

REVIEW ARTICLE

A Review on Covid-19 And Cancer Based On Current Evidence

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ABSTRACT

Both COVID-19 and cancer are crucial problems with major public health implications. Because of their increasing prevalence and the fact that they carry an increased risk for morbidity and mortality, a potential association between COVID-19 and cancer has been presumed. As various studies concerning COVID-19 issues have been published, the objective of this review is to appraise critically the literature to clarify the association between COVID-19 and cancer. More extensive research in this field is needed to improve awareness and minimize the chance of potential complications.

Keywords: COVID-19, SARS-CoV-2, cancer, risk, acute respiratory distress syndrome

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had electrified the world by the presence of deadly infectious disease which is also known as coronavirus disease 2019 (COVID-19). World Health Organization (WHO), had briefed the media during the opening remarks related to COVID-19 and declared that 1,524,162 patients had been confirmed to be infected by this virus including 92,941 death had been reported. What makes this news more puzzling was that 213 countries had been affected which means this disease had been spreading throughout the world. The virus which is also known as SARS-CoV-2 tends to attack the respiratory tract and consequently causing the patients to experience acute respiratory distress. 80% of the patients had been reported to have mild symptoms and have good progress towards recovery. The remaining patients had been recorded to have severe infection together with dyspnoea, low oxygen saturation in the blood circulation and may be at a critical state with multiple organs failure (1). Few pieces of research have mentioned that cancer patients who had been infected by SARS-CoV-2 could experience severe clinical course and this may indicate that this category of patients referred to the remaining patients that had been mentioned before.

Basically, cancer is a condition where there is an

occurrence of series of mutations in a gene that causes the specific gene to carry out an abnormal function. It was also had been proved that some chemical compounds have the ability to form a gene mutation and cancer cell inside the human body. The chemical compound can exist in the forms of tobacco smoke, alcohol, exposure to excessive sunlight as well as tanning bed (2). For example, a habit of smoking may lead the person to have lung cancer since the cigarette contains carcinogenic chemical compounds (3). Once the gene had undergone a mutation, it will contribute to few genetic disorders as well as oncogene generation. These including point mutation which may cause the patient to develop into colon cancer by having a mutation at Ras gene, having a chromosomal translocation at Bcr gene and Abl oncogene causing a chronic blood cancer and deletion that occurs at Erb-B gene causing breast cancer to appear. Usually elderly may have a higher chance to have chronic blood cancer due to genetic material exchange between chromosome 22 and chromosome 9. From this condition, there will be a specific released biomarker known as p115. It usually can be detected in 95% of chronic blood cancer patients and this may help the physician to recognize a specific diagnosis for this patient (4). During the pandemic, a follow-up that should be attended by the patient had been postponed in order to minimize the risk of infection as the cancer patient has a high risk to be infected by SARS-CoV-2. From a study done by Maringe et al., in 2020, they estimated that due to several issues such as changes in terms of health-seeking behaviour as well as lack of access to diagnostic service from this national pandemic measures will contribute to an extra larger number of deaths

comes from the patient who has breast, colorectal, lung and oesophageal cancer (5). In this study, we reviewed the relationship between COVID-19 and cancer in order to have clearer look at this matter.

CANCER

Cancer is one of the serious or major public health threats that involving worldwide. In addition, it is also the second leading cause of death amongst the population in the United States. Research done by Cancer Statistic in 2016 stated that the expected frequency of death that may occur in 2016 was about 595,690 since it was corresponding to the amount of death occur per day in 2016 which is 1600 people. The commonest factors of cancer death in females were due to breast, colorectum and bronchus cancer. Nevertheless, for males, the main causes that caused cancer death were colorectal, bronchus and prostate cancer. These 4 types of cancers represented approximately 46% of all cancer deaths. Another 27% of cases of cancer death come from lung cancer (6). Regarding the lifetime probability for each gender were also different. The probability of males diagnosed with invasive cancer was higher (42%) compare to females (38%). It is still not well understood about the factor that increased high susceptibility in men, however to some extent, factors such as endogenous hormones, environmental exposures may influence the lifetime probability for each individual to develop into invasive cancer. In terms of the age of the cancer patient, it was found that adults who were younger than 50 years old specifically women (5.4%) have a higher risk compared to males (3.4%) to have cancer. This is relatively due to the high burden of young women to have cancer like genital, thyroid and breast cancer at this specific age (6).

