Abstract:

Purpose
COVID-19 infection resulting from (SARS-CoV-2) began to spread across the globe in early 2020. Patients with hematologic malignancies are supposed to have increased risk of mortality from COVID-19 infection. From Pakistan, we report the analysis of the outcome and interaction between patient demographics and tumor subtype and COVID-19 infection and hematological malignancy.

Patients and Methods
This is a multicenter, retrospective study included adult patients with history of hematological malignancy who were tested positive for COVID-19 presented at the oncology department of 5 tertiary care hospitals in Pakistan from February 2020 to August 2020. The primary objective was to determine overall clinical outcome, the patient characteristics, clinical presentations, treatments administered, and mortality rate stratified by age, type of malignancy and oncological treatment status for COVID-19 in patients with hematological malignancy.

Results

107 patients with hematological malignancy and COVID-19 positive presented to the hospital during study period. The median age was 35 years. The most represented malignancies were acute leukemia (28.9%), non-Hodgkin’s lymphomas (28.9%) with predominantly B cell lymphomas and Hodgkin’s lymphoma. Most frequently symptoms were respiratory (41%), fever (32.7%) and diarrhea (4.6%). Around 45.8% patients were admitted to the hospital for acute care while 54.2% had mild disease and were advised home isolation. Overall mortality of the entire cohort was 28%, of which 51% were admitted in a hospital. When stratified for age, increased mortality was reported with age greater than 50 years (10.2%) and those with acute leukemia (9.3%). In addition, a mortality rate of 19.6% was seen in those who were on active oncological treatment.

Conclusion
Taken together, this data supports the emerging consensus that patients with hematologic malignancies experience significant morbidity and mortality resulting from COVID-19 infection.

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Hematological malignancies and COVID-19 infection

Title:

“Outcomes of COVID-19 infection in patients with hematological malignancies- A multicenter analysis from Pakistan”

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**ABSTRACT**
Hematological malignancies and COVID-19 infection

Purpose

COVID-19 infection resulting from (SARS-CoV-2), began to spread across the globe in early 2020. Patients with hematologic malignancies are supposed to have increased risk of mortality from COVID-19 infection. From Pakistan, we report the analysis of the outcome and interaction between patient demographics and tumor subtype and COVID-19 infection and hematological malignancy.

Patients and Methods

This is a multicenter, retrospective study which included adult patients with a history of hematological malignancy who were tested positive for COVID-19 presenting at the oncology department of 5 tertiary care hospitals in Pakistan from February 2020 to August 2020. The primary objective was to determine overall clinical outcome, the patient characteristics, clinical presentations, treatments administered, and mortality rate stratified by age, type of malignancy and oncological treatment status for COVID-19 in patients with hematological malignancy.

Results

107 patients with hematological malignancy and COVID-19 positive presented to the hospital during study period. The median age was 35 years. The most represented malignancies were acute leukemia (28.9%), non-Hodgkin’s lymphomas (28.9%) with predominantly B cell lymphomas and Hodgkin’s lymphoma. Most frequently symptoms were respiratory (41%), fever (32.7%) and diarrhea (4.6%). Around 45.8% patients were admitted to the hospital for acute care while 54.2% had mild disease and were advised home isolation. Overall mortality of the entire cohort was 28%. Of which 51% were admitted in hospital. When stratified for age, increased mortality was reported with age greater than 50 years (10.2%) and those with acute leukemia
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(9.3%). In addition, a mortality rate of 19.6% was seen in those who were on active oncological treatment.

**Conclusion:**

Taken together, this data supports the emerging consensus that patients with hematologic malignancies experience significant morbidity and mortality resulting from COVID-19 infection.

Keywords: Hematological malignancy, Outcome, Mortality, Hospital.

**INTRODUCTION**

The SARS-Cov-2 or COVID-19 also known as novel coronavirus has become a global threat and healthcare concern. Since its outbreak in China at the end of 2019, the pandemic has affected more than a 100 million people worldwide. Although the outbreak is likely to have started from a zoonotic spread, it soon became clear that person-to-person transmission occurs mainly through respiratory droplets and direct contact with diseased person or indirect contact with fomites in the environment. Many people have mild symptoms while others have no symptoms at all, but still actively carry and transmit the virus. However, some do develop severe symptoms such as respiratory failure, cytokine release syndrome, and multi-organ failure.

