Journal of Institute of Science and Technology, 27(1), 37-49 (2022)
ISSN: 2467-9062 (print), e-ISSN: 2467-9240
https://doi.org/10.3126/jist.v27i1.42652

Research Article

AN INITIAL SPATIOTEMPORAL ASSESSMENT OF COVID-19 CLUSTERS IN NEPAL

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*(**Received**: January 25, 2022; **Revised**: April 15, 2022; **Accepted**: April 15, 2022)*

ABSTRACT

Nepal has been strongly influenced by the COVID-19 pandemic and struggling to contain it with multiple interventions. We assessed the spatiotemporal dynamics of COVID-19 in the context of various restrictions imposed to contain the disease transmission by employing prospective spatiotemporal analysis with SaTScan statistics. We explored active and emerging disease clusters using the prospective space-time scanning with the Discrete Poisson model for two time periods using COVID-19 cases reported to the Ministry of Health and Population (MoHP), Government of Nepal during 23 January – 21 July, and 23 January – 29 November 2020 taking the cutoff date of 21 July (end date of nationwide lockdown). The results revealed that COVID-19 dynamics in the early transmission stage were slower and confined to a few districts. However, since the third week of April, transmission spread rapidly across the districts of Madhesh and Sudurpaschim Provinces. Despite nationwide lockdown, nine statistically significant active and emerging clusters were detected between 23 January and 21 July 2020, whereas seven emerging clusters were observed for an extended period to 29 November. After lifting the nationwide lockdown, COVID-19 clusters developed had a many-fold higher relative risk than during the lockdown period. The most likely cluster was located in the capital city, the Kathmandu valley, making it the highest-risk active cluster since August. Movement restriction appears to be the most effective non-pharmaceutical intervention against the COVID-19 in countries with limited health care facilities. Our findings could be valuable to the health authorities within Nepal and beyond to better allocate resources and improve interventions on the pandemic for containing it efficiently.

Keywords: Disease clusters, geospatial dynamics, pandemic, SARS-CoV-2, SaTScan

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious disease with an initial estimated average basic reproductive rate (R_0) of 3.28 (Liu et al., 2020) that has been substantially reduced by the multiple intervention approaches (You et al., 2020). However, the unrestrained transmission of SARS-CoV-2 in many parts of the world is creating evolutionary changes to the virus developing its new variants (Abdool Karim & de Oliveira, 2021; Kandeel *et al.*, 2021) and recurring waves of the COVID-19 with a higher infection rate (Ranjan *et al.*, 2021; Viana *et al.*, 2022). With a massive global effort to fast-track the development of vaccines, there are several vaccines currently authorized for use (Creech *et al.*, 2021). Vaccination is the ultimate long-term solution against COVID-19 (Bubar *et al.*, 2021), however, the low- and middle-income countries have struggled to obtain even a minimum number of vaccine doses (Creech *et al.*, 2021).

Analogous to many countries in the world, Nepal has hugely suffered from the COVID-19 pandemic (Liu *et al.*, 2020; Panthee *et al.*, 2020). The first case of the disease was reported on 23 January 2020 in a 32 years old male in Kathmandu (Pun *et al.*, 2020; Shrestha *et al.*, 2020). After the lag period of two months, the second positive case was reported on 23 March 2020 (Piryani *et al.*, 2020). Subsequently, the number of disease victims gradually increased and almost all the cases in the earlier days were among the people who returned from Europe, the Middle-East countries and others. The geographical distribution of the COVID-19 cases within the Nepal territory is not uniform. Communities that are associated with poverty in densely populated growing cities are estimated more vulnerable to infection (Khanal *et al.*, 2020). Additionally, disease intervention efforts are not equal among the local administrative units of Nepal and so is the pattern of spread of the COVID-19.

The magnitude and timing of the interventions matter for the mitigation of the disease outbreak (Dehning *et al*., 2020). When the second COVID-19 case was recorded in Nepal and the number of cases was also rising in India, the Nepal Government closed all international flights and borders on 23 March 2020 (Sapkota *et al*., 2020). The very next day, a nationwide lockdown was further enforced that continued till 21 July 2020. Besides the diagnosis, isolation and treatment of the COVID-19 patients, the Government of Nepal employed multiple public health measures such as border closure, lockdown, social distancing, and personal hygiene, which aided Nepal in avoiding the spread of the novel coronavirus during the initial days (Basnet *et al*., 2020; Dhakal & Karki, 2020). Physical distancing measures, such as the closure of schools and colleges, retail businesses, and restaurants; cancellation of public events; as well as constraints on individual movements and social interactions; etc. are now in place in many countries intending to reduce transmission of SARS-CoV-2 (Cowling *et al*., 2020; Davies *et al*., 2020; Yang *et al*., 2020). Among other measures, travel restrictions, physical distancing, home quarantine, centralized quarantine, compulsion on mask-wearing in public places, universal symptom survey, implementation of testing, isolation, and contact tracing probably slowed the transmission dynamics significantly (Davies *et al*., 2020; Fang *et al*., 2020; Pan *et al*., 2020). Despite continuous lockdown enforced for 120 days, the outbreak of the COVID-19 is reemerging and the country is severely affected by the second wave of the disease. Although multiple non-pharmaceutical intervention measures have been employed, their implementation is poor and efficacy have never been assessed in Nepal.