The total cancer death rate rises in the 20th century, mainly caused by the rapid death of lung cancer patients who mainly came from males. The rising case of lung cancer appeared as a consequence of the high usage of tobacco (7). A lot of preventions have been made in terms of constant and steady reduction of smoking habit, treatment, as well as early detection contributed about 23% drop in cases of cancer death due to lung cancer. It is interesting to note before 1941, the death rate came across as higher in females compared to males due to uterine cancer. Uterine cancer usually involved both the uterine corpus and uterine cervix. This phenomenon leads to a major cause of death among women in the early 20th century. Nonetheless, there was quite a drastic decline in cancer death specifically in uterine cancer cases for more than 80% between 1930 to 2012. This is mainly attributable to the Papanicolaou test widespread among the population toward the early detection and prevention of uterine cancer. Similar to the previous fact, stomach cancer has also undergone rapid decline which only accounted for about 20% and 30% of female and male death respectively in the 1930s as well as 2% only

in 2012. Even though, the decreased in cancer death of stomach cancer is not fully understood, one of the main factors was the lower prevalence of *Helicobacter pylori* infection.

Furthermore, brain cancer had surpassed leukaemia to be the most leading death cause among adolescents and children. However, from 1970 to 2012, the death rate among this age group had declined particularly for leukaemia about 76% compared to 31% for a brain tumour and other nervous systems as a result of therapeutic advances to treat a patient with leukaemia (8). The majority of the children who have cancer came from patients who have leukaemia (30%) where about 76% of them have lymphoid leukaemia. Next, brain cancer and other nervous systems which represented about 26% among the children were the second common type of cancer experienced by the children, proceed with soft tissue sarcomas for about 7%, neuroblastoma (6%), non – Hodgkin lymphoma (6%), Wilms tumour (5%) as well as Hodgkin tumour (3%) (8).

COVID-19 OUTBREAK

Since 12th December 2019, there was a continuous occurrence of acute respiratory distress disease appeared in Wuhan City, was told to be originating from Hunan South China Seafood market (9). Chinese scientists had isolated the unknown virus sample from the patient with acute respiratory distress on 7 January 2020. After sequencing its genome using the next gene sequencing tool, they found that the unknown viral genome was 70% similar to the homology of severe acute respiratory syndrome coronavirus. In addition, that specific unknown viral also has similarity for about 95% to coronavirus RaTG13 of Yunan bat (10).

SARS-CoV-2 is a large, enveloped, spherical, single-stranded RNA virus genome and beta coronavirus (11). It is also made up of 4 important structural proteins which are membrane (M), nucleocapsid (N) protein, envelope (E) and spike glycoprotein (S) (12). The spike glycoprotein normally will be used by the SARS-CoV-2 to inhibit the neutralizing antibody's activity. Usually, the neutralizing antibody plays role in preventing the viral particle from adhering to the host cells in order to infect the cells. For further info regarding the pathogenesis on how it infects the host cells, is due to S protein. It consists of S1 and S2 domains. When there is an interaction between the S1 domain and the receptor at the host cell which is known as Angiotensin-Converting Enzyme 2. This simultaneously will change the conformational shapes in a component of S protein. S2 domain help in the process of fusion between virus membrane and host cell membranes, which allows the virus to enter the host cells (13). SARS-CoV-2 structures and characteristics are found to be different from MERS-SARS and SAR-CoV and being explained as below (Table I) (14,15,16,17,18).