Since COVID-19 began to spread across the globe in early 2020, patients with co-morbidities and cancer are more susceptible to marked complications of viral infection. Cancer patients are more prone to increased risk of infections than individuals without cancer because of immunosuppression by the malignancy itself and anticancer treatments, such as chemotherapy or surgery, and have a poorer prognosis. Cai et al have reported that patients with metastatic disease, hematological malignancy or lung cancer are at particularly high risk of severe
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complications, requiring intensive care unit (ICU) admission, invasive mechanical ventilation and even death. Furthermore, active treatment such as surgery and immunotherapy are associated with a significantly increased risk (hazard ratios of 6.22 and 4.82) respectively, for poor outcomes.\(^7\) Zhang et al reported a higher rate of adverse events (53.6\%) and mortality (28.6\%) in those who had their last anti-tumor treatment within 14 days of the infection (HR = 4.079, 95\% CI 1.086–15.322, \(P = 0.037\)). We do know that patients with hematological malignancies can have an underlying immune dysfunction and are vulnerable to viral and other infections.\(^9\)

Additionally, treatments which include cytotoxic agents, immunomodulators, hematopoietic stem cell transplantation, and chimeric antigen receptor T-cell therapy, are profoundly immunosuppressive. In addition, patients with hematologic malignancies have multiple risk factors of particular concern in the context of COVID-19 infection such as advanced age, underlying or treatment-induced comorbid illnesses like hypertension and diabetes, and chronic lymphopenia. These factors make this patient population particularly susceptible to an adverse outcome.

Public health measures have been universally instituted to control the disease spread and aim to decrease preventable hospital admissions. In addition it is recommended that patients receiving anticancer treatment should have vigorous screening for COVID-19.\(^8\) However, cancer care encompasses a diverse array of primary tumor types and stages, affecting all age groups of patients, with different prognosis and outcomes. Therefore, labelling all patients with cancer as susceptible to COVID-19 is probably neither reasonable nor informative.

For patients with hematologic malignancies, overall risk of morbidity and mortality resulting from COVID-19 infection, as well as how this risk varies as a function of age, disease status,
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type of malignancy, and cancer therapy is being studied. However, data from low- and middle-income countries is sparse. It is hypothesized that lower rates of testing and contact tracing and dearth of medical facilities adequately equipped to manage complicated covid infections can potentially result in higher morbidity and mortality in this high-risk population.

From Pakistan, we report the analysis of the interaction between patient demographics and tumor subtype and COVID-19 infection and outcomes in patients with hematological malignancy. This is a multicenter analysis from five tertiary care hospitals in Pakistan, all of whom have an established cancer center.

METHODS

We retrospectively collected data on all the patients with a history of hematological malignancies that tested positive for COVID-19 by RT-PCR and presented at the oncology department of 5 tertiary care hospitals in Pakistan: Aga Khan University Hospital Karachi, Armed Forces Bone Marrow Transplant Centre Rawalpindi, Hameed Latif Hospital Lahore, Shifa International Hospital Islamabad and Shaukat Khanum Memorial Cancer Hospital Lahore from February 2020 to August 2020. Demographic, clinical, treatment and laboratory data and serial samples for viral RNA detection were extracted from medical records.

Patients with a clinical or radiological diagnosis of COVID-19, without a positive RT-PCR test were not included in this analysis.

Outcomes

The primary objective of the study is to determine overall clinical outcomes of COVID-19 infection in patients with hematological malignancy. Secondary objectives of the study are to
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determine the patient characteristics, clinical presentations, treatments administered, and
mortality rate stratified by age, type of hematological malignancy and oncological treatment status.

**Statistical Analysis**

The data was entered and analyzed by using SPSS version 23. Calculated medians for all
continuous variables and frequencies with percentages for categorical variables. Chi-square test
was performed to check the association between the age and mortality.

