

## Original Research Article

# Incidence, Risk Factors and Mortality of COVID-19 among Cancer Patients: A Meta-Analysis

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**Abstract:** Cancer is among the fatal diseases caused by abnormal cell growth from one organ that can invade and destroy adjacent organs. These abnormally growing cells are caused by defects in the gene sequence of the living organisms. These unregulated, proliferating cells exceed their normal boundaries to infiltrate adjacent bodily tissues and/or move to other organs. Cancer is the second leading cause of death globally, responsible for more than 10 million deaths in 2020 alone. Cancer is the second most common non-communicable disease to cause death. Currently, the health systems around the world are facing a huge challenge in finding a proper cure for cancer. Lung cancer is the leading cause of cancer deaths in China, followed by liver cancer, stomach cancer, esophageal cancer, and cardiovascular disorders, which together account for 43% of all deaths. Currently; the health system is facing huge challenge on the proper cure for cancer. This is because cancer is not one disease but many disorders that share a profound growth dysregulation of cells. The peculiar traits of cancer, including altered cellular metabolism, unlimited capacity for replication, sustained angiogenesis, the ability to invade and metastasize, the ability to evade apoptosis, self-sufficiency in growth signals, evasion of immune surveillance, and insensitivity to growth-inhibitory signals, are to chastise for this growth dysregulation. Due to their poor general health, concurrent illnesses, a systemic immunosuppressive condition brought on by cancer itself, and some drugs as conventional immune checkpoint inhibitors (ICIs) used to treat cancer, cancer patients are more vulnerable to different infectious diseases. Hence, cancer patients are more vulnerable to coronavirus infection. The main goal of this study was to conduct a meta-analysis of COVID-19 incidence, risk factors, and mortality among diverse cancer patients. We narrowed our attention to both inpatients and outpatients with Covid-19 symptoms during the outbreak. Google Scholar, Science Direct, and PubMed were four online databases we used to search for and locate the relevant cohort studies. We heavily drew from research that involved cancer patients who were impacted by COVID-19 between January 2020 and March 2023. According to 21 studies involving 492,115 individuals, the overall COVID-19 incidence was 27% (95% CI: 0.243–0.296), I<sup>2</sup>=99.98%, p0.001). According to a pooled meta-analysis; Lung cancer (OR 2.0, 95% CI 1.38-2.90, P0.0001), hematologic cancer (OR 1.46, 95% CI 1.09-1.97, P0.0001), and late-stage cancer (OR 1.72, 95% CI 1.24-2.39, P 0.0001) were recorded as risk factors for COVID-19. Mortality was assessed in 11 studies involving 10311 COVID-19 positive cancer patients and 198047 COVID-19 positive non-cancer participants. During a median follow-up of 1 to 2 months, 1915 (18%) cancer patients passed away, compared to 9867 (5%) non-cancer participants; this difference was statistically significant (OR =6.3, 95 percent CI: 5.81-6.84, P 0.00001, I<sup>2</sup>=99%). We found that COVID-19 is more common to cancer affected individuals than in non-cancer patients, with a 6-month incidence rate of 27%. The risk factors for COVID-19 include lung cancer, hematologic cancer, anticancer treatments, late-stage malignancies, and advanced age. COVID-19 has a higher mortality rate in cancer patients when compared to non-cancer patients.

**Keywords:** COVID-19, Lung cancer, hematologic cancer, Conventional Immune Checkpoint Inhibitors (ICIs), mortality, risk factor.