SARS-CoV-2 usually has the potential to be transmitted from one person to another person. In addition, the person also can be infected by SARS-CoV-2 when ingesting infected animal or meat either in a semi-cooked or raw form. COVID-19 was categorized as a zoonotic disease due to its characteristic where the virus enables to undergo mutation as well as allowing it to replicates and infect the person. Normally, the virus is able to spread from symptomatic as well as asymptomatic patients through oral fluid droplets specifically airborne such as coughing and sneezing (19).

Apart from that, there are several symptoms that may appear when the person had been infected by this virus. Commonly, the patient may experience fever, fatigue and malaise as well as cough. Several patients may have mild symptoms such as runny nose, flu, muscle pain, sore throat or sometimes diarrhoea. In the worst condition, the patient may have organ failure, for instance, kidney failure, acute respiratory infection or it can be severe pneumonia as well as septic shock which

will eventually lead the person to progress towards death (19). Nonetheless, there are infected persons who do not show any symptoms and do not feel sick. These individuals are categorized as asymptomatic carriers and they are still able to transmit the disease to another healthy person. The person who is highly susceptible toward this virus are commonly elderly, children, pregnant ladies and people who have a chronic disease such as diabetes, heart disease, kidney, and liver disease. Furthermore, the person who has been infected by HIV, cancer, have a smoking habit and autoimmune disease, they are labelled as an immune-compromised patient which is also highly vulnerable to this virus.

To date, World Health Organization (WHO) gives us the facts on the many forms of vaccines such as Corminaty, Coronavac, AstraZeneca and many more. Being vaccinated does not mean that we are completely protected, particularly with the new emerging variants and research is still ongoing in clinical and pre-clinical development on the effectiveness (20).

Table II: The similarities and differences between the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

	SARS-CoV	MERS-SARS	SARS-CoV-2
Coronavirinae Genera	b-coronavirus, lineage B	b-coronavirus, lineage C	b-coronavirus, lineage B
Virus type	RNA virus	RNA virus	RNA virus
Total length of DNA sequence	29,751	30,111	29,903
Discovery (y)	2002	2012	2019
Origin	Guangdong, China	Arabian Peninsula	Wuhan, China
Total number of cases worldwide (WHO report)	>8000	2494	2230,439 (Till 17 th April 2020)
Total number of affected countries (WHO report)	26	27	210
Total number of death cases (WHO report)	916	858	150837 (As of April 2020)
Mortality	>10%	34.4%	2.10%
Transmission mode	Droplets (coughing, sneezing) Close contact with an infected person	Droplets (coughing, sneezing) Close contact with an infected person	Droplets (coughing, sneezing) Close contact with an infected person or asymptomatic ones
Transmission medium	Animal to human Human to human	Animal to human Human to human	Animal to human Human to human
Transmission region	Globally	Regionally	Globally
Cellular receptor	Angiotensin-Converting Enzyme 2 (ACE2)	Dipeptidyl peptidase 4 (DPP4)	Angiotensin-Converting Enzyme 2 (ACE2)
Reservoir	Palm Civets and Bats	Bats and Camels	Bats
Receptor binding domain (RBD)	C-domain	C-domain	C-domain
IFN γ inhibitor	Yes	Yes	Unknown
Viral replication efficiency	High	Higher	Higher
Pathogenicity	Higher	High	High
Clinical symptoms (WHO report)	Fever, malaise, myalgia, headache, diarrhea and shivering (rigors)	Fever, cough, shortness of breath	Fever, tiredness, dry cough
Prevention	Hand wash Wear mask and gloves Physical distancing	Hand wash Wear mask and gloves Physical distancing	Hand wash Wear mask and gloves Physical distancing
Treatment	Glucocorticoid and Interferon	No vaccine or specific treatment	No specific antiviral treatment

MERS-CoV = Middle East respiratory syndrome coronavirus; SARS-CoV = severe acute respiratory syndrome coronavirus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

But, there is yet not any ultimate antiviral therapy had been approved by WHO to be effective in combatting COVID-19. Despite this, several existed medications can be repurposed to ease the symptoms of COVID-19 and later will treat the patient from this disease (Table II) (20,21). World Health Organisation had established and emphasised strict guidelines for this pandemic. The precautionary measures that should be taken by the community to prevent the infection are avoiding any handshakes, practising handwashing regularly, wearing masks when going outside of the home, the social distance between each other for about 1 m to 2 m apart as well as self-quarantine when the person starts to have any similar symptoms to COVID-19. The public also had been advised to avoid having unnecessary visits to high-risk areas. All these alternatives should be practised in addition to suppressing the viral infection from spreading widely (22).