**RESULTS**

**Baseline characteristics**

From February till August 2020, we identified 107 patients with hematological malignancy who
presented to the hospital with a positive COVID-19 PCR test. Most of the patients’ entries were
from Shaukat Khanum Memorial Cancer Hospital (50%) followed by Shifa International
Hospital (20%), Aga Khan University Hospital (16%), Armed Forces Bone Marrow Transplant
Centre Rawalpindi (11%), Hameed Latif Hospital Lahore (3%). 49 (45.8%) patients were
admitted to the hospital for acute care while 54.2% had mild disease and were advised home
isolation.

Baseline patient’s characteristics are shown in (Table 1). At the time of COVID-19 diagnosis,
median age was 35 years (14-68). 39% of patients were younger than 30 years, while 34% and
28% were between age 30- 50 years and age >50 years, respectively. Two-thirds of the
patients were female (67%). About 79% of patients had no comorbidities

other than the hematological malignancy. Other co-morbidities included hypertension in 17%
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and diabetes in 9% of the patients. The most common malignancies were acute leukemia (28.9%), Non-Hodgkin’s lymphoma (28.9%) with predominantly B cell lymphomas and Classical Hodgkin’s lymphoma. Most of the patients were receiving active treatment (63%), mainly chemotherapy (41.1%), chemo-immunotherapy (16.8%), tyrosine kinase inhibitors (4.7%), and radiation therapy (0.9%). 8 patients had a prior history of stem cell transplant of which 7 were on immunosuppressive drugs. The median time to a positive covid PCR for patients on active treatment was 19 days (range 3-43 days).

Table 1: Baseline characteristics of the study population.

| Demographic Characteristics of Patients |   |
|-----------------------------------------|--|
| Age (years) Range                       | 35 (14 – 68) |
| Sex                                     | n  %         |
| Male                                    | 35 (32.7%)  |
| Female                                  | 72 (67.3%)  |
| Co-morbidity                            |             |
| Diabetes                                | 9 (8.4%)    |
| Hypertension                            | 17 (15.8%)  |
| Ischemic Heart disease                  | 1 (0.9%)    |
| Chronic Kidney disease                  | 1 (0.9%)    |
| No - comorbid                           | 79 (73.8%)  |
| Primary Malignancy                      |             |
| ALL                                     | 14 (13.1%)  |
### Hematological malignancies and COVID-19 infection

| Condition                     | Count | Percentage |
|-------------------------------|-------|------------|
| AML                           | 13    | (12.2%)    |
| CML                           | 5     | (4.6%)     |
| CLL                           | 7     | (6.5%)     |
| SLL                           | 1     | (0.9%)     |
| HCL                           | 1     | (0.9%)     |
| Hodgkin’s lymphoma            | 19    | (17.7%)    |

**Non-Hodgkin’s lymphoma**

| Condition                     | Count | Percentage |
|-------------------------------|-------|------------|
| B cell lymphoma               | 25    | (23.3%)    |
| T cell lymphoma               | 4     | (3.73%)    |
| MDS                           | 4     | (2.8%)     |
| Multiple myeloma              | 8     | (7.4%)     |
| HLH                           | 1     | (0.9%)     |
| ITP                           | 1     | (0.9%)     |
| Histiocytic sarcoma           | 1     | (0.9%)     |

**On Active cancer treatment**

| Chemo immunotherapy           | Count | Percentage |
|-------------------------------|-------|------------|
| Yes                           | 68    | (63.6%)    |
| No                            | 39    | (36.4%)    |

| Chemo immunotherapy           | Count | Percentage |
|-------------------------------|-------|------------|
| R CHOP                        | 9     | (50%)      |
| R- Bendamustine               | 2     | (11%)      |
| R-ICE                         | 3     | (16.6%)    |
### Hematological malignancies and COVID-19 infection

| Treatment                        | Count | Percentage |
|----------------------------------|-------|------------|
| R-CEOP                           | 1     | (5.5%)     |
| R-EPOCH                          | 2     | (11%)      |
| Rituximab                        | 1     | (5.5%)     |
| TKI                              | 5     | (4.7%)     |
| IV chemotherapy                  | 44    | (41.1%)    |
| CVP                              | 1     | (2.2%)     |
| Idarubicin + cytarabine          | 10    | (22.7%)    |
| BFM protocol                     | 4     | (9.09%)    |
| HyperCVAD                        | 9     | (20.4%)    |
| ABVD                             | 10    | (22.7%)    |
| Bendamustine                     | 2     | (4.54%)    |
| VRD                              | 4     | (9.09%)    |
| Cyclophosphamide + bortezomib    | 2     | (4.54%)    |
| Lenalidomide + carfilzomib       | 2     | (4.54%)    |
| Radiation                        | 1     | (0.9%)     |

