR-19a, miR-92a, miR-425, **miR-210**, **miR-221**	let-7b, miR-127-3p, **miR-320**, let-7c, miR-652, **miR-378**, **miR-143***, **miR-99a**, **miR-497**, **miR-376a-3p**, **miR-145**, miR-574-3p, miR-193b, miR-221, **miR-140-3p**, **miR-100**, **miR-22**, miR-324, miR-423-3p, **miR-145***, **let-7d**, miR-193a-5p, miR-423-5p, miR-28-5p, **miR-125b**, miR-376c, miR-185, **miR-452**, **miR-125a**, miR-451	80	6	Massively parallel sequencing	Volinia et al, PNAS, 2012

The expression of miRNAs and the histology of breast cancer are related. It has been demonstrated that miR-213 and miR-203 are associated to cancer progression and that miR-30 corresponds with progesterone and estrogen receptor status. Let-7 miRNA isoform differential expression is linked to histopathological traits such PR status (let-7c), lymph node metastasis (let-7f-1, let-7a-3, and let-7a-2), and a high proliferation index (let-7c, let-7d) (Iorio et al., 2005). The miRNA panel generated by Iorio exhibited substantial overlap with the miRNAs discovered by Mattie and colleagues in relation to breast tumours categorised according to HER2 status or ER/PR status (Mattie et al., 2006). Numerous studies on miRNAs in breast cancer have demonstrated their involvement in a variety of biological functions and phenotypes. Three miRNAs were identified to be overexpressed in tumors lacking ER expression (Zhao et al., 2008), indicating that these

molecules control ER expression. By examining the expression patterns of coding genes and miRNAs, breast cancer can be divided into histological (Blenkiron et al., 2007).

MicroRNAs have demonstrated significant potential as biomarkers in clinical settings. One of the benefits of nanoparticles is their remarkable stability, which facilitates their isolation from diverse cell or tissue types owing to their diminutive dimensions. Research has indicated that miRNAs exhibit a high degree of conservation even in sections that have been archived for a decade and fixed in formalin and paraffin (Li et al., 2007). A small amount of total RNA is required for quantitative reverse transcription PCR (qRT-PCR) analysis and in situ hybridization on conventional paraffin sections in order to identify miRNAs. Furthermore, it is possible to quantify miRNAs in whole blood or serum samples that are present in the circulatory system (Heneghan et al., 2010). Numerous inquiries have detected microRNAs (miRNAs) that are exclusive to cancer and demonstrate elevated concentrations in the circulatory system of individuals afflicted by the ailment. The identification of these miRNAs presents the possibility of utilising them as non-intrusive indicators to appraise the condition of disease and appraise the efficacy of treatment. The analysis of circulating miRNAs presents a viable option for the non-invasive monitoring and detection of cancer-related alterations, obviating the need for invasive procedures like tissue biopsies. This development holds significant potential for clinical applications.

2.3. Triple Negative Breast Cancer

Breast cancers that do not show expression of the hormone receptors ER, PR, or HER2 are referred to as triple-negative breast cancers (TNBC) (Lehmann & Pietenpol., 2011). The incidence of these tumours is responsible for approximately 20% of all instances of invasive breast cancer (Makki., 2015). TNBCs may have many histopathological features that may lead to an aggressive clinical course. Although these features are not specific to TNBCs, they are frequently encountered. Occurrence at a young age, larger tumor size, higher histological grade, large geographical necrosis areas, and lymph node involvement are among the features frequently observed in these tumors (Thike et al., 2010). TNBC is also linked to a greater chance of dying, metastasis, and disease recurrence (Lin et al., 2008). Disease progression in TNBC patients shows visceral organ metastasis in the early period, whereas patients with hormone-positive tumors show bone and soft tissue metastases in the later period (Davis et al., 2014).

Non-specific type invasive carcinoma (NST) makes up the majority of TNBC, Other histological subtypes with triple-negative characteristics include metaplastic carcinoma, invasive

lobular cancer, medullary carcinoma, apocrine carcinoma, myoepithelial carcinoma, adenoid cystic carcinoma, and secretory carcinoma (Badve et al., 2011). Cytotoxic treatment is necessary since these tumors don't express HER2 and have negative hormone receptors. Even while some patients benefit from systemic chemotherapy, individuals who have a poor response, in particular, require focused treatment options (Yao et al., 2017). Future treatments for these patients may include immunomodulatory medications and PARP inhibitors, which stands for poly (ADP-ribose) polymerase (Cortazar et al., 2014).

Seventy-five percent of individual patients who have had Triple-negative breast cancer have a phenotypic appearance that is comparable to that of basal cells (Perou., 2011). However, it is known that not all basal-like cancers are TNBC. According to the gene expression profile, 77% of cases with basal-like phenotypes have triple-negative phenotypes (Lachapelle & Foulkes., 2011).

According to their findings, there are six unique molecular subtypes of triple-negative breast cancer (TNBC) that may be identified by analyzing the patterns of gene expression: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen and these results imply that knowledge of the subtype-specific chemotherapy responses may be useful in future clinical trials of personalised tumor therapies (Lehmann et al., 2011).

2.3.1. Triple-Negative Breast Cancer Risk Factors

Empirical research has demonstrated a higher incidence of triple-negative breast tumours (TNBCs) among certain populations. Specifically, studies have indicated that patients who are younger, pre-menopausal, and of African American or Hispanic descent exhibit a greater prevalence of TNBCs (Foulkes et al., 2010). It has been shown that several characteristics, including an earlier age at the first full-term pregnancy (below 26 years), a higher number of births (above four), and a more recent childbirth (within five years of diagnosis), increase the susceptibility to triple-negative breast cancer (TNBC) (Yang et al., 2007). Breastfeeding has been shown to reduce a woman's chance of acquiring triple-negative breast cancer, which is inversely related to this risk, this holds true regardless of how many children a woman breastfeeds or how long on average each kid breastfeeds for (TNBC) (Foulkes et al., 2010). According to Millikan et al.'s findings, after controlling for all reproductive factors, elevated parity and absence of breastfeeding were the primary factors associated with an augmented likelihood of developing triple-negative, or basal-like, breast cancer (Millikan et al., 2008).

There is no evidence to support a connection between prior alcohol or cigarette use and the risk of acquiring TNBC. However, numerous studies have found a link between BMI and the subtype of breast cancer (Widschwendter et al., 2015). In pre-menopausal women, weight, and body mass index (BMI) are inversely correlated with the likelihood of developing triple-negative breast cancer. According to an observed correlation, the risk of developing TNBC rises by 5% for every additional 5 kg of weight. Like this, every 5-kg increase in body mass index is accompanied by a 16% increase in risk (Chen et al., 2016). TNBC women had higher pre-menopausal BMIs and waist-to-hip ratios than non-TNBC subtypes, BMI affects TNBC in pre- and post-menopausal women (Millikan et al., 2008). Widschwendter et al. found that TNBC was identified more commonly in highly obese individuals (BMI >40 kg/m2), Severely obese TNBC patients showed lower OS and DFS than normal-weight individuals or underweight (Widschwendter et al., 2015). Bonsang-Kitzis et al. found that BMI affected NACT patients' prognoses. Although all groups showed negative lymph nodes following NACT, individuals with a BMI of 30 kg/m2 or more had a worse outcome (Bonsang-Kitzis et al., 2015).

2.3.2. Molecular Heterogeneity of TNBC

Researchers have looked deeply into the mutational profile of breast cancer and found that BRCA mutations are more prevalent in TNBC than in non-TNBC, Importantly, BRCA1 mutations have been found in up to 15.6% of individuals with TNBC cases (Zhang et al., 2015). Having a mutation in one of the BRCA genes is a well-known risk factor for hereditary breast cancer, since it increases the likelihood that a woman will acquire breast cancer at some point in her life (Ahmad., 2019). Women with germline mutations in the BRCA genes are also at a higher risk for developing TNBC, as are those with mutations in BARD1, PALB2, and RAD51(Shimelis et al., 2018). Copy number alterations (CNAs) have also been discovered in the genes PARK2, RB1, PTEN, and EGFR. In addition, numerous genes known to be frequently mutated have been identified (Shah et al., 2012) Among them are TP53, PIK3CA, USH2A, MYO3D, PTEN, and RB1. Establishing categorization criteria has helped to better describe the molecular biology of TNBC (Lehmann et al., 2011) have devised a well-accepted classification system that proposes the existence of six separate transcriptional subtypes. After further study, the first six subtypes were consolidated into four main groups (Lehmann et al., 2016). TNBC classification is based on age at diagnosis, histology, tumour grade, and geographic progression. These features distinguish basal-like 1 (BL1), basal-like 2 (BL2), luminal androgen receptor (LAR), and mesenchymal (M) cases from

one another. Gene, mRNA, BL1 patients have considerably higher levels of pathway expression related to the cell cycle, division, proliferation, and DNA damage response. The highest favorable response of any TNBC subtype investigated was observed in patients treated with neoadjuvant therapy for TNBC, with pathological complete response (pCR) rates of 41%. Additionally, this subtype of TNBC had the highest overall survival (OS) rate in comparison to other subtypes. In BL2, the growth factor signaling pathways Wnt/-catenin and epidermal growth factor (EGF) are more active. Genes associated in hormonally controlled pathways, such as androgen and oestrogen metabolism, are expressed more frequently in the LAR subtype. This subtype displayed higher levels of androgen receptor (AR) expression compared to non-LAR TNBC. Luminal androgen receptor (LAR), a subtype of triple-negative breast cancer (TNBC), tumours are often globular in shape and have a propensity to metastasis to the bone. Rho signaling, differentiation, and epithelial-to-mesenchymal transition (EMT) pathways are all amplified in M subtypes. The lungs are a common target for metastases of this kind. LAR instances are more symptomatic of the ERBB2-enriched subtype, whereas BL1, BL2, and M cases show a substantial fraction of basal-like breast cancer (Lehman et al., 2011; Lehman et al., 2016). These subtypes allow for further in-depth research into triple-negative breast cancer and give more proof of the disease's substantial variety.

2.3.3. TNBC and MicroRNAs

It has recently come to light that microRNAs play a part in TNBC (Ng et al., 2013). Research conducted using primary TNBC tissue samples in addition to normal tissue samples uncovered 116 miRNAs that were dysregulated, the miR-106b, the miR-17/92 cluster, and the miR-200 family were the microRNAs that showed the greatest elevation. (miR-200a, miR-200b, and miR-200c), miR-21, and miR-155. The microRNAs that were most significantly downregulated were let-7b, let-7c, miR-126, miR-145, and miR-205 (Cascione et al., 2013).

For instance, it has been demonstrated that miR-205, a gene that functions as a tumour suppressor, is expressed less in TNBCs (Piovan et al., 2012). It is known that the expression of miR-205 is increased when the tumor suppressor gene TP53, which is typically reduced in cancers, is expressed (Tran et al., 2013). MiR-205 expression was found to be widely down-regulated in several TNBC cell lines, and it has been demonstrated that this expression lowers in vitro cell proliferation and clonogenic ability (Plantamura et al., 2020).

MiR-203 and miR-200c are other microRNAs that can inhibit the growth of tumors (Hisamori et al., 2022). The production of a protein known as X-linked inhibitor of apoptosis

(XIAP) was shown to be inhibited by both microRNAs, which reduced the amount of cell proliferation and migration. In addition, it was found that miR-203 prevents cancer cells from proliferating and spreading (Wang et al., 2012).

TNBC relies heavily on one of the most well-known oncomiRs, known as miR-21 (Najjary et al., 2020). There is a correlation between high miR-21 levels and a bad prognosis, as shown by the results of a study that employed 49 main TNBC samples and 34 matched tumour-associated normal samples, The research was conducted on tumours caused by triple-negative breast cancer, Within the same body of research, investigators concluded that miR-221 and miR-210 have a strong connection with one another (Radojicic et al., 2011).

Table 2.2. miRNAs associated with TNBC and the list of microRNAs associated with TNBC (D'Ippolito&Iorio.,2013).

MicroRNA	Validated target(s)	Main biological function(s) in TNBC
Tumor suppressor		
miR-200a/b	Zeb1/Zeb2, Suz 12, EphA2	Stimulation of differentiation in undifferentiated mammary epithelial cell line
miR-200c	Zeb1/Zeb2	Inhibition of EMT
	MSN; FN1	Suppression of migration
	TrkB	Reversion of anoikisis resistance
miR-205	E2F1; LAMC1	Reduction of proliferation, cell cycle and tumor growth
miR-203	BIRC5	Reduction of proliferation
	LASP1	Inhibition of migration
miR-31	WAVE3; RhoA; Radexin	Reduction of metastatic potential
	PRKCE	Induction of apoptosis and enhancement of chemo- and radiosensitivity
miR-34a	AXL	Impairment of migration
OncomiR		
miR-181a/b	Bim	Inhibition of anoikisis
	ATM	Impairment of DNA double-strand-breaks repair
MiR-146 and miR-146b-5p	BRCA1	control of BRCA1-mediated proliferation and homologous recombination
miR-182	PFN1	Inhibition of cell proliferation and invasion Induction of apoptosis

2.4. Clear Cell Renal Cell Carcinoma

ccRCC develops in the proximal convoluted tubule of the kidney and is one of its subtypes, which is a component of the kidney's extremely minute ducts that are responsible for excreting waste materials into the urine (Najar., 2018). For adults, clear cell renal cell carcinoma (ccRCC)

accounts for 90–95 percent of all cases (Goyal et al., 2013). The first therapy consists of either the partial or total removal of the kidney that is most frequently afflicted (s) (Rajab., 2019). The 5-year survival rate is between 65 to 90 per cent for patients whose cancer has not progressed beyond the kidneys, and it reduces dramatically after the disease has moved beyond the kidneys, However, by the time individuals are identified with ccRCC, the illness has progressed significantly since the body is so skilled at masking its symptoms (Vini & Harmer., 2002). Early signs of ccRCC contain blood in urine, flank discomfort, heaviness in the belly or legs, weight loss, fever, elevated blood pressure, night sweats, and a general sense of malaise (Marchioni et al., 2021). The lymph nodes, lungs, liver, adrenal glands, brain, or bones are the locations in which an RCC metastasis is most frequently found (Dudani et al., 2021). Metastatic ccRCC now has a better prognosis thanks to immunotherapy and targeted treatment (Girardi et al., 2020).

2.4.1. Epidemiology of ccRCC

Geographical, demographic, and, to a lesser extent, genetic variables influence the occurrence of the illness differently, Despite the fact that there are a few obvious causes for concern, the significance and relevance of possible risk variables remain contentious (Escuider et al., 2016). The incidence of ccRCC in the world has been increasing by approximately 2-3% per decade until recent years when the number of new cases has remained stable (Bhatt & Finelli., 2014). In addition, the incidence of ccRCC varies by gender, age, and ethnicity and It is roughly 1.6 times more prevalent in males than in women, and the great majority are diagnosed beyond the age of 65. Although the specific reason for the increased frequency among men in industrialised nations is unknown, it may be connected to hereditary factors, environmental variables such as smoking, and working circumstances (Ciccarese et al., 2016). According to reports, the prevalence of ccRCC is much lower among Asians than among whites and African nations have the lowest ccRCC incidence, whereas Black Americans in the United States have the highest ccRCC incidence (Ridge et al., 2014). ccRCC is far more prevalent in industrialised nations than in poor nations and North America, Europe, and Australia /New Zealand are the regions with the highest prevalence (Padala et al., 2020).

After Urinary tract and prostate cancers, ccRCC is the third most prevalent cause of mortality among urological malignancies, in addition, its clinical history is the most fatal among urological malignancies (Hu et al., 2019). According to studies conducted worldwide, ccRCC ranks ninth in cancer incidence and 337,860 new cases were identified in 2012 (Capitanio & Montorsi.,

2016). The World Health Organization (WHO) reported that approximately 121,629 new cases were diagnosed in Europe in 2012 and 75,676 of these cases were male (Torre et al., 2015).