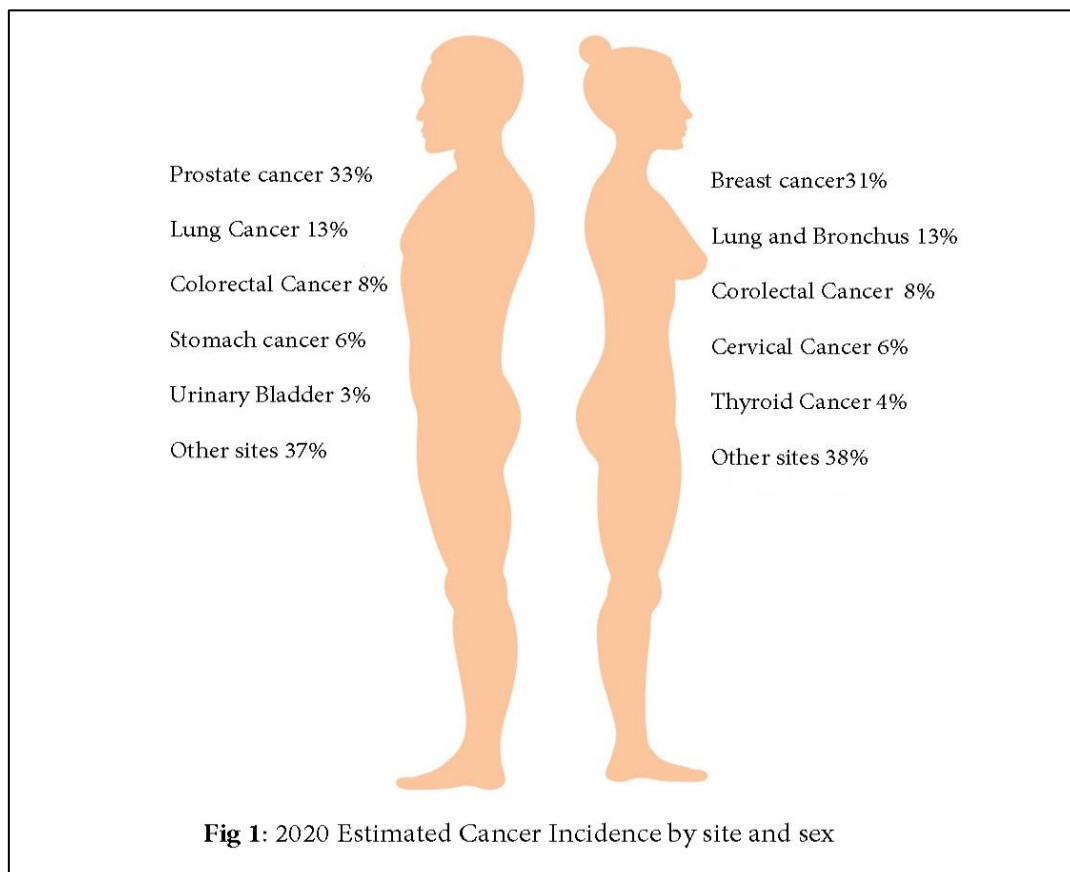
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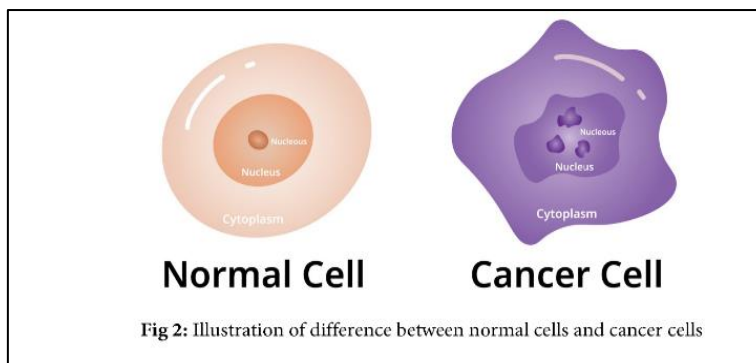
## 1. INTRODUCTION

Cancer is among the deadly non-communicable diseases caused by abnormal cell growth with the ability to invade the surrounding tissues and even the other distant organs. These uncontrolled growing cells, go beyond their usual boundaries and invade other adjoining parts of the body, and/or spread to other organs [1]. More than 10 million people died from cancer in 2020 alone, making it the second biggest cause of death in the world [2]. The second-leading cause of death from non-communicable diseases in the US is cancer, only cardiovascular diseases take the first position [3]. Lung cancer is the most common type of cancer, followed by liver cancer, stomach cancer, esophageal cancer, and cardiovascular disorders, which together cause 43% of all deaths in China [4].

To date, the health systems all over the globe are facing strong obstacle in finding the cure for cancer. This is because cancer is not one disease but many disorders that share a profound growth dysregulation of cells. This growth dysregulation is caused by the bizarre characteristics of cancer, such as altered cellular

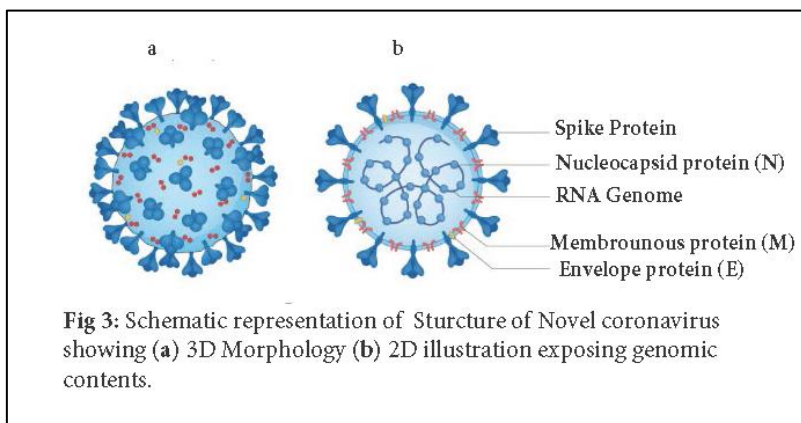
metabolism, limitless replicative potential, sustained angiogenesis, the ability to invade and metastasize, the evasion of apoptosis, self-sufficiency in growth signals, evasion of immune surveillance, and insensitivity to growth-inhibitory signals [5]. Cancer patients are more susceptible to various infectious diseases due to their poor overall health status, coexisting diseases, a systemic immunosuppressive state caused by cancer itself, and some medications such as Conventional immune checkpoint inhibitors (ICIs) used to treat cancer [6-8]. Also, cancer cells produce a heterogeneous group of immature myeloid cells called Myeloid-derived suppressor cells (MDSCs). These cells have strong anti-T-cell activity. Hence, MDSCs can impair antitumor immunity while promoting invasion, angiogenesis, and metastases [9]. As a result, cancer patients are more likely than other populations to contract SARS-Cov-2 and could face more challenging outcomes. Compared to women, who are more prone to acquire breast, colorectal, lung, cervical, and thyroid cancer, men are more likely to develop lung cancer, prostate cancer, colorectal cancer, and stomach cancer [1, 2].