CANCER PATIENTS IN SARS-COV INFECTION

In China specifically on the date 12th February 2020, it is reported to have 42747 cases and 1017 deaths due to rapid transmission of a virus known as SARS-CoV-2. Simultaneously, the same cases had been reported in other 25 countries. For instance, developing countries such as the United States, Spain as well as Japan. This causing the latest public health emergency of international concern to be proclaimed by the World Health Organization due to a new novel of coronavirus caused by this specific virus (23). As opposed to Middle East Respiratory Syndrome (MERS) and Severe Acute

Respiratory Distress (SARS), COVID-19 had resulted in a bigger number of deaths. Patients who died due to COVID-19 were reported not having only respiratory failure, but also having multiple organs failure which leads them to progress to death. This proved that COVID-19 brought severe destruction in the patient's body compared to a patient with MERS and SARS (23).

Additionally, it was proved that SARS-CoV RNA can be found abundantly in a stool sample. It had been proved that ACE2 protein can be found mainly at the brush border of enterocytes situated at most parts of the small intestine such as the duodenum, jejunum and ileum. Nevertheless, ACE2 cannot be found in the gastric and colon due to the absence of brush-border staining (24). ACE2 protein was one of the receptors for SARS-CoV to invade the host cell. Researchers found that SAR-CoV can be found abundantly at the site of the small intestine and this strengthens the fact that it is possible for this specific virus to be transmitted through faecal-oral route transmission. Aforementioned in the facts above, there is another research done by To KF in 2004. The researcher proved that ACE2 protein also can be found profusely on smooth muscle and endothelial cells at almost all parts of organs in the body. This fact suggested that once the virus was circulating throughout the blood circulation, it may spread and invade most of the organs throughout the body. This means that any inflammatory changes and vascular abnormalities experience by the patient at various parts of the organ may therefore be linked to the systemic toxic effect that had been caused by SAR-CoV (25).

Table II: Drugs and their potential mechanisms for inhibiting SARS-CoV-2 infection in humans

Drugs	Mechanism
Remdesivir	Blocks viral RNA dependent RNA polymerase activity
Chloroquine and Hydroxychloroquine	Inhibits endocytosis
Ropinavir and Lopinavir	Inhibits RNA translation process
Camostat Mesylate	Inhibits enzymatic activity of type 2 transmembrane serine protease
Darunavir	Blocks viral replication
BCR-ABL kinase inhibitor imatinib	Inhibits fusion of virions with the endosomal membrane
Arbidol	Inhibits membrane fusion of virus envelope
Ribavarin	Inhibits viral synthesis and mRNA capping
Ribavarin plus interferon beta	Shuts down viral replication
Umifenovir	Inhibits fusion of virions with the endosomal membrane
Oseltamivir	Inhibits RNA translation process
Interferon-beta	Triggers the activation of innate antiviral immunity
Favipiravir	Blocks viral RNA dependent RNA polymerase activity
Monoclonal antibody	Inhibits viral infection via binding to the virus

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Most of the patient that had been infected by this virus were diagnosed to have necrosis located at spleen and lymph nodes. Lymphopenia was one of the cases that can be found in patients with SAR-CoV (26). It is a condition where the amount of lymphocytes in the patient's blood is very low. The lymphocyte is one of the main components that play roles in the defence system of the body, usually by fighting the infection and produce a sign of inflammation. Nonetheless, lymphopenia not only can be found in a patient who has been infected by COVID-19, but this condition also consistently presents in a patient who had been contracted with severe disease. This showed that the condition, lymphopenia might not be a great marker to prove that patient is being infected by COVID-19 (27). Furthermore, it also had been found that SARS-CoV may cause a clinical manifestation such as inflammation of several organs such as the heart, kidney, adrenal gland and liver. In addition to that, systemic vasculitis, apoptosis and swelling of endothelium cells also may occur (28). From these above findings, it can be concluded that ACE2 protein that can be found abundantly throughout the body may cause the destruction of various organs and became one of the routes for the virus to infect the host cells.