Pharmaceutical interventions alone are not enough to contain the COVID-19, hence, countries augmented them with non-pharmaceutical approaches. However, how different combinations of interventions, timings, and extents have yielded desired outcomes to curb the disease transmission remains unclear (Cowling *et al*., 2020; Davies *et al*., 2020; MacIntyre & Wang, 2020; Pan *et al*., 2020). The level of vulnerability to the COVID-19 differed among the communities based on the demographic, socioeconomic, accessibility to the health facilities, prevalence of pulmonary and cardiac disorders, etc. (Khanal *et al*., 2020). One of the important drivers of the spreading of infectious diseases is the human movement, tracking of which using data sources such as public transportation (bus, train, and flight), social-media data, and mobile-phone data could be critical for the prediction of virus transmission, the identification of risk area, and decisions about control measure (Zhou *et al*., 2020). Therefore, it is important to analyze the spatiotemporal pattern of the COVID-19 outbreak in the light of human dynamics and non-pharmaceutical interventions.

The epidemic crisis management demands estimation of the actual effects of interventions taken not only to make rapid adjustments but also to adapt short-term forecasts (Dehning *et al*., 2020). Nepal offers an opportunity to assess the impact of non-pharmaceutical interventions on COVID-19 that could be rolled out in resource-limited settings in other countries. Therefore, this study aimed to assess the spatiotemporal dynamics of COVID-19 in the context of various restrictions imposed as preventive measures to contain the disease transmission. We explored active and emerging disease clusters using the prospective space-time scanning (Desjardins *et al*., 2020; Masrur *et al*., 2020) for two time periods, 23 January – 21 July (the end date of nationwide lockdown), and 23 January – 29 November 2020 taking the cutoff date of 21 July. In addition, we investigated biweekly space-time propagation of transmission for locating risk and newly emerged clusters along the timeline accounting for the two-weeks incubation period of the SARS-CoV-2.

METHODS

Study design

This prospective clustering study is based on the assumption that the COVID-19 clusters and their relative risks differ with the different level of interventions employed. We divided the study period (23 January to 29 November 2020) into two parts based on the national level lockdown employed by the federal government of Nepal. The country was shut down on 23 March 2020, which was lifted five months later in 21 July 2020. Using daily COVID-19 positive cases and a gridded population dataset for the spatial resolution at the district level, we investigated emerging district-level clusters and the progression of relative risk of the pandemic in Nepal.

Variables and models

This study used three different data sets: daily COVID-19 positive cases, gridded population data set for each district and spatial coverage of the districts. Temporal dynamics of the disease was visualized using the epidemic curve and restrictions enforced in different spatiotemporal scales. The spatial distribution of cumulative cases of reported COVID-19 and incidence rate for two temporal windows from 23 January to 29 November 2020 with the cutoff date of 21 July 2020 is presented through the choropleth mapping technique. Geospatial analysis has been used to characterize the spatiotemporal dynamics of COVID-19 in Nepal. We chose prospective space-time analysis to detect emerging or active space-time clusters that are still occurring at the end of the study period based on the discrete Poisson model (Kulldorff, 1997;2001). We chose the discrete Poisson probability model to account for heterogeneous distribution of COVID-19 transmission across space and time (Kim & Castro, 2020; Masrur *et al*., 2020).

Data collection and processing
This study was conducted covering the entire 77 districts of Nepal (Figure. 1) using three different datasets. COVID-19 cases reported to the Ministry of Health and Population (MoHP), Government of Nepal was the first of its kind. This dataset contains daily COVID-19 positive cases, death and recovery aggregated at districts. The COVID-19 cases were tested using the RT-PCR in various labs distributed across the country. We extracted reported positive cases and joined them with district shapefile collected from National Spatial Data Infrastructure Clearing House (http://nationalgeoportal.gov.np/) of Department of Survey, Government of Nepal. In addition, we obtained gridded population dataset in 100-meter spatial resolution for the year 2020 from the Worldpop geoportal (https://www.worldpop.org). We summarized it for each district using the zonal statistics tool of the Arc GIS 10.5 (ESRI, 2011) which was used later as a base population to assess underlying risk to COVID-19 in the district.