2.4.2. Etiology of ccRCC

The lifestyle choices that people make provide the greatest threat of developing ccRCC and It is thought that smoking, being overweight, and having high blood pressure each have a part in fifty per cent of all cases (Szymańska et al., 2010). Much research has studied the link between ccRCC and exposure to chemicals, including polycyclic aromatic hydrocarbons (PAHs), asbestos, cadmium, lead, chlorinated solvents, petrochemicals, but no definitive results have been produced (Karami et al., 2012). Nearly fifty per cent of all kidney tumours relate to one's BMI (BMI) of more than thirty kilogrammes per square metre. Moreover, the incidence of ccRCC rises by 20-35% for each 5 kg/m2 increase in BMI (Wang and Xu., 2014). This connection demonstrates that being obese is a significant risk factor for several life-threatening disorders, some of which include cancer, cardiovascular disease, and renal disease (Adams et al., 2017). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) over an extended period is an additional potential risk factor (Bjorkman., 1999). In addition, research indicates that the chance of getting ccRCC is double in women who have had a hysterectomy compared to women who have not (Karami et al., 2012). Studies have shown that those who are related to people who have ccRCC have a two- to fourfold greater risk of developing the condition themselves, there is a possibility that a person's susceptibility to infection is somewhat influenced by genetic variables (Purdue et al., 2011). ccRCC risk may be increased by having a family history of hereditary papillary renal carcinoma, hereditary leiomyomatosis, hyperparathyroidism-jaw tumour syndrome, familial papillary thyroid cancer, von Hippel-Lindau (VHL) disease, or sickle cell anaemia (Moch., 2013). However, genetic etiology is not the most important disease affecting risk and in patients with a renal cystic disease requiring dialysis, the risk of ccRCC is 30 times higher in comparison to the rest of the population (Szymańska et al., 2010).

2.4.3. Classification of ccRCC

In 2004, WHO made a classification of RCC which can be considered as a summary of Mainz and Hidelberg's classification (Table 2.3.). In this classification, various categories were created by considering the results of pathological and genetic analyses (Lopez-Beltran et al., 2006).

Table 2.3. Summary of Mainz and Hidelberg's classification (Lopez-Beltran et al., 2006).

Benign	**Malign**
Papillary	Transparent Cell RCC
Oncocytoma	Multilocular Clear Cell RCC
	Papillary RCC
	Chromophobe RCC
	Bellini Collecting Duct Carcinoma
	Renal Medullary Carcinoma
	Xpll Translocation Carcinoma
	Carcinoma Associated with Neuroblastoma
	Mucinous Tubular and Spindle Cell Carcinoma
	Unclassifiable RCC

2.4.4. ccRCC Genetics

ccRCC differs from kidney cancer involving the renal pelvis or renal medulla in that it only occurs in the cells that extend into the renal bed (i.e. the renal tubules). In some families predisposed to ccRCC, genetically based variants have been identified as the cause of the inherited cancer risk. These genetic background variants are estimated to account for only 5 to 8 per cent of RCC cases overall. Other undiscovered genes and Other genetic factors in the background may contribute to the development of ccRCC together with non-genetic risk factors (Shuch et al., 2013).

ccRCC can occur in both sporadic and inherited cases (Moore et al., 2011). The four main ccRCC syndromes defined as inherited in a manner that is determined to be autosomal dominant are listed below (Shuch et al., 2013):

- VHL syndrome
- RCC and hereditary leiomyomatosis (CLRCC)
- Papillary renal cell carcinoma hereditary (CPRCC).
- BHD syndrome.

The Cancer Genome Atlas Consortium has analysed more than 400 ccRCC patients, comparing healthy kidney tissue with kidney tumours. On average, fewer than twenty deoxyribonucleic acid (DNA) copy number alterations were found in ccRCC. Copy number alterations are abnormal numbers of copies of one or more parts of a cell's DNA. These changes

cause a quantitative imbalance in the genome (Zarrei et al., 2015). This number is far lower than the DNA copy number variations seen in breast and colon malignancies, Nonetheless, all chromosomal arms had more copy number alterations than colon and breast cancer (Poulogiannis et al., 2010). 10% to 20% of RCC instances have been shown to have RNA fusions, the great majority of which have been characterised for the very first time, These RNA fusions are thought to be the result of translocation (Zarrei et al., 2015). With the help of whole genome or exome sequencing, more than 100 ccRCC instances were examined. One to two somatically acquired single nucleotide variants or minor insertions and deletions per megabase pair, the majority of which occur outside of the coding sections, are characteristics of RCC. Random mutations occur in protein-coding regions, which make up roughly 1% of the genome (Brugarolas., 2014).

Research attempting to identify the chromosomal irregularities that cause RCC has identified many loci of critical importance. Loss of heterozygosity results In many hereditary cancer syndromes, wild-type alleles are lost due to somatic mutation (Gatto et al., 2014). The most common losses of heterozygosity are: 30 large fragments loss (along 3p21-36), 1 interstitial deletion (along 3p12-14, 3p21-22, 3p24.1- 24.2, and 3p24.3) in addition to a number of chromosomal losses (8p12-pter, 6q23.3-27, 14q24.1-qter, 9q32-qter, 10q22.3-qter, 9p13.3-pter, 4q28.3-qter and 13q12.1-21.1) (Chen et al., 2009). After the detection of 3p loss in RCC, significant correlations were found between cytogenetic changes and histopathological subtypes of RCC (Singh & Kadam., 2013). The general frequency of chromosome 3p heterozygosity loss observed in RCC is 53%. Examination of the relationship between the histopathological phenotypes of ccRCC and the incidence of 3p loss showed that the loss of heterozygosity in tumors with transparent cell type was 75% (12/16) and that the loss of heterozygosity in this cell type was more frequent than in granular cell type tumors (14%, 1/7) ($p < 0.01$) (Favazza et al., 2017). ccRCC-associated deletions positioned at the third chromosome's short arm.

The loss of heterozygosity in this region demonstrates that cases of ccRCC are strongly associated with the presence of tumour suppressor genes on the short arm of chromosome 3. VHL, ITPR1, PPARG, GPD1L, ABHD5, IMPDH2, CHDH, DRR1, PDHB, and FHIT are a few of the genes that have been identified as being present in these genomic regions (Singh & Kadam., 2013) (Figure 2.13). The following is a summary of these genes' functions**:**

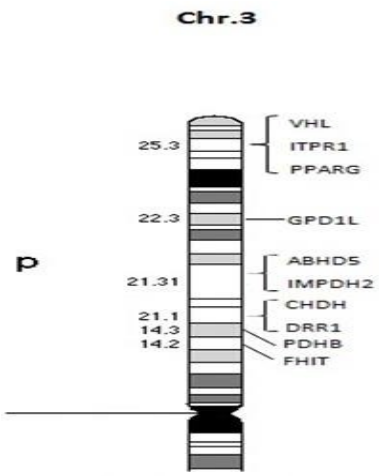

Figure 2.13. ccRCC-specific deletion genes positioned at the third chromosome's short arm (Singh & Kadam., 2013).

2.4.4.1. VHL Gene

The majority of RCC cases (90%) are characterised by two allelic losses of the VHL gene (Batavia et al., 2019). Cancers such as haemangioblastomas, pheochromocytomas, pancreatic malignancies, and renal cell carcinomas are all linked to von Hippel-Lindau syndrome, a disorder that is inherited in an autosomal dominant manner and raises a person's chance of getting the aforementioned illnesses (Richard et al., 2013). RCC is a prevalent cause of mortality in sporadic and non-familial individuals with this mutation type, manifesting as bilateral and multifocal tumors at an early age. In unaffected areas, patients with VHL deletion inherit a mutation in just one allele of the VHL gene, whereas afflicted cells, tissues, and organs have a mutation in the other allele. Thus, RCCs in this disease are typically early-onset and multifocal (Singh & Kadam., 2013).

The questioned gene produces a protein that is a component of a complex that also contains the proteins elongin B, elongin C, and cullin-2 (Kamura et al., 1999). The protein in question demonstrates activity as a ubiquitin ligase E3 and has been linked to the degradation of hypoxia-induced factor (HIF) via the process of ubiquitination (Wang & Xu., 2014).

2.4.4.2. ITPR1 Gene

This gene, when activated, causes calcium to be released from the endoplasmic reticulum. The protein that it encodes, an intracellular receptor for inositol 1,4,5-triphosphate, is encoded by this gene (Ding et al., 2002). ITPR1 is a new target of HIF2α, which regulates its mRNA and protein expression, HIF2α may cause RCC tumor development via ITPR1, RCC VHL mutations

may activate the HIF2α/ITPR1 axis, which controls antitumor immunity, tumor cell survival, and cell proliferation (Messai et al., 2014).

2.4.4.3. PPARG Gene

PPARG is a nuclear receptor that controls the body's lipid balance and has been hypothesised to have a role in the genesis of many diseases, including diabetes and obesity (Barish et al., 2006). PPARG also suppresses tumor development, progression, and metastasis. This gene encodes a transcription factor that can enter the nucleus and bind to DNA. It regulates several genes as a heterodimer with RXR protein. Several mechanisms, including PPARG activation, mediate omega-3 fatty acids' anti-cancer properties. Colon, breast, lung, and prostate tumors express PPARG. PPARG activation inhibits cancer cell growth in vitro. PPARG naturally binds fatty acids. Fatty acids stimulate PPARG and then suppress cancer cell proliferation. α-linolenic acid (ALA) reduces RCC cell growth via two concurrent signalling pathways: PPARG activation and COX-2 inhibition (Yang et al., 2013).

2.4.4.4. GPD1L Gene

This gene's cytoplasmic protein interacts with sodium channels in the plasma membrane to catalyze the transformation of sn-glycerol 3-phosphate into glycerone phosphate (Valdivia et al., 2009). Although it is located in one of the deletion loci of chromosome three associated with RCC, it has not been pathophysiologically associated with RCC before. However, hypoxia-induced positive feedback loop increases HIF1α stability through miR-210 repression of GPDL1 (Kelly et al., 2011). This HIF-mediated GPDL1 suppression may shed light on its possible association with RCC (Valdivia et al., 2009).

2.4.4.5. ABHD5 Gene

The protein that is produced by this gene is involved in the manufacture of phosphatidic acid and triggers the storage of triacylglycerol on the intracellular level (Lutkewitte & Finck., 2020). Despite the fact that it is situated in one of the sites on chromosome three that has been linked to deletion in RCC, the ABHD5 gene has not yet been shown to be pathophysiologically connected with renal cell carcinoma (Dmitriev et al., 2014).

2.4.4.6. IMPDH2 Gene

This gene's protein limits de novo guanine nucleotide production and is necessary for DNA and RNA synthesis, prostate cancer and other neoplasms upregulate IMPDH2, the enzyme that

controls the speed at which guanine nucleotides are made from scratch (Barfeld et al., 2015). Overexpressed IMPDH2 can be utilised to diagnose and treat kidney and bladder cancer. Proliferating cells including cancer cells express IMPDH2 (Szwed et al., 2021).

2.4.4.7. CHDH Gene

This gene encodes a protein that is localised in mitochondria and participates in choline production (Fagone & Jackowski., 2013). Despite the importance of this gene's higher mRNA and protein expression in renal tissues relative to other tissues in providing crucial information about RCC, no relationship between the two has yet been discovered (Johnson et al., 2012).

2.4.4.8. DRR1 Gene

The protein encoded by this gene has a function in preventing cell proliferation and development when transfected into cell lines where it is not normally expressed (Liu et al., 2009). It is possible that a loss of DRR1 gene expression is a critical step in the progression of RCC and other malignancies (Wang et al., 2000).

2.4.4.9. PDHB Gene

Involved in the process of conversion of pyruvate to acetyl coenzyme A, the compound of prussic acid dehydrogenase connects the glycolytic route to the tricarboxylic acid cycle, While it is situated in one of the chromosome 3 deletion locations linked with RCC, it has not been previously related with the pathophysiology of RCC (Saunier et al., 2016).

2.4.4.10. FHIT Gene

The enzyme that catalyses the hydrolysis of adenosine 5',5"-P1, P3-triphosphate encoded by this gene is involved in purine metabolism and this fragile gene region on chromosome 3 causes many different translocations. The FHIT gene, located in the fragile site, aphidicolin type, fra (3) One of the first and most often changed genes in most human malignancies is FRA3B, Most FHIT-negative cancers start in epithelial cells, however, the FHIT gene isn't the most susceptible locus there (Kvasha et al., 2008). In fact, recent studies have shown that the FHIT gene is involved in both apoptosis and the epithelial-mesenchymal transition (Epithelial-Mesenchymal Transition, EMT) (Jinesh & Brohl., 2022). is a gene that acts as a tumor suppressor and plays a part in cancer prevention, More recent investigations have found that the product of the FHIT gene, which is called Fhit, has a novel role in the body as a "gatekeeper" (Waters et al., 2014). Loss of function of this protein has been shown to result in nucleotide imbalance, spontaneous replication stress, and

DNA breakage. As a result of "checkpoint blindness" caused by Fhit loss-induced DNA damage, cells might enable oncogenic mutations throughout successive cell cycles and DNA damage rises, resulting in genomic instability that accelerates clonal proliferation. Hence, the absence of Fhit activity promotes a mutator phenotype. Recent research on the absence of Fhit and the subsequent genomic instability provides evidence that the FHIT gene is a mutator gene. Inactivation of the FHIT gene in RCC may be caused by hypermethylation of the FHIT cytosine-phosphate-guanine (CpG) island (Kvasha et al., 2008).

2.4.5. miRNAs in ccRCC

The primary miRNAs (pri-miRNAs) are first translated into lengthy coding or noncoding RNA segments in the nucleus by RNA polymerase II (Bortolin-Cavaille et al., 2009). Prim-miRNAs target segments with a stem-loop that are 70–100 nucleotides long. The DiGeorge Syndrome Critical Region 8 (DGCR8), a complex of ribonuclease (RNase) type III and double-stranded RNA (dsRNA) binding protein, cleaves these pri-miRNAs (Lin & Gregory., 2015). These small RNA molecules, which have the structure of a stem-loop, are referred to as precursor miRNAs (pre-miRNAs), they are also known by the name's RNase, Drosha, and the DGCR8 protein microprocessor complex (Kataoka et al., 2009). Pre-miRNAs leave the nucleus and are transported into the cytoplasm after being bundled with exportin-5 and RAS-associated nuclear guanosine triphosphate (RAS Associated Nuclear-Guanosine Triphosphate, or RAN-GTP), In order to generate a double-stranded miRNA duplex, pre-miRNAs are processed by Dicer, a double-stranded RNA cutter (Double Stranded RNase, or dsRNase) type III (Svobodova et al., 2016). The ATP-dependent RNA-induced silencing complex (RISC) loading complex (RLC) transports the miRNA duplex into the RISC, where it is then cleaved in half; one sequence leaves the RLC, while the other remains to complete the RISC structure and serve as a capture template for mRNA targets (Ha & Kim., 2014). Mature RISC typically acts to repress gene expression after transcription (Filipowicz et al., 2005). Through the catalytic area (RNase III domain) of Argonot proteins, the main element of the RICS complex, the mature RISC complex cleaves and destroys mRNAs that exhibit a high degree of complementarity with the mould sequence (Kwak et al., 2010). The 7-methylguanosine cap and several adenylation sites are damaged by the DCP1-DCP2 and CNOT complexes, which are parts of the RISC complex and reduce the stability of target mRNAs for partially complementary targets (Norbury., 2013). Target gene translation is typically hampered by the RISC complex, and certain miRNAs inhibit translation. Adenine and uracil-rich areas bind to

miR-369-3 and the fragile X mental retardation, autosomal homolog 1 (FXR1) transcription 3' untranslated region (3'UTR), which causes TNF translation when there is starvation (Riaz et al., 2015). This process explains the role of the RISC complex at the molecular level in the regulation of translation (Morris & Mattick., 2014).