In the context of risk for the cancer patient to get SARS-CoV infection, it was reported that the person who has cancer have higher susceptibility to contract SAR-CoV infection compare to the individual without cancer. Malignancy of cancer and anticancer treatment for instance surgery and chemotherapy contribute the patient to have a systemic immunosuppressive state (29, 31). This can be concluded that cancer patient may have a higher risk to have COVID-19 infection and may experience poorer prognosis once they get infected compare to a non-cancer patient. From research done by Liang et al., on 2020, it was found among all the type of cancer, the patient with lung cancer was more susceptible to get an infection. Moreover, patients with a previous history of surgery and chemotherapy are clinically proven to have a higher risk to get infected by COVID-19. In the case of a severe event of COVID-19 cases, it is usually experienced by older age patients. This showed that ages are also one of the factors that may cause the person to have a high risk to get infected by this virus (30).

Since the patient who has cancer might have a higher risk to get a COVID-19 infection, physicians should provide a timely reminder that more attention should be given to the patient with cancer, in order to avoid any sudden rapid deterioration. From a similar article, few major strategies had been proposed to protect the patient who had been involved in this COVID-19 crisis or any future attack of severe infectious disease. First and foremost, an intention that had been made to postpone any adjuvating chemotherapy or elective surgery for a patient with stable cancer should be considered in a specific endemic area. Secondly, a patient with cancer as well as a cancer survivor should receive a provision of strong personal protection to protect them from infection. Last but not least, the physician should consider more effective and intensive surveillance for cancer patients who had been infected by SARS-CoV-2, particularly on a patient with other comorbidities and the elderly (30).

COVID-19 PREVALENCE AND MORTALITY IN PATIENTS WITH CANCERS

From this research done by Lee et al., in 2020 found that patients with haematological malignancies, for example, lymphoma, myeloma and leukaemia were quite overrepresented. Due to this matter, there is perhaps a prior suggestion stated that this category of patients may have a high susceptibility to contract COVID-19 infection (31, 32). Besides, patients with extranodal natural killer or T cell lymphoma, Waldenstrom macroglobulinemia and unspecified neoplasm of lymphoid, haematopoietic and related tissue were also largely overrepresented. However, this research was quite contradictory to the previous research that had been mentioned above, in this research, they found that patients with haematological malignancies have a much

greater risk to contract infection of COVID-19 clinical phenotype. They also had been reported to require more intensive supportive intervention as well as have a high probability to suffer the risk of death compare to the patient without haematologic malignancies (31).

In addition to that, after taking into account age and sex, the patient who has leukaemia have a higher risk of death due to COVID-19. Contradistinction to a patient who had breast cancer or any malignancies related to the female genital tract, they have a significantly lower risk to get COVID-19 infection and death due to this infection (31). The result from this research was similar to the research done by He W et al., in 2020 and Yang K et al., in 2020. They also found that there was an increase in amount or mortality occurred among patients who have haematological malignancies and at the same time contracted a COVID-19 infection (33, 34). A patient who had received at least 4 weeks or current chemotherapy and has haematologic malignancies contribute to a higher risk for them to have COVID-19 (34). Patients with cancer and COVID-19 were more likely to deteriorate into severe illness than those without cancer (35).

RISK OF COVID-19 FOR PATIENTS WITH CANCER

COVID-19 was very contagious to the public and it may potentially cause mortality as well as morbidity after being exposed to infection source. Based on research published by Chen N et al., in 2020, There was a quite high proportion of cancer patients can be found in a cohort of COVID-19. This showed that the person who has cancer may develop to have COVID-19 (36). In some findings, they also found that an increase in age actually gives a higher outcome of COVID-19. It had been reported that the patient who has cancer and at a median age of 63.1 years old have a significantly higher chance to get infected by this virus rather than the non-cancer patient (37).