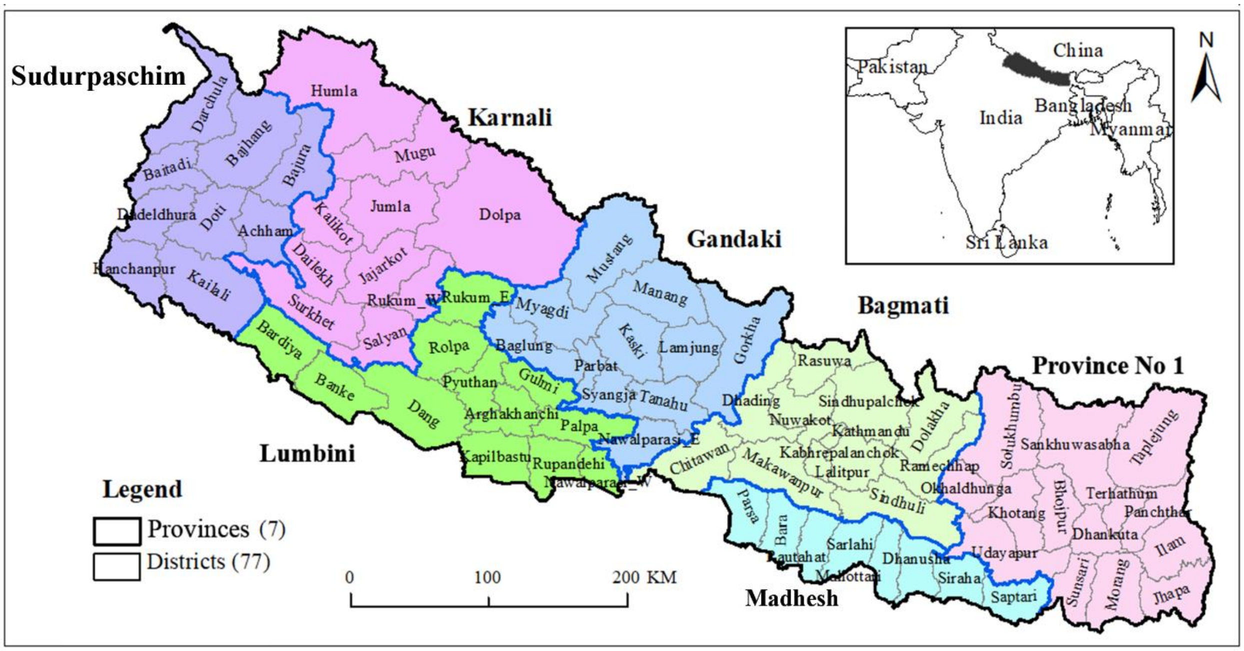

Figure 1. Location map of Nepal showing the seven provinces and 77 districts.

Statistical analysis
The spatial scan statistic (SaTScan) (Kulldorff, 1997) is a widely used method for geographical disease surveillance that detects and determines the statistical significance of geographical clusters without having to prespecify the cluster size or location. The retrospective analysis on the SaTScan can identify all past and current significant clustering events throughout the study period (Kulldorff, 1997). To quantify spatiotemporal dynamics of the COVID-19 pandemic in Nepal, we used the SatScan approach using the SaTScan version 9.6 (Kulldorff, 2018). The SaTScan statistics has been used widely to identify significant spatial/ temporal and spatiotemporal disease clusters including COVID-19 in different regions of the world (Acharya *et al.*, 2016; Desjardins *et al.*, 2020; Masrur *et al.*, 2020). The SaTScan scans across time and/or space using a moving window to identify possible clusters by comparing the number of observed cases and expected cases assuming random distribution inside the window at each location. A scanning window is a time interval for purely temporal scan, a circle or ellipse in spatial scan and a cylinder in space-time scan where base of a cylinder represents space dimension and height represents the temporal dimension (Kulldorff, 2001; Kulldorff, 2018).

We performed prospective space-time clustering analysis on daily reported cases of COVID-19 aggregated on 77 districts. As we were interested to locate elevated risk zones to the COVID-19, a high rate was chosen for further analysis. We set the upper bounds to have a maximum spatial and temporal scanning window size of 10% of the population at-risk to avoid extremely large clusters; and 50% of the study period, respectively. We utilized Monte Carlo testing with 9999 replications to assess the statistical significance of space-time clusters with a default 'P' of 0.05.

To understand the space-time propagation of the transmission, we computed the difference of relative risk between two-study periods and also detected emerging clusters with shorter temporal scans through biweekly cumulative prospective scanning approach accounting for two weeks incubation period (Desjardins *et al.*, 2020) for locating the risk and newly emerged high-risk areas along the timeline.

RESULTS

General overview of the COVID-19 in Nepal

A total of 231,978 cases of COVID-19 were reported in Nepal as of 29 November 2020 out of 1,727,836 tests done by RT-PCR. Among the total infected people, 152,235 (66%) were males and 79,743 (34%) were females. The fatality rate and recovery rate in Nepal due to COVID-19 were 0.6% and 91.6%, respectively.