Short non-coding RNA species called miRNAs control the transcriptional level of gene expression (Dykes & Emanueli., 2017). Recent studies have shown that epigenetic processes like DNA methylation and histone modification regulate the expression of miRNAs like miR-9, miR-34a, miR-124, miR-134, miR-147, miR-148, and miR-203 in addition to having an impact on the expression of protein-coding genes. Contrarily, a different subset of microRNAs is in charge of controlling the expression of crucial epigenetic regulators such as DNA methyltransferases, histone deacetylases, and polycomb group genes. This feedback network between miRNAs and epigenetic pathways appears to form an epigenetic-miRNA regulatory loop, which appears to organize the gene expression profile and repress numerous disease processes as well as normal physiological functioning (Pagano et al., 2013).

According to several types of research, miRNAs that are overexpressed are indicators of many disorders including cancer (Ouyang et al., 2014). Profiling of miRNA expression has been found to be linked with tumour growth, progression, and treatment response, indicating their potential use as biomarkers for diagnosis, prognosis, and prediction (Schwarzenbach., 2015). In addition, there has been a rise in the number of research indicating that miRNAs can perform the functions of either potential oncogenes or tumour suppressor genes (Ouyang et al., 2014). On this basis, miRNA-based anti-cancer medicines that aim to improve disease response and increase cure rates have either The benefit of miRNA-focused techniques is the capacity to simultaneously target various effectors of cell differentiation, proliferation, and survival pathways (Baer et al., 2013).

3. MATERIAL AND METHODS

3.1. Datasets

The data sets used in this thesis study were obtained from the publicly accessible National Centre for Biotechnology Information Gene Expression Omnibus (NCBI-GEO) (https://www.ncbi.nlm.nih.gov/geo/) (Barrett et al., 2012). The NCBI-GEO data set is publicly accessible; our study does not require ethics committee approval. The scheme of the methodology of the study is shown in Table 3.1. Among the datasets scanned using different filters in the search engine of the NCBI-GEO database, those suitable for the study were determined. The keywords (Covid-19, breast cancer, triple-negative breast cancer, clear cell renal cell carcinoma). Among the data sets, the ones included in the study were selected by evaluating them on various criteria. The criteria used for selecting data sets for both diseases were: (i) tissue sample or whole blood sample; (ii) case-control study (iii) no drug use (iv) same microarray platform. Studies that did not meet all these criteria were excluded. The GSE164805 dataset consisted of 10 individuals with COVID-19, including 5 with severe symptoms and 5 with mild symptoms, along with 5 control subjects. In the GSE139038 dataset, there were a total of 65 samples, including 41 breast tumors (24 in early stages and 17 locally advanced), 18 adjacent normal tissue samples (paired normal), and 6 apparently normal samples from breasts that had undergone non-malignant condition surgeries. The GSE45498 dataset contained 165 primary tumors, 59 adjacent normal samples, and 54 lymph node metastatic samples for Triple-negative breast cancer. Lastly, the GSE105261 dataset included samples of Clear cell renal cell carcinoma (ccRCC), comprising 9 normal samples, 9 primary ccRCC samples, and 26 metastatic ccRCC samples.

Table 3.1. Dataset information used in the study.

GEO ID	Tissue type	Case-control group	Experiment Type	Platform
GSE164805	Peripheral blood mononuclear cells	5 severe, 5 mild COVID-19- 5 Control	"Expression profiling by array"	" Agilent-085982 Arraystar human lncRNA V5 microarray"
GSE139038	Breast tissue	65 Breast Cancer- 6 Control	"Expression profiling by array"	"Print_1437 "
GSE45498	Breast tissue	224 TNBC – 59 Controls	"Expression profiling by array"	NanoString nCounter mRNA Human Cancer Reference Kit
GSE105261	Renal tissue	37 ccRCC– 9 Controls	"Expression profiling by array"	Illumina HumanHT-12 V4.0 expression beadchip

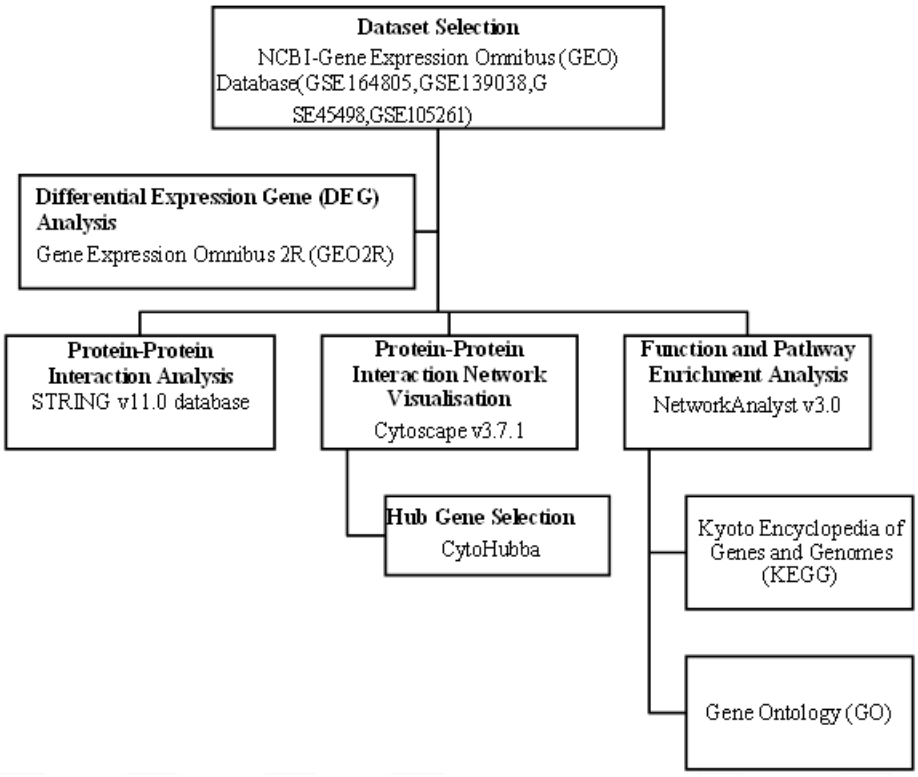

Figure 3.1. Workflow of the thesis

3.2. Identification of DEGs and Common DEGs

The criteria used for identifying DEGs is p-value < 0.01, log2FC ≥ 1 (up-regulated DEGs) or p-value < 0.01 and log2FC ≤ -1 (down-regulated DEGs). DEGs were identified in GSE164805 dataset in three groups: 5 Severe COVID-19 patients and 5 controls, 5 mild COVID-19 patients and 5 controls, and all 10 COVID-19 (mild and severe) patients and 5 controls. DEGs were identified 65 breast cancer patients and 6 controls, 224 triple negative breast cancer patients and 59 controls, 37 ccRCC patients and 9 controls: Common DEGs for severe COVID-19-breast cancer, mild COVID-19-breast cancer, COVID-19-breast cancer were shown by the Venn diagrams.

3.3. Protein-Protein Interaction (PPI) Network Analysis and Identification of Top 10 hub Genes

The present study employed the Search Tool for the Interacting Genes (STRING) database to investigate the protein-protein interactions (PPI) of the differentially expressed genes (DEGs) that were shared among the groups (Szklarczyk et al., 2019). The DEGs were identified using a common approach. The PPI network was created by selecting a combined score of 0.7 for the PPI. Subsequently, the Cytohubba plugin integrated within the Cytoscape (v3.9.1) software was employed to visually represent and ascertain the hub genes that were filtered based on the Degree term (Lin et al., 2008). Hub genes, alternatively referred to as network hub genes, are genetic elements that possess a pivotal function within gene regulatory networks or protein-protein interaction networks, These networks exhibit strong interconnections and are recognised for their substantial influence on diverse biological processes (Wang et al., 2007). In the context of protein-protein interaction networks, hub genes can be defined as proteins that exhibit a high degree of connectivity by interacting with multiple other proteins. These proteins are commonly implicated in crucial cellular processes, including signal transduction, molecular transportation, and enzymatic functions (Chapple et al., 2015). Hub genes play a critical role in preserving the integrity of protein-protein interaction networks and coordinating the essential protein interactions involved in diverse biological processes (Wang et al., 2007). The ability to identify hub genes is crucial to understanding the underlying workings of complex biological systems, Hub genes may be used as diagnostic tools or therapeutic targets in the treatment and study of illness because alterations in hub gene expression or function may disrupt normal network functioning, they may play a role in the development of illness. The functional modules and hierarchical structure of biological networks may be better understood by analyzing hub genes (Diaz-Beltran et al., 2013).

3.4. Functional Enrichment Analysis

The study employed the Database for Annotation, Visualisation and Integrated Discovery (DAVID) database, which can be accessed at (https://david.ncifcrf.gov/), to conduct Gene Ontology (GO) function analysis, with a particular focus on biological processes (BP), molecular functions (MF), and cellular components (CC). Furthermore, the research performed an analysis of the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways (Huang et al., 2009). Functional and pathway analyses were conducted on each group separately.

3.5. Identification of TFs and miRNAs

The study formulated hypotheses concerning the associations between hub genes and miRNAs, hub genes and transcription factors (TFs), and the interactions between TFs and miRNAs. The establishment of the interaction between transcription factors (TFs) and hub genes was accomplished by utilising the TRRUST v.2 database, as described by (Han et al. 2018). The miRNA Data Integration Portal (mirDIP) version v4.1 database was utilised by (Tokar et al., 2018) to generate the miRNA-hub gene interaction. Within each category. The TRUSST v2 software is a highly valuable tool for the identification of pertinent transcription factors (TFs) implicated in diverse human diseases. The MirDIP v4.1 database is an invaluable repository that encompasses a multitude of predictions regarding interactions between human miRNA and hub genes. These predictions have been sourced from a comprehensive collection of 30 distinct repositories. The study conducted an analysis of TF-miRNA regulations and performed functional over-representation analyses of the miRNAs using the TransmiR v2.0 database (Tong et al., 2019). The TransmiR database serves as a valuable resource in the identification of regulatory interactions between transcription factors (TFs) and microRNAs (miRNAs). The compilation of information in this study encompasses a range of sources, such as published literature, ChIP-seq data, and predicted TF-miRNA regulations.

4. RESULTS AND DISCUSSION

4.1. Identification of DEGs and Common DEGs

A total of 16 differentially expressed genes (DEGs) were identified to be commonly expressed in both COVID-19 and TNBC. Additionally, 17 DEGs were identified as commonly expressed between mild COVID-19 and TNBC, while 25 DEGs were found to be commonly expressed between severe COVID-19 and TNBC. The study identified 409 differentially expressed genes (DEGs) that were commonly shared between COVID-19 and clear cell renal cell carcinoma (ccRCC). Additionally, 314 DEGs were found to be commonly expressed between mild COVID-19 and ccRCC, while 736 DEGs were commonly expressed between severe COVID-19 and ccRCC. A total of 327 DEGs were identified to be commonly expressed in both COVID-19 and breast cancer. Additionally, 243 DEGs were identified as commonly expressed between mild COVID-19 and breast cancer, while 549 DEGs were found to be commonly expressed between severe COVID-19 and breast cancer.

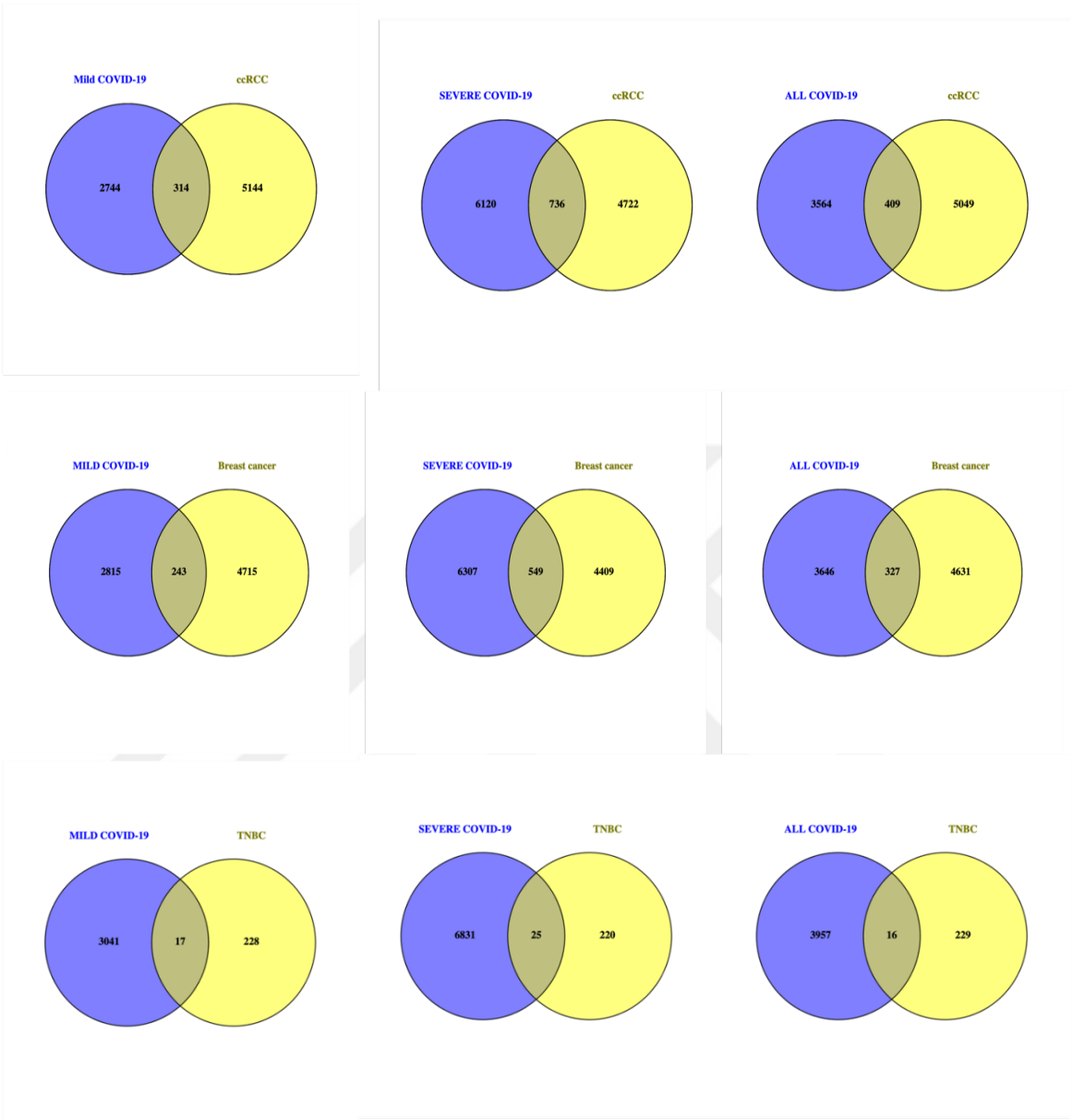

Figure 4.1. Venn diagram of, COVID-19 and ccRCC, COVID-19 and breast cancer, COVID-19 and TNBC

4.2. PPI network analysis and identification of top 5 hub genes in COVID-19 and TNBC and COVID-19 and ccRCC

The top 5 hub genes for severe COVID-19-TNBC are *ESR1, NOTCH1, MMP9, CD44* and *IGF1*. The top 5 hub genes for mild COVID-19-TNBC are *IL1B, IL1A, IGF1, FGF1,* and *FLT1*. The top 5 hub genes for COVID-19-TNBC are *NOTCH1, IL1B, IGF1, MMP9*, and *IL1A* (Table 4.1., Table 4.2, Table 4.3).

