Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and Malignancy: Exploration of the possible genetic and epigenetic interlinks and overview of the vaccination scenario

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ABSTRACT

Background: Malignancy is one of the prime global causes of mortality. Cancer Patients suffering from SARS-CoV-2 have demonstrated higher rates of severe complications exacerbating towards death. Possible genetic and epigenetic alterations may exist in cancer patients which have the potential to contribute towards their increased vulnerability towards COVID-19.

Method: An exhaustive literature search using 'COVID-19′, 'SARS-CoV-2′, 'Cancer', 'Malignancy', 'Relationships', Interlinks', 'Genetic', 'Epigenetic', 'Epidemiological studies', 'Clinical Studies', 'Vaccination', 'Vaccine scenario' were conducted in PubMed and EMBASE till 2nd June 2021.

Result: In this narrative review, 17 epidemiological studies were listed which focused on clinical parameters of several malignancy patient cohorts who contracted COVID-19. Besides, genetic and epigenetic alterations seen among cancer patients are also discussed which may plausibly increase the vulnerability of cancer patients to SARS-CoV-2 infection. Also, global vaccination scenario among malignant patients along with the necessity to prioritize them in the vaccination campaigns are also elaborated.

Conclusion: Genetic and epigenetic modifications present in ACE2, TMPRSS2, IL-6 and several cytokines require more in-depth research to elucidate the shared mechanisms of malignancy and SARS-CoV-2.

Table of abbreviations

SARS CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
COVID-19	Corona Virus Disease-19
SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
DM	Diabetes Mellitus
HTN	Hypertension
WHO	World Health Organization
WBC	White Blood Cell
MSK	Memorial Sloan Kettering
COPD	Chronic Obstructive Pulmonary Disease
ICU	Intensive Care Unit
TERAVOLT	Thoracic Cancers International COVID-19 Collaboration
LEOSS	Lean European Open Survey on SARS-CoV-2 infected patients
CKD	Chronic Kidney Disease
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
NHL	Non-Hodgkin lymphoma
MDS	Myelodysplastic Syndromes
MPN	Myeloproliferative Neoplasms
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
MM	Multiple Myeloma
CML	Chronic Myelogenous Leukemia
SCLC	Small Cell Lung Cancer
NSCLC	Non-Small Cell Lung Cancer
CLD	Chronic Liver Disease
CHD	Coronary Heart Disease
HBV	Hepatitis B Virus
MI	Myocardial Infarction
PVD	Peripheral vascular disease
HCQ	Hydroxychloroquine
PC	Prostate cancer
AR	Androgen receptor
TMPRSS2	Transmembrane protease serine 2
ACE2	Angiotensin Converting Enzyme-2
ADT	Androgen-Deprivation Therapy

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RAAS	Renin-Angiotensin-Aldosterone System
IL-6	Interleukin-6
IL-6R	Interleukin-6 Receptor
ARDS	Acute Respiratory Distress Syndrome
MAS	Macrophage Activation Syndrome
hACE2	Human ACE2
ISG	Interferon Stimulated Gene
Sirtuin 1	SIRT1
CSF	Colony Stimulating Factor
GF	Growth Factor
GI	Gastrointestinal
NCI	National Cancer Institute
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
ESCA	Esophageal carcinoma,
GBM	Glioblastoma multiforme,
HNSC	Head and Neck squamous cell carcinoma,
LGG	Brain Lower Grade Glioma,
PAAD	Pancreatic adenocarcinomA,
SKCM	Skin Cutaneous Melanoma,
STAD	Stomach Adenocarcinoma (STAD)
THYM	Thymoma
COAD	Colon adenocarcinoma,
KIRP	Kidney renal papillary cell carcinoma,
READ	Rectum adenocarcinoma
CESC	Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma
KICH	Kidney Chromophobe,
PRAD	Prostate Adenocarcinoma
UCEC	Uterine corpus endometrial carcinoma
UCS	Uterine Carcinosarcoma
LUAD	Lung Adenocarcinoma
BRCA	Breast Invasive Carcinoma
LIHC	Liver Hepatocellular Carcinoma
LUSC	Lung Squamous Cell Carcinoma
scRNA-seq	single-cell RNA-sequencing
EUA	Emergency Use Authorization
AACR	American Association for Cancer Research
ASCO	American Society of Clinical Oncology
AACI	Association of American Cancer Institutes
CDC	centre for Disease Control and Prevention
ESMO	European Society for Medical Oncology
SITC	Society for Immunotherapy of Cancer
SEOM	Spanish Medical Oncology Society
NCCN	National Comprehensive Cancer Network
EPR	Enhanced Permeation and Retention
DLT	Dose Limiting Toxicity
LMIC	Low to Middle Income Country
GI	Gastrointestinal
TKI	Tyrosine Kinase Inhibitor
FDA	Food and Drug Administration
EMA	European Medicines Agency
CTSL/B	Cathepsin L/B
GEPIA	Gene Expression Profiling Interactive Analyses , CRP:C Reactive Protein

1. Introduction

After being reported for the 1st time in Wuhan, China in December 2019 as a pneumonia with unknown etiology; Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) has caused a havoc as a pandemic with a total of 170,747,372 cases and 3,555,726 deaths till 2nd June 2021 [1–3]. According to genetic sequencing, this RNA genome containing virus is closely similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [4, 5].

Cancer is one of the associated comorbidities responsible for higher mortality rates seen in COVID-19 patients [6–11]. According to World Health Organization (WHO), as one of the foremost causes of mortality, malignancy remains in the 1st or 2nd position for causing death before the age of 70 in 112 countries [12, 13]. COVID-19 has brought catastrophic consequences for cancer patients due to the occurrence of impediments in diagnosis, recurrent checkups and treatment options. Discontinued cancer screening has escalated the number of malignancy associated deaths as belated diagnosis and treatment has made previously treatable tumors harder to treat. A prime example of COVID associated cataclysm is the humongous number of more than 4•6 million people on waiting lists for surgery in UK only which is a waiting period 100 times higher compared to that of the normal times. [14]. Altered immunological state with increased inflammatory pathways [15], higher expression of host genes which are pivotal in viral activation and amplification, [16, 17] and host epigenetic alterations associated with viral infections may contribute to the higher susceptibilities seen in cancer patients suffering from Covid-19 [18–20]. Overexpression of host genes such as ACE2, TMPRSS2 has stirred much interest in scientific communities due to their roles in viral SARS-CoV2 pathogenesis along with their associations with malignancy. Epigenetic alterations associated with ACE2, IL-6 need in-depth investigation to understand their contribution in COVID-19 pathogenesis [18-20]. Although, vaccines have given us a ray of hope against the battle of COVID-19; the lack of participation of vulnerable cancer patient cohorts in vaccine trials is a concerning issue. Cancer patients should be vaccinated on priority basis and clinical data regarding vaccination need to be meticulously recorded so that any complications or deviation related to vaccines in these patients can be identified.This review tries to delineate some plausible connection between malignancy and COVID-19 susceptibility from both genetic and epigenetic perspectives along with an investigation in the vaccination programs, especially the scenario observed among cancer patients. 17 epidemiological studies focused on malignancy patients suffering from COVID-19 are enlisted here and distinct features of those studies are discussed too. [6–11, 21–31]. This narrative review work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