Behind this fact, there were actually several reasons leading the cancer patient to be highly susceptible to contract the infection. One of the factors was the cancer patient that had already set their follow-up for treatment had to delay the appointment and this caused them to be unable to receive necessary treatment or medical service due to this pandemic phase. In addition to this, in January 2020, more than 30,000 doctors had been sent to ease the process of treating COVID-19 patients in Wuhan. This scenario had simultaneously affected the reputation of medical services outside of those regions. Moreover, the patients had been advised not to visit any hospital. This was done to protect the public from having risk to get an infection since most of the COVID-19 patients were being placed at the hospital. As the cases of COVID-19 had worsened day by day, the country had enforced quarantine. This results from some clinical trials being delayed. From this, it complicated the hospital attendance to rearrange back

the continuity of care and treatment for the patient. They also have to prepare well to receive any emergencies cases such as severe complications that suddenly appear by cancer patients. Furthermore, a patient who received an immune checkpoint inhibitor unfortunately may have a higher risk to experience an adverse effect. This is because they are unable to receive adequate treatment promptly and lead to having a rapid tumour progression and disrupt their survival rate (38).

COVID-19 SUSCEPTIBILITY, SEVERITY MAY VARY BY TUMOUR TYPES

In research done by Lee LYW et al., in 2020, involving 1044 participants and all of the participants contracted both cancer and SARS-CoV-2 infection. From this research, it had been stated that all causes of case fatality rate were corresponding to the age of the patient. The case fatality rate rises significantly from 0.10 which came among the patient at the age of 40 – 49 years old to 0.48 which came from the patient at least at the age of 80 years old. Gender also may affect the case fatality rate. It was proved that the case of fatality in men was significantly higher in men compared to women (39).

As for the tumour subtypes analysis, there was a significant increase in the case of fatality rate level in a person with leukaemia compare to the group of patients who have digestive tract tumours. Furthermore, patients with COVID-19 and haematological malignancies were found to be at significantly higher risk to get a severe or critical COVID-19 course compared to their counterpart which was non-haematological cancer. This group of patients may need non-invasive ventilation, high-flow oxygen as well as admission to the intensive care unit. They also found out that patients with haematological cancer and who had undergone chemotherapy as a treatment within 4 weeks of COVID-19 diagnosis have a higher risk to face death. An extremely usage of a myelosuppressive treatment regimen and disruption of an immunological action inside a leukaemia patient may contribute the patient to have multiple risks. For example, as regards an initial infection of SARS-CoV-2. Immunological disruption gives the virus a foothold in order for them to infect the patient's host cells. Additionally, they may also experience a critical sequel such as multiple organs failure along with cytokine storm (39).

Recently, an article written by Yu J et al. had been published in 2020. This article is attentively written about the effects of COVID-19 infection in a person with haematological cancer (40). This study had been carried out in Wuhan. From this study, they espied that among 128 COVID-19 patients that had been hospitalised, approximately 10% of them have haematological cancer. An expectation had been made from this study expecting that the person who has an immune disease such as lymphoid leukaemia and lymphomas

have a higher risk to be infected by SARS-CoV-2 and having COVID-19 in contrast to a patient with myeloid cancer such as myelodysplastic syndromes and acute myeloid leukaemia. As a knowledge, they also found out that the patient with haematological cancer that had been hospitalized and having COVID-19 infection have a high case fatality rate principally related to the bacterial coinfections. This was accordant with the high possibility of a decrease in granulocyte concentration in the patients' blood due to their disease or treatment thereof (40).