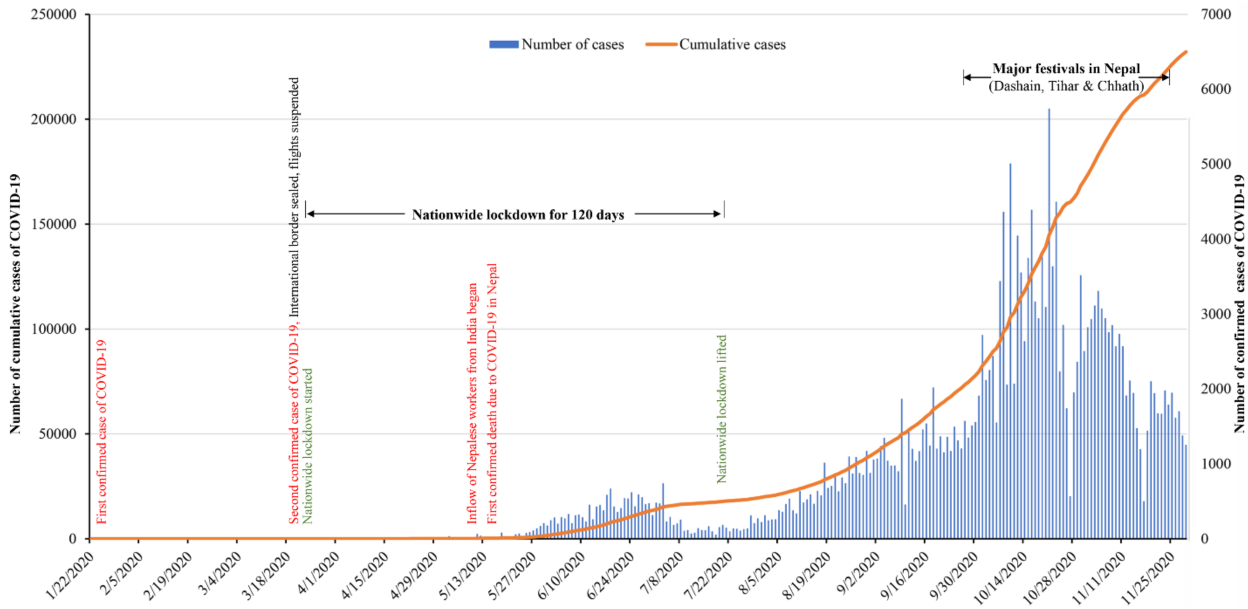

Figure 2. Epidictic curve of reported COVID-19 cases in Nepal. The primary axis (left) is cumulative count of reported cases and secondary axis (right) is daily reported count.

The temporal dynamics of the epidemic is presented in Fig. 2. The epidemic curve started to ascend only after the third week of April, which was almost four months later the detection of the first case on 23 January 2020. However, sporadically COVID-19 cases were detected from different districts despite the nationwide lockdown started on 24 March. From the third week of May the epidemic curve started to rise abruptly and the trend continued until June last. In this period, a significantly higher number of migrant workers returned home from India. Once the number of returns from India decreased slowly the positive case also shrunk rapidly. However, the number of COVID-19 cases increased substantially again after lifting the nationwide lockdown on 21st July 2020. The exponential increase in the disease cases continued during the entire festival season (September, October) in Nepal and peaked during the second half of October 2020. Then, the number of cases declined considerably.

The spatial distribution of cumulative cases and district level incidence rate of COVID-19 reported before and after the cutoff date is presented in Figures 3a and 3b, respectively. By July 21, the epidemic was more intense in several western districts such as Dailekh, Doti, Achham and Bajura and low lying Tarai districts bordering India including Rautahat, Kailali, Mahotari and Sarlahi, although it was already spread across the country. The spatial pattern of the incidence rate was slightly different than the patterns of total cumulative cases which were determined by the population distribution. Bajura, Doti, Achham, Dailekh were districts with higher incidence. Higher incidence rates were also reported from Palpa, Parbat and Arghaghkanchi districts of Gandaki Province. By 29 November, the epidemic had become more intense across the country (Figure 3b). The highest number of cases were reported from Kathmandu followed by Bhaktapur, Lalitpur, Sunsari and Morang districts while the least cases were reported from Manang, Nawalparasi West, Dolpa and Humla. In the same period, the highest incidence was observed in Lalitpur, Kavrepalanchowk, Bhaktapur, Surkhet and Kathmandu where the incidence was above 125/10000.

