

# The Risk and Impact of COVID-19 Pandemic on Immunosuppressed Patients: Cancer, HIV, and Solid Organ Transplant Recipients

Ali Haider Mohammed<sup>1\*</sup>, Ali Blebil<sup>1</sup>, Juman Dujaili<sup>1</sup>, and Bassam A. Rasool-Hassan<sup>2</sup>

<sup>1</sup>School of Pharmacy, Monash University Malaysia, Selangor, Malaysia; <sup>2</sup>Department of Pharmacy, Al Rafidain University College, Baghdad, Iraq

## Abstract

*Toward the end of the year 2019, there was the eruption of an acute respiratory syndrome, which is widely referred as coronavirus disease (COVID-19) from Wuhan, Hubei Province. The disease causes a range of respiratory illnesses, which are fatal. The COVID-19 disease has spread globally and has significantly impacted the health delivery systems, travel regulations, and economic activities and has posed and upsurge of responsibilities for the frontline healthcare workers. Due to the nature of the COVID-19 disease, it has typically caused complications which include pneumonia, multiple organ dysfunction together with renal failure, and acute respiratory distress syndrome. As of date, there is no approved vaccine or treatment for COVID-19 though there are ongoing research studies to formulate a treatment. COVID-19 is highly contagious, and the risk of infection is higher for patients with immunosuppressed patients than regular patients. The immunosuppressed conditions include cancer, HIV, and patients with solid organ transplants (SOT). This paper aims to review the risk and impact of COVID-19 on immunosuppressed patients, with a focus on cancer, HIV, and patients with SOT and the essence of special parameters for their care and management. Despite the fatal effects of this global pandemic, the findings of this study indicate the high risk which immunosuppressed patients have to contract the disease; thus, the governments and health delivery systems have to offer them extra support and treatment. (AIDS Rev. 2020;22:151-157)*

Corresponding author: Ali Haider Mohammed, alishanshool93@gmail.com

## Key words

**COVID-19. Cancer. HIV. Solid organ transplants.**

### \*Correspondence to:

Ali Haider Mohammed  
E-mail: alishanshool93@gmail.com

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## Introduction

The COVID-19 global pandemic broke out from Wuhan, Hubei province of China in December 2019 and has since spread rapidly, even faster than its predecessors severe acute respiratory syndrome-related coronavirus (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV). As of June 25, 2020, the disease has infected over 9 million people, with over two hundred thousand deaths. COVID-19, which is caused by a novel SARS-CoV-2, causes a group of diseases which range from mild to severe. Some of the diseases are zoonotic which means that they are transmitted between animals and humans. This contagious disease is transmitted through breathing in infected droplets from another human or animal that is infected by the disease. The virus incubates in the carrier's body for approximately 14 days before symptoms are evident. Despite its high level of contagion, the virus has a lower fatality rate. This has led to the various legislations of the infected countries worldwide imposing strict restrictions to lower the rate of infection and transmission, in an effort to contain the disease. Some of the regulations include a worldwide lockdown of all sectors and industries except for essential services, international travel ban, and the mandatory wearing of facial masks to reduce infection rates<sup>1</sup>. Upon infection, it has been reported that about 20% of the patients' progress from mild to moderate symptoms, while 5% proceed to more severe diseases. The countries which have recorded the highest rate of infection so far have been the US, Spain, China, South Korea, and Mainland Europe. Notably, individuals who have exceeded 60 years of age have had a higher risk of contracting the disease. This is highlighted in the case of Italy, where 90% of the deceased patients were over 70 years old, while the remaining 10% were over 90 years old. COVID-19 has been spreading more rapidly in the areas where there are patients with human immunodeficiency virus (HIV), malaria, and dengue which are dominant in areas such as Latin America and Africa. These regions are recording a high number of new cases where the patients have the aforementioned underlying conditions. Patients with diabetes, underlying cardiovascular, and respiratory illnesses were also classified as high-risk profile patients. Besides, people with weakened immune systems are at higher risk of getting severely sick from COVID-19. They may also remain infectious for a longer period than others with COVID-19. Despite