Table 4.1. Top 5 hub genes in All COVID-19 and TNBC in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
NOTCH1	22.33	3.0	9.83	0.428	8	0.439	0.270	6.595	125	3.25	48
IL1B	19.66	3.0	10	0.607	8	0.495	0.406	6.644	248	3.317	48
IGF1	18.33	1.0	10	0.607	8	0.495	0.406	6.686	248	3.317	44
MMP9	18.33	1.0	10	0.607	8	0.495	0.406	6.675	248	3.317	44
IL1A	14.33	3.0	9.33	0.523	7	0523	0.270	6.34	123	3.182	36

Table 4.2. Top 5 hub genes in mild COVID-19 and TNBC in the PPI network

Gene ID	Betweneness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
IL1B	31.066	4.0	9.0	0.380	7.0	0.292	0.352	6.329	18.0	2.887	66
IL1A	27.266	3.0	8.33	0.333	6.0	0.324	0.235	5.833	11.0	2.759	50
IGF1	12.266	1.0	8.5	0.533	6.0	0.380	0.352	6.159	18.0	2.823	42
FGF1	7.6	2.0	7.83	0.6	5.0	0.388	0.235	5.999	14.0	2.695	22
FLT1	10.33	1.0	7.16	0.5	4.0	0.463	0.235	5.537	7.0	2.566	20

Table 4.3. Top 5 hub genes in severe COVID-19 and TNBC in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
ESR1	147.367	7.0	20.0	0.338	17.0	0.372	0.48	10.757	6044	2.796	312
NOTCH1	103.784	6.0	19.0	0.42857	15.0	0.506	0.48	10.572	7569	2.713	228
MMP9	44.223	2.0	18.5	0.538	14.0	0.551	0.48	10.635	7706	2.671	138
CD44	68.789	4.0	18.5	0.516	14.0	0.600	0.48	10.734	7687	2.671	150
IGF1	13.584	1.0	17.5	0.666	12.0	0.643	0.48	10.262	7584	2.587	66

The top 5 genes between COVID-19 and ccRCC are *TTK, CCNB1, ASPM, RAD51AP1,* and *NCAPG.* The top 5 genes between severe COVID-19 and ccRCC are *ASPM, CCL5, CCNB1, CENPE,* and ESR1. The top 5 genes between mild COVID-19 and ccRCC are *CDCA3, ASPM, ANLN, TTK,* and *BARD1* (Table 4.4, Table 4.5, Table 4.6). PPI enrichment value is 1.62e-05, PPI enrichment value is 1.18e-06.

Table 4.4. Top 5 hub genes in All COVID-19 and ccRCC in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
TTK	4121.35	9.0	86.32	0.29	21.0	0.55	0.0704	83.52	58473	8.45	18714
CCNB1	8404.67	31.0	92.35	0.38	19.0	0.65	0.0792	83.91	58612	8.67	27946
ASPM	1085.46	3.0	84.41	0.45	18.0	0.51	0.0704	83.73	58602	8.43	7522
RAD511AP1	2421.53	5.0	86.06	0.47	17.0	0.58	0.0792	83.73	57137	8.52	9364
NCAPG	549.07	5.0	84.77	0.57	16.0	0.61	0.0792	83.87	58638	8.49	5368

Table 4.5. Top 5 hub genes in Severe COVID-19 and ccRCC in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
ASPM	4121.35	9.0	86.32	0.29	21.0	0.55	0.0704	83.52	58473	8.45	18714
CCL5	8404.67	31	92.35	0.38	19.0	0.65	0.0792	83.91	58612	8.67	27946
CCNB1	1085.46	3.0	84.41	0.45	18.0	0.51	0.0704	83.73	58602	8.43	7522
CENPE	2421.53	5.0	86.06	0.47	17.0	0.58	0.0792	83.73	57137	8.52	9364
ESR1	549.07	5.0	84.77	0.57	16.0	0.61	0.0792	83.87	58638	8.49	5368

Table 4.6. Top 5 hub genes in Mild COVID-19 and ccRCC in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
CDCA3	4121.35	9.0	86.32	0.29	21.0	0.55	0.0704	83.52	58473	8.45	18714
ASPM	8404.67	31.0	92.35	0.38	19.0	0.65	0.0792	83.91	58612	8.67	27946
ANLN	1085.46	3.0	84.41	0.45	18.0	0.51	0.0704	83.73	58602	8.43	7522
TTK	2421.53	5.0	86.06	0.47	17.0	0.58	0.0792	83.73	57137	8.52	9364
BARD1	549.07	5.0	84.77	0.57	16.0	0.61	0.0792	83.87	58638	8.49	5368

The top 5 genes in all COVID-19 and breast cancer patients are *TOP2A, MMP9, IGF1, PXN*, and *SPP1*. The top 5 genes in mild COVID-19 and breast cancer patients are *TYMS, TOP2A, CCNB1, TTK*, and *ASPM*. The top 5 genes in severe COVID-19 and breast cancer patients are *MMP9*, IGF1, *RAC1, RPS16*, and *CCNB1* (Table 4.7, Table 4.8 and Table 4.9).

Table 4.7. Top 5 hub genes in All COVID-19 and breast cancer in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
TOP 2A	119795	402	267	0.07	78	0.13	0.11	136	495455	75	8.3
MPP9	15710	16	217	0.16	46	0.28	0.11	16	590724	44	7.9
IGF1	4320	3	206	0.27	35	0.39	0.11	3	597154	35	7.8
PXN	7075	12	205	0.24	29	0.34	0.09	12	86947	28	7.8
SPP1	6587	22	207	0.31	28	0.4	0.11	22	584810	28	7.9

Table 4.8. Top 5 hub genes in mild COVID-19 and breast cancer in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
TYMS	306508	241	681	0.06	150	0.14	0.15	189	7813199	149	9.1
TOP2A	150981	93	607	0.05	89	0.12	0.13	157	4043536	81	8.8
CCNB1	184878	96	577	0.02	82	0.16	0.15	124	491	36	8.7
TTK	116209	43	617	0.07	81	0.16	0.15	171	82477	74	8.9
ASPM	63760	16	587	0.15	76	0.28	0.15	175	5750204	74	8.7

Table 4.9. Top 5 hub genes in severe COVID-19 and breast cancer in the PPI network

Gene ID	Betweenness	BottleNeck	Closeness	Clustering Coefficient	Degree	DMNC	EcCentricity	EPC	MCC	Radiality	Stress
MMP9	41775	22	575	0.16	67	0.31	0.15	174	5365203	64	8.7
IGF1	31485	14	556	0.2	63	0.36	0.15	171	1.24	61	8.6
RAC1	19330	18	549	0.23	55	0.4	0.15	167	1.22	53	8.6
RPS16	56026	26	540	0.14	51	0.23	0.15	131	388506	49	8.7
CCNB1	54898	17	544	0.07	50	0.17	0.15	126	746	38	8.6

4.3. Functional Enrichment Analysis

The top 5 GO terms in the BP category are “Positive regulation of transcription from RNA polymerase II promoter”, “Positive regulation of gene expression”, “Positive regulation of cell migration”, “Positive regulation of cell proliferation” and “Positive regulation of transcription, DNA-templated” for all COVID-19 and TNBC. The top 5 GO terms in the CC category are “Extracellular region”, “Extracellular space”, “Extracellular exosome”, and “Cell surface” for all COVID-19 and TNBC. The top GO terms in the MF category are “Integrin binding”, “Cytokine activity”, “Interleukin-1 receptor binding”, “Insulin-like growth factor receptor binding” and “Protein binding” for all COVID-19 and TNBC. The top 5 KEGG terms are “Pathways in cancer”,

"Endocrine resistance", "Breast cancer", "Ovarian steroidogenesis" and "Proteoglycans in cancer for all COVID-19 and TNBC (Table 4.10).

Table 4.10. The top 5 GO terms (BP, MF, CC) and KEGG pathways for all COVID-19 and TNBC

Category	Term	Count	p-value
GOTERM_BP	Positive regulation of transcription from RNA polymerase II promoter	8 TOP2A, ETS1, WNT1, FGF1, IGF1, IL1A, IL1B, NOTCH1	1.5e-5
GOTERM_BP	Positive regulation of gene expression	6 ETS1, FGF1, IGF1, IL1A, IL1B, NOTCH1	3.5e-5
GOTERM_BP	Positive regulation of cell migration	5 FGF1, IGF1, IL1B, MMP9, NOTCH1	4.1e-5
GOTERM_BP	Positive regulation of cell proliferation	6 ETS1, WNT1, FGF1, IGF1, IL1B, NOTCH1	4.5e-5
GOTERM_BP	Positive regulation of transcription, DNA-templated	6 ETS1, WNT1, IGF1, IL1B, NOTCH1, SPP1	1.6e-4
GOTERM_CC	Extracellular region	11 GNAS, TIMP3, WFDC2, WNT1, FGF1, IGF1, IL1A, IL1B, MMP9, NOTCH1, SPP1	2.6e-7
GOTERM_CC	Extracellular space	9 TIPM3, WFDC2, WNT1, FGF1, IGF1, IL1A, IL1B, MMP9, SPP1	2.1e-5
GOTERM_CC	Extracellular exosome	6 GNAS, WFDC2, WNT1, MMP9, PTPRG, SPP1	1.7e-2
GOTERM_CC	Cell surface	3 WNT1, IL1A, NOTCH1	7.8e-2
GOTERM_MF	Integrin binding	4 FGF1, IGF1, IL1B, SPP1	2.6e-4
GOTERM_MF	Cytokine activity	4 WNT1, IL1A, IL1B, SPP1	4.3e-4
GOTERM_MF	Interleukin-1 receptor binding	2 IL1A, IL1B	1.2e-2
GOTERM_MF	Insulin-like growth factor receptor binding	2 GNAS, IGF1	1.3e-2
GOTERM_MF	Protein binding	15 TOP2A, ETS1,GNAS,TIMP3,WFDC2,CDKN2B,CYP1A1,FGF1,IGF1, IL1A,IL1B,MMP9,NOTCH1,PTPRG,SPP1	2.0e-2
KEGG PATHWAY	Pathways in cancer	8 ETS1, GNAS, WNT1, CDKN2B, FGF1, IGF1, MMP9, NOTCH1	5.6e-6
KEGG PATHWAY	Endocrine resistance	4 GNAS, IGF1, MMP9, NOTCH1	4.3e-4
KEGG PATHWAY	Breast cancer	4 WNT1, FGF1, IGF1, NOTCH1	1.4e-3
KEGG PATHWAY	Ovarian steroidogenesis	3 GNAS, CYP1A1, IGF1	2.8e-3

KEGG PATHWAY	Proteoglycans in cancer	4 TIMP3, WNT1, IGF1, MMP9	3.7e-3

The top 5 GO terms in the BP category are “Positive regulation of cell proliferation”, “Positive regulation of cell migration”, “Positive regulation of transcription from RNA polymerase II promoter”, “Positive regulation of cell proliferation” and “Embryo implantation” for severe COVID-19 and TNBC. The top 5 GO terms in the CC category are “Extracellular region”, “Apical plasma membrane”, “Extracellular exosome”, “Golgi apparatus” for all COVID-19 and TNBC. The top GO terms in the MF category are “Enzyme binding”, “Protein binding”, “Integrin binding”, “Growth factor activity” and “Cytokine activity” for severe COVID-19 and TNBC. The top 5 KEGG terms are “Pathways in cancer”, “Human papillomavirus infection”, “Breast cancer”, “Ovarian steroidogenesis” and “Proteoglycans in cancer” for severe COVID-19 and TNBC (Table 4.11).

Table 4.11. The top 5 GO terms (BP, MF, CC) and KEGG pathways for mild COVID and TNBC

Category	Term	Count	p-value
GOTERM_BP	Positive regulation of mitotic nuclear division	4 IGF1, IL1A, IL1B, PDGFRB	1.9e-6
GOTERM_BP	Positive regulation of angiogenesis	5 ETS1, FGF1, FLT1, IL1A, IL1B	8.4e-6
GOTERM_BP	Positive regulation of MAP kinase activity	4 FGF1, FLT1, IL1B, PDHFRB	3.7e-5
GOTERM_BP	Positive regulation of cell migration	5 FGF1, FLT1, IGF1, IL1B, PDGFRB	5.4e-5
GOTERM_BP	Positive regulation of cell proliferation	6 ETS1, FGF1, FLT1, IGF1, IL1B, PDGFRB	6.3e-5
GOTERM_CC	Extracellular space	8 TIMP3, WFDC2, FGF1, FLT1, IGF1, IL1A, IL1B, TGFBI	3.5e-4
GOTERM_CC	Extracellular region	8 GNAS, TIMP3, WFDC2, FGF1, IGF1, IL1A, IL1B, TGFBI	6.2e-4
GOTERM_CC	Nucleus	11 TOP2A, ETS1, GNAS, PIM1, TIMP3, CDKN2B, FGF1, IL1A, PDGFRB, TYMS	5.7e-3
GOTERM_CC	Extracellular matrix	3 TIMP3, FGF1, TGFBI	1.7e-2
GOTERM_CC	Cytoplasm	9 TOP2A, ETS1, GNAS, PIM1, CDKN2B, GFG1, IRF1, PDGFRB, TYMS	4.4e-2
GOTERM_MF	Integrin binding	4 FGF1, IGF1, IL1B, TGFBI	3.1e-4
GOTERM_MF	Interleukin-1 receptor binding	2 IL1A, IL1B	1.3e-2
GOTERM_MF	Insulin-like growth factor receptor binding	2 GNAS, IGF1	1.3e-2
GOTERM_MF	Protein binding	16 TOP2A,ETS1,GNAS,PIM1,TIMP3,WFDC2,CDKN2B,CYP1A1, FGF1,FLT1,IGF1,IRF1,IL1A,IL1B,PDGFRB,TGFBI	1.4e-2
GOTERM_MF	Growth factor binding	2 FLT1, PDGFRB	3.1e-2
KEGG PATHWAY	MAPK signaling pathway	6 FGF1,FLT1,IGF1,IL1A,IL1B,PDGFRB	8.8e-5
KEGG PATHWAY	Pathways in cancer	7 ETS1, GNAS, PIM1, CDKN2B, FGF1, IGF1, PDGFRB	1.4e-4

KEGG PATHWAY	Rap1 signaling pathway	5 GNAS, FGF1, FLT1, IGF1, PDGFRB	3.4e-4
KEGG PATHWAY	Ras signaling pathway	5 ETS1, FGF1, FL1, IGF1, PDGFRB	5.3e-4

Category	**Term**	**Count**	**p-value**
KEGG PATHWAY	Ovarian steroidogenesis	3 GNAS, CYP1A1, IGF1	3.3e-3

The top 5 GO terms in the BP category are “Positive regulation of transcription from RNA polymerase II promoter”, “Positive regulation of gene expression”, “Positive regulation of cell migration”, “Positive regulation of cell proliferation” and “Positive regulation of transcription, DNA-templated” for all COVID-19 and TNBC. The top 5 GO terms in CC category are “Extracellular region”, “Extracellular space”, “Extracellular exosome”, “Cell surface” for all COVID-19 and TNBC. The top GO terms in MF category are “Integrin binding”, “Cytokine activity”, “Interleukin-1 receptor binding”, “Insulin-like growth factor receptor binding” and “Protein binding” for all COVID-19 and TNBC. The top 5 KEGG terms are “Pathways in cancer”, “Endocrine resistance”, “Breast cancer”, “Ovarian steroidogenesis” and “Proteoglycans in cancer for all COVID-19 and TNBC (Table 4.12).