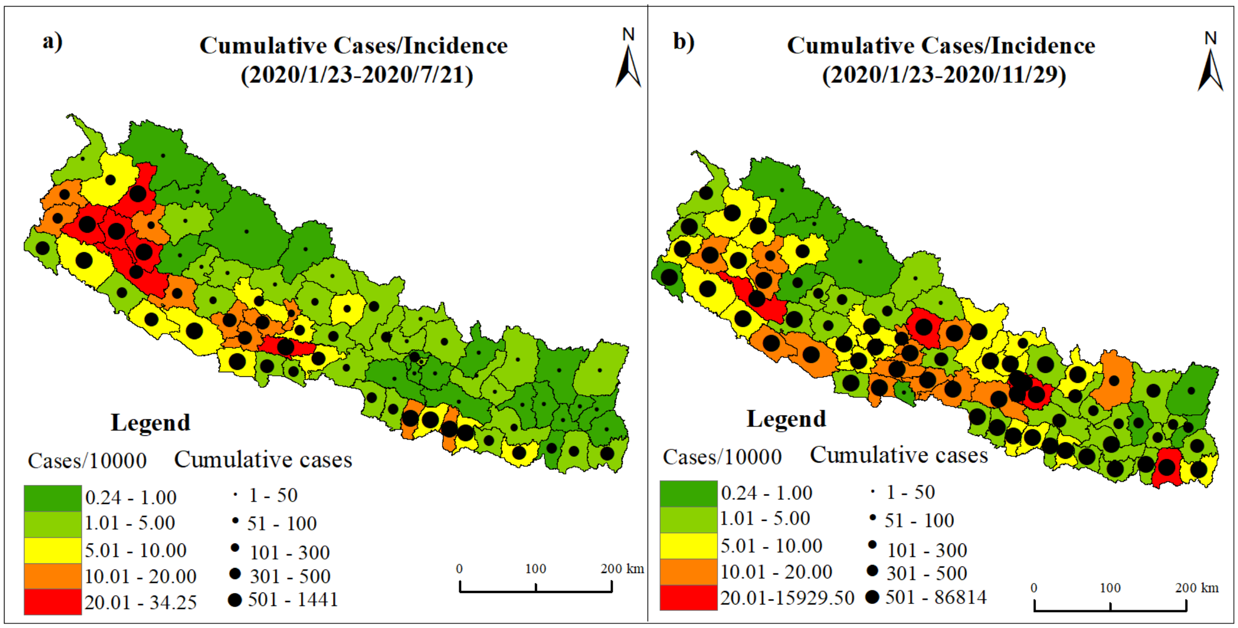

Figure 3. Spatial distribution of cumulative number and rate of incidence/10000 of COVID-19 cases from a) 23 January – 21 July and b) 23 January – 29 November 2020

Emerging district level clusters: 23 January-21 July 2020

Nine statistically significant emerging space-time clusters of COVID-19 were detected at the district level between 23 January and 21 July 2020 in Nepal. Table 1 provides the characteristics of these clusters with varying size, relative risk and onset time and duration. The most likely cluster i.e. cluster 1 and other secondary clusters; 3, 4 and 5 emerged from June 12 while clusters 6, 7 and 8 lately emerged almost at the end of the study period. The relative risk of these clusters also varied significantly. For example, the RR of cluster 1 (most likely cluster) was 16.95 while those of the cluster 2 and 3 were 9.87 and 9.81, respectively. Cluster 5, 8 and 9 were low-risk clusters with RR less than 3.00.

Table 1. District level emerging space-time clusters of COVID-19 from 23 January to 21 July 2020 in Nepal (RR: relative risk). All results are statistically significant at P<0.001.

Cluster	Radius	Start Date	End Date	# Districts	Observed	Expected	RR
1	82.89	2020/6/12	2020/7/21	11	4574	361.58	16.95
2	145.18	2020/6/14	2020/7/21	19	2884	344.79	9.87
3	53.05	2020/6/12	2020/7/21	5	2843	341.13	9.81
4	0.00	2020/6/12	2020/7/21	1	307	67.52	4.61
5	44.18	2020/6/12	2020/7/21	3	386	222.55	1.75
6	27.29	2020/7/21	2020/7/21	3	36	8.08	4.46
7	51.75	2020/7/16	2020/7/21	2	22	2.97	7.40
8	51.33	2020/7/20	2020/7/21	4	81	36.07	2.25
9	0.00	2020/6/23	2020/7/21	1	50	20.77	2.41

Figure 4a shows the locations and spatial patterns of the nine emerging space-time clusters of COVID-19 at the district level in Nepal between January 23 and July 23, 2020. Cluster-1 contains 11 districts of Karnali and Sudurpaschim provinces. Cluster 2, the first secondary cluster, is the largest cluster with a 145 km radius and covers 19 districts of western Nepal. Cluster 3, 5 and 6 were smaller compared to the first two clusters with radii

53, 44 and 27 km and the number of districts inside the clusters were 5, 3 and 3, respectively. Cluster 4 and 9 were single district clusters of Saptari and Sindhupalchok, correspondingly. There were 28 out of 77 districts outside these 9-emerging clusters having RR=0; at the time of this analysis, they were non-emerging COVID-19 risk districts.