2. Method

A literature search was conducted in the PubMed, Embase using keywords ‘COVID-19′, ‘SARS-CoV-2′, ‘Cancer’, ‘Malignancy’, ‘Relationships’, Interlinks’, ‘Genetic’, ‘Epigenetic’, ‘Epidemiological studies’, ‘Clinical Studies’, ‘Vaccination’ and ‘COVID-19 vaccine’. The flowchart describes the summarized process. An initial search rendered 102 articles. 23 epidemiological papers were found in the initial search. After exclusion of 5 studies due to either of being meta-analyses or lacking most of the attributes represented on Table 1, 17 clinical studies consisting of case studies and large cohort studies conducted on cancer patients who were suffering from COVID-19 were chosen. These studies were mainly included based on the available information provided on patient size, symptoms, associated comorbidities, type of cancers, cancer and COVID-19 treatments. 23 studies focused on vaccine information regarding cancer patient were included. Either genetic or epigenetic or studies about both of them narrating interlinks with COVID-19 summed up a total number of 56 studies. 5 papers were excluded due to containment of repetitive information. So, the final assortment of papers consisting of epidemiological studies, vaccine scenario of cancer patients and genetic and epigenetic linking between malignancy and COVID-19 reached a total of 91. Fig. 1

3. Epidemiological studies on cancer patients suffering from COVID-19

Table 01 amasses clinical parameters (malignancy type, subtype and respective number of patients, symptoms, associated comorbidities and treatment options) of 17 such studies which focused on COVID-19 patients suffering from different types of malignancies. 23.53% ($n = 04$) of

Table 1
Clinical features of cancer patients suffering from COVID-19.

Type of cancer *n*= number of patients	Subtypes [*n*=number of patients]	Clinical features	Comorbidities (*n*=number of patients)	Cancer Treatments	COVID-19 Treatments	References
1. Lung [case study]	Advanced adeno-carcinoma [57-year-old Chinese male]	Fever, cough, shortness of breath, myalgia, diarrhea, patchy shadows in both lung (CT scan)	Not given	Targeted therapy with gefitinib since February 2016, Osimertinib monotherapy since 2017, radiotherapy for enlarged lymph in 2019	Cefoselis, oseltamivir, meropenem, teicoplanin, moxifloxacin, antiviral treatment with (lopinavir/ritonavir) [continued osimertinib during COVID-19 treatment]	[6]
2. Solid, hematological [218]	**i] Solid (164)** 1] Genitourinary [46] 2. Breast [28] 3. Colorectal [21] 4. Gynecologic [13] 5. Lung [11] 6. Head and neck [08] 7. Neurologic [08] 8. Upper GI [08] 9. Hepatobiliary [07] 10. Bone/soft tissue [05] 11. Neuroendocrine [03] 12. Pancreas [03] 13. Skin [03] **ii] Hematological:** [54] 1. NHL [15] 2. MDS [05] 3. MPN [07] 4. ALL [04] 5. AML [01] 6. MM [13] 7. CML [01] 8. Hodgkin lymphoma [05] **iii] Myeloid malignancy** [14] **Iv] Lymphoid malignancy** [40]	Decreased platelet count, WBC, hemoglobin, total lymphocyte count, Elevated ferritin, D-Dimer, LDH	1. DM (80) 2. HTN (147) 3. Chronic lung disease (62) 4. CKD (54) 5. CAD (43) 5. CHF (33)	Chemotherapy, Immunotherapy, radiotherapy	ICU admission, ventilator support, hemodialysis	[7]
3. Case study Lung)	Advanced SCLC with a grade IV neutropenia [58 year-old Caucasian male]	Lower neutrophils, lymphopenia, high D-dimer value, lower left lobe atelectasis and diffuse bilateral infiltration	No CVD history	ECOG 2 performance status. Topotecan as second line therapy	Oxygen (FiO2 8 L/min), hydroxychloroquine and meropenem for 7 days, granulocyte stimulating growth factor (G-CSF) for 5 days, 1 mg daily dexamethasone, for anorexia-cachexia	[8]
4. Lung [45 cancer including 17 lung cancer patients in 1878]	1. NSCLC [16] 2. SCLC [01]	Fever, cough, myalgia, dyspnea, diarrhea	1.HTN (10) 2. DM (2) 3. CKD (1) 4. COPD (9) 5. Obesity (3)	Active Chemotherapy, Tyrosine kinase Inhibitors (TKI), new diagnosis, immunotherapy, surgery	Lopinavir/ritonavir + Hydroxichloroquine, Hydroxichloroquine + azithromycin, Lopinavir/ritonavir + Hydroxichloroquine + azithromycin, Hydroxichloroquine.	[9]
5. Lung [102]	1. NSCLC [94] 2. SCLC [07]	Cough, dyspnea, fever. GI symptoms	1. COPD (24) 2. Non-COPD lung disease (28) 3.Obesity (30) 4. HTN (57) 5. CHF (07) 6. DM (27)	PD-(L)1 blockade therapy, chemotherapy + PD-(L)1 blockade, TKI	Hospitalization, admission of ICU/receipt of intubation, receipt of intubation and mechanical ventilation	[10]
6. 28 cancer patients among 1276 COVID patients	1. Lung [07] 2. esophagus [04] 3. Breast [03] 4.Laryngocarcinoma [02] 5. Liver [02] 6. Prostatic [02] 7. Cervical [01] 8. Gastric [01] 9. Colon [01] 10. Rectum [01]	Fever, cough, fatigue, dyspnea, myalgia, diarrhea, chest pain	1. DM (04) 2. Chronic CVDs (04) 3. COPD (01) 4. CLD (02)	Chemotherapy, targeted therapy, radiotherapy, immunotherapy, chemotherapy+ immunotherapy	Oxygen therapy, invasive mechanical ventilation, one or combination of antiviral agents, systemic corticosteroids, intravenous immunoglobin, antibiotic treatment	[11]

(*continued on next page*)

Table 1 (*continued*)