Table 4.12. The top 5 GO terms (BP, MF, CC) and KEGG pathways for severe COVID and TNBC

Category	**Term**	**Count**	**p-value**
GOTERM_BP	Positive regulation of cell proliferation	10 ETS1,LIF,WNT10B,FGF1,IGF1,IL4,NOTCH1,NPM1,PTHLH ,PDGFRB	1.1e-8
GOTERM_BP	Positive regulation of cell migration	7 FGF1, IGF1, IL4, LAMB1, MMP9, NOTCH1, PDGFRB	6.7e-7
GOTERM_BP	Positive regulation of transcription from RNA polymerase II promoter	11 TOP2A,ETS1,LIF,LMO2,MYBL2,ESR1,FGF1,IGF1,IL4,NOTCH1 ,NPM1	7.8e-7
GOTERM_BP	Positive regulation of cell proliferation	7 ETS1, LIF, CDKN2B, NOTCH1, NPM1, PTHLH, PTGS2	1.7e-5
GOTERM_BP	Embryo implantation	4 LIF, MMP9, PTGS2, SPP1	1.9e-5
GOTERM_CC	Extracellular region	13 GNAS,LIF,TIMP3,WNT10B,FGF1,GUSB,IGF1,IL4,LAMB1, MMP9,NOTCH1,PTHLH,SPP1	1.2e-6
GOTERM_CC	Extracellular space	11 LIF,TIMP3,WNT10B, FGF1,GUSB,IGF1,IL4,LAMB1,MMP9, PTHLH,SPP1	3.1e-5
GOTERM_CC	Apical plasma membrane	4 CD44, GNAS, NOTCH1, PDGFRB	9.5e-3
GOTERM_CC	Extracellular exosome	7 CD44, GNAS, GUSB, LAMB1, MMP9, PTPRG, SPP1	3.8e-2

GOTERM_CC	Golgi apparatus	5 CD44, ESR1, PTHLH, PDGFRB, SPP1	4.1e-2
GOTERM_MF	Enzyme binding	6 TOP2A, CYP1A1,ESR1,NOTCH1,PDGFRB,PTGS2	1.1e-4
GOTERM_MF	Protein binding	24 CD44,TOP2A,ETS1,GNAS,LIF,LMO2,MYBL2,TIMP3,WNT10B, CDKN2B, CYP1A1,ESR1,FGF1,IGF1,IL4,LAMB1, MMP9, NOTCH1,NPM1,PTHLH,PDGFRB,PTGS2,PTPRG,SPP1	7.9e-4

Category	**Term**	**Count**	**p-value**
GOTERM_MF	Integrin binding	4 FGF1, IGF1, LAMB1, SPP1	1.1e-3
GOTERM_MF	Growth factor activity	4 LIF, FGF1, IGF1, IL4	1.2e-3
GOTERM_MF	Cytokine activity	4 LIF, WNT10B, IL4, SPP1	1.8e-3
KEGG PATHWAY	Pathways in cancer	13 ETS1,GNAS,WNT10B,CDKN2B,ESR1,FGF1,IGF1,IL4,LAMB1, MMP9,NOTCH1,PDGFRB,PTGS2	1.7e-9
KEGG PATHWAY	Endocrine resistance	5 GNAS, ESR1, IGF1, MMP9, NOTCH1	1.2e-4
KEGG PATHWAY	Proteoglycans in cancer	6 CD44, TIMP3, WNT10B, ESR1, IGF1, MMP9	1.7e-4
KEGG PATHWAY	Human papillomavirus infection	7 GNAS, WNT10B, LAMB1, NOTCH1, PDGFRB, PTGS2, SPP1	1.8e-4
KEGG PATHWAY	Ovarian steroidogenesis	4 GNAS, CYP1A1, IGF1, PTGS2	3.2e-4

The top 5 GO terms in the BP category are “Negative regulation of cholesterol storage”, “Memory”, “Regulation of small GTPase mediated signal transduction”, “Phospholipid homeostasis” and “Cardiac muscle tissue development” for all COVID-19 and ccRCC. The top 5 GO terms in the CC category are “Glutamatergic synapse”, “Bicellular tight junction”, “Cytoplasmic vesicle”, “Plasma membrane” for all COVID-19 and ccRCC. The top GO terms in MF category are “Integrin binding”, “Protein binding”, “Interleukin-1 receptor binding”, “Insulin-like growth factor receptor binding” and “Protein binding” for all COVID-19 and ccRCC. The top 5 KEGG terms are “Carbon metabolism”, “Pathways in cancer”, “Synaptic vesicle cycle”, “Rap1 signaling pathway” and “ Breast cancer” for all COVID-19 and ccRCC (Table 4.13).

Table 4.13. The top 5 GO terms (BP, MF, CC) and KEGG pathways for all COVID and ccRCC

Category	**Term**	**Count**	**p-value**
GOTERM_BP	Negative regulation of cholesterol storage	4 ABCA1, ABCG1, CES1, TREM2	9.0e-4
GOTERM_BP	Memory	8 PAK6, CSMD1, ADGRF1, FGF13, KLK8, PAK6, TREM2	1.1e-3
GOTERM_BP	Regulation of small GTPase mediated signal transduction	9 FDG2, ARHGAP22, ARHGAP26, ARHGEF3, STARD13, CHN1, ECT2, SIPA1L2, TRIO	1.6e-3
GOTERM_BP	Phospholipid homeostasis	4 ABCA1, ABCG1, FABP3, LIPG	3.4e-3

GOTERM_BP	Cardiac muscle tissue development	4 NPRL3, TBX2, ALDH1A2, RBP4	4.1e-3
GOTERM_CC	Glutamatergic synapse	18 RAC1, ARHGAP22, SH3GL2, SLITRK4, WNT7A, AP2M1, CAPS2, CDKL5, DRD1, GPM6A, IL1RAP, LPAR1, KCNJ2, PACSIN2, PRKCZ, PTPRD, TRIO	1.7e-3

Category	**Term**	**Count**	**p-value**
GOTERM_CC	Bicellular tight junction	9 ARHGAP17, ANK3, CCDC85C, ECT2, ILDR1, MPDZ, PRKCZ, SHROOM2	2.8e-3
GOTERM_CC	Cytoplasmic vesicle	14 RAC1, RHCG, RHOBTB3, AP2M1, ADGRF1, AZIN2, CAPS2, CAV2, COEO7, DYSF, GRIP1, JMY, MYO6, SLC1A3	6.7e-3
GOTERM_CC	Plasma membrane	120 ADAM30, ART1, ABCA1, ABCG1, ATP6V1D, CLEC2B, CD160, CD300LG, HELB, EPM2A,….	9.1e-3
GOTERM_CC	Cytoplasm	124 AKAP3, BNIPL, BARD1, PAK6, CHAC2, HELB, LIG1, EPM2A, ETS1, FTO, FGD2, GRK2, GTPBP6, ….	1.6e-2
GOTERM_MF	Protein binding	281 ARAF, AKAP3, ARFIP1, ABCA1, ABCG1, ATP6V1D, BNIPL, BCL2L14, BARD1, BBS10,…..	3.6e-4
GOTERM_MF	Phospholipid binding	9 ARFIP1, ABCG1, ARHGAP26, AMPH, DYSF, LPAR1, PLA2G7, PACSIN2, TREM2	2.7e-3
GOTERM_MF	GTPase activator activity	14 NPRL3, RASAL2, ARHGAP17, ARHGAP22, ARHGAP26, STARD13, TBC1D13, TBC1D4, TBC1D9B, CHN1, ECT2, RGS10, RGS14, SIPA1L2	5.6e-3
GOTERM_MF	4 iron, 4 sulfur cluster binding	5 NDUFS8, NDUFV1, ACO1, MOCS1, RTEL1	1.3e-2
GOTERM_MF	Sequence-specific DNA binding	14 ETS1, NFE2L2, PBX4, RORB, TBX2, ATF3, ESRRB, FOXA3, IRX2, NR1D2, PGBD1, RAG2, ZEB2, ZBTB14	1.9e-2
KEGG PATHWAY	Carbon metabolism	8 ACO1, ACOX1, GOT2, IDH3A, OGDHL, PGP, PCCA, TKFC	1.0e-2
KEGG PATHWAY	Pathways in cancer	20 ARAF, ETS1, GNGT2, NFE2L2, RLAB, RAC1, WNT7A, ADCY3, COL4A5, CDKN2B, EDNRA, FGF1, FGF9, FZD10, GADD45G, HES5, HEY1, KNG1, LPAR1, MMP9	1.4e-2
KEGG PATHWAY	Synaptic vesicle cycle	6 ATP6V1D, TCIRG1, AP2M1, CPLX4, SLC1A3, STX1B	2.3e-2
KEGG PATHWAY	Rap1 signaling pathway	10 RALB, RAC1, ADCY3, FGF1, FGF9, LPAR1, PRKCZ, PRKD1, RGS14, SIPA1L2	3.1.e-2
KEGG PATHWAY	Breast cancer	8 ARAF, WNT7A, FGF1, FGF9, FZD10, GADD45G, HES5, HEY1	3.4e-2

The Top 5 GO terms in the BP category are “Neuron migration”, “Regulation of small GTPase mediated signal transduction”, “Neuron projection extension”, “Regulation of resting membrane potential” and “Regulation of pH” for severe COVID-19 and ccRCC. The top 5 the GO terms in the CC category are “Bicellular tight junction”, “Cytoplasmic vesicle”, “Basolateral plasma membrane”, “Plasma membrane” for severe COVID-19, and ccRCC. The top GO terms in MF category are “Protein binding”, “GTPase activator activity”, “Interleukin-1 receptor binding”, “NAD+ nucleosidase activity” and “Protein binding” for severe COVID-19 and ccRCC. The top 5 KEGG terms are “Breast cancer”, “2-oxocarboxylic acid metabolism”, “Axon guidance”, “Renal cell carcinoma” and “Pathways in cancer” for severe COVID-19 and ccRCC (Table 4.14).

Table 4.14. The top 5 GO terms (BP, MF, CC) and KEGG pathways for severe COVID and ccRCC

Category	Term	Count	p-value
GOTERM_BP	Neuron migration	14 RAC1, SDCCAG8, ASPM, COL3A1, CDKL5, ELP3, FGF13, GPM6A, MEF2C, NDNF, NDE1, PEX13, TRIM46, TUBB2B	1.9e-4
GOTERM_BP	Regulation of small GTPase mediated signal transduction	13 FGD2, ARHGAP11B, ARHGAP22, ARHGAP26, ARHGEF10, ARHGEF3, STARD13, CHN1,E CT2, ITSN1, PREX1, SIPA1L2, TRIO	6.1e-4
GOTERM_BP	Neuron projection extension	6 PAK6, EMX1, FLRT3, ITGA4, PAK6, PRKCZ	1.2e-3
GOTERM_BP	Regulation of pH	5 ATP12AA, RHCG, SLC26A4, SLC9A5, SLC9A9	1.6e-3
GOTERM_BP	Regulation of resting membrane potential	4 KCNJ10, KCJ2, KCNK5, TREM2	3.7e-3
GOTERM_CC	Bicellular tight junction	14 MARVELD3, ARHGAP17, ANK3, CGNL1, CLDN7, CCDC85C, EPCAM, ECT2, ILDR1, MPDZ, PRKCZ, SHROOM2, TJP2, USP53	3.8e-4
GOTERM_CC	Cytoplasmic vesicle	24 ATP2C2, BICD1, BTK, GIPC1, MARVELD3, RAB25, RAC1, RHCG, RHOBTB3, AP2M1, ADD2, ADGRF1, CAPS2, CAV2, DYSF, LGALS8, GRIP1, LGALS8, GRIP1, JMY, MYO6, PDGFRB, SLC1A3, SLC9A4, SPRED1, UBQLN4	4.6e-4
GOTERM_CC	Basolateral plasma membrane	19 ABCC5, ATP12A, ATP2C2, CD300LG, RHCG, ANK3, AQPA, AQP2, AQP9, CDH16, CA9, CLDN7, EPCAM, KCNJ10, SLC16A3, SLC4A1, SLC4A9, SLC9A4, UMOD	1.4e-3
GOTERM_CC	Plasma membrane	211 XRN1, ADAM30, ART1, ART4, ABCA1, ABCC5, ATP6V1D, ATP12A, ATP2C2, BTK, CLEC2B, CD160	1.9e-3
GOTERM_CC	Integral component of plasma membrane	65 ABCA1, ABCC5, CLEC2B, CD1C, CD2, CD84, CD9, GPR34, RHCG, ADCY3, ADGRD1, AQP1, AQP2, AQP9	9.5e-3
GOTERM_MF	Protein binding	490 XRN1, MTRR, ARAF, AKAP3, ABAI3, ARFIP1, AKT3, ALG3, ABCA1, ATP6V1D, ATP2C2, BCLAF1, BNIP3L	2.5e-5
GOTERM_MF	GTPase activator activity	23 ACAP2, NPRL3, RASAL2, RAP1GDS1, ARHGAP11B, ARHGAP17, ARHGAP22, ARHGAP26, ARHGAP42, STARD13	6.4e-4
GOTERM_MF	NAD+ nucleosidase activity	6 IL1RAP, IL1RL1, PIK3AP1, TLR1, TLR6, TLR8	2.2e-3
GOTERM_MF	Receptor binding	26 ABCA1, CD160, CD2, GIPC1, HHLA2, NCK1, RSPO3, SMARCD3, WNT7A, ANGPTL2, APLN, BEX5, BTN3A2, CALCA, FZD1, GUSB, KNG1, MFAP4, PIK3AP1, PDGFRB, PLXNC1, PTPRD, RARRES2, SEMA3G, STX1B, TLR6	4.9e-3
GOTERM_MF	4 iron, 4 sulfur cluster binding	7 NDUFS8, NDUFV1, ACO1, ELP3, MOCS1, RSAD2, RTEL1	5.1e-3
KEGG PATHWAY	Breast cancer	13 ARAF, AKT3, WNT7A, DLL4, ESR1, FGF1, FGF9, FZD1, FZD10, GADD45G, HEY1, HEYL, NCOA1	1.1e-2
KEGG PATHWAY	2-oxocarboxylic acid metabolism	4 ACO1, ACY1, GOT2, IDH3A	3.5e-2

KEGG PATHWAY	Axon guidance	13 PAK6, NCK1, RAC1, NFATC2, PAK6, PLXNA2, PLXNB1, PLXNC1, PRKCZ, SEMA3B, SEMA3G, SEMA5A, UNC5B	4.8e-2
KEGG PATHWAY	Renal cell carcinoma	7 ARAF, AKT3, PAK6, ETS1, RAC1, FLCN, PAK6	4.9e-2

Category	**Term**	**Count**	**p-value**
KEGG PATHWAY	Pathways in cancer	29 ARAF, AKT3, CKS1B, ETS1, GNGT2, NFE2L2, RALB, RAC1, WNT7A, ADCY3, COL4A5, CUL1, CDKN12, DLL4, EDNRA, ESR1, FGF1, FGF9, FZD1, FZD10, GADD45G, HEYL, KNG1, LAMB3, LPAR1, MMP9, NCOA1, PDGFRB	5.5e-2

The top 5 GO terms in the BP category are “Regulation of innate immune response”, “Memory”, “Response to virus”, “Defense response to virus” and “Positive regulation of interferon-beta production” for mild COVID-19 and ccRCC. The top 5 the GO terms in CC category are “Cytoplasm”, “Cell projection”, “Cytoplasmic vesicle”, “Cytosol” for all COVID-19 and TNBC. The top GO terms in MF category are “Protein binding”, “Lipase activity”, “Lipid binding”, “4 iron, 4 sulfur cluster binding” and “Phospholipid binding” for mild COVID-19 and ccRCC. The top 5 KEGG terms are “Axon guidance”, “Metabolic pathways”, “Steroid biosynthesis”, “Ras signaling pathway” and “ Proteoglycans in cancer for mild COVID-19 and ccRCC (Table 4.15).