Coronavirus Disease-2019 (COVID-19) is one of the deadliest respiratory tract diseases caused by Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2); the first case of COVID-19 was observed in Wuhan, China, in December 2019 [10-12]. Coronaviruses are enclosed, non-segmented, positive-sense, single-stranded RNA viruses that are commonly found in humans and other mammals. They are a member of the family Coronaviridae and the order Nidovirales [11, 13-15]. There are two categories of coronaviruses: alpha- and beta-coronaviruses that can be transferred to humans and some rodents by bats [16].

Clinical symptoms of COVID-19 include venous thromboembolism (VTE), anorexia, shortness of breath, dry cough, fatigue, and diffuse intravascular coagulation (DIC) [17-20]. Laboratory testing on some COVID-19 patients indicated elevated neutrophil, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and C-reactive protein levels as well as decreased albumin and platelet levels [18, 21, 22]. Another study reveals increased Ferritin levels in all severely ill COVID-19 patients and increased D-dimer levels in some patients [20, 23, 24].



The current published statistics show that older people are more affected by COVID-19 than young children [19]. Due to the high amount of hACE2 in the blood of male elders than female, COVID-19 affect more men than women [25]. Evidence suggests SARS-CoV-2 can induce immune dysfunction and a hyperinflammatory state [10, 26]. This occurs as a result of SARS-CoV-2's spike protein binding to its target cells via ACE-2 receptors, which results in multiorgan failure [26]. According to studies, lower temperatures increase the prevalence of the coronavirus, but higher temperatures decrease the prevalence of COVID-19 [27-29]. Hematologic cancer, lung cancer, and metastatic cancer are currently considered to be strong independent predictors of COVID-19 in cancer patients, according to various published evidence [30-32]. However, according to the recent studies, there are high heterogeneity in the risk factors for COVID-19 [33, 34]. In this study, we employed meta-analysis

techniques to determine the incidence of COVID-19 in cancer affected individuals across various study populations. Additionally, we combined the outcomes of multivariate logistic regression models to calculate the risk variables for COVID-19 development in various cancer patients.

**2. THE AIM OF THE STUDY**

The main aim of this study is to analyze the incidence rate of COVID-19 in cancer patients, the commonest risk factors for developing COVID-19 among cancer patients, and computing the fatality rate of cancer patients with COVID-19 compared to non-cancer patients with COVID-19.

**3. MATERIALS AND METHODS**

**3.1. Study eligibility criteria**

To reach our major outcome of interest, we included retrospective and prospective cohort studies

analysing the relationship between incidence, risk factors, and death from COVID-19 infection for various cancers. We included the studies which published data mainly on lung cancer, hematologic cancer, metastatic cancer, and late stage of cancer who were on cancer treatment when they were tested positive for COVID-19 during the outbreak [7, 8, 30, 32, 35-44]. We also exclude all the randomized controlled trials, case report, case-control studies, and cross-sectional studies. To avoid heterogeneous results, we excluded pediatrics only studies, surgery patients, pregnant women and those with co-infections. Systematic review, editorials, short communications, and letter to editor were also excluded. We included only English written human based peer reviewed published articles. And to avoid data uncertainty, we excluded all unpublished articles.

We didn't use electronic inquiry to investigate the articles; we manually investigated all identified articles used in this meta-analysis. All titles and abstracts were independently extracted by two reviewers and all the controversial matters were resolved by discussion. Potential risk factors for the development of COVID-19 among cancer patients were: lung cancer, hematologic cancers, chronic lymphocytic leukemia (CLL), metastatic cancer, age of the affected individual, and advanced stages of cancer [32, 43, 45-50].