	11.Naso-pharynx [1] 12. Endometrial [01] 13. Ovarian [01] 14. Testis [01]					
07. 105 patients with cancer and 536 age-matched non-cancer patients	1. Lung [22] 2. Gastro-intestinal [13] 3. Breast [11] 4. Thyroid [11] 5. Blood [09] 6. Cervix [06] 7. Esophagus [06]	Fever, dry cough, sputum production, fatigue, myalgia. nausea or vomiting, chest distress, headache, sore throat	1. HTN (30) 2. CVD (12) 3. Diabetes (07) 4.Cerebrovascular Disease (05) 5. CKD (06) 6. CLD (07)	Cancer treatments within 40 days (surgery radiotherapy, chemotherapy, targeted therapy, immunotherapy)	Antibiotics, antiviral treatments, systemic glucocorticoids, oxygen therapy, mechanical ventilation	[21]
8. Solid tumors [52]	1. Lung [10] 2. Breast [09] 3. Rectal [08] 4.Colon [05] 5. Cervical [04] 6. Thyroid [03] 7.Gastric [02] 8. Liver [02] 9. Prostate [02] 10. Other [07]	Fever, dry cough, chest distress, fatigue, headache, dyspnea, pharyngalgia, myalgia and diarrhea	1. HTN (17) 2. Diabetes (07) 3. CHD (05) 4. CVD (04) 5. COPD (04), 6. chronic HBV (2), 7. Cirrhosis (01), 8.chronic renal insufficiency (01) 9.hypothyroidism (01)	Chemotherapy, cancer immunotherapy	Antiviral therapy, antibiotic therapy, Gglucocorticoid therapy, immunoglobulin, oxygen support	[22]
9. Breast (. RNA-positive subgroup 2. RNA negative, CT scan) [76 among 15,600 treated in 4 months]	1. HR+ [39] 2. Triple-negative [10] 3. HER2+ [10]	**Fever,** cough, dyspnea, decreased saturation, GI disorders, headache, possible nosocomial infection	1. Obesity (10) 2. smokers (04) 3. Chronic lung disease (02) 4. Diabetes (10) 5. HTN (21) 6. Heart disease (08) 7. Systemic disease (03)	Surgery, chemotherapy (Epirubicin and cyclophosphamide), Paclitaxel/ docetaxel), radiation, endocrine therapy, anti-estrogens and targeted therapy.	Antibiotics. Corticosteroids, No patients received hydroxychloroquine, antiviral, or immunomodulating drugs as frontline treatment at admission	[23]
10. several [110]	1. Melanoma [64] 2. NSCLC [17[3. RCC [10] 4. Other [19]	Fever, cough, dyspnea,	1. CVD (30) 2. DM (16) 3. pulmonary disease (13) 4. renal disease (06)	1. (nivolumab, pembrolizumab, spartalizumab, atezolizumab or durvalumab 2. combination anti-PD-(L) 1 and anti-CTLA-4 (nivolumab–ipilimumab, durvalumab–tremelimumab or pembrolizumab–MK1308	HCQ, azithromycin, azithromycin+ HCQ, oxygen therapy, mechanical ventilation, antibiotics, antivirals, glucocorticoids, anti-IL6 agents, intravenous immunoglobulins	[24]
11. Breast [35]	35 breast cancer against a control group of 55 COVID-19 patients without cancer and 81 COVID-19 patients with other types of cancer]	Fever, cough,fatigue, chest tightness myalgia, diarrhea, chills, shortness of breath	1. HTN (06) 2. Myelo-suppression (04) 3. Diabetes (04) 4. Anemia (03) 5. CVD (02) 6.Cerebrovascular diseases (01) 7. Liver dysfunction (01) 8. Chronic bronchitis (01)	Chemotherapy, radiotherapy, targeted therapy	Antiviral therapy, antibiotic therapy, glucocorticoid, immuno-modulatory drug, traditional Chinese medicine	[25]
12. Early breast cancer	Invasive ductal carcinoma: [53-years-old female]	blood tests (lymphocyte count and subpopulation, D-dimer, coagulation indices, and blood inflammatory indices) were regular with positive Sars-CoV-2 tests (totally four swab	NA	Neoadjuvant, Endocrine therapy	No treatment given for COVID-19.	[26]
13.lung	(NSCLC) 1. male (62 age) 2. male (52 age)	1. asymptomatic (1st patient) 2. fever, dry cough, ground glass opacities	NA	Targeted alectinib therapy **1st patient** and lorlatinib treatment (**2nd patient)**	No specific covid-19 medication (**1st patient**), antibiotic treatment with azithromycin and ceftriaxone for **2nd patient**	[27]
14. LEOSS (Lean European Open Survey on SARS-CoV-2 Infected Patients) registry	**435 cancer patients and 2636 non-cancer patients** i. Solid tumor [256] 1. Gastrointestinal [60], 2. Lung [36] 3. Gynecological [39] 4. breast [21] ii. Solid tumor,	Fever, dry cough, dyspnea, excessive tiredness	1. Hemiplegia (15) 2. Dementia (48) 3.CVD (59) 4. MI (36) 5. PVD (34) 6.HTN (25) 7. CAD (81) 8. COPD (39)	Chemotherapy high-dose steroids, targeted therapy, other immune-suppressive therapy, surgery, radiation	ICU admission	[28]

(*continued on next page*)

Table 1 (*continued*)

	metastasized [95] iii. Lymphoma [76] 1. NHL [71] IV. Leukemia [48] 1. AML [14]		9. Asthma (15) 10. Other chronic pulmonary disease (27) 11. Connective tissue disease (3) 12. Peptic ulcer disease (19) 13. CLD (5) 14. Liver cirrhosis (6) 15.Diabetes (104) 16. CKD (87) 17. Acute kidney injury (25) 18. Organ transplantation (5)			
15. Breast [27 out of 4515 covid paitents]	[27]	Cough, fever shortness of breath fatigue diarrhea and myalgia	1.HTN (15) 2. Diabetes (06) 3. Pulmonary disease (06)	1 chemotherapy without targeted agents for early stage Breast cancer 2. single-agent hormone therapy	3. supplemental oxygen, 4. none needed intensive care-level support, including intubation or dialysis	[29]
16. CCC19 database 928 patients	I] Solid tumours 758 1. Breast [191] 2. Prostate [152] 3. Gastrointestinal [108] 4. Thoracic 91 5. gynecological [49] 6. Renal cell carcinoma [45] 7. Endocrine [39] 8. Melanoma [38] 9. Head and neck [30] 10. Sarcoma [24] 11. Nervous system [12] 12. Solid tumor, not otherwise specified [43] ii] Haematological malignancies [204] 1. Lymphoid neoplasms [102] 2. Low-grade NHL [54] 3. High-grade NHL [27] 4. ALL [6] 5. Multiple myeloma [55] 6. Myeloid neoplasms [42] 7. AML [13] 8. hematological malignancy, not otherwise specified [6]	Not given	The type of comorbidity not given	Non-cytotoxic therapy, targeted therapy, endocrine, immunotherapy, radiotherapy.	HCQ alone, azithromycin alone, Azithromycin + HCQ	[30]
17, TERAVOLT [thoracic malignancies] [200]	1. NSCLC [151] 2. SCLC [29] 3. Thymic carcinoma [08] 4. Carcinoid or neuroendocrine [04] 5. Malignant pleural mesothelioma [08]	Fever (>37•5 °C), dyspnea, cough Fatigue, headache, diarrhea, myalgia, nasal congestion, loss of smell or taste, conjunctival congestion	1. Autoimmune disease (6) 2. Chronic hepatitis (3) 3. CKD (15) 4. COPD (51) 5. Diabetes (29) 6. HTN [93] 7. Lung fibrosis (3) 8. cerebrovascular disease (10) 9. ischaemic heart disease (30) 10. Tuberculosis (3) 11. HBV (8) 12. hepatitis C (5)	TKI, chemotherapy, immune checkpoint inhibitors, chemotherapy and immune checkpoint inhibitors	ACE inhibitors, angiotensin II receptor blockers, NSAID, steroids, immune-suppressive drugs, aspirin, anticoagulants	[31]

DM: Diabetes Mellitus, HTN: Hypertension, WBC: White Blood Cell, COPD: Chronic Obstructive Pulmonary Disease, TERAVOLT: Thoracic Cancers International COVID-19 Collaboration, LEOSS: Lean European Open Survey on SARS-CoV-2 infected patients, CKD: Chronic Kidney Disease, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, NHL: Non-Hodgkin lymphoma, MDS: Myelodysplastic Syndromes, MPN: Myeloproliferative Neoplasms, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myelogenous Leukemia, MM: Multiple Myeloma, CML: Chronic Myelogenous Leukemia, SCLC: Small Cell Lung Cancer, NSCLC: Non-Small Cell Lung Cancer, CLD: Chronic Liver Disease, CHD: Coronary Heart Disease, HCQ: Hydroxychloroquine, HBV: Hepatitis B Virus, MI: Myocardial Infarction. PVD: Peripheral vascular disease, GI: Gastrointestinal, NSAID: Nonsteroidal anti-inflammatory drug, TKI: Tyrosine Kinase Inhibitors.