Table 4.15. The top 5 GO terms (BP, MF, CC) and KEGG pathways for mild COVID and ccRCC

Category	**Term**	**Count**	**p-value**
GOTERM_BP	Regulation of innate immune response	5 NFE2L2, IRF1, RNF135, TREM2, TKFC	1.8e-4
GOTERM_BP	Memory	8 PAK6, CSMD1, ADGRF1, DRD1, FGF13, KLK8, PAK6, TREM2	2.1e-4
GOTERM_BP	Response to virus	8 OAS2, OAS3, CYP1A1, IFIT1, IFIT2, IFIT3, LAMTOR5, TLR8	8.7e-4
GOTERM_BP	Defense response to virus	11 OAS2, OAS3, AGBL5, APOBEC3B, APOBEC3G, IFI44L, IFIT1, IFIT2, IFIT3, IRF1, TLR8	1.6e-3
GOTERM_BP	Positive regulation of interferon-beta production	5 OAS2, OAS3, IRF1, RNF135, TLR8	2.5e-3
GOTERM_CC	Cytoplasm	108 OAS2, OAS3, PDPK1, AKAP3, AGBL5, BMP2K, BARD1, PAK6, DLGAP5, HELB, ETS1, FCHO2, GRK2, GMDS	2.0e-4
GOTERM_CC	Cell projection	10 PDPK1, RAC1, ARHGEF5, RHOBTB3, SH3GL2, LPXN, LAPTMB4, RHOD, RTN4RL1, TRIO	1.1e-3
GOTERM_CC	Cytoplasmic vesicle	12 PDPK1, RAC1, RHOBTB3, AP2M1, ADGRF1, AZIN2, CAPS2, CORO7, DYSF, GRIP1, PDGFRB, RHOD	5.9e-3
GOTERM_CC	Cytosol	97 OAS2, OAS3, PDPK1, AGBL5, ATP6V1D, DLGAP5, FBXL6, FCHO2, GRK2, GMDS, NDUFV1	9.0e-3
GOTERM_CC	Nucleus	103 PDPK1, AKAP3, AGBL5, BMP2K, BARD1, DLGAP5, HELB, ETS1, FBXL6	1.3e-2

GOTERM_MF	Protein binding	209 OAS2, OAS3, PDPK1, AKAP3, ABCG1, ATP6V1D, BARD1, CLEC2B, CD160, CD300LG, CD70	1.7e-2
GOTERM_MF	Lipase activity	3 LIPA, LIPG, PLA1A	2.7e-2
GOTERM_MF	Lipid binding	8 ARHGEF5, SH3GL2, STARD13, AP2M1, CAPS2, FABP3, PLEJHA2, TREM2	3.0e-2
Category	**Term**	**Count**	**p-value**
GOTERM_MF	4 iron, 4 sulfur cluster binding	4 NDUFV1, AO1, MOCS1, RTEL1	3.2e-2
GOTERM_MF	Phospholipid binding	6 ABCG1, ARHGAP26, AMPH, DYSF, PLA2G7, TREM2	3.6e-2
KEGG PATHWAY	Axon guidance	8 PDPK1, PAK6, RAC1, PAK6, RHOD, SEMA3B, SEMA5A, UNC5B	3.5e-2
KEGG PATHWAY	Metabolic pathways	36 BDH1, ATP6V1D, GMDS, ASAH1, NDUFV1, NDUFA4L2, SETMAZ, ST3GAL4, TCIRG1, ACO1, ADH1C, AZIN2	3.6e-2
KEGG PATHWAY	Steroid biosynthesis	3 CYP27B1, LIPA, TM7SF2	4.4e-2
KEGG PATHWAY	Ras signaling pathway	9 PAK6, ETS1, GNGT2, RASAL2, RAC1, FGF1, PAK6, PLA1A, PDGFRB	4.6e-2
KEGG PATHWAY	mTOR signaling pathway	7 PDPK1, ATP6VD1, WNT7A, EIF4E1B, FZD10, LAMTOR5, RPS6KA6	4.9e-2

The top 5 GO terms in the BP category are “Tetrahydafolate interconversion”, “Negative regulation of ubiquitin protein ligase activity”, “Cytoplasmic translation”, “Translation” and “Negative regulation of activin receptor signaling pathway” for mild COVID-19 and breast cancer. The top 5 GO terms in CC category are “Cytosolic ribosome”, “Cytosol”, “Extracellular region”, “Cytosolic large ribosomal subunit” and “Cytoplasm” for all COVID-19 and breast cancer. The top GO terms in MF category are “Ubiquitin ligase inhibitor activity”, “Metal ion binding”, “Serine-type endopeptidase activity”, “Structural constituent of ribosome” and “Oxygen transporter activity” for mild COVID-19 and breast cancer. The top 5 KEGG terms are “One carbon pool by folate”, “Coronavirus disease- COVID-19”, “Ribosome”, “Amoebiasis” and “Focal adhesion” for mild COVID-19 and breast cancer (Table 4.16).

Table 4.16. The top 5 GO terms (BP, MF, CC) and KEGG pathways for mild COVID-19 and breast cancer

Category	**Term**	**Count**	**p-value**
GOTERM_BP	Tetrahydrofolate interconversion	4 MTHFD1L, MTHFD2, MTHFR, TYMS	1.7e-4
GOTERM_BP	Negative regulation of ubiquitin protein ligase activity	4 RPL11, RPL23, RPS20, USP44	3.9e-4
GOTERM_BP	Cytoplasmic translation	7 RPL11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23	5.9e-4

GOTERM_BP	Translation	9 GUF1, RPL11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23, RPS4Y1	4.1e-3
GOTERM_BP	Negative regulation of activin receptor signaling pathway	3 CER1, C3CER1, FST	4.5e-3

Category	**Term**	**Count**	**p-value**
GOTERM_CC	Cytosolic ribosome	7 RPLS11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23	2.4e-4
GOTERM_CC	Cytosol	87 OAS2, NT5DC3, AKAP7, BACH2, COPE, EPHB6, ERRFI1, FBXL13, FBXL6, FCHO2, FXR2	7.1e-4
GOTERM_CC	Extracellular region	39 ADAMTS6, CXCL1, CXCL3, C1QTNF9, COMMD3, EGFL8, EPHB6, F10, TIPM3, TNFSF12	3.6e-3
GOTERM_CC	Cytosolic large ribosomal subunit	5 FXR2, RPL11, RPL13A, RPL19, RPL23	4.7e-3
GOTERM_CC	Cytoplasm	82 OAS2, TOP2A, ERRFI1, FAM20A, FCHO2, FXR2, GPR88, GTPBP6, LARP6, NFE2L2, NEK1, NEK2	1.1e-2
GOTERM_MF	Ubiquitin ligase inhibitor activity	3 RPL11, RPL23, RPS20	5.0e-3
GOTERM_MF	Metal ion binding	48 OAS2, NT5DC3, ADATTS6, COMMD3, TOP2A, GTPBP6, KLF8, LONRF1, NEK1, NEK2, NEK3, PDLIM2, PHF3, PHF7	5.1e-3
GOTERM_MF	Serine-type endopeptidase activity	8 F10, CTSG, CTSS, F10, IMMP2L, MBTPS1, TMPRSS2, TMPRSS2	8.1e-3
GOTERM_MF	Structural constituent of ribosome	8 RPL11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23, RPS4Y1	8.5e-3
GOTERM_MF	Oxygen transporter activity	3 HBB, HBD, HBD	1.6e-2
KEGG PATHWAY	One carbon pool by folate	4 MTHFD1L, MTHFD2, MTHFR, TYMS	2.9e-3
KEGG PATHWAY	Coronavirus disease- COVID-19	10 OAS2, RPL11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23, RPS4Y1, TMPRSS2	6.8e-3
KEGG PATHWAY	Ribosome	8 RPL11, RPL13A, RPL19, RPL23, RPS17, RPS20, RPS23, RPS4Y1	1.1e-2
KEGG PATHWAY	Amoebiasis	6 CXCL1, CXCL3, CTSG, COL4A5, PRDX1, PLCB1	1.7e-2
KEGG PATHWAY	Focal adhesion	8 RAC1, ACTB, COL4A5, FLT1, IGF1, PXN, PDGFRB, PPP1CA	2.8e-2

The top 5 GO terms in the BP category are “Angiogenesis”, “Regulation of G-protein coupled receptor protein signaling pathway”, “Outflow tract morphogenesis”, “Cytoplasmic translation” and “Cell adhesion” for severe COVID-19 and breast cancer. The top 5 the GO terms in CC category are “Extracellular space”, “Cytosol”, “Plasma membrane”, “Cytosol” for all COVID-19 and breast cancer. The top the GO terms in MF category are “Protein binding”, “Lipase activity”, “Lipid binding”, “4 iron, 4 sulfur cluster binding” and “Phospholipid binding” for severe COVID-19 and breast cancer. The top 5 KEGG terms are “Axon guidance”, “Metabolic pathways”,

"Steroid biosynthesis", "Ras signaling pathway" and " Proteoglycans in cancer for severe COVID-19 and breast cancer (Table 4.17).

Table 4.17. The top 5 GO terms (BP, MF, CC) and KEGG pathways for severe COVID and breast cancer

Category	Term	Count	p-value
GOTERM_BP	Angiogenesis	19 EGFL7, ARHGAP22, SOX17, TBX1, WNT7A, BMPR1A, CALD1, DLL4, EDN2, FGF1, FGF9, FZD5, HEY1, JAM3, MCAM, OVOL2, PDGFRB, PTGS2, RAMP1	1.1e-4
GOTERM_BP	Regulation of G-protein coupled receptor protein signaling pathway	8 GNG4, TULP3, PLCB1, RAMP1, RGS10, RGS3, RGS5, RGS6	2.5e-4
GOTERM_BP	Outflow tract morphogenesis	8 EYA1, SOX17, TBX1, TBX3, BMPR1A, DHRS3, FZD1, MEF2C	3.7e-4
GOTERM_BP	Cytoplasmic translation	10 RPL11, RPL19, RPL23, RPL35A, RPL7A, RPS16, RPS17, RPS20, RPS23, SARS1	6.2e-4
GOTERM_BP	Cell adhesion	29 CD164, EGFL7, RAC1, AMELX, CNTN3, CNTNAP3, FEZ1, FOLR2, ITGA4, ICAM2, JAM3, LAMA1	8.7e-4
GOTERM_CC	Extracellular space	81 CXCL14, C1QTNF1, C1QTNF3, CD1C, EGFL7, FCGR3A, IGFL2, S100A14, S100B, SPARCL1, TIPM3	2.5e-5
GOTERM_CC	Cytosol	183 NT5DC3, ATIC, AKAP7, ARL4C, BACH2,BBS1, CEACAM7, COPE, COPZ2, DISC1, EPHB6, EMP2A, ERRFI1, FBXL13	1.2e-4
GOTERM_CC	Plasma membrane	175 ATIC, AKAP7, ADAM29, ARL4C, ABCA1, CLEC1A, CLEC2B, C1QTNF1, CD164, CD1C, CD2, CD300LG, CEACAM7	3.1e-4
GOTERM_CC	Extracellular region	81 ADAMTS6, C1QTNF1, CD164, CD2, CEACAM7, COMMD3, EGFL7, EPHB6, IFI30, IGFL2, F10, RSPO3	4.0e-4
GOTERM_CC	Cytosolic ribosome	9 RPL11, RPL19, RPL23, RPL35A, RPL7A, RPS16, RPS17, RPS20, RPS23	7.9e-4
Category	**Term**	**Count**	**p-value**
GOTERM_MF	Metal ion binding	103 NT5D3, ADAMTS6, COMMD3, TOP2A, EYA1, FTO, GNAZ, GLIS3, GTPBP6, ISL2, KLF8, LMO2	3.7e-4
GOTERM_MF	Transcriptional repressor activity, RNA polymerase II transcription regulatory region sequence-specific binding	382 AKAP7, ARL4C, ABCA1,BCAR3, BNIP3L, BACH2, BBS1, CXCL14, CLEC14A, CLEC1A, CLEC2B	1.1e-3
GOTERM_MF	Oxygen transporter activity	20 BACH2, GLIS3, KLF8, NFE2L3, TBX15, TBX3, ZFP37, ETF3, DACH1, HEY1, NFATC3, NR2C1, OVOL2, PEG3, ZBTB20, ZNF248, ZNF281, ZNF436, ZNF529, ZNF559	2.6e-3
GOTERM_MF	Wnt-protein activity	4 CYGB, HBB, HBD, HBD	9.0e-3
GOTERM_MF	Heparan sulfate proteoglycan binding	5 FAZD1, FZD10, FZD5, RECK, SFRP4	1.1e-2

KEGG PATHWAY	Focal adhesion	16 RAC1, ACTB, CAV2, COL4A5, FLNC, IGF1, ITGA4, LAMA1, LAMB1, LAMB3, PARVA, PDGFRB, PPP1CA, SPP1, THBS4, VEGFC	1.6e-3
KEGG PATHWAY	Proteoglycans in cancer	16 RAC1, TIMP3, WNT7A, ACTB, CAV2, ESR1, EIF4B, FLNC, FZD1, FZD10, FZD5, HPSE2, IGF1, MMP9, MRAS, PPP1CA	2.0e-3
KEGG PATHWAY	Renin secretion	8 AQP1, EDN2, EDN3, EDNRA, PLCB1, KCNJ2, PTGER4, PPP3CC	5.7e-3
KEGG PATHWAY	Pathways in cancer	28 CKS1B, GNG4, NFE2L2, RAC1, WNT7A, WNT7A, ADCY3, COL4A5, DLL4, EDNRA, ESR1, FGF1	8.8e-3
Category	**Term**	**Count**	**p-value**
KEGG PATHWAY	Fluid shear stress and atherosclerosis	11 NFE2L2, RAC1, ACTB, BMPR1A, CAV2, GSTT1, IL1R1, MMP9, MAP2K4, MEF2C, THBD	1.2e-2

The top 5 GO terms in the BP category are “Regulation of G-protein coupled receptor protein signaling pathway”, “Embryonic camera-type eye development”, “Canonical Wnt signaling pathway”, “Negative regulation of ubiquitin protein ligase activity” and “Cell adhesion” for all COVID-19 and breast cancer. The top 5 GO terms in CC category are “Extracellular region”, “Extracellular space”, “Cytosol”, “Extracellular exosome” for all COVID-19 and breast cancer. The top GO terms in MF category are “Heparan sulfate proteoglycan binding”, “Transcriptional repressor activity, RNA polymerase II transcription regulatory region sequence-specific binding”, “Ubiquitin ligase inhibitor activity”, “GTPase activator activity” and “Metalloendopeptidase activity” for mild COVID-19 and breast cancer. The top 5 KEGG terms are “Proteoglycans in cancer”, “Renin secretion”, “Vascular smooth muscle contraction”, “Focal adhesion” and “Wnt signaling pathway” for all COVID-19 and breast cancer (Table 4.18).

Table 4.18. The top 5 GO terms (BP, MF, CC) and KEGG pathways for all COVID and breast cancer

Category	**Term**	**Count**	**p-value**
GOTERM_BP	Regulation of G-protein coupled receptor protein signaling pathway	7 GNG4, TULP3, PLCB1, RAPM1, RGS10, RGS3, RGS6	9.2e-5
GOTERM_BP	Embryonic camera-type eye development	4 TULP3, WDR19, ALDH1A2, ALDH1A3	7.2e-4
GOTERM_BP	Canonical Wnt signaling pathway	8 DISC1, RSPO3, WNT7A, EDNRA, FGF9, FZD10, RECK, SFRP4	8.7e-4
GOTERM_BP	Negative regulation of ubiquitin protein ligase activity	4 RPL11, RPL23, RPS20, USP44	9.3e-4
GOTERM_BP	Cell adhesion	20 RAC1, AMELX, CNTAP3, DPP4, FOLR2, ICAM2, LAMA1, LPXN, MFAP4, NLGN3	1.1e-3
GOTERM_CC	Extracellular region	55 ADAMTS6, C1QTNF1, C1QTNF6, COMMD3, EPHB6, IGFFL2, F10, RSPO3, S100B, SPARCL1	1.3e-4

GOTERM_CC	Extracellular space	50 CXCL14, C1QTNF1, FAM20A, FCGR3A, IGFL2, S100B, SPARCL1, TIMP3, TIMP4, ULBP2	3.8e-4
GOTERM_CC	Cytosol	112 NT5DC3, ATIC, AKAP7, BACH2, BBS1, COPE, DISC1, E2F8, EPHB6, EPM2A, ERRFI1, FBXL13, FBXL6	6.5e-4
GOTERM_CC	Cytosolic ribosome	7 RPL11, RPL19, RPL23, RPL35A, RPS17, RPS20, RPS23	1.1e-3
GOTERM_CC	Extracellular exosome	51 ATIC, FAM20A, FCGR3A, GNG4, RAC1, ST3GAL1, STEAP4, TNFRSF8, WNT7A, ACO1, ACTB, ACTG2	3.6e-3

Category	**Term**	**Count**	**p-value**
GOTERM_MF	Heparan sulfate proteoglycan binding	4 CFH, FST, HPSE2, SEMA5A	3.3e-3
GOTERM_MF	Transcriptional repressor activity, RNA polymerase II transcription regulatory region sequence-specific binding	14 BACH2, E2F8, KLF8, ZFP37, ATF3, HEY1, NFATC3, NR1D2, NR2C1, PEG3, TFEC, ZBTB20, ZNF281, Z F436	3.3e-3
GOTERM_MF	Ubiquitin ligase inhibitor activity	3 RPL11, RPL23, RPS20	8.6e-3
GOTERM_MF	GTPase activator activity	11 ERRFI1, IQGAP3, ARHGAP22, STARD13, TBC1D12, TBC1D13, ECT2, PLCB1, RGS10, RGS3, RGS6	1.9e-2
GOTERM_MF	Metalloendopeptidase activity	3 TIMP3, TIMP4, RECK	2.7e-2
KEGG PATHWAY	Proteoglycans in cancer	12 RAC1, TIMP3, WNT7A, ACTB, CAV2, FZD10, HPSE2, IGF1, MMP9, MRAS, PXN, PPP1CA	8.6e-4
KEGG PATHWAY	Renin secretion	6 EDN2, EDN3, EDNRA, KCJ2, PTGER4	6.e-3
KEGG PATHWAY	Vascular smooth muscle contraction	8 ACTG2, ADCY3, EDN2, EDN3, EDNRA, PLCB1, PPP1CA, RAMP2	8.7e-3
KEGG PATHWAY	Focal adhesion	10 RAC1, ACTB, CAV2, COL4A5, IGF1, LAMA1, PARVA, PXN, PPP1CA, SPP1	8.8e-3
KEGG PATHWAY	Wnt signaling pathway	9 RSPO3, RAC1, SOX17, WNT7A, CER1, FZD10, NFAT3, PLCB1, SFRP4	9.7e-3

4.4. Identification of transcription factors and miRNAs regulating the hub genes

To discover the regulatory networks and mechanisms of the hub genes, TFs, DEGs, and finally miRNAs were analyzed. Hence, the miRTarBase and JASPAR databases are used to search for miRNAs and TFs that influence top 5 hub genes at thelevels of posttranscriptional and transcriptional, respectively. The miRNAs and TFs that target hub genes are discovered in each group (Table 4.19, Table 4.20, Table 4.21, Table 4.22, Table 4.23, Table 4.24, Table 4.25, Table 4.26 and Table 4.27).