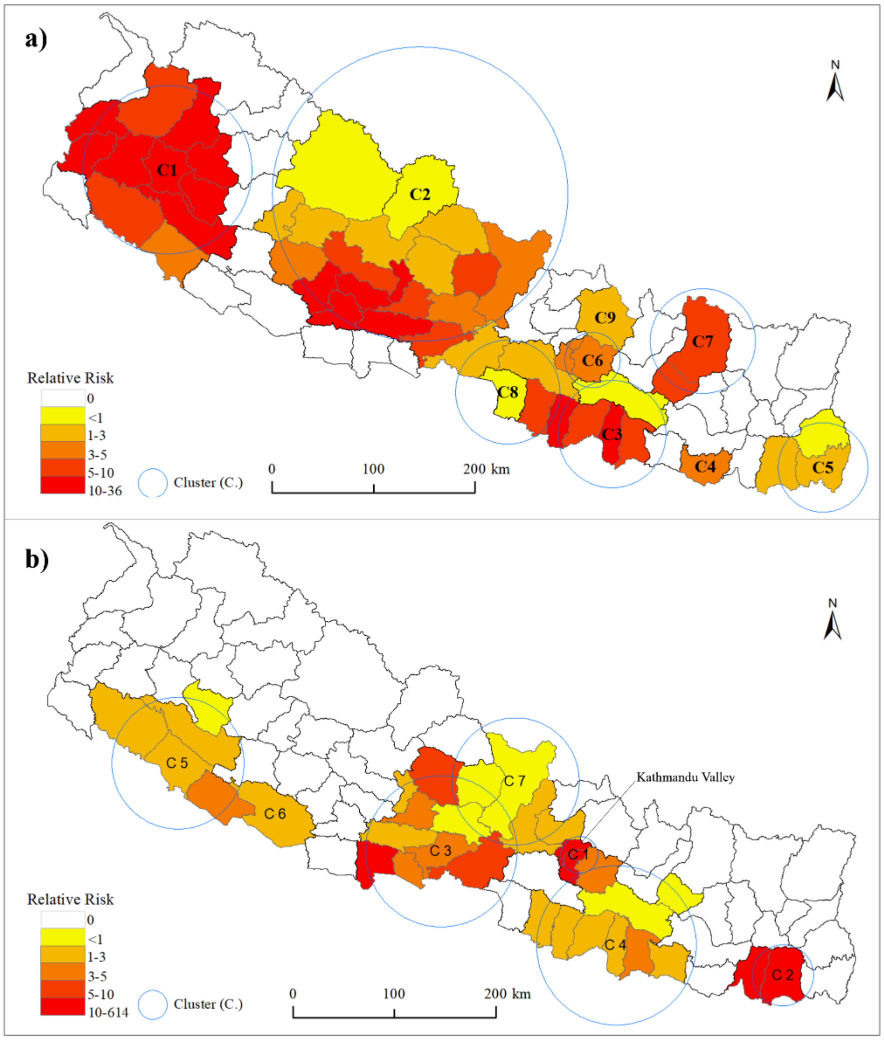

Figure 4. Spatial distribution of emerging space-time clusters of COVID-19 at District level. a) From 23 January – 21 July 2020; and b) 23 January – 29 November 2020.

Emerging district level clusters: 23 January-29 November 2020

Seven statistically significant emerging space-time clusters were detected between 23 January and 29 November 2020. Table 2 summarizes the characteristics of these clusters in terms of size, onset time, duration and relative risk level. Clusters 1, 2, and 4 emerged during the first and second week of August persisted till the end of the study period while clusters 6 and 7 were emerged lately and persisted shorter. Relative risk also varied significantly among these clusters. Cluster-1 which is a most likely cluster (RR =393.17) had the highest relative risk followed by clusters 2, and 3; while the remaining clusters 4, 5, 6, and 7 were the clusters with lower relative risk.

Figure 4b illustrates the extent and spatial distribution of the seven emerging space-time clusters of COVID-19 at the district level in Nepal between 23 January and 29 November 2020. Cluster-4 is the largest cluster with a 78 km radius, which contains seven districts of Madhesh Province and Okhaldhunga and Kavrepalanchowk districts followed by cluster-3, cluster-5 and cluster-7. The most likely cluster (Cluster-1) was located in central Nepal covering three districts of the Kathmandu valley; Kathmandu, Bhakatapur and Lalitpur. Cluster-6 was the single district cluster in Dang district of the Lumbini Province.

Table 2. District level emerging space-time clusters of COVID-19 from 23 January to 29 November 2020 in Nepal (RR: relative risk). All results are statistically significant at P<0.001.

Cluster	Radius	Start Date	End Date	# Districts	Observed	Expected	RR
1	18.129	2020/8/16	2020/11/29	3	105966	495	393.173
2	30.046	2020/8/11	2020/11/29	2	19795	1647	13.047
3	74.460	2020/8/30	2020/11/29	9	25276	5690	4.863
4	78.443	2020/8/8	2020/11/29	9	13735	6715	2.111
5	64.671	2020/9/4	2020/11/29	5	9837	4870	2.065
6	0.000	2020/10/6	2020/11/29	1	2261	843	2.697
7	62.590	2020/10/7	2020/11/29	4	3103	2280	1.366

Figure 4b also elucidates the elevated risk of 33 districts lying inside these clusters with varying risk levels ranging from 1.1 (Cluster-7) to 393.173 (Cluster-1). Kathmandu, Bhaktapur and Lalitpur were the districts with a higher relative risk (RR> 50). The number of the districts with moderate relative risk was 5 (RR= 5–15) while lower risks (RR= 1–5) were observed in 25 districts. Other 44 districts of Nepal exhibited no elevated risk of exposure (RR = 0) to the COVID-19 infection.