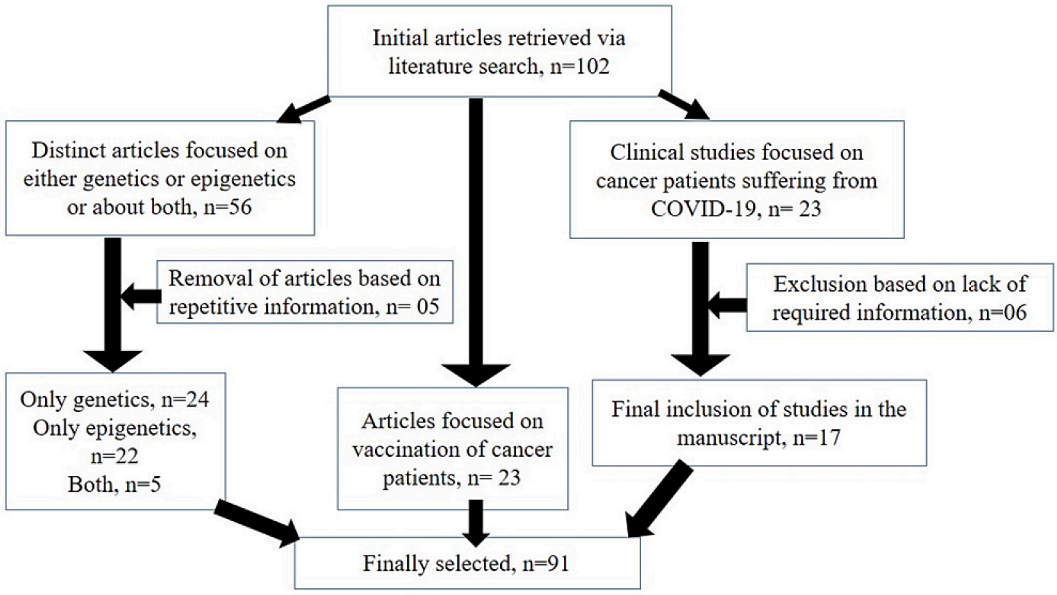

Fig. 1. Methodology of paper selection.

all studies were case studies and among those, 75% focused on lung cancer; remaining 01 case discussed about a breast cancer patient ailing from SARS-CoV-2 infection. Among the 13 large population studies, breast, lung and thoracic cancers each predominated 23.08%, 15.38% and 7.69%, respectively. Remaining 07 studies focused on multiple types of solid and hematological malignancies.

From a study conducted in the Montefiore Health System in New York on 218 cancer patients suffering from COVID-19 (March 18, 2020-April 8, 2020); 164 (75%) and 54 (25%) patients suffered from solid tumor and hematologic malignancies, respectively. The cohort primarily composed of adult male patients (59.07%) had a median age of 69 years (10–92 years). Among the solid tumor types, although the percentage of alive patients was higher than that of their dead counterparts (Alive: 75%); pancreas patients (Dead: 67%) had the highest mortality rate followed by lung patients (Dead: 55%). But the number of lung patients ($n = 11$) was 3-folds more than that of the pancreas patients ($n = 03$). There was no significant association of gender-bias or ethnicity with mortality observed in this particular study. According to the laboratory findings, relative anemia occurring before COVID-19 and lower hemoglobin levels, increased total white blood cell (WBC) counts, higher absolute neutrophil counts occurring after COVID-19 infection were associated with increased mortality [7]. Compared to this study consisting of multiple malignancy types, another study conducted at Memorial Sloan Kettering Cancer Center (MSK), New York (12 March 2020 - 6 May 2020) only focused on lung cancer patients [$n = 102$]. Among the 11% mortality observed here, smoking history, Chronic Obstructive Pulmonary Disease (COPD), and HTN were found to be significantly associated with mortality. An interesting observation of this study was the investigation to elucidate the association between HLA-A and HLA-B alleles with outcomes. Patients with mild ($n = 29$) or severe ($n = 17$) disease were compared with the control cohort of 5166 patients and almost similar frequencies of HLA-A and HLA-B alleles were found in study and control cohorts. HLA-B44 was found to be more dominantly present among patients with severe COVID-19, but the association between HLA-B44 and severity was statistically inconspicuous. [9].

In a multicenter study, [Tongji Sino-French New Town Hospital, Union Red Cross Hospital and Union West Hospital], [13 January 2020-26 February 2020], 28 (2.2%) patients were found to have cancer amid a total of 1276 patients. Among the predominantly male (60.7%) study population with a median age was 65 (56–70 years), lung (25.0%), oesophageal (14.3%) and breast cancers (10.7%) were the most frequent type of cancer, respectively. In this cohort, severe complication, resultant Intensive Care Unit (ICU) admission, life-threatening complication and mortality occurred at 53.6%, 21.4%, 35.7% and 28.6%, respectively. Compared to the non-cancer population, anemia and hypoproteinaemia were repeatedly found in this cancer cohort. These features were construed to be a major consequence of nutritional depletion with concurrent adverse consequences on the already poor immune-competent cancer patients. 28.6% of study population developed COVID-19 infection during hospitalization [11].

In another multicenter case-control study consisting of 14 hospitals in Wuhan, China [January 1, 2020- February 24, 2020], 105 COVID-19 patients with cancer were enrolled. Lung, gastrointestinal, breast, thyroid and hematologic cancers were present at 20.95, 12.38, 10.48, 10.48 and 8.57 percentile among the 102 patients, respectively. One of the study findings was that metastatic cancer (stage IV) had statistically proven greater susceptibility towards death [Odds Ratio (OR), 5.58; 95% Confidence Interval (CI) (1.71–18.23); $P = 0.01$], ICU admission [OR, 6.59; 95% CI (2.32–18.72); $P < 0.01$], and use of invasive mechanical ventilation [OR, 55.42; 95% CI (13.21–232.47); $P < 0.01$] whereas their non-metastatic counterparts did not exhibit any such statistical significant associations on account of any of the three abovementioned parameters. This study also found hematologic and lung cancer to be the 1st and 2nd highest mortality causing malignancies, respectively. 55.56% of patients with hematologic cancer had severe immunosuppression, which was construed as the foremost reason leading towards exacerbated conditions in COVID-19 patients [21].

TERAVOLT registry [Thoracic Cancers International COVID-19 Collaboration] is a multicenter observational study spanning 42 institutes over 8 countries [March 26- April 12, 2020]. Majority of 200 patients were male, white, or current or former smokers with a median age was 68 years (61•8–75•0). Non-Small Cell Lung Carcinoma (NSCLC) (76%) followed by Small Cell Lung Carcinoma (SCLC) (15%) were the major 2 types of malignancies present. In multivariable analysis, only smoking habit was significantly associated with mortality threats. In this study, most death incidents occurred during hospitalization but only 13 (09%) of 147 patients in the cohort were admitted to the ICU, 09 of whom received mechanical ventilation. [31]. Similar to TERAVOLT, Lean European Open Survey on SARS-CoV-2 infected patients (LEOSS) registry was another multicenter-based [March 16- August 31 2020,] study with a study population of 435 cancer patients among a total of 3071 COVID-19 patients. In contrast with TERAVOLT, its focus was not

only confined in the thoracic malignancies. Among this male-dominant study population, 98% was hospitalized. 55% and 27% exacerbated to critical condition and ICU hospitalization, respectively. Among the 119 ICU-admitted patients, 65.5% required mechanical ventilation. In the group of 119 patients treated in ICU, death of 47 (39.5%) patients was attributed to COVID-19 [28].