COVID-19 being a global pandemic, it has to be noted that the risk profile differs in the geographical areas, based on the diverse age structures and underlying illnesses and conditions. In general, the symptoms of COVID-19 include a high fever, cough, fatigue, breathing impediments, and malaise. The disease can have mild symptoms in the elderly and those with underlying conditions, while it can also progress to severe conditions such as pneumonia, acute respiratory distress syndrome, and multiple organ failure<sup>1,2</sup>. To date, there is no approved treatment or vaccine for COVID-19 yet, so the disease is being managed by measures that are being implemented to reduce infection rates, stop the transmission, and management of the confirmed cases. The medical facilities are using ventilators for oxygen therapy, fever remedies, hydration methods, and general pain management. In cases where there is bacterial co-infection, antibiotics are being administered to the patients<sup>3</sup>. Several clinical trials have been researching on the possible medications to treat the disease which include remdesivir, numerous other antiviral agents, and immunotherapies as well as vaccines continue to be investigated and developed as potential therapies<sup>4</sup>.

## COVID-19 and cancer

It is found that cancer patients are susceptible to malignancy; therefore, their immunosuppressive state exposes them to the risk of pathogens in their respiratory system and pneumonia. Despite the few studies on malignancy and COVID-19, the study of Liang et al. reveals the results of 18 cases of COVID-19 oncology patients. Out of the 18 patients, 4 of them had undergone chemotherapy within a month of infection and 12 were having their follow-up treatments from tumor removal. The other two patients' prior condition was unknown. The study stated that these patients were more prone to experiencing COVID-19 in its severe form, which was characterized by being admitted into intensive care, oxygen therapy, and possibly death. These patients' chances of being infected were 4 times higher than those without cancer. Therefore, the myelosuppressive effects of chemotherapy and of metastatic malignancy were considered; thus, it is feasible to propose how these patients are more prone to infection and severe symptoms<sup>5</sup>.

Another major risk which the cancer patients face is the disruption of reception of medical facilities and access for cancer patients. Hospitals are burdened with the high rate and volumes of infected patients. A

large percentage of cancer infections have been receiving delayed treatment due to the large volumes of patients which the hospitals are receiving since the outbreak of COVID-19. There has been a 39-90% decrease of screening of breast, prostate, cervical, and lung cancer in early April compared to the prior months. The projections by the American Cancer Society were that approximately 5000 new cases of cancer would be identified. Given the fatal effects of COVID-19 on cancer patients, oncology specialists have the onus to be actively involved in measures to mitigate the cases of COVID-19 among patients by appropriating extensive health care to the patients, the correct usage of social distancing and the appropriate time-lapse for diagnosis and treatment<sup>6</sup>.

Taking 28 cases of cancer patients with COVID-19 from three hospitals in Wuhan, an assessment of the risk factors was undertaken, considering intensive care admission, oxygen therapy, and possible death. The findings from this study indicated that these patients have a high risk of deteriorating even into death. With this in mind, it is recommended to extensively be educated on COVID-19 to prevent infection in the first place. The patients need to exercise extreme caution and hygiene whenever they are exposed to social occasions or any instance where they may be infected. The cancer patients are strongly urged to adhere to their treatment and medication regardless the outbreak of the pandemic. Upon diagnosis or testing positive for COVID-19, the patients should be monitored in how they would take treatment for both conditions without compromising the efficacy of the other. The patients should be on high alert should they experience symptoms such as coughing, shortness of breath, and dizziness<sup>6</sup>.

Furthermore, it has been noted that COVID-19 has a very high fatality rate among the aged people, and people living with co-morbidity. Even those patients who have recovered from cancer are still at a high risk of being infected. Therefore, since the pandemic is still progressing, it is important to have special conditions to cater for these vulnerable patients, given that the extent of severity of this virus has not yet been quantified. In addition, there is a need to consider the increased possibility of succumbing to the severe symptoms of COVID-19 before oncologic treatments, which include surgery, systemic chemotherapy, or radiation therapy. Figure 1 provides simplified guidelines for frontline personnel that may be exposed to cancer patients during the COVID-19 pandemic. It would be important to note the categories of cancer which need

immediate treatment, and those which can afford to be dealt with gradually. For example, solid tumors (lung or pancreatic cancer) with other hematologic cancers (acute leukemia) need to be diagnosed and treated urgently. Other cancers which would be in the initial stages such as (breast, prostate, cervical, and non-melanoma skin) can be dealt with gradual treatment. The results from these findings are still inconclusive; therefore, it is not yet advisable to propose universal treatments for such cases. It is recommended to continue investigating the cases of cancer intersecting with COVID-19 to obtain more substantiated results that would be worth applying<sup>7</sup>.