Table 4.19. Transcription factors of the hub genes in all COVID-19 and TNBC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	KLF5	Kruppel-like factor 5 (intestinal)	3	1.42e-07	3.7e-06

2	JUN	Jun proto-oncogene	4	6.31e-06	7.32e-05
3	SIRT1	Sirtuin 1	3	8.45e-06	7.32e-05
4	EP300	(E1A) binding protein (p300)	3	1.35e-05	8.77e-05
5	ELF3	E74-like factor three (3) (epithelial-specific,ets domain transcription factor)	2	2.42e-05	0.000126
6	RELA	v-rel reticuloendotheliosis homozygous oncolytic virus A (avian)	4	9.92e-05	0.000372
#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
7	NFKB1	kappa nuclear factor light polypeptide gene enhancer at B cells 1	4	0.000102	0.000372
8	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	2	0.000114	0.000372
9	AHR	aryl hydrocarbon receptor	2	0.000154	0.000445
10	RARA	retinoic acid receptor, alpha	2	0.000217	0.000563
11	DNMT1	DNA (cytosine-5-)-methyltransferase 1	2	0.000309	0.00073
12	NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	2	0.000466	0.000958
13	PPARA	peroxisome proliferator-activated receptor alpha	2	0.00049	0.000958
14	KLF4	Kruppel-like factor 4 (gut)	2	0.000516	0.000958
15	SP1	Sp1 transcription factor	4	0.000553	0.000959
16	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	2	0.000839	0.00136
17	BRCA1	breast cancer 1, early onset	2	0.00105	0.00143
18	FOS	FBJ murine osteosarcoma viral oncogene homolog	2	0.00105	0.00143
19	WT1	Wilms tumor 1	2	0.00105	0.00143
20	PPARG	peroxisome proliferator-activated receptor gamma	2	0.0014	0.00182
21	HDAC1	histone deacetylase 1	2	0.00162	0.00191
22	TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	2	0.00162	0.00191
23	STAT1	signal transducer and activator of transcription 1, 91kDa	2	0.00226	0.00255
24	YY1	YY1 transcription factor	2	0.00264	0.00286
25	E2F1	E2F transcription factor 1	2	0.00563	0.00585
26	STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	2	0.0063	0.0063

Table 4.20. Transcription factors of the hub genes in mild COVID-19 and TNBC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	E2F1	E2F transcription factor 1	4	5.38e-06	0.000118
2	ESR1	estrogen receptor 1	3	4.1e-05	0.000304
3	STAT4	signal transducer and activator of transcription 4	2	4.18e-05	0.000304
4	STAT1	signal transducer and activator of transcription 1, 91kDa	3	5.53e-05	0.000304

5	RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	4	0.000128	0.000482
6	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	4	0.000131	0.000482
7	AHR	aryl hydrocarbon receptor	2	0.000175	0.000549
8	ATF1	activating transcription factor 1	2	0.000208	0.00055
9	RARA	retinoic acid receptor, alpha	2	0.000245	0.00055
10	STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	3	0.000263	0.00055
11	JUN	jun proto-oncogene	3	0.000302	0.00055
12	YBX1	Y box binding protein 1	2	0.000327	0.00055
13	DNMT1	DNA (cytosine-5-)-methyltransferase 1	2	0.00035	0.00055
14	RB1	retinoblastoma 1	2	0.00035	0.00055
15	TP53	tumor protein p53	3	0.000401	0.000588
16	KLF4	Kruppel-like factor 4 (gut)	2	0.000584	0.000803
17	EP300	E1A binding protein p300	2	0.00114	0.00137
18	BRCA1	breast cancer 1, early onset	2	0.00118	0.00137
19	WT1	Wilms tumor 1	2	0.00118	0.00137
20	USF1	upstream transcription factor 1	2	0.00154	0.00169
21	YY1	YY1 transcription factor	2	0.00298	0.00313
22	SP1	Sp1 transcription factor	3	0.00814	0.00814

Table 4.21. Transcription factors of the hub genes in severe COVID-19 and TNBC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	SP1	Sp1 transcription factor	9	5.05e-09	2.53e-07
2	HDAC1	histone deacetylase 1	5	3.27e-08	8.18e-07
3	ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	3	1.72e-07	2.86e-06
4	KLF5	Kruppel-like factor 5 (intestinal)	3	5.82e-07	7.28e-06
5	EP300	E1A binding protein p300	4	8.39e-07	8.39e-06
6	TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	4	2.19e-06	1.83e-05
7	DNMT1	DNA (cytosine-5-)-methyltransferase 1	3	9.01e-06	6.43e-05
8	PPARA	peroxisome proliferator-activated receptor alpha	3	1.82e-05	0.000114
9	IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	2	2.52e-05	0.00014
10	NCOR1	nuclear receptor corepressor 1	2	3.52e-05	0.000175
11	RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	5	4.08e-05	0.000175

12	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	5	4.21e-05	0.000175
13	STAT5B	signal transducer and activator of transcription 5B	2	4.7e-05	0.000181
14	BRCA1	breast cancer 1, early onset	3	5.73e-05	0.000201
15	EGR2	early growth response 2	2	6.03e-05	0.000201
16	PPARG	peroxisome proliferator-activated receptor gamma	3	8.89e-05	0.000278
17	STAT5A	signal transducer and activator of transcription 5A	2	0.00013	0.000383
18	SNAI2	snail homolog 2 (Drosophila)	2	0.000152	0.000422
#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
19	ING4	inhibitor of growth family, member 4	2	0.000175	0.000438
20	JUNB	jun B proto-oncogene	2	0.000175	0.000438
21	HMGA1	high mobility group AT-hook 1	2	0.000226	0.000539
22	ARNT	aryl hydrocarbon receptor nuclear translocator	2	0.000316	0.000717
23	CTNNB1	catenin (cadherin-associated protein), beta 1, 88kDa	2	0.000383	0.000798
24	ETV4	ets variant 4	2	0.000383	0.000798
25	MTA1	metastasis associated 1	2	0.000457	0.000914
26	CREBBP	CREB binding protein	2	0.000496	0.000919
27	PGR	progesterone receptor	2	0.000496	0.000919
28	RARA	retinoic acid receptor, alpha	2	0.000537	0.000959
29	CIITA	class II, major histocompatibility complex, transactivator	2	0.000765	0.00128
30	SMAD3	SMAD family member 3	2	0.000765	0.00128
31	STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	3	0.00085	0.00137
32	TWIST1	twist basic helix-loop-helix transcription factor 1	2	0.000976	0.00148
33	JUN	jun proto-oncogene	3	0.000977	0.00148
34	STAT6	signal transducer and activator of transcription 6, interleukin-4 induced	2	0.00103	0.00152
35	GATA3	GATA binding protein 3	2	0.00115	0.00155
36	NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	2	0.00115	0.00155
37	POU2F1	POU class 2 homeobox 1	2	0.00115	0.00155
38	MYCN	v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	2	0.00161	0.00212
39	SIRT1	sirtuin 1	2	0.00183	0.00235
40	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	2	0.00206	0.00258
41	FOS	FBJ murine osteosarcoma viral oncogene homolog	2	0.00257	0.00306
42	WT1	Wilms tumor 1	2	0.00257	0.00306
43	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	2	0.00285	0.00331
44	USF1	upstream transcription factor 1	2	0.00333	0.00378
45	ESR1	estrogen receptor 1	2	0.00452	0.00503

46	ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)	2	0.00488	0.0053
47	STAT1	signal transducer and activator of transcription 1, 91kDa	2	0.0055	0.00585
48	YY1	YY1 transcription factor	2	0.00642	0.00669
49	E2F1	E2F transcription factor 1	2	0.0135	0.0138
50	TP53	tumor protein p53	2	0.0198	0.0198

Table 4.22. Transcription factors of the hub genes in all COVID-19 and ccRCC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	KLF5	Kruppel-like factor 5 (intestinal)	4	0.000115	0.00495
2	NR1H3	nuclear receptor subfamily 1, group H, member 3	2	0.00417	0.0897
3	CUX1	cut-like homeobox 1	2	0.0112	0.135
4	RARA	retinoic acid receptor, alpha	3	0.0164	0.135
5	SPDEF	SAM pointed domain containing ets transcription factor	2	0.0175	0.135
6	CIITA	class II, major histocompatibility complex, transactivator	3	0.0264	0.135
7	DNMT1	DNA (cytosine-5-)-methyltransferase 1	3	0.0264	0.135
8	PTTG1	pituitary tumor-transforming 1	2	0.0382	0.135
9	RFX1	regulatory factor X, 1 (influences HLA class II expression)	2	0.0382	0.135
10	RFXANK	regulatory factor X-associated ankyrin-containing protein	2	0.0382	0.135
11	RFXAP	regulatory factor X-associated protein	2	0.0382	0.135
12	USF1	upstream transcription factor 1	4	0.0468	0.135
13	PPARA	peroxisome proliferator-activated receptor alpha	3	0.0475	0.135
14	BCL6	B-cell CLL/lymphoma 6	2	0.0481	0.135
15	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	2	0.0481	0.135

Table 4.23. Transcription factors of the hub genes in mild COVID-19 and ccRCC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	KLF5	Kruppel-like factor 5 (intestinal)	3	0.000991	0.027
2	RFX1	regulatory factor X, 1 (influences HLA class II expression)	3	0.00154	0.027

3	RARA	retinoic acid receptor, alpha	3	0.00775	0.0737
4	YBX1	Y box binding protein 1	3	0.0115	0.0737
5	STAT2	signal transducer and activator of transcription 2, 113kDa	2	0.0124	0.0737
6	CIITA	class II, major histocompatibility complex, transactivator	3	0.0126	0.0737
7	USF1	upstream transcription factor 1	4	0.0194	0.0756
8	PTTG1	pituitary tumor-transforming 1	2	0.0228	0.0756
9	RFXANK	regulatory factor X-associated ankyrin-containing protein	2	0.0228	0.0756
10	RFXAP	regulatory factor X-associated protein	2	0.0228	0.0756
#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
11	KLF4	Kruppel-like factor 4 (gut)	3	0.0251	0.0756
12	TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	4	0.0259	0.0756
13	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	2	0.0289	0.0779
14	RFX5	regulatory factor X, 5 (influences HLA class II expression)	2	0.0322	0.0805
15	KLF6	Kruppel-like factor 6	2	0.0392	0.0914
16	TP53	tumor protein p53	6	0.0461	0.0961
17	REL	v-rel reticuloendotheliosis viral oncogene homolog (avian)	2	0.0467	0.0961

Table 4.24. Transcription factors of the hub genes in severe COVID-19 and ccRCC

#	Key TF	Description	# of overlapped genes	P value	FDR
1	RARA	retinoic acid receptor, alpha	3	0.00346	0.045
2	RFXANK	regulatory factor X-associated ankyrin-containing protein	2	0.0132	0.0572
3	RFXAP	regulatory factor X-associated protein	2	0.0132	0.0572
4	RFX5	regulatory factor X, 5 (influences HLA class II expression)	2	0.0188	0.061

Table 4.25. Transcription factors of the hub genes in all COVID-19 and breast cancer

#	Key TF	Description	# of overlapped genes	P value	FDR
1	BRCA1	breast cancer 1, early onset	5	0.00273	0.0417
2	ELF4	E74-like factor 4 (ets domain transcription factor)	2	0.00275	0.0417
3	SP1	Sp1 transcription factor	17	0.00288	0.0417
4	KLF6	Kruppel-like factor 6	3	0.00441	0.0417
5	KLF4	Kruppel-like factor 4 (gut)	4	0.00453	0.0417
6	CUX1	cut-like homeobox 1	2	0.00746	0.0449
7	ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	2	0.00948	0.0449

8	NKX2-5	NK2 homeobox 5	2	0.00948	0.0449
9	ERG	v-ets erythroblastosis virus E26 oncogene homolog (avian)	3	0.0104	0.0449
10	NFIC	nuclear factor I/C (CCAAT-binding transcription factor)	3	0.0104	0.0449
11	NKX3-1	NK3 homeobox 1	2	0.0117	0.0449
12	POU2F2	POU class 2 homeobox 2	2	0.0117	0.0449
13	YBX1	Y box binding protein 1	3	0.0139	0.0491
14	KLF5	Kruppel-like factor 5 (intestinal)	2	0.0197	0.0603
15	NFYC	nuclear transcription factor Y, gamma	2	0.0197	0.0603
16	NFYB	nuclear transcription factor Y, beta	2	0.0227	0.0652
#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
17	PTTG1	pituitary tumor-transforming 1	2	0.0259	0.07
18	NFE2L2	nuclear factor (erythroid-derived 2)-like 2	2	0.0292	0.0718
19	HDAC1	histone deacetylase 1	4	0.0322	0.0718
20	TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	4	0.0322	0.0718
21	FOXM1	forkhead box M1	2	0.0328	0.0718
22	SP3	Sp3 transcription factor	5	0.0429	0.0849
23	NFYA	nuclear transcription factor Y, alpha	2	0.0443	0.0849
24	RXRA	retinoid X receptor, alpha	2	0.0443	0.0849

Table 4.26. Transcription factors of the hub genes in mild COVID-19 and breast cancer

#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
1	YBX1	Y box binding protein 1	4	0.000522	0.0116
2	BRCA1	breast cancer 1, early onset	5	0.00075	0.0116
3	NKX3-1	NK3 homeobox 1	2	0.00667	0.0655
4	NFYC	nuclear transcription factor Y, gamma	2	0.0113	0.0655
5	NFYB	nuclear transcription factor Y, beta	2	0.013	0.0655
6	PTTG1	pituitary tumor-transforming 1	2	0.0149	0.0655
7	NFE2L2	nuclear factor (erythroid-derived 2)-like 2	2	0.0169	0.0655
#	**Key TF**	**Description**	**# of overlapped genes**	**P value**	**FDR**
8	FOXM1	forkhead box M1	2	0.019	0.0655
9	HMGA1	high mobility group AT-hook 1	2	0.019	0.0655
10	NFYA	nuclear transcription factor Y, alpha	2	0.0259	0.0804
11	E2F4	E2F transcription factor 4, p107/p130-binding	2	0.0337	0.0894
12	ATF1	activating transcription factor 1	2	0.0364	0.0894
13	SP1	Sp1 transcription factor	11	0.0375	0.0894
14	NFIC	nuclear factor I/C (CCAAT-binding transcription factor)	2	0.0452	0.1
15	USF1	upstream transcription factor 1	3	0.0489	0.101