Another retrospective study comprising of 05 designated COVID-19 tertiary hospitals in Wuhan, China comprised of 35 breast cancer patients with COVID-19, 81 other types of cancer patients with COVID-19, and 55 COVID-19 patients without cancer [January 17, 2020- May 18, 2020]. These 35 female patients had a median age was 56 years (42–62) and 68.6% of the 35 patients were asymptomatic at the onset of COVID-19. Lymphopenia, thrombocytosis, increased levels of neutrophil count and elevated monocytes were present at 52.6, 10.5, 15.8 and 15.8%, respectively. Age, comorbidities, and abnormal chest CT findings were statistically relevant with COVID-19 disease severity and plausibly contributed to the progression of the infection. Another multivariate analysis illustrated age as the only factor (OR, 1.325; 95% CI, 1.075–1.634; $P = 0.008$) with plausible effect on the severity of COVID-19 in breast cancer patients. [25].

Another large-scale study conducted at Institut Curie hospitals comprised of 76 breast cancer patients suffering from COVID-19 [March 13, 2020- April 25, 2020]. 18% of the 59 RT-PCR positive patients developed COVID-19 symptoms after being hospitalized. A noticeable feature of this particular study was the sub-classification of cancer treatments into early and metastatic groups. In the early breast cancer patients, under the chemotherapy treatment option, Epirubicin+cyclophosphamide and Paclitaxel/docetaxel were prescribed to 10 and 04 individuals, respectively. In contrast to that, under the same treatment class in the metastatic group, Capecitabine, Paclitaxel/docetaxel, Epirubicin+cyclophosphamide, Vinorelbine, Eribulin, Gemcitabine and Carboplatin were given to 11, 09, 01, 02, 02, 03 and 04 individuals, respectively. Another conspicuous difference is observed between these two groups in case of targeted therapy. In the early breast cancer group, Trastuzumab, Pertuzumab and Trastuzumab emtansine were given to 04, 02 and 02 patients, respectively. Compared to that in the metastatic group, CDK4/6 inhibitor, Trastuzumab, Pertuzumab, Everolimus [was recommended to stop using it at the start of pandemic] were given to 14. 07, 06 and 02 individuals, respectively. [23]

Although the 17 studies mentioned in table 1 varied among themselves on account of objectives and studied parameters; nonetheless, the table tried to summarize the severity of malignancy among COVID-19 patients.

4. Genetic interlinks between cancer and COVID-19

Cancer patients with COVID-19 have showed higher mortality rates compared to their non-cancer counterparts [27–31]. Due to the heterogeneity of cancer type, diverse malignancy-related mutations and mechanisms, a general mechanism responsible for higher susceptibility among SARS-CoV2 infected cancer patients has not been yet postulated. But several studies are being conducted with a focus to pinpoint the intertwined relationships between different types of malignancies and SARS-CoV-2 infection from various angles [32, 35]

4.1. Pan-cancer analyses

SARS-Cov-2 gains entry into host cell via binding of viral spike S protein to host membrane receptor ACE2 leading to bisection of S is into S1, S2 subunits by host cell proteases such as CTSL/B (Cathepsin L/B). This cleavage expedites the fusion between the cell and viral membranes for concurrent viral activation. [16] Priming of the (S) protein by the Transmembrane Protease Serine 2 (TMPRSS2) is also needed which is facilitated by severing S. [17] In a study conducted by Li et al. tanscriptional level analysis using GEPIA (Gene Expression Profiling Interactive Analyses) [32, 33], showed augmented expression of CTSL in nine types of tumors [Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBC), Esophageal Carcinoma (ESCA), Glioblastoma Multiforme (GBM), Head and Neck Squamous Cell Carcinoma (HNSC), Brain Lower Grade Glioma (LGG), Pancreatic Adenocarcinoma (PAAD), Skin Cutaneous Melanoma (SKCM), Stomach Adenocarcinoma (STAD) and Thymoma (THYM)]. ACE2 was also found to be upregulated in Colon Adenocarcinoma (COAD), Kidney Renal Papillary Cell Carcinoma (KIRP), PAAD, Rectum Adenocarcinoma (READ) and STAD. This study also narrowed down specific mutations in upregulated genes using c-BioPortal analysis [34]. Genomic amplification of CTSB and CTSL proteases are responsible for the overexpression of these two genes in STAD. In case of ACE2, mutations may play a regulatory role in gene expression in STAD and PAAD. In this particular study, increased expression of both ACE2 and CTSL/B in PAAD and STAD may indicate a greater infection risk for SARS-CoV-2 in PAAD and STAD which needs further validation using a clinical trial.

In another pan-cancer analysis, [35]. CTSL was upregulated in the same 9 cancer types similar to the findings of Li at al [32]. They also showed TMPRSS2 to be upregulated in Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC), COAD, Kidney Chromophobe (KICH), Prostate Adenocarcinoma (PRAD), READ, Uterine Corpus Endometrial Carcinoma (UCEC) and Uterine Carcinosarcoma (UCS). The finding of high expression of TMPRSS2 in PRAD, a type of prostate cancer was validated by its abundant expression in prostate secretory epithelium [36, 37]. Prostate Cancer (PC), the second leading cause of cancer deaths in North America revolves predominantly around a transcriptional cascade system focusing on Androgen receptor (AR) [38]. Consequently, therapies have been targeting AR to inhibit the progression of PC [39] because the androgens facilitates the normal development and function of prostate via AR [40, 41]. Due to its high abundance, TMPRSS2-ERG gene fusions is also a biomarker of PC [36, 37]. Stopsack et al. coined the question of whether the increased TMPRSS2 expression in prostate is involved with sexual dimorphism of COVID-19 [42]. Such dimorphism along with the increased AR expressions via suppressed regulatory pathways may make PC patients more vulnerable to COVID-19 infection [42, 43].These hypotheses can be corroborated by the higher mortality rate seen in male during this pandemic [42]. It can be further strengthened by a 4-fold lower SARS-CoV-2 infection in PC patients undergoing androgen-deprivation therapy (ADT) compared with the cohort not receiving the therapy or even other cancer types [44]. Additionally, many drugs such as Camostat, Nafamostat, and Bromhexine with the ability to directly attack and regulate TMPRSS2 expression are currently in the clinical trial pipelines against COVID-19 patients [45]. Exploiting the overexpression of TMPRSS2 can be a fruitful therapeutic target not only against COVID-19 but also against PC [46].

Another similar study was conducted by Hoang et al. [47] where they tried to assess the expression level of ACE2 and TMPRSS2 in 6 cancer types [Lung Adenocarcinoma (LUAD), Breast Invasive Carcinoma (BRCA), COAD, PRAD, STAD, and Liver Hepatocellular Carcinoma (LIHC)] and compared those values found in malignancies to that of non-cancer patients. With GEPIA2 [33], they found that mRNA levels of ACE2 expression were significantly higher in COAD and STAD which is similar to the findings of Li et al. [32]. mRNA levels of TMPRSS2 expression were significantly lower in BRCA, but higher in COAD and PRAD, compared with the control group. In terms of the TMPRSS2 too, the findings were similar to that of Li et al. and Katopodis et al. [32, 35]. Another interesting fact is that they tried to narrow down the affected pathways. KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis for ACE2 and top 100 co-expressed genes showed that the most significant pathways were phenylalanine metabolism ($p = 0.003$), tryptophan metabolism ($p = 0.001$), vitamin digestion and absorption ($p < 0.001$), steroid hormone biosynthesis ($p = 0.003$), fat digestion and absorption ($p = 0.001$), and Renin-Angiotensin System (RAAS) ($p = 0.006$) [47]. Such extensive involvement of metabolic pathways was also supported by a metabolism-linked hypothesis

regarding NAMPT/ NAD and RAAS and this hypothesis seems to materialize a connection between cardiovascular function [48], lung failure and [49] SARS infections [50]. Both viral infections and malignancy have the ability to modify NAMPT/NAD cascade which insinuates the possibility that metabolic modulation of aberrant cell growth may influence the patient's response to COVID disease [51].