### **COVID-19 and HIV**

HIV compromises an individual's immune system through the infection combined with destruction of the T helper lymphocytes or CD4+ T cells, and this results to immune suppression which makes one more susceptible to infection<sup>8</sup>. By 2019, the number of people infected with HIV globally was approximately 36.8 million thus the disease needs a substantial amount of attention. Regardless of the progressive antiretroviral therapy (ART), nearly 1 million people die from HIV in 2019. The patients of HIV are prone to non-contagious diseases which affect the cardiovascular system. They were also high numbers of HIV-related deaths which succumbed to influenza. For this reason, HIV patients have a high risk of contracting COVID-19<sup>2</sup>. HIV and COVID-19 are similar because both illnesses do not have any approved cures yet. The response of the people globally will help in shaping the pandemic trajectory of COVID-19 as much as it did for HIV. HIV causes more deaths than COVID-19, as some patients recover from COVID-19 before they have severe illnesses. HIV is transmitted largely by sexual activity and needle sharing, while COVID-19 is transmitted through physical interaction with infected patients and poor hygiene. Cases of people living with HIV (PLHIV) doubled within a period of 6-12 months while for COVID-19, the time-lapse was only within days of infection, due to its high level of contagion<sup>9</sup>. Table 1 shows a comparison between HIV and SARS-CoV-2<sup>10</sup>.

Averages of the 37 million people infected with HIV are all at risk of contracting COVID-19. Using 1178 HIV patients from Wuhan, an investigation was done to measure the effected of COVID-19 on their immune systems. The study showed how 8 of the patients tested positive for COVID-19. The patients had a low to undetectable viral load, despite having a high CD4

Decision Regarding Immediate Cancer Treatment During COVID-19 Crisis		Risk for Significant Morbidity From COVID-19 (comorbidities need to be considered)		
		Low (<50 y/o)	Medium (50-70 y/o)	High (>70 y/o)
Risk of Progression With Cancer Care Delay	<b>Low (safe to delay &gt;3 mo)</b> Surgery: Nonmelanoma skin cancer HR+, HER2-, postmenopausal non-locally advanced breast cancer (needs neoadjuvant endocrine therapy on board) Low- or intermediate-risk prostate cancer Type 1 endometrial cancer Low-grade urothelial cancer Most thyroid cancers <3-cm renal mass Stage IA1 cervical cancer  Hematology/Oncology: Chronic hematologic cancer  Radiation Oncology: Nonmelanoma skin cancer HR+, HER2-, postmenopausal non-locally advanced breast cancer (needs neoadjuvant endocrine therapy on board) Low- or intermediate-risk prostate cancer Low-grade lymphoma			
	<b>Intermediate (delay of ~3 mo acceptable)</b> Surgery: High-risk prostate cancer (consider starting androgen deprivation if significant delay) Colon cancer with low risk for imminent obstruction Stage IA2 cervical cancer Low-risk melanoma  Hematology/Oncology: Chemotherapy for advanced breast, colon, lung cancer  Radiation Oncology: Postresection endometrial cancer High-risk prostate cancer (start androgen deprivation)			
	<b>High (ideally, no delay)</b> Surgery: ≥2-cm lung mass Colon cancer with imminent obstruction Type 2 endometrial cancer Pancreatic mass suspicious for malignancy Ovarian masses suspicious for malignancy Liver mass suspicious for malignancy High-risk non-muscle invasive or muscle-invasive urothelial cancer >T1b localized kidney cancer Stage IB cervical cancer Non-low-grade sarcomas  Hematology/Oncology: Chemotherapy for testicular, rectal, all non-low-grade hematologic cancers Non-low grade sarcomas Small cell lung cancer Most head and neck cancers, except thyroid  Radiation Oncology: Lung cancer Rectal cancer Head and neck cancers Gynecologic cancers Non-low-grade sarcomas			

Proceed with immediate treatment  
 Balanced risks and benefits of immediate treatment  
 Delay immediate treatment

Figure 1. Guidelines for decision-making for cancer treatment during the COVID-19 global pandemic.