### 3.2. Search Strategy

Between January 1, 2020, and May 31, 2022, we thoroughly searched online databases like PubMed, Google Scholar, and Science Direct for relevant papers. "Cancer" and "COVID-19" were among the search phrases we used, along with outcome terms like incidence, risk factor, and death. The following search criteria were created and used in our advanced search: "Cancer" AND "COVID-19" AND ("incidence" OR "risk factor" OR "mortality"). The studies were included if they met all of the following criteria: reported incidence, risk factors, and mortality of COVID-19 exclusively on the patients who were confirmed to have cancer at the time of the COVID-19 outbreak. Review articles and case studies weren't included in our analysis. We manually searched the references lists of the relevant publications that we identified.

### 3.3. Data Extraction Process

After an initial title and abstract search, two reviewers independently assessed entire papers for inclusion and exclusion criteria. The information that was extracted covered the following topics: confirmation of SARS-CoV-2 infection in cancer patients, study design, time and location of data collection, author name, publication year, country, total reported cases, total mortality, age, type of cancer, and stage of cancer. We used PRISMA checklist to present the results of our analysis [51].

### 3.4. Study Quality Assessment

The quality of the included cohort studies was evaluated using the Newcastle-Ottawa Scale (NOS) [52]. In order to evaluate the quality of the included studies, three key criteria were used: the method used to select the study participants, the coordination of effective confounding variables, and the evaluation of the results. Out of a possible maximum of nine points, articles scoring more than five were deemed to be of high quality [53].

### 3.5. Meta-analysis of incidence and mortality of COVID-19

We computed incidence analysis using the proportion of cancer patients who developed COVID-19 with an OpenMeta analyst. Additionally, we combined the risk factor hazard ratios using the generic inverse variance approach for mortality analysis with dichotomous data, and we computed the Mantel-Haenszel odds ratios (OR) using the number of occurrences in the intervention and control groups of each study. We calculated Mortality estimates using Revman Review Manager version 5.4. The results are presented as least squares means with 95% confidence intervals (CI). All statistical tests reported in this study were two-sided, and  $P < 0.05$  was considered statistically significant.

### 3.6 Assessment of Heterogeneity

We evaluated the heterogeneity of the study using Higgins'  $I^2$  value. Subgroup analysis based on age and cancer type was used to identify significant heterogeneity among the results of the included studies. Significant heterogeneity was defined as an  $I^2 > 50\%$ , after which we used a random-effects model for the analysis. In the cases where  $I^2 \leq 50\%$ , we used a fixed-effects model for the analysis.

### 3.7. Sensitivity Analysis

To find the effect of a single study on the overall study result; we performed a sensitivity analysis by deleting one study at a time to see if the results could be influenced by a single study or studies with a high risk of bias. However, to assess the outcome and ascertain its impact, we used Revman Review Manager version 5.4. The Newcastle-Ottawa Scale was used to evaluate the quality of the evidence in order to give trustworthy evidence for clinical choices (NOS). Funnel plot was used to detect the publication bias [54].

## 4. RESULTS

### 4.1 Description of studies

From the three databases PubMed, Science Direct, and Google Scholar, we found a total of 1235 relevant articles. We then retrieved only 350 articles after thorough screening of the title and abstract from the relevant studies. 50 out of 350 articles were chosen for full text evaluation. After multivariate analysis of the factors, only lung cancer, hematologic cancers, systemic anti-cancer therapy, chronic lymphocytic

leukemia (CLL), metastatic cancer, age of the affected individual, and advanced stages of cancer were considered for final evaluation [32, 41, 42, 44, 46, 48-50]. Only 21 papers with a total of 492,115 participants reported the incidence, risk factors, and mortality of COVID-19 among cancer patients as primary and secondary outcomes. The other 29 publications were not included because of insufficient data, poor study design, and duplication. Finally, this meta-analysis included 21 cohort studies (Fig. 1). All of the included studies' characteristics were listed in table (See Table 1).

**4.2. The incidence of COVID-19 in various cancer patients**

In the 21 remaining studies with 492,115 cancer patients, a total of 7,756 were diagnosed with COVID-19. We present the likelihood of COVID-19 infections in cancer patients in Figure 2. Using Open Meta-Analyst software, we pooled the estimated incidence from reported proportions in individual studies. Using the binary random-effect model, a significant summary estimate (0.229; 95% CI: 0.202-0.256) was found, demonstrating that there is a significant risk of developing COVID-19 among various cancer patients (p<0.001).