The abovementioned pan-cancer analyses focused on a plethora of cancer types. But the study by Sagkan et al. [52] was solely focused on lung cancer in which comparative mRNA expression of ACE2, TMPRSS2, CD147/BSG and FURIN/PCSK3 genes were performed to determine their expressional dissimilarity among 483 LUAD and 486 Lung Squamous Cell Carcinoma (LUSC) patients and healthy counterparts. Although ACE2 and CD147/BSG gene expression levels were high in both cancer groups, those were statistically insignificant. Among the LUSC patients, downregulation of TMPRSS2 expression was significantly lower compared to their healthy counterparts. [52].

All these in-silico studies mainly estimate the expression levels of such genes which play pivotal roles in COVID-19 infection [32, 35, 47]. The reason of such differential expression of these genes in cancer and non-cancer populations plausibly can shed more light on the phenomenon of higher mortality and vulnerability rates observed in cancer patients suffering from COVID-19 compared to those of their non-cancer COVID-19 counterparts. This data need to be validated with in-vivo studies so that the holistic approach can pave the way to provide better treatment options for this more vulnerable cancer patients suffering from COVID-19 or similar viral infections.

4.2. COVID-19 and colorectal cancer

Gastrointestinal (GI) symptoms such as diarrhea, anorexia, nausea, and vomiting have been observed in patients suffering from COVID-19 [6, 9–11]. Fecal samples also contained SARS-CoV-2 RNA which remained longer in feces compared to those found in respiratory tracts. [53]. Microscopic examinations of enterocytes in cultured human small intestinal organoids also showed to be infected by SARS-CoV-2 [54]. In this study conducted by Liu et al. [55] probable susceptibility of colorectal cancer patients to SARS-CoV-2 was investigated by looking into expressional analyses of ACE2 and TMPRSS2 in colorectal cancer tissue using bulk and single-cell RNA-sequencing (scRNA-seq). Bulk RNA-sequencing profiling showed that ACE2 and TMPRSS2 were expressed at increased levels in human colorectal tumor and normal tissue samples compared to the human tumor or normal tissue samples of lung, esophagus, stomach, and liver (P for all <0.05]. This finding insinuates the colorectum to be a likely route of infection with SARS-CoV-2 in addition to the lungs. Systematic exploration of the expression of ACE2 and TMPRSS2 in human tumor and normal colorectal tissues by utilizing both bulk and scRNA-seq datasets revealed both receptors to be highly expressed in colorectal epithelial cells. Extended probing divulged that patients with colorectal cancer suffering from COVID-19 were more likely to have lymphopenia and higher respiratory rates and hypersensitive C-reactive protein (CRP) levels than were patients with non-cancer COVID-19 population. These results suggest of the vulnerability of patients with colorectal cancer to infection with SARS-CoV-2. [55]

4.3. Immunological interlinks of malignancy and SARS-CoV2 infection

'Cytokine Release Syndrome', a distinct feature of both SARS-CoV-2 infection and cancer refers to the unimpeded overabundance of cytokines which can lead to vascular leakage, coagulopathy, organ dysfunction, and death [56]. IL-6 (Interleukin-6) is a vital component of the unrestricted cytokine storm seen in COVID-19 and is also deemed as a mediator in the transition of malignancy of lungs [56, 57]. Inflammation and carcinogen exposure (example: tobacco smoking) expedites NF-kB signaling pathway which induces KRAS mutations to trigger direct expression of IL-6 on lung epithelial cells [58]. Overexpressed IL-6 espouses lung cancer proliferation and migration through STAT3 signaling [59]. With SARS-CoV-2 infection, Escalated amounts of IL-6 has been found to be associated with disease severity, increased viral load and a contributing factor to complications such as 'Acute Respiratory Distress Syndrome' (ARDS) [60].

One noticeable feature of the hyper-inflammatory response is the predominance of innate immune response, Macrophage Activation Syndrome (MAS), which is characterized by lymphopenia and multi-organ failure [61]. Another interesting finding is that with severity and progression of lung cancer, IL-6 producing cell types can alter. This finding was substantiated by an in vitro 2D lung organoid model in which the early stage IL-6 production in alveolar type II transited to macrophages in the latter infection stage when they became the predominant IL-6 producing cell-type [62]. This MAS induced hyper-inflammation seen in both COVID-19 and cancer patients can be salvaged to an extent with immune checkpoint inhibitors with the elective treatments of steroids [63]. Due to the significant role of IL-6 in both COVID-19 and lung cancer pathogenesis, a detailed protocol about the medication of IL-6 in COVID-19 patients suffering from lung cancer must be established. National Cancer Institute (NCI), along with its clinical trial networks, is recommending tocilizumab, a monoclonal antibody against IL-6R, to lung cancer patients suffering from complications of COVID-19 [64]. A phase II clinical trial (NCT04370834) is in pipeline to assess the efficacy of tocilizumab in patients with COVID-19 and hematopoietic and lymphoid cell malignancies or solid organ malignancies [56]. With the noteworthy role of macrophages in the COVID-19 severity, it is also important to find medications to mitigate its effects. 'Macrophage Polarization' is regarded as a phenomenon by which macrophages produce distinct functional phenotypes as a reaction to specific micro-environmental stimuli and signals polarization [65-66]. Macrophages can be polarized into classically activated (M1) and alternatively activated (M2) macrophages. Hydroxychloroquine (HCQ), a repurposed COVID-19 medicine can cause macrophage polarization by modifying M1 to M2 [67], which eventually would support tumor progression [58]. Such prominent role of macrophages in tumor progression and COVID-19 hyper-inflammation suggests the possible usefulness of macrophage-depleting drugs, such as clodronate and zoledronic acid [68].

4.4. Malignancy specific biomarkers associated with COVID-19

The study presided over by Vanni et al. [69] tried to understand more about the prognostic value of blood tests in a small cohort of 97 Italian cancer patients suffering from SARS-CoV-2 infection where the cohort was divided into 2 groups [moderate, severe]. Despite the reported lower lymphocyte count in severe group, it was proved to be statistically insignificant. Additionally procalcitonin, D-dimer and IL-6 did not reach statistical significance between the 2 sub-groups. Only the CRP (C-Reactive Protein) admission level showed a similar pattern to the general population, with a significantly higher value in the severe group. These unexpected results could be explained by the complex interactions between the hosts' immune system and tumor cells [15, 70, 71]. Despite the small cohort, preexistent immunological impairment of oncological patients seems to affect the host immune reaction towards SARS-CoV-2. Another study conducted at Montefiore Health System among 218 American patients showed elevated D-dimer, lactate, and lactate dehydrogenase (LDH) to reach statistical significance correlated with dying [7]. In the study at MSK center [10], Elevated initial creatinine was associated with increased severity ($P = 0.002$ for ICU/intubation/DNI; $P = 0.002$ for death) [10]. From these studies, it can be inferred that to provide better treatments, previous oncological history should be taken into consideration in times of admitting such patients in the hospitals [69].