count. The results of this study indicated that a relatively normal immune system leads to strong infection, and the pathological changes leading to evident symptoms. Similarly, it also indicated that a compromised immune system with a lower CD4 counts level exempts one from exhibiting the typical symptoms of the disease. The results of the study indicate the validity of the hypothesis that an immune-suppressed system protects the body from an attack of the viruses, for example, SARS and MERS. This can explain why HIV and acquired immune deficiency syndrome (AIDS) patients do not experience a majority of the early symptoms of COVID-19, which can validate the early inclusion of corticosteroids in treating the virus. The findings also suggest that when lopinavir/ritonavir (LPV/r) is used, it can protect frontline workers and volunteers from infection with the virus, as it can be used as a preventative drug<sup>11</sup>. However, a recent case series, included eight patients with COVID-19, were treated with lopinavir 400 mg/ritonavir 100 mg orally

twice daily, demonstrated that the plasma drug concentrations that were achieved using typical doses of LPV/r are far below the levels that may be needed to inhibit SARS-CoV-2<sup>12</sup>. Therefore, LPV/r does not work effectively against COVID-19 and adds toxicity; hence, ART of HIV/AIDS patients with COVID-19 needs to be revised and adjusted to ensure better outcomes and improve patients' quality of life.

Given the large scale and volume of daily infections, there has been a significant upsurge in the barriers and challenges to the HIV care continuum. First, due to global lockdown implementation, here has been decreased access to HIV facilities which include routine testing to identify new cases. This is counterproductive to the goal of UNICEF to have up to 90% of people infected patients knowing their status. This is counterproductive because testing leads the patients to know their status, starting treatment, and possibly lowering the rate of transmissions. Despite self-testing kits being available, counseling, and other additional facilities are

**Table 1. Major differences between HIV-1 (AIDS) and SARS-CoV-2 (COVID-19) infections**

HIV-1		SARS-CoV-2
Disease	AIDS (immunodeficiency)	COVID-19 (pneumonia and respiratory distress)
Origin country	Cameroon and Gabon	China
Year beginning	1981	2019
Zoonosis	Chimps and gorillas	Bats and pangolin
Genome	dsRNA, 10,000 Kb	ssRNA, 30,000 Kb
Mutation rate	$4 \times 10^{-3}$ /site/year	$1 \times 10^{-3}$ /base/year
Infectivity	Life-long	10 days
Fatality rate	> 90% (in the absence of ART)	< 1% (support: O <sub>2</sub> + ventilation)
Transmission	Parenteral, sexual, vertical	Droplets (airborne or contact)
Diagnosis	Plasma PCR, blood serology	Nasopharyngeal swab PCR, blood serology
Infected people	78 million (49% alive)	> 3.5 million (99% alive)
Length	Chronic (lifelong)	Acute (self-limited)
Receptor	CD4 and CCR5/CXCR4 at T lymphocytes	ACE-2 at pneumocytes type II

PCR: polymerase chain reaction.

needed to make this exercise more effective. Second, timely help and care for HIV patients have greatly declined<sup>13</sup>. There is need for some HIV patients to have their ARV treatment while in hospital supervision and care, but thus has been delayed because the allocation of resources is giving first preference to containing the global pandemic. Finally, the ART therapy programs are being compromised as no one knows when and how the lockdown will progress, and how this would affect hospital visits for all patients<sup>11</sup>. This was indicated from a study in China which investigated the status of PLHIV during the COVID-19 global pandemic, a questionnaire was distributed electronically, with 18 as the minimum age requirement and being on ARV treatment as a compulsory option. From the pool of 1014 respondents, 32.64% were facing inadequacy in their treatment due to limited movement and were also running short of their vital medications. Fifty-three respondents from Hubei province required ARV replenishment while 64.15% failed to access their medications after being turned away at traffic police stations. Therefore, PLHIV needs to be enlightened on the HIV-specific protective strategies during the COVID-19

pandemic and alerted of other ways of replenishing their ART. In this light, it is essential for studies to be conducted on effect of the COVID-19 on PLHIV as a means of being prepared and alert in the pandemic<sup>14</sup>.