#### Symptoms at onset

| Symptom                          | Count | Percentage |
|----------------------------------|-------|------------|
| Fever                            | 35    | (32.7%)    |
| Respiratory symptoms             | 44    | (41.1%)    |
| GI symptoms                      | 5     | (4.6%)     |
| Others                           | 5     | (4.6%)     |
Presenting symptoms and treatment of COVID-19

As shown in Table 1, we investigated presenting features of all patients with COVID-19 infection. The most common presenting symptoms were respiratory (41% - cough, dyspnea), fever (32.7%) and diarrhea (4.6%), while 16.8% patients were asymptomatic. In terms of exposure, about 69.2% of patients did not report to have any known contact or travel exposure history; however, 16% and 14% reported to have travel and contact exposure, respectively. 75% of the 49 patients admitted to the hospital were classified as moderate to severe covid infection. 80% of these patients fulfilled the criteria of cytokine release syndrome. Lymphopenia was seen in 40% of these patients. The most common COVID19–specific therapies in our dataset were symptomatic treatment with steroids (60%) and anticoagulation (35%). Tocilizumab was used in 6.5%, remdesivir in 2.8% and hydroxychloroquine 3.7% of patients. Of the 49 hospitalized patients, 9% and 15% of the patients needed noninvasive and invasive ventilation respectively.

Outcomes of COVID-19 infection

Overall mortality of the study cohort was 28%. Of the 107 patients, 49 patients (45%) required admission to the hospital. The mortality rate in the admitted patients was 51%. 17 patients were transferred to intensive care unit and the mortality rate amongst these patients was 86%. 46.9% recovered from their illness and were discharged home. Average length of hospital stay was 12 days (1-38 days). When stratified for age, the mortality was 7.4%, 5.6% and 10.2% in the age groups 10-30 years, 31-50 years, and 51-70 years respectively. In our cohort the highest

| Symptom          | Count | Percentage |
|------------------|-------|------------|
| Respiratory      | 41    | 41.0%      |
| Fever            | 32.7  | 32.7%      |
| Diarrhea         | 4.6   | 4.6%       |
| Asymptomatic     | 18    | 16.8%      |
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mortality was seen in patients with acute leukemia (12.1%) followed by Non-Hodgkin's lymphoma (5.6%), chronic leukemia (3.7%) and multiple myeloma (3.7%). In addition, a mortality rate of 19.6% was seen in those who were on active oncological treatment. (Table 2)

Mortality rate in patients receiving intravenous chemotherapy alone was about 14% and 4.6% receiving chemoimmunotherapy. Subsequent PCR data in the infected patients was available for only 17 patients. In those, the average time to a negative PCR result was 19 days (6-40 days).

**Table 2: Stratification of Mortality**

| Overall Mortality | N     | DEATH |
|-------------------|-------|-------|
| Overall patients  | 107 (100%) | 30 (28%) |
| Hospital admission| 49 (45.8%) | 25 (51%) |
| Home isolation    | 58 (54.2%) | 0 (0.0%) |

**Mortality stratified by Age**

|        | N     | DEATH |
|--------|-------|-------|
| 10-30 yrs | 41 (38.3%) | 8 (7.4%) |
| 31-50 yrs | 37 (34.5%) | 6 (5.6%) |
| 51-70 yrs | 29 (27.1%) | 11 (10.2%) |