Progression of relative risk of COVID-19 in Nepal

The changing patterns of relative risk (RR) over two emerging periods have been shown in Figure 5. An abrupt reduction of RR was observed in 11 districts of which most of the districts belonged to cluster-1 and cluster-2 during 23 January- 21 July. A rapid rise of RR (>5) was also noticed in three districts of Kathmandu valley, Sunsari and Rupandehi; while moderate rise and fall in RR were observed in 13 and 20 districts symbolized by light red and light green, respectively. Some districts with RR = 0 over the two periods indicated no difference in relative risk which were regarded as "non-emerging" COVID-19 districts. However, it should be noted that these districts had also experienced elevated risk during the study period. Some of them became emerging clusters (with elevated RR) at some point in time when scanned over a shorter temporal window (Fig. 6).

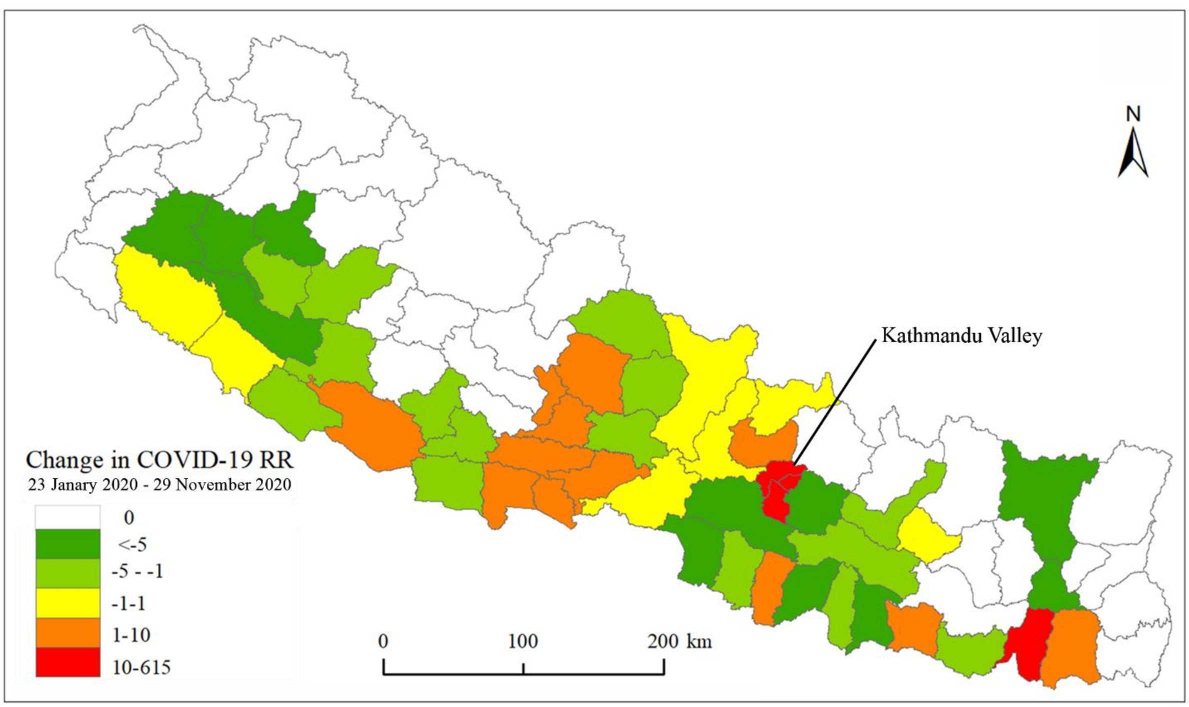

Figure 5. Changes in relative risk (RR) of COVID-19 between two emerging periods 23 January – 21 July and 23 January – 29 November 2020 in Nepal

Biweekly spatiotemporal variations of COVID-19 transmission at the district level in Nepal from 23 January to 29 November 2020 have been shown in Figure 6. This short temporal window scanning enabled us to assess the space-time progression of COVID-19 by locating dispersing risk and newly emerged high-risk areas along the timeline.