PATIENTS CHARACTERISTICS AND CLINICAL OUTCOMES

As regarding the clinical manifestation demonstrated by the COVID-19 with cancer, they have similar clinical manifestations as COVID-19 patients without cancer. Additionally, this study also had conducted research to observe the survival analysis of subjects who were on the occurrence of severe condition including admission to intensive care unit, utilization of mechanical ventilation and having severe clinical symptoms. They found out that this category of patients experiences a rapid deterioration in terms of survival than in those who were non-cancerous. In this study, they had compared different observations between various types of cancer. Lung cancer was found to be the most frequent type of cancer represent among the patient. It represents about 20.95% among all types of cancer. Then, followed by gastrointestinal cancer about 12.38%, breast cancer which is about 10.48%, thyroid cancer for 10.48% and the least percentage constituted by a group known as hematologic cancer which is approximately 8.57%(39,40).

CANCER TYPES

Patients who had been infected by COVID-19 and have haematological cancer for instance leukaemia, myeloma and lymphoma have a comparative high death risk, high risk to experience severe or critical symptoms, high admission rate in an intensive care unit as well as high prospect to utilize the invasive mechanical ventilation. As contradistinction, patients who had been infected with COVID-19 and have lung cancer were reported to be the second-highest risk level to experience critical and severe symptoms, admission rate to intensive care unit, probability in the utilization of invasive mechanical ventilation and death rate (40).

In spite of the fact that the patients who had contracted COVID-19 only have a relatively low death rate for about 2% to 3% in the general population, yet, COVID-19 patients with cancer may have 3-fold higher death rates and much higher severity of illness compare to COVID-19 patients without cancer (41). This research done by Zheng RS et al., done in 2019 proved a similar result from the previously explained research. The data

revealed that the severity of COVID-19 infection in patients was significantly related to the types of tumours experienced by the patient. Analysis that had been made from this study signified that the highest severity of the infection and highest death rates may be contracted in patients with haematological cancer and followed by the lung cancer patient who became the second-highest risk of having high severity and death rates.

Patients with haematological cancer comprised myeloma, leukaemia and lymphoma were said to have further compromised in the immune system compared to the patient with solid tumours (42). The COVID-19 patients with haematological cancer will have rapidly deteriorate in terms of clinical courses once they have been contracted by SARS-CoV-2. This occurred as a result of dysfunctional lymphocyte, plasma cells as well as white blood cells which will simultaneously lower the immunological function of these specific patients. This could contribute as one of the main factors causing COVID-19 patients with haematological prone to experience high severity and death rates and also severe complications. The study done by Raab MS et al. in 2009 proved that 55.56% of the patients with haematological cancer encountered severe immunosuppression which could lead them to produce deteriorated outcomes (43). However, among various types of solid tumours, it was found that lung cancer was the most risk category of cancer that may affect the severity of patients that had been infected by SARS-CoV-2. This is because severe infection and worst decreased in lung function in a patient with lung cancer may contribute a worse outcome to the subpopulation which may lead them to have multi-fold and high risk of death, admission to intensive care unit, severe and critical clinical manifestation and utilization of mechanical ventilation (44).

CANCER STAGE

Study by Mengyuan et al. found out that the patient with metastatic cancer and at the stage of IV had a higher risk of death, admission to intensive care unit, chance to require utilization mechanical ventilation and experience severe and critical symptoms than non-metastatic cancer patients. Contrarily they also spotted that non-metastatic cancer patients did not demonstrate significant differences compared to the patient without cancer. Besides, differentiation also had been made between the COVID-19 patient who has no cancer and COVID-19 patients who have lung cancer as well as other cancers with lung metastasis. They discovered that the COVID-19 patients with lung cancer or other types of cancers with lung metastasis have a higher risk of death and, utilization of mechanical ventilation, admission to intensive care unit and experienced severe and critical symptoms compare to non-cancer patients. Lastly, the data reported shown that COVID-19 patients with other cancer without metastasis had no statistical differences when this category had been compared with

patients without cancer (45).