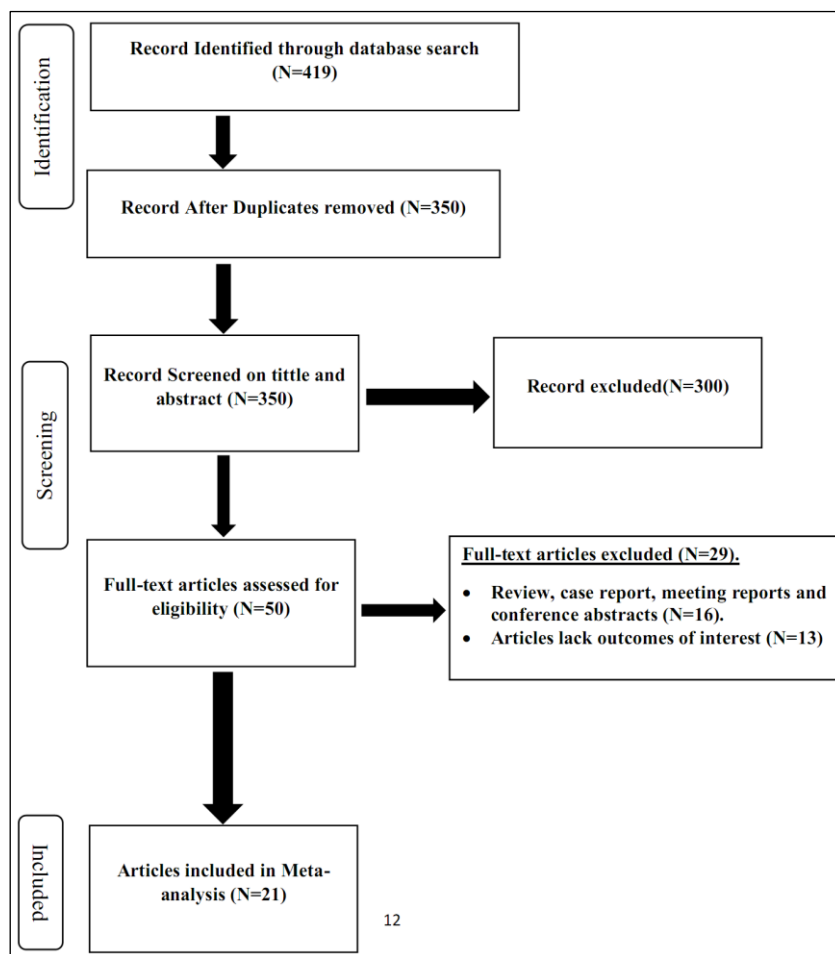
**4.3 Risk factors associated with COVID-19 infection among cancer patients**

We did an analysis for lung cancer (OR=2.0, 95% CI; 1.38-2.90, P<0.00001), hematologic cancers (OR = 1.46, 95% CI; 1.09-1.97, P < 0.00001), metastatic cancer, and advanced stages of other cancers (OR=1.72, 95%CI: 1.24- 2.39, P < 0.0001, showed that all these factors were significantly associated with COVID-19 infection (Figure 3).

**4.4. Mortality rate among COVID-19 infected cancer patients**

After screening a total of 10311 COVID-19 patients with cancer and 198047 COVID-19 patients without cancer, we found that 1915 COVID-19 affected cancer patients and 9867 COVID-19 affected non-cancer patients resulted in death. Statistical analysis confirmed that COVID-19 was significantly associated with mortality in cancer patients (OR = 6.3; 95% CI: 5.81-6.84) as compared with those without cancer patients (Figure 4).

The figure below shows the steps towards the retrieval of the articles used.



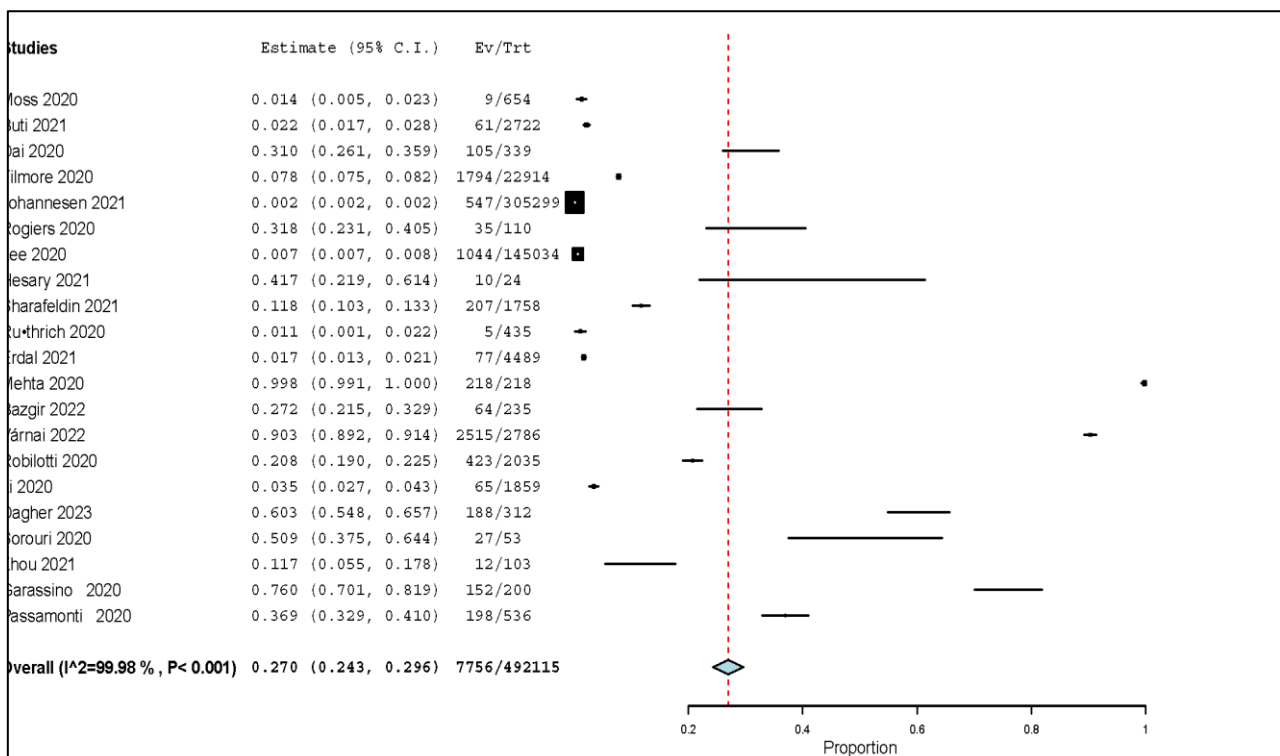
**Figure 4: PRISMA flow chart of Methodological Studies**