Table 4.27. Transcription factors of the hub genes in severe COVID-19 and breast cancer

#	Key TF	Description	# of overlapped genes	P value	FDR
1	BRCA1	breast cancer 1, early onset	6	0.00348	0.122
2	ELF4	E74-like factor 4 (ets domain transcription factor)	2	0.00636	0.122
3	NCOR1	nuclear receptor corepressor 1	2	0.0129	0.122
4	KLF6	Kruppel-like factor 6	3	0.0142	0.122
5	CUX1	cut-like homeobox 1	2	0.0169	0.122
#	Key TF	Description	# of overlapped genes	P value	FDR
6	STAT5B	signal transducer and activator of transcription 5B	2	0.0169	0.122
7	KLF4	Kruppel-like factor 4 (gut)	4	0.0195	0.122
8	BTF3	basic transcription factor 3	2	0.0214	0.122
9	ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	2	0.0214	0.122
10	NKX2-5	NK2 homeobox 5	2	0.0214	0.122
11	NKX3-1	NK3 homeobox 1	2	0.0263	0.136
12	TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	5	0.0369	0.136
13	SP1	Sp1 transcription factor	19	0.0389	0.136
14	YBX1	Y box binding protein 1	3	0.0418	0.136
15	HDAC7	histone deacetylase 7	2	0.0433	0.136
16	KLF5	Kruppel-like factor 5 (intestinal)	2	0.0433	0.136
17	NFYC	nuclear transcription factor Y, gamma	2	0.0433	0.136
18	DNMT1	DNA (cytosine-5-)-methyltransferase 1	3	0.0455	0.136
19	SMAD3	SMAD family member 3	3	0.0455	0.136
20	NFYB	nuclear transcription factor Y, beta	2	0.0497	0.142

A total of 293 miRNAs targeting at least two pivotal genes were identified through the COVID-19 and TNBC point-class mapping. A total of 341 miRNAs targeting at least two hub genes were identified by outcome category assignment for COVID-19 and moderate TNBC. A total of 484 miRNAs at least targeting two critical genes were identified by assigning the results category “COVID-19 severe” and “TNBC high” in the mirDIP tool. (Table 4.28).

Table 4.28. Targeting miRNAs of the top 5 hub genes for all COVID-19 and TNBC

	miRNAs	**Target genes**
	hsa-miR-1227-5p	*IGF1, NOTCH1*
	hsa-miR-1287-5p	*IGF1, ESR1*

	hsa-miR-130a-3p	*ESR1, IGF1*
	hsa-miR-130b-3p	*ESR1, IGF1*
	hsa-miR-1471	*IGF1, NOTCH1*
	hsa-miR-18a-3p	*ESR1, NOTCH1*
	hsa-miR-18a-5p	*ESR1, IGF1*
	hsa-miR-18b-5p	*ESR1, IGF1*
	hsa-miR-190a-5p	*IGF1, ESR1*
	hsa-miR-190b-5p	*IGF1, ESR1*
	hsa-miR-1915-3p	*CD44, ESR1*
	hsa-miR-19a-3p	*ESR1, IGF1*
	miRNAs	**Target genes**
	hsa-miR-19b-3p	*ESR1, IGF1*
	hsa-miR-301a-3p	*ESR1, IGF1*
	hsa-miR-301b-3p	*ESR1, IGF1*
	hsa-miR-3666	*ESR1, IGF1*
Severe COVID-19 and TNBC	hsa-miR-374a-3p	*ESR1, IGF1*
	hsa-miR-3978	*ESR1, CD44*
	hsa-miR-4295	*ESR1, IGF1*
	hsa-miR-454-3p	*ESR1, IGF1*
	hsa-miR-4735-3p	*ESR1, IGF1*
	hsa-miR-4781-3p	*IGF1, MMP9*
	hsa-miR-509-3p	*NOTCH1, IGF1*
	hsa-miR-517a-3p	*ESR1, IGF1*
	hsa-miR-542-5p	*ESR1, CD44*
	hsa-miR-568	*IGF1, NOTCH1*
	hsa-miR-577	*CD44, NOTCH1*
	hsa-miR-583	*IGF1, ESR1*
	hsa-miR-595	*ESR1, IGF1*
	hsa-miR-609	*ESR1, IGF1*
	hsa-miR-625-5p	*ESR1, IGF1*
	hsa-miR-629-5p	*IGF1, CD44*
	hsa-miR-632	*IGF1, ESR1*
	hsa-miR-6499-3p	*ESR1,NOTCH1*
	hsa-miR-6730-5p	*IGF1, CD44*
	hsa-miR-6780a-3p	*NOTCH1, IGF1*
	hsa-miR-6817-5p	*NOTCH1, IGF1*
	miRNAs	**Target genes**
	hsa-miR-1250-3p	*IGF1, FLT1*
	hsa-miR-329-5p	*IGF1, FLT1*
	hsa-miR-3620-5p	*FGF1, FLT1*
	hsa-miR-4435	*IGF1, FGF1*
	hsa-miR-4439	*FLT1, FGF1*
	hsa-miR-4735-3p	*IGF1, FGF1*
	hsa-miR-509-3p	*IGF1, IL1A*

Mild COVID-19 and TNBC	hsa-miR-548s	*FGF1, IGF1*
	hsa-miR-578	*FLT1, IGF1*
	hsa-miR-609	*IL1A, IGF1*
	hsa-miR-629-5p	*IGF1, FGF1*
	hsa-miR-6750-5p	*FGF1, IGF1*
	hsa-miR-6831-3p	*IL1A, IGF1*
	hsa-miR-7855-5p	*FLT1, IGF1*
COVID-19 and TNBC	hsa-miR-6817-5p	IGF1, NOTCH1
	hsa-miR-568	IGF2, IL1A
	hsa-miR-1471	IL1A, NOTCH1

A total of 44 miRNAs at least targeting two hub genes that were identified throgh score category assignment for all ccRCC and COVID-19, by adjusting the outcome category to mild COVID-19 and ccRCC, a total of 36 miRNAs at least targeting two pivotal genes were identified, also, a total of 195 miRNAs at least targeting two hub genes were identified by assigning the outcome category as severe COVID-19 and ccRCC. hsa-miR-4661-5p is the only miRNA that target 2 hub genes between all COVID-19 and ccRCC.

A total of 274 miRNAs at least targeting two pivotal genes that identified throgh defining the outcome category as 'breast cancer' and 'all COVID-19 diseases'. Also a total of 55 miRNAs at least targeting two focal genes that identified throgh defining the outcome category as breast cancer and mild COVID-19, by assigning score categories. A total of 256 miRNAs at least targeting two hub genes were identified as severe COVID-19 and breast cancer (Table 4.29)

Table 4.29. Targeting miRNAs of the top 5 hub genes for all COVID-19 and breast cancer

	miRNAs	**Target genes**
Severe COVID-19 and breast cancer	hsa-miR-3688-3p	*RAC1, IGF1*
	hsa-miR-4695-5p	*RAC1, IGF1*
	hsa-miR-483-3p	*IGF1, MMP9*
	hsa-miR-509-3p	*RAC1, IGF1*
Mild COVID-19 and breast cancer	None	
COVID-19 and breast cancer	hsa-miR-1301-5p	*IGF1, TOP2A*
	hsa-miR-6502-5p	*IGF1, TOP2A*
	hsa-miR-6769a-5p	*IGF1, PXN*
	hsa-miR-6769b-5p	*IGF1, PXN*
	hsa-miR-8063	*PXN, IGF1*

Emerging research suggests that individuals afflicted with chronic and complex medical conditions, including breast cancer, triple-negative breast cancer, and clear cell renal cell carcinoma, may exhibit heightened vulnerability to severe manifestations of COVID-19 due to pre-existing pathological conditions. Hence, it is imperative to investigate the molecular anomalies that contribute to the escalation of disease severity in COVID-19 patients with comorbidities. Therefore, it is crucial to understand the correlation between COVID-19 and concurrent medical conditions in order to effectively manage the disease and develop efficient treatment strategies.

In this research endeavour, an in-depth bioinformatics analysis was undertaken to enhance comprehension of the overlapping mechanisms, shared genes, transcription factors (TFs), and microRNAs (miRNAs) between COVID-19 and breast cancer, specifically triple-negative breast cancer, as well as clear cell renal cell carcinoma. Furthermore, we also examined whether the severity of COVID-19 has differential effects on the specific shared mechanisms and biomarkers between patients with COVID-19-TNBC and COVID-19-ccRCC. The datasets were categorised into three groups for each disease by applying sample filtering. The study examines the presence of severe COVID-19-TNBC, mild COVID-19-TNBC, and COVID-19-TNBC, as well as severe COVID-19-ccRCC, mild COVID-19-ccRCC, and COVID-19-ccRCC.

A total of 25 differentially expressed genes (DEGs) have been identified in severe COVID-19-TNBC, while 17 DEGs have been found in mild COVID-19-TNBC datasets. Additionally, there are 16 DEGs that are common to all COVID-19-TNBC cases. A total of 736 differentially expressed genes (DEGs) have been identified in severe COVID-19-ccRCC, while 314 DEGs have been identified in mild COVID-19-ccRCC. Additionally, 409 DEGs have been found to be common across all cases of COVID-19-ccRCC. Furthermore, a PPI network was constructed in order to ascertain the five most prominent hub genes within said network. The five most prominent hub genes associated with severe COVID-19-TNBC (Triple-Negative Breast Cancer) are *ESR1, NOTCH1, MMP9, CD44,* and *IGF1*. Conversely, the top five hub genes for mild COVID-19-TNBC are *IL1B, IL1A, IGF1, FGF1*, and *FLT1*.

Lastly, the hub genes most closely linked to COVID-19-TNBC in general are *NOTCH1, IL1B, IGF1, MMP9,* and *IL1A*. Insulin-like Growth Factor 1 (IGF1) is identified as a shared hub gene in both severe and mild cases of COVID-19 in patients with Triple-Negative Breast Cancer (TNBC). The majority of hub genes exhibited differential expression between mild and severe COVID-19-TNBC patients, indicating that the severity of COVID-19 is associated with distinct

underlying mechanisms. Prior research has also revealed that variations in biomarkers are associated with the severity of COVID-19 (Broman et al., 2021). In addition, we have identified a selection of ten hub genes that exhibit potential as diagnostic and therapeutic biomarkers for both COVID-19 and ccRCC. The five most significant hub genes associated with severe COVID-19-ccRCC are *ASPM, CCL5, CCNB1, CENPE*, and *ESR1*. Similarly, for mild COVID-19-ccRCC, the top five hub genes are *CDCA3, ASPM, ANLN, TTK,* and *BARD1*. Lastly, for COVID-19-ccRCC in general, the prominent hub genes are *TTK, CCNB1, ASPM, RAD51AP1,* and *NCAPG*. The gene *ASPM* is identified as the sole hub gene that is commonly associated with both severe COVID-19-ccRCC and mild COVID-19-ccRCC.

The functional enrichment analysis revealed that the top five Gene Ontology terms in the Biological Process category that exhibited significant associations were "Positive regulation of transcription from RNA polymerase II promoter," "Positive regulation of gene expression," "Positive regulation of cell migration," "Positive regulation of cell proliferation," and "Positive regulation of transcription, DNA-templated" for both COVID-19 and TNBC. The Cellular Component (CC) category for both COVID-19 and TNBC exhibits five prominent Gene Ontology (GO) terms, namely "Extracellular region," "Extracellular space," "Extracellular exosome," and "Cell surface." The Molecular Function (MF) category exhibits several notable Gene Ontology (GO) terms that are prominent in both COVID-19 and TNBC. These terms include "Integrin binding," "Cytokine activity," "Interleukin-1 receptor binding," "Insulin-like growth factor receptor binding," and "Protein binding." According to Table 4.4, the five most notable KEGG terms in relation to both COVID-19 and TNBC are "Pathways in cancer," "Endocrine resistance," "Breast cancer," "Ovarian steroidogenesis," and "Proteoglycans in cancer."

This study represents the inaugural investigation into the potential common mechanisms, biomarkers, transcription factors (TFs), and microRNAs (miRNAs) shared between patients with COVID-19 and those with triple-negative breast cancer (TNBC), as well as between patients with COVID-19 and those with clear cell renal cell carcinoma (ccRCC). The findings of this study would provide valuable insights into the management approaches for individuals diagnosed with triple-negative breast cancer (TNBC) and COVID-19, as well as those with clear cell renal cell carcinoma (ccRCC) and COVID-19, taking into account the varying degrees of severity associated with the COVID-19 infection.

5. CONCLUSION AND ADVICE

The COVID-19 pandemic poses a significant global risk to the overall welfare of the general populace. The origin of COVID-19 can be ascribed to the viral pathogen known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The current global pandemic caused by the SARS-CoV-2 virus has significant ramifications for individuals who have been diagnosed with cancer. Individuals who have weakened immune systems are more susceptible to experiencing severe complications and an elevated likelihood of mortality linked to the virus. A considerable body of empirical research has yielded evidence that suggests a significant mortality rate among individuals diagnosed with cancer who have also contracted COVID-19. Hence, a notable association can be discerned between the oncological ailment of cancer and the viral infection induced by the COVID-19 virus. The identification of shared pathological mechanisms holds considerable importance.

Breast cancer demonstrates an incidence rate of 24.2% and a prevalence rate of 15% among the various types of cancers that impact the female population. Cancer is the predominant manifestation of malignancy, characterised by significant mortality rates. Triple negative breast cancers are distinguished by the lack of expression of the oestrogen receptor (ESR1), progesterone receptor (PGR1), and ERBB2 receptor. Triple negative breast cancer (TNBC) is a distinct subtype of breast cancer that manifests in approximately 15% of women who receive a diagnosis of renal cell carcinoma. Renal cell carcinoma is widely acknowledged as the primary type of kidney cancer, comprising different histologic subtypes. Clear cell renal cell carcinoma (ccRCC) is the primary histological subtype observed in cases of renal cancer, accounting for approximately 80% of all instances of renal cell carcinoma (RCC).

This thesis provides a thorough analysis of potential common mechanisms, biomarkers, transcription factors (TFs), and microRNAs (miRNAs) shared among individuals with COVID-19

and breast cancer, COVID-19 and triple negative breast cancer, and COVID-19 and clear cell renal cell carcinoma. The primary objective of this study was to investigate and evaluate the association between the COVID-19 virus and three specific forms of cancer. The examination of potential disparities in shared mechanisms and biomarkers across various cancer types, with regards to the severity of COVID-19, presents an opportunity to advance the discovery of customised therapeutic approaches for a wide range of cancer types. In light of the prevailing decrease in the pandemic status of COVID-19, it would be advantageous to conduct an investigation into the shared biological pathways that are frequently observed in diverse forms of cancer. The execution of such an investigation would augment our understanding of the interaction between various types of cancer and the COVID-19 virus. The exploration of novel personalised treatment modalities for patients with various forms of cancer shows promise through the investigation of potential mechanisms and biomarkers.

Furthermore, this study has successfully identified common biomarkers and pathways in breast cancer, triple negative breast cancer, and clear cell renal carcinoma. The current investigation enabled the recognition of common biomarkers among different subtypes of breast cancer, as well as the revelation of potential markers and biological pathways that are shared between breast cancer and clear cell renal cell carcinoma. This thesis presents an original study that establishes a correlation between the COVID-19 virus and diverse forms of cancer. Furthermore, this study provides a comprehensive analysis of the prevailing biomarkers and biological pathways that are frequently observed in breast cancer, triple negative breast cancer, and clear cell renal cell carcinoma.

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BACKGROUND

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