CANCER TREATMENT

Among all of the COVID-19 patients that had been observed, about 12.26% of the patient had undergone radiotherapy, 14.15% treated by using chemotherapy, 7.62% had performed surgery, 3.81% had a targeted therapy and about 5.71% had done immunotherapy within 40 days before the onset of COVID-19 symptoms started to appear (45). The observation from this current study stated that the patients who have undergone immunotherapy tend to have high rates of death and a high chance to progress into a critical and severe illness. Additionally, the patient who has received surgery manifested higher death rates, demonstrate severe and critical symptoms, required utilization of mechanical ventilation and admission to intensive care unit compared to the patients who received other anticancer therapy except for immunotherapy. Nonetheless, COVID-19 with a cancer patient who received radiotherapy before did not show any statistically significant differences compared to the COVID-19 patient without cancer (45).

Patients with cancer may undergo a various range of treatments. In addition to that, different types of treatment used by the patient determined the severity and death rate of cancer patients after being infected by SARS-CoV-2. Nonetheless, immunotherapy was presumed to have an effective effect to help cancer patients in treating the existed tumour. They believed that immunotherapy assisted in preventing the cancer cells from escaping against the immune system (45). But from a study done by Huang Y in 2018, the dissimilitude to patients with cancer and received other types of treatment, the cancer patient with immunotherapy treatment demonstrated higher death risk and severity of illness which was contradicted with the previous fact that had been mentioned and this was a very puzzling finding (46). The patient who received immunotherapy was said to have a chance of experiencing severe illness compared to a patient who received other treatment because, immunotherapy has the ability to recruit a large number of cytokines to be released in the blood circulation, which sometimes can become toxic to the normal cells in the body, for instance, epithelial cells (46). Pathologic study had been observed in COVID-19 patients. According to this study, the factor that implicated the patient to have acute respiratory distress syndrome was as a result of desquamation of pneumocyte and hyaline membrane formation (47). Moreover, it was also reported that cytokine storm that occurred in the patient who received immunotherapy and concurrently induced acute respiratory distress syndrome in patients was one of the main causes for the death of patients with cancer and SARS-CoV-2 infection (48).

COVID-19 patients with cancer that were under active treatment as well as not under active treatment did

not show significant differences in terms of clinical outcomes. Nevertheless, they had reported that there were statistically significant differences between COVID-19 patients with cancer but without active treatment and COVID-19 patients who have no history of cancer. From this result, it can be specified that the COVID-19 patients who have a history of cancer as well as under active treatment may experience severe clinical course compared to the patients without cancer. The feasible factor for this statement could be due to anaemia, dyspnoea and hypoproteinaemia which were cancer-related complications that will be experienced during the early phase of COVID-19 (49). From this, it can be considered that a patient who has a history of cancer and even a cancer survivor had a lifetime effect which required them to receive a continuous follow-up routine after primary resection. Therefore, in a nutshell, during this pandemic of COVID-19, clinical patient management should perform equivalent attention to patients of COVID-19 as well as a patient who has a history of cancer or even the cancer patient who are under therapeutics.

CONCLUSION

In a nutshell, it can be concluded that there were several factors that may be experienced by the COVID-19 patients to progress to severe clinical course. Various research had proved that COVID-19 patients who have haematological cancer have a high risk to get a severe and critical symptom of infection, a high chance of getting admitted to intensive unit care, a higher risk of death and may require the utilization of mechanical ventilation. It was also found that immunotherapy may cause the patient who receives this specific treatment to have a higher risk to get into critical illness compared to the patient who receives other cancer treatment. Additionally, COVID-19 patients with metastasis cancer or to be more specific, stage 4 cancer have higher death rates compared to non-metastasis patients.

Therefore, during this pandemic, it is suggested to provide better protection for these categories of patients and give extra online medical counselling to give them support since most of the surgery or treatment had been postponed during this pandemic. Nevertheless, it is better to rethink the decision on whether or not to postpone any cancer therapy and treatment that had been planned on each of the cancer patients. This can be decided by classifying them according to the risk to the patient and the current condition of the patient. This matter should be emphasized as delay in treatment may lead the tumour to progress very rapidly and in the long run causing the patients to develop poorer outcomes.

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