5. Epigenetic interlinking between malignancies and SARS-CoV-2

Tremendous progress in sequencing-based technologies has made it possible to detect neoplasm specific epigenetic signatures and epigenetic heterogeneity which are mostly observed in solid tumors [72]. Using suitable controls and genome-wide profiling, cancer-associated changes of DNA methylation, global hypomethylation, and focal hypermethylation were determined as early marks in tumorigenesis. Alterations accumulating in the epigenome can therefore be used to predict cancer risks. [73, 74].

5.1. Epigenetics of the pan-cancer analyses

Some recent studies are trying to explain SARS-CoV-2 disease severity from an epigenetic perspective. According to data derived from several studies, epigenetic modifications indeed have been found to contribute significantly in the severity progression of COVID-19 [51, 56, 57] via altering the overall process from the initial viral interaction with host ACE2, to the subsequent viral pathophysiology [75–77].

Some pan-cancer analyses also tried to investigate epigenetic changes associated with the pivotal host genes to comprehend more about their differential expressions. To explore the influence of epigenetic modification on the mRNA levels for CTSL and ACE2 in PAAD and STAD, CpG probes targeted the promoters of the CTSL and ACE2 genes, respectively [32]. With a combination of Methylation450k profiles and the DiseaseMeth database [78]; the results demonstrated that DNA methylation of CTSL is significantly decreased in PAAD but not in STAD when compared with normal tissues. DNMIVD (DNA Methylation Interactive Visualization Database) analyses showed negative correlation of ACE2 methylation with PAAD and STAD [79]. Using the Ualcan database, expression of ACE2 from GEPIA were correlated with the methylation status. For most of the cancers there was a strong correlation of the gene expression with its promoter methylation status in agreement with the findings for ACE-2 [35] [80]. CTSL in COAD and READ has a higher beta value and resultant lower expression of the gene. In case of STAD, the lower methylation of the promoter, leads to higher expression. In LUSC and BRCA, the very high methylation rate of the TMPRSS2 gene leads to a very low expression level, while the very low methylation rate of the same gene in PRAD and READ lead to very high numbers of gene transcripts [35]. In terms of different cancer types, the same epigenetic mark can be associated with diverse expression levels. Without incorporation of large-scale wet lab experimentations with such in-silico analyses, a comprehensive picture about the significance of epigenetic changes to link up malignancy and COVID-19 is harder to manifest.

5.2. Consequences of epigenetic changes in IL-6 and ACE2 associated with COVID-19

Yao et al. conducted a study to elucidate the regulatory effect of chromosome 3p21.31 (genetic susceptibility locus for COVID-19) [81] in immune cell lines (THP-1, HL-60, Jurkat, and K562 resembling human monocytes, promyelocyte, T lymphocytes, and erythroid respectively) [18]. With CRISPR/Cas9 mediated genomic deletion, CCR9 and SLC6A20 were found to be target genes in the locus. Their investigation revealed six fine-mapped variants (rs34326463, rs76374459, rs73064425, rs13081482, rs35652899, and rs35044562) overlapping human T-cell specific primed enhancers. These findings insinuate of an epigenetic regulatory mechanism that can influence the T cell functions towards SARS-Cov-2 infection [18].

IL-6 can regulate the expression and functions of multiple genes by inhibiting methyltransferases, DNMT1 and DNMT3B [19, 20]. In inflammation-induced ARDS, [82] IL-6 is activated in dendritic cells by the acetylation of transcription factor KLF4 [83]. A combination of epigenetic phosphorylation and acetylation marks on Herpes virus encoded viral IL-6 can induce STAT3 activity [84]. All these prior studies strengthen the assumption that IL-6 may be epigenetically altered in case of COVID-19 infection. To test such assumption, using Chip-Seq and ATAC-Seq datasets from 839 and 157 cell/tissue types of humans and mice through ENCODE respectively (https://www.encodeproject.org/) [85]; Sang et al. discovered significant comparative existence of H3K4me3 and H3K27ac markers between IL-6 and ACE2 gene promoters in various humans and mouse samples. Interestingly, such epigenetic enrichment were found in greater quantity in these human genes compared to their mouse orthologs. In both distal and proximal regions of the hACE2 (Human ACE2) gene promoters, 2–3-fold more positive histone modifications marking insinuate of higher ACE2 activation and transcription compared to their mouse counterparts. According to their findings, elevated expression of non-ISGs (Interferon Stimulated Genes) such as IL-6 and ACE2 could be biomarkers for the exacerbation of inflammation underlying some viral infections, especially those similar to SARS-CoV-2, which dysregulate the physiological function of ACE2 in the RAAS-centric body system [76].

In another study, using four different public databases for lung tissues, Chlamydas et al. found gender-specific DNA methylation at two CpGs sites of the *ACE2* gene [86]. Using Illumina DNA methylation array data from samples of different biological ages, one CpG (cg085599149) near the *ACE2* transcription start site was discovered which displayed decreased methylation level during aging [87]. Prior studies also reported fluctuations in methylation levels in association with aging, age-related inflammation and immune response. In accord with these observations, DNA methylation was deemed as one of the main mechanisms appropriated by MERS-CoV to alter host adaptive immune response. Such findings corroborate with higher mortality incidents observed in aging population infected with COVID-19 [87, 88]. COVID-19 patients suffering from endometrial carcinoma or renal papillary cell carcinoma showed curtailed levels of ACE2 due to hypomethylation and concurrent impaired immune infiltration [89].

Another epigenetic enzyme histone deacetylase Sirtuin 1 (SIRT1), which can exert modulation on ACE2; has been found to be upregulated in the lung of patients with severe COVID-19 comorbidities [90].

Besides, ACE2 and IL-6, in SARS-CoV-2 infected patients, the surge of cytokines such as interleukins, colony stimulating factors (CSFs), and growth factors (GFs) also have been found to contain increased epigenetic modifications [91, 92]. Another Transcriptome analysis and system biology predictive study conducted by Khademul et al. created protein networks to observe host and viral protein interaction and projected the role of host epigenetic regulators in the dysregulation conferring towards disease severity [93]. According to their study, SARS-CoV-2 proteins can target several epigenetic factors, such as HDAC2, DNMT1, CUL2, MOV10, RBX1 and TLE1, to alter the hypoxia related responses. Epigenetic factors contributes remarkably in maintenance of lung pathobiology, and aberrations in their regulation can exacerbate towards many lung diseases such as COPD progression [94, 95].

5.3. Epigenetic changes associated with vaccination

Another mentionable epigenetic findings relevant to COVID-19 infection is associated with vaccination. Exposure to live Bacillus Calmette–Guérin (BCG) vaccine is found to boost pathogen-agnostic antimicrobial resistance in myeloid cells via changes in chromatin conformations. Resultant conformational modifications in innate immune cells can confer epigenetic change in form of a pattern of exposed enhancers and promoters of host-defense genes. Such epigenetic changes may plausibly show accelerated responsiveness in its ability to influence gene expression which may show resistance against infectious diseases, including Covid-19. [96, 97].