**Mortality stratified by type of malignancy**
Hematological malignancies and COVID-19 infection

| Disease                  | Total | Death   |
|--------------------------|-------|---------|
| **Acute Leukemia**       | 31 (28.9%) | 13 (12.1%) |
| ALL                      | 17 (11.2%) | 4 (3.2%) |
| AML/MDS                  |       | 9 (8.5%) |
| **Chronic Leukemia**     | 13 (12%) | 4 (3.7%) |
| CLL                      | 8 (7%) | 3 (2.8%) |
| CML                      | 4 (3.7%) | 1 (0.9%) |
| **HCL**                  | 1 (0.9%) | 1 (0.9%) |
| **Hodgkin’s lymphoma**   | 19 (17.7%) | 3 (1.8%) |
| **Non-Hodgkin’s lymphoma** | 31 (27%) | 6 (5.6%) |
| **Multiple Myeloma**     | 7 (7.4%) | 4 (3.7%) |
| **HLH**                  | 1 (0.9%) | 0 (0.0%) |
| **ITP**                  | 1 (0.9%) | 0 (0.0%) |

Mortality stratified by active oncological
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| treatment | Yes | 68 (63%) | 21 (19.6%) |
|-----------|-----|----------|------------|
| Mortality stratified by type of treatment | | | |
| TKI | 5 (4.7%) | 1 (0.9%) |
| Intravenous chemotherapy | 44 (41.4%) | 15 (14%) |
| Chemo immunotherapy | 18 (16.8%) | 5 (4.6%) |
| Radiation | 1 (0.9%) | 0 (0.0%) |
| Surveillance | 39 (36.4%) | 4 (3.7%) |

**DISCUSSION**

Worldwide, health-care systems are facing an uphill task of dealing with the COVID-19 pandemic, a situation that is going to remain a challenge to all clinicians. The incidence of covid-19 and outcomes in cancer patients is a topic of great interest. It is evident now that the covid-19 will be a global health care issue for the foreseeable future, and it is imperative that clinicians understand the complexity of presentations and outcomes of patients with concomitant health issues that make them vulnerable for severe complications. Our study has mainly focused on outcomes of COVID-19 with hematological malignancies in a resource constrained environment and it’s the first multicenter analysis from Pakistan.

ASH Research Collaborative COVID-19 Registry analysis states that patients with hematologic malignancies have a higher mortality resulting from COVID-19 than in the general population. They reported an overall mortality of 28%, increasing to 42% in patients with moderate to severe infection.\textsuperscript{10-11-12} Recently published study from Italy stated a mortality of 37% patients with hematological malignancy and COVID-19, with higher risk amongst those with older age, progressive disease, or severe infection\textsuperscript{13-14}. Another multicenter study, analyzing outcomes in cancer patients from China reported mortality of 20%, with 41% mortality in the 22 patients with
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Hematologic malignancies. UK Myeloma Forum published their results of 75 patients with COVID-19 and multiple myeloma, with a mortality of 55%. In our study, the overall mortality mirrors the data of these studies with an overall mortality of 23% and increasing to approximately 51% in the hospitalized patients and 86% in ICU patients. 50% of deaths were seen in patients younger than 50 years. This is most likely due to the fact that approximately 70% of our patients were in that age group. Therefore, this is likely over represented. It was interesting to note the relatively low numbers of patients of older age admitted to the hospital in our cohort. It could be hypothesized that treatment was deferred for the older patients with multiple co-morbidities in the initial months of the pandemic if they had a relatively stable clinical course. However, it would be interesting to study the outcomes of patients who had their treatment deferred.