**Table 1: Characteristics of included studies**

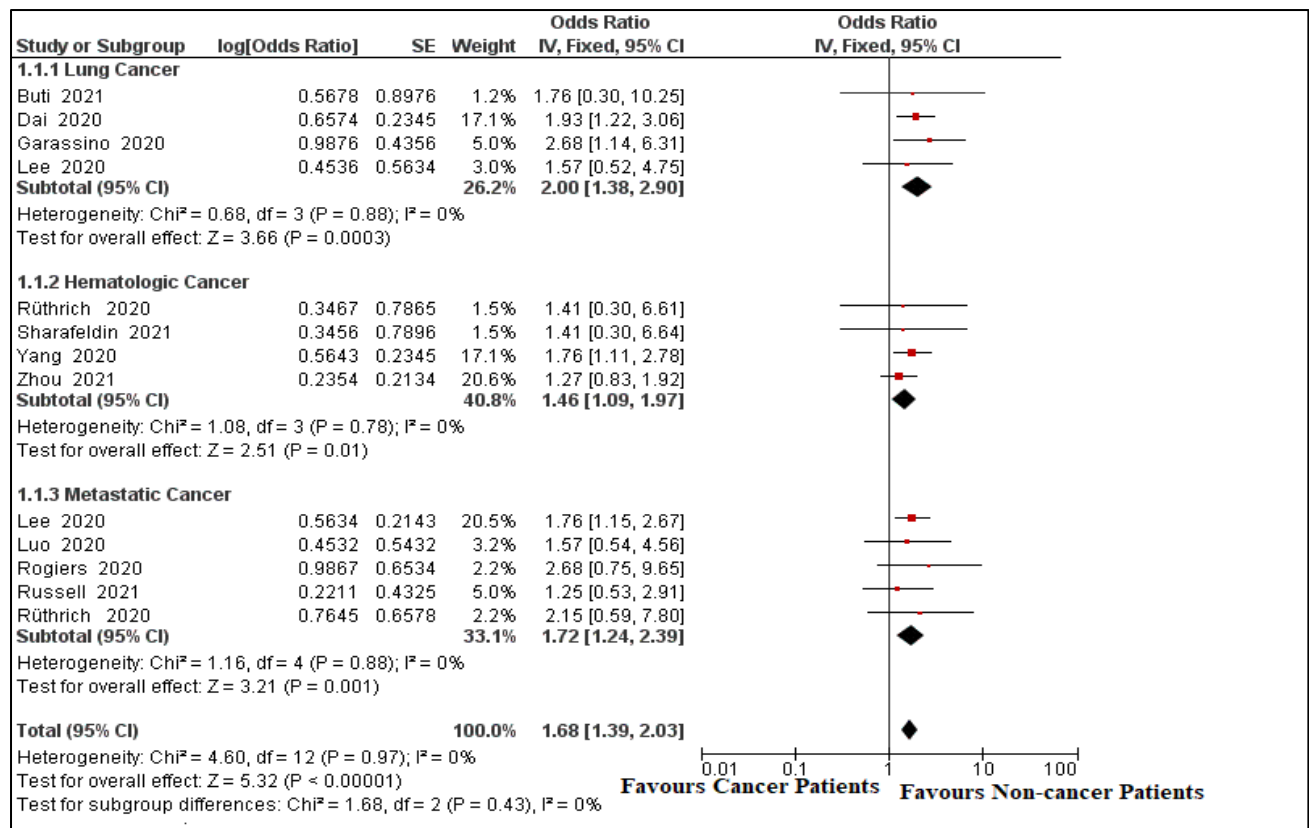
Study ID	Country	Study Period	Sample Size	NOS Score
Moss, (2020) [93]	UK	7-15 May 2020	654	7
Buti, (2021) [94]	Italy	Feb-April 2020	61	7
Dai, (2020) [30]	China	1Jan- 24Feb 2020	105	7
Fillmore, (2020) [95]	USA	May2020	22914	7
Johannesen, (2021) [96]	Norway	Jan 1 – May 31 2020	8410	6
Garassino, (2020) [97]	Italy	March26 – April12, 2020	200	7
Rogiers, (2021) [98]	North America, Australia &Europe	March5- May 15, 2020	110	6
Lee, (2020) [43]	UK	March 18 – May8, 2020	1044	6
Luo, (2020) [99]	USA	March 12 – May 6, 2020	102	6
Chavez-MacGregor, (2020) [100]	USA	Jan1 – Dec 31, 2020	507,307	7
Pinato, (2022) [10]	Europe	2020-2021	2795	7
Jee, (2020) [102]	USA	March – April 2020	309	6
Kuderer, (2020) [103]	USA, Canada & Spain	March17 – April16, 2020	928	6
Lee, (2021) [104]	UK, USA & Sweden	March 29 – May 8, 2020	23,266	7
Sharafeldin, (2021) [105]	USA	Jan 2020 – March, 2021	373,780	7
Russell, (2021) [106]	UK	February – July, 2020	306	7
Yang, (2020) [107]	China	Jan 13 – March 18, 2020	205	7
Zhou, (2021) [108]	China	Feb 10 – April 15, 2020	103	7
Passamonti, (2020) [109]	Italy	Feb 25 – May 18, 2020	536	7
Rüthrich, (2020) [110]	Germany	March16 – August 31, 2020	435	7