6. Impact of COVID-19 vaccines in cancer patients

6.1. Prioritizing cancer patients for vaccination

With emergency use authorization (EUA) from FDA for nucleoside-modified mRNA-based vaccines Moderna and Pfizer, we have seen the glimmering hope against the battle of COVID-19 pandemic [98, 99]. Unfortunately, even with over 60 different COVID-19 vaccines at different stages of clinical development, on issue of the safety, tolerability and efficacy of COVID-19 vaccines in cancer patients, there exists a data paucity due to the exclusion of patients with active malignancies from most of the vaccination trials [100]. As a proof to that statement, the participation of only 3.7% cancer patients among 43,540 participants enrolled in the trial of BNT162b2 can be mentioned [101]. More relevant data generation on the efficacy and safety regarding the COVID-19 vaccines in patients with cancer, especially patients undergoing active cancer therapy should be prioritized. Due to the associated greater risk of fatality and complications, patients with cancer are considered a high-priority subgroup for COVID-19 vaccination. Realizing that, organizations such as American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO) and the Association of American Cancer Institutes (AACI), have urged the Centres for Disease Control and Prevention (CDC) to prioritize patients with cancer for COVID-19 vaccination [102–104]. Similar phenomenon was observed in Europe as well where all type of cancer patients including those receiving active therapies were recommended to get vaccination. This scene was bolstered by the advisory preliminary reports of the European Society for Medical Oncology (ESMO), the Society for Immunotherapy of Cancer (SITC), the Spanish Medical Oncology Society (SEOM) and the National Comprehensive Cancer Network (NCCN) COVID-19–20 [105–107].

6.2. Reports from COVID-19 and cancer taskforce

After ensuring the cancer patient group as a priority group for vaccination, an inequitable distribution of COVID-19 vaccines should also be maintained, especially in Low and Middle-Income Countries (LMICs). A global system like COVAX is trying to ensure unbiased vaccine distribution in LMICs but only can cover 20% of the populations of recipient countries [108]. To understand more about the implication of COVID-19 on the vulnerable malignancy patients, COVID-19 and Cancer Taskforce commenced the investigation into the current global availability of COVID-19 vaccines and the variety of national strategies for covering cancer patients and health-care workers till March 31, 2021 [109]. A diversified global picture ranging from well-advanced vaccination programs for patients with cancer (UK) to countries without any vaccine supplies (Iraq and Guatemala) came into being by the Taskforce's reports. Another mentionable finding is the variability seen among countries on the mass vaccination campaigns in terms of planning, procurement, and distribution of COVID-19 vaccines. Of the 29 countries with access to any type of COVID-19 vaccine, patients with cancer are prioritized only in 9 (26%). Regrettably, with mentionable exception as the VOICE, a multi-center, multi-cohort study based in Netherland which consist of patients with solid malignancies receiving active anticancer treatment who have been vaccinated against COVID-19; very few national systemic data collection from patients with cancer receiving COVID-19 vaccines exist [110]. The inability to access vaccines is the single most cataclysmic obstacle to receive vaccines for many patients with cancer in some of the most vulnerable settings. But lack of proper management and failure in inclusiveness of cancer patients in mass vaccination campaigns are found to exist in well-resourced health systems too. Prioritized, fast COVID-19 vaccination of health-care workers and cancer patients is indispensable to alleviate the existing delay in providing proper cancer treatment.

6.3. Recommendations regarding vaccination for patients of oncological clinical trials

Oncological clinical trials are of paramount importance for providing new, better, improved treatments in various rare malignancy types but a drastic decline in patient enrolment has been observed across oncology trials of all phases (from trials of screening and/or prevention strategies to phase I, II and III trials) [111, 112] during the pandemic. The necessity of regulatory protocol modification by organizations like FDA and the EMA (European Medicines Agency) are required to maximize patient safety during the COVID-19 pandemic [113, 114]. Patients with cancer including those enrolled on clinical trials, should be prioritized for COVID-19 vaccination. The timing of vaccination of patients enrolled on phase I trial should be based on the category of the anticancer treatment and the stage of the trial with being vigilant about any perplexing variables that can incite detrimental effects due to investigational drugs or vaccines, especially during the dose-limiting toxicity (DLT) window [115]. To minimize the search to pinpoint the cause of resultant hypersensitivity as the consequence of either the investigational oncological drug or that of the vaccine administration, the timing of vaccination can be calculated early based on the mechanism of action of the anticancer agents. Patients with solid tumors or hematological malignancies who are recipient of cytotoxic therapies, targeted therapies, hormone therapies and/or immunotherapies should be vaccinated against COVID-19 at the earliest available opportunity exempting only those patients who received transplantation or adoptive cell therapies. In these exempted patients, vaccination can be delayed for $\geq$3 months to enable these patients to regain adequate immune function [116].

6.4. Consequences of EPR effect on liposome carried based vaccines

A very interesting problem of vaccination can be the EPR [Enhanced Permeation and Retention] effect, a phenomenon where lipid based nanoparticles easily leave the blood flow and reach cancer cells provided that their size is less than 200 nm. Reduced lymphatic drainage also contribute to the accumulation of such nanoparticles in the tumor microenvironment after leaking out of the blood vessels [117, 118]. Two of the advanced, successful vaccine candidates (Moderna mRNA-1273 and Pfizer BNT162b2) are both delivered enclosed in liposomes (<200 nm particles) which theoretically make them vulnerable to the EPR effect resulting in a possible misplaced accumulation of the target therapeutics in tumor surroundings [98, 99]. The possibility of this occurrence taking place in solid tumor patients is a concerning issue regarding COVID-19 vaccination which unfortunately has limited clinical data about active cancer patients; mostly because their lesser participation in the clinical trials. If this EPR effect actually materializes; COVID-19 vaccines, especially the carrier liposomes should be modified. But an assuring fact is that COVID-19 vaccines are administered by the intramuscular (IM) route, and the preclinical data suggest that encapsulated proteins in liposomes administered intramuscularly do not amass at a neoplastic site and systemically is distributed across the body [119]. Nonetheless, the efficacy of the promising mRNA COVID-19 vaccines administered enclosed in nano-lipid carriers should be assessed cautiously among solid tumor patients and associated clinical data should be rigorously listed and monitored [120].

7. Conclusion

To understand the higher mortality rates observed in cancer patients who suffered from SARS-CoV-2 infection, an in-depth understanding of the possible genetic and epigenetic interlinks between these two disease entities can play a significant role. The heterogeneity in cancer types, causative mutations and mechanisms make it difficult to narrow down such intertwined pathways. In this review paper, the altered immunological changes, differential expression of pivotal host genes of COVID-19 in different cancer types are discussed from both genetic and

epigenetic perspectives with a hope to shed some light on why cancer patients are more vulnerable to COVID-19 infection. In case of an unprecedented calamity like COVID-19, cancer patients are at a greater disadvantage due to lack of sufficient knowledge of possible links between the two etiologies. The aim of the narrative review paper is to draw the attention of the readers to the possibility that genetic and epigenetic alterations existing in malignant pathways may be responsible for the increased complications seen among cancer patients suffering from COVID-19 In the latter part of the review, the necessity to prioritize cancer patients in vaccination camping is discussed and the pathetic global scenario of vaccination among this vulnerable group is also explored. The need to vaccinate cancer patients can't be overemphasized as they are already found to be more affected by COVID-19 infection. Also, any changes in clinical parameters or biomarkers associated with vaccination among cancer patients need to be assiduously recorded. These data may help to find possible biomarkers which may vary significantly owing to viral infections. Required modifications or improvements of vaccines can also be possible with collection of such clinical data. This review works with different aspects of cancer such as genetic, epigenetic changes, epidemiological studies, biomarkers, vaccination scenario in association with SARS-CoV-2. As the limitation of the review, the inclusion of a wide range of topics can be addressed which may seem a bit broad at a first glance. But it is deemed necessary to include such a variety of topics to create a holistic picture of cancer in association with SARS-CoV2 infection.

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