### COVID-19 and solid organ transplanted (SOT) recipients

There is a high possibility that SOT recipients are more susceptible to SARS-CoV2 infection and its dire conditions. At the time of the global pandemic, organ transplant recipients are living with immune-suppressed system. Their response to infection and treatment is not similar with the normal population; therefore, special arrangements are necessary to give them relevant aid and assistance. However, the statistics of patients with both COVID-19 and SOT patients are still limited<sup>15</sup>. A case was reported of a 52-year-old Chinese kidney transplant (KT) recipient, who successfully recovered from COVID-19. Their treatment was progressive due to limitation of immunosuppression maintenance and reduced dosages of methylprednisolone, nebulized interferon- $\alpha$ , and

polyclonal intravenous immunoglobulin therapy. Another case from Spain did not reveal the fate of the patient 12 days after infection. With reference to similar viral respiratory tract infections, including the 2009 H1N1 influenza pandemic, it was noted that there were more cases of pneumonia and respiratory distress syndromes among SOT receivers infected with COVID-19 in comparison with the non-transplant people<sup>16</sup>. Another study was in the US to measure the baseline characteristics, clinical presentation, antiviral, and immunosuppressive management among SOT patients with SARSCoV2 infection. The study comprised of 90 patients in which 46 were kidney recipients, 17 lung, 13 liver, 9 heart, and 5 dual organ transplants. Popular symptoms included fever (70%), cough (59%), and dyspnoea (43%). In this light, 16 patients were deceased (18% overall, 24% of hospitalized, and 52% of ICU) and 37 (54%) were released. The findings of this study suggested how transplant patients posed an increased risk of severe disease and poor outcomes<sup>17</sup>. Moreover, Ruiz et al. conducted a study in Spain, including 18 SOTs (kidney (44.4%), liver (33.3%), and heart (22.2%) recipients diagnosed with COVID-19 to measure clinical characteristics, management, and outcome of COVID-19 after SOT. Fever (83.3%) and radiographic abnormalities in form of unilateral or bilateral/multifocal consolidations (72.2%) were present among the dominant symptoms. Notably SOT patients (30.8%) succumbed to respiratory failure before follow-up of 18 days they started to experience symptoms of the virus. The mortality rate among SOT patients before starting medications and therapy 27.8% and C-reactive protein levels at various points were significantly higher among recipients that experienced unfavorable outcomes. Therefore, it substantiated that SOT patients posed an increased risk of poor clinical outcomes, severe event, and possibly death<sup>16</sup>.

In addition, immunosuppression plays a contributing factor in initiating an improper immune response and reducing cytokine release syndrome. However, the cases addressing this phenomenon are still limited. In Wuhan, China, there was a patient who successfully recovered from COVID-19, yet they had a renal transplant 12 years ago and were administered methylprednisolone due to their immune suppression. In the scenario of lung transplantation, the SARS-CoV2 infection mainly inhabits the allograft which leads to an increase of inflammatory cells, thus large steroid therapy treatments would be needed in the initial stages of infection. This type of scenario requires

more substantiated studies<sup>18</sup>. According to Bartiromo et al. a 36-year-old patient with a KT initially experienced a dry cough and malaise, until she was tested and came out positive with COVID-19. She ended up having pneumonia, and this was a result of her interacting with her mother who was already infected with the disease. The mother was asymptomatic; however, she was treated with hydroxychloroquine and LPV/r; however, this was substituted with darunavir/cobicistat within 48 h as the patient experienced diarrhea. The patient was taking tacrolimus and steroid treatment for her immune system; however, tacrolimus trough level was higher than normal, so she ended up taking the steroid treatment only. Within 14 days the pneumonia condition subsided, while 3 follow-up RT-PCR tests for SARS-CoV-2 were programmed as a possible cure for COVID-19. The participants of this study propose that COVID-19 can be eliminated by conducting rhinopharyngeal swab on the KT patients who are exhibiting symptoms of the virus. Therefore, it is a matter of urgency to research and identify efficient antiviral treatments and measure the response of the immune system as a means to formulated immunomodulatory for the diverse groups of SOT patients<sup>15</sup>.

## Conclusion

The effect of persistent immunosuppression on the progression of COVID-19 is still inconclusive. However, it is evident that the effects are significantly high due to the relationship between inflammatory responses and significant organ failure. Despite the fatal effects of this global pandemic, the findings of this study indicate the high risk which immunosuppressed patients have to contract the disease thus the governments and health delivery systems have to offer them extra support and treatment. Ongoing studies should continue to investigate how the SARs-CoV-2 infection affects immunosuppressed patients with cancer, HIV and SOT patients in comparison with immunocompetent patients.

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