Figure below shows the incidence of COVID-19 among Cancer patients.



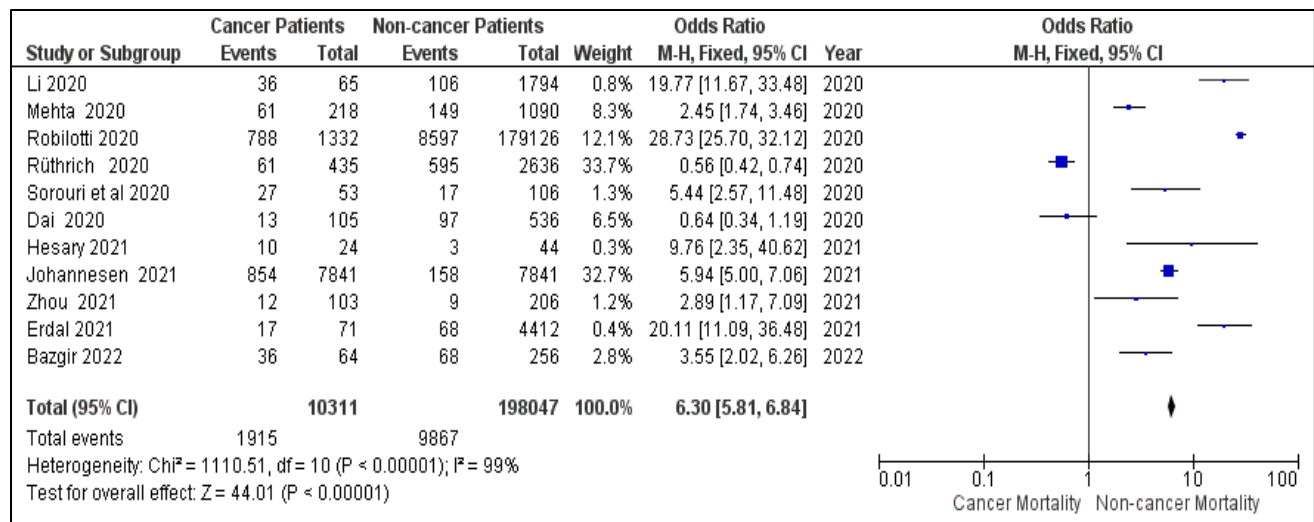
**Figure 5: A meta-analysis of incidence of COVID-19 among Cancer Patients**

Figure below shows the risk factors that are associated with developing COVID-19 among Cancer patients



**Figure 6: Meta-analysis of the reported risk factors associated with development of COVID-19 in Cancer patients**

Figure below shows the mortality rate of COVID-19 among Cancer and non-cancer patients.