Several other findings from our cohort are noteworthy. We analyzed the demographics of COVID-19 patients with hematological malignancy and explored the effect of cytotoxic chemotherapy and various chemo immunotherapy and targeted treatments on the trajectory of COVID-19. The incidence of COVID-19 was found to be more frequent in acute leukemias (29%) followed by non-Hodgkin’s lymphoma (27%) and Hodgkin’s lymphoma (18%). Furthermore, an increase in mortality has been reported in myeloid malignancies (MDS/AML/MPN) than lymphoid neoplasms (NHL/CLL/ALL/MM/HL) (43% vs. 35%), which is similar to that seen in our study population. Majority of our study patients were on active treatment and reported a mortality rate of 19.6% in contrast to 10% among patients on surveillance. Interestingly a higher mortality rate (14%) was seen in patients receiving chemotherapy alone compared to a 4.6% receiving chemoimmunotherapy.
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The most common COVID-19–specific therapies in our dataset were symptomatic treatment with steroids and anticoagulation, tocilizumab (6.5%), remdesivir (2.8%), hydroxychloroquine (3.7%). The use of tocilizumab and remdesivir in our cohort were low when compared to other studies. One reason is that our data collection started in the early days of the pandemic when these drugs were not used regularly. Additionally, the availability of the drugs was sparse until the mid of 2020. Remdisivir was given emergency use authorization in May 2020 and gained full FDA approval in October 2020. It only then has this drug become widely available for use.

Morbidity rates from COVID-19 in patients with cancer who are admitted to the hospital are high particularly in older patients and those with hematological malignancies. But not all cancer patients are affected equally. These findings allow clinicians to risk stratify their patients; whether symptomatic or not; and make decisions on social isolation and shielding at appropriate levels. Our data and many other studies demonstrate that patients with hematological malignancies, particularly acute leukemias, are at a high risk for severe COVID-19 infection and mortality. Therefore, preemptive testing, early recognition of infections and prompt management at a facility with expertise to manage complications is of paramount importance. In addition, protective measures such as universal masks, social distancing and shielding this susceptible population from COVID-19 exposure is mandatory. Many sites have implemented use of telemedicine to on-site physical distancing, and these practices should continue if COVID-19 prevalence remains high.

Our study has some limitations. Our analyses are based on patients with hematological malignancy who sought help from centers where they were receiving their treatment. Therefore, this cohort did not capture the outcomes of patients who presented for management at a different
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hospital. This is particularly true for patients who live in another cities or towns and most likely obtained treatment closer to home. Also, we likely missed patients on long term follow-up who approached their local GP or hospital. We, too, were unable to capture those patients who were asymptomatic and found to have COVID-19 positive on screening. In addition, patients who are on hospice care were not reported or included in this study. Therefore, it is not possible to accurately quantify the burden of infection in patients with hematological malignancy. Nonetheless, this dataset provides the glimpse of outcomes of patients who presented to a tertiary care hospital in Pakistan where both state of art management for covid infection and the primary malignancy was available. Majority of our patients were on active treatment and these results help prognosticate; patients who require intensive care carry a very grim prognosis. Data such as ours are especially important in formulating guidelines that are country/region specific regarding management of covid infections in a specific subset of patients. This is of importance in guiding management decisions in situations where resources are limited, and medical care is not covered by private insurance.

The expertise in management of covid infection has evolved over the last year. Early use of dexamethasone, remdesivir and anticoagulation has resulted in improved outcomes. Nonetheless, determine the incidence and severity of infections in cancer patients who have been adequately vaccinated.

In summary, this study of patients with hematological malignancy and COVID-19 accentuates several significant considerations for clinical care and emphasizes the urgent need for more data. Longer-term follow-up and larger sample sizes are needed to understand the effect of SARS-CoV-2 on outcomes in patients with hematological malignancy.
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**Abbreviations**

CI - Confidence Interval

HR - Hazard Ratio

ICU - Intensive Care Unit

NHL - Non-Hodgkin’s Lymphoma

RT-PCR - Real Time Polymerase Chain Reaction

UK - United Kingdom

**Declaration**

**Competing interests:**

No Potential conflict of interest exist.

**Funding Disclosure**

The authors have not received any kind of funding for this research study from any institution or agency.

**Ethics approval:**

Ethical approval was obtained from Ethical Review Committee of the Aga Khan University Hospital, Karachi, Pakistan.

**Availability of Data and Materials**
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The data is available to the corresponding authors and can be provided on the reasonable request.

Author’s contribution

A.Z.- Conceptualization, Writing original draft

D.K, S.S- Data Curation & Formal Analysis

H.S., R.I., A.M, Z.A. K.B- Methodology & Writing original draft

H.N., Q.C., S.B- Writing original draft

M.M- Supervision & Writing, reviewing final draft.
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