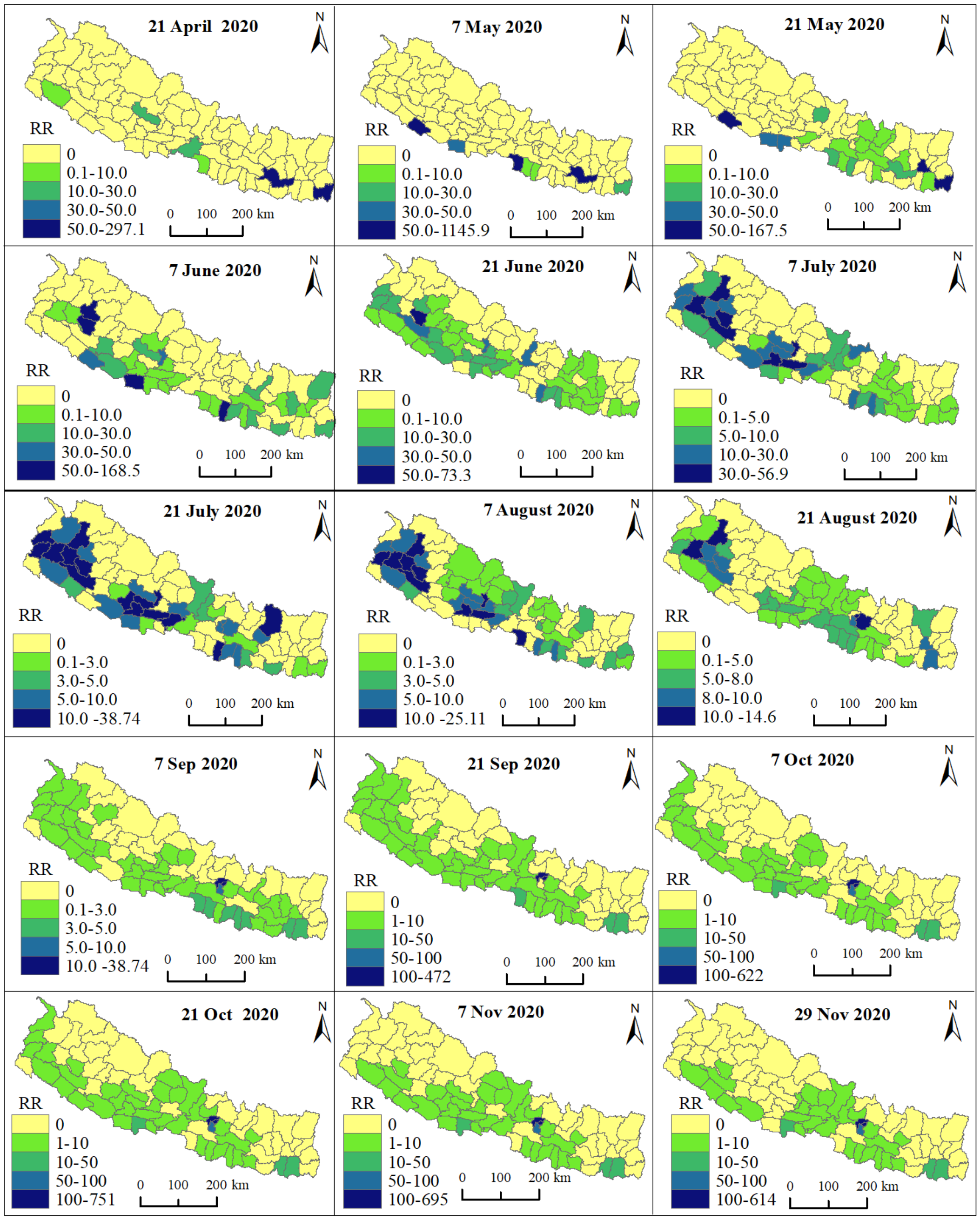

Figure 6. Space-time propagation of COVID-19 relative risk in different weeks in Nepal (RR- relative risk)

The elevated risk of COVID-19 transmission was observed on 21 April for the first time in Nepal although sporadic cases were reported from different districts since its first report on 23 January 2020. At this time, only six districts had elevated risk with significant variation in RR. The RR of Udayapur was extremely high (RR=297) followed by Jhapa (RR=68). The relative risk of Baglung, Chitawan, Kailali, Parsa and Nawalparasi East were moderately low (RR<20). This was the first cluster level transmission (14 cases) of COVID-19 suspected in

Udayapur district of Nepal with a migration history of infected people from India. Two weeks later Banke and Parsa districts bordering India became hotspots while the risk of transmission in Udaypur persisted continuously (RR=86). By May 21, the elevated risk expanded in 21 districts with a significant spatial variation on RR. Dhankuta and Jhapa emerged as new hotspots while the elevated risk of Banke remained constantly high (RR= 100). The COVID-19 transmission further spread in the next two weeks, till 07 June and the number of elevated risk (RR>1) districts reached 32. At this time Kalikot and Dailekh districts became hotspots (RR>150) while the risk of Rautahat and Kapilvastu was also significantly high (RR>50). In the later weeks, the elevated risk of COVID-19 further expanded but the unexpectedly high RR was more stable. From the beginning of July, the districts with higher relative risk further expanded on the proximity of Dailekh and Kailkot and the vicinity of Palpa and Syangja which continue until the first week of August. By August 21, the elevated RR was expanded to 56 districts. In early September, elevated risks were observed in 48 districts with large variations of RR. For instance, the RR of Kathmandu district was 372.48 followed by Bhaktapur with RR 113. While in 19 districts, the RR was lower than 5. The risk pattern in the following weeks was more or less similar with the continuously highest risk in the Kathmandu valley until the end of the study period.

DISCUSSION

COVID-19 pandemic has greatly affected the south-Asian countries including Nepal where the number of cases are still (first week of June 2021) increasing exponentially (MoHP, 2021). This study employed prospective space-