**Figure 7: Meta-analysis of risk of Death of COVID-19 among Cancer patients compared to non-cancer patients**

### 5. DISCUSSION

This analysis incorporated findings from 21 published studies including 492,115 cancer patients, 7,756 of whom had the COVID-19 infection. This number is equivalent to an incidence of 27% during 1-6 months of follow-up. After consideration of several confounding factors (multivariate models), we found that older patients >60 years, lung cancer patients, cancer patients using conventional immune checkpoint inhibitors (ICIs), stage IV cancer, and hematologic

cancer patients were the risk factors for COVID-19 among cancer patients [55, 56]. In addition, we found that COVID-19 increases the mortality in cancer patients [40].

Only a small number of cancer patients were COVID-19 free during our study period, despite the virus' estimated incidence risk of 27%. The present study is a wake-up-call to educate these patients and their families about the disease process, which may

include social distancing, using soap to wash hand, sterilizing hand, and the proper application of face masks [57-62]. To prevent sudden mortality in asymptomatic individuals, it is advised that all cancer patients have serial COVID-19 tests and vaccine. Our study revealed that lung cancer, elderly individuals, hematologic cancer, and advanced stages of cancer are all risk factors for COVID-19 infections. Additionally, these cancer patients have a very high COVID-19 fatality rate [63]. We recommend that the medical treatment of COVID-19 focus on virus penetration into host cells and viral replication within the human host because the goals of COVID-19 therapy are to reduce viral load and prevent the consequences of an immune response.

According to studies, corona virus enters the cell through the attachment of the Spike protein to the angiotensin converting enzyme-2 (ACE-2) receptor of the host cells [62, 64], proliferate using protease enzyme [65-67], replicate and transcript using RNA-dependent RNA polymerase (RdRp) enzyme [68-70], and penetrate into host's cell nucleus for replication by binding to importin (*IMP*)  $\alpha$  and  $\beta 1$  [71-73]. Hence, medical treatment of COVID-19 must focus on blocking the aforementioned factors. Remdesivir inhibit viral replication by blocking chain termination in RNA viruses [74, 75], ivermectin can restrict viral penetration by inhibiting viral protein binding to the Importin (*IMP*)  $\alpha$  and  $\beta 1$  [76, 77], lopinavir/ritonavir inhibit synthesis of viral protein [78, 79], and tocilizumab reverse vascular permeability to affected individual [80].

Cancer patients treated with tocilizumab: an IL-6R antagonist, show less symptoms when infected by COVID-19, this is because this medicine can reverse the vascular permeability in the lungs [21, 80, 81]. While cancer patients treated with anticancer medication such as conventional immune checkpoint inhibitors (ICIs) show severe infection rate [8]. That is to say, Patients who are immunocompromised are vulnerable to COVID-19 infections. Hence, COVID-19 infection is serious threat to the patients with cancer as to all immunocompromised patients. Our study speculated that tocilizumab can block the inflammatory mediators resulting in decreasing vascular permeability, remdesivir and ivermectin block viral replication to lower the viral load. These two mechanisms can concomitantly relieve the symptoms of COVID-19.

But medical treatment should be the second line management as mentioned before; preventive measures are of greater importance because; prevention is better than cure. Hence, more emphases should be stressed to the social distancing, use of hand sanitizer, self-isolation, face masks [82]. The WHO has also offered suggestions for preventing infections, such as fundamental advice on properly preparing meat and eggs, washing our hands, and covering our mouths and noses while coughing or sneezing [83]. Although

COVID-19 has been proven to infect people of all ages, the fatality risk is higher in the elderly (those over 60), people with pre-existing medical conditions, including cancer, and people who have compromised immune systems [84]. So far there are various vaccines developed to prevent and control COVID-19 infections and spreading [85]. The primary goal of these vaccines is to reduce the rate of infection in the population at risk [86]. But the ability of those vaccines to stop or reduce infections differ [87, 88]. This is due to the different technology used to engineer those different types of vaccines.

Regardless of the type of cancer, stage IV cancer patients are likely to have COVID-19 [89]. Advanced stage cancers are normally characterized with worse clinical status and prolonged hospital admissions and even death [90, 91]. Cancer patients tend to develop COVID-19 symptoms easily and faster compared with the non-cancer population. Over 25% of cancer patients experience COVID-19 onset in the early weeks of the pandemic compared with other individuals [92]. The present study has shown that the correlation between age and the development of COVID-19 in the cancer population over the period of follow-up indicates that COVID-19 should be expected more in the elder patients than in the general population, suggesting that individuals over 60 years of age must be protected at all costs against COVID-19 infections.

## 6. LIMITATIONS

In regards to this study, it should be taken into consideration the fact that the study comprises of both prospective and retrospective observational studies; hence estimates from this study should be taken with caution. In addition, the included studies had a heterogeneous follow-up period, ranging from short periods of about 1 month to long periods of about 6 months. Another drawback is that we were only able to find English-language articles. Because of data insufficiency, some risk factors were not included in this study. The strength of the study is that we included a total of 21 studies with a total of 492,115 cancer patients. Therefore, despite the heterogeneous individual studies, the sample size gives the estimates some degree of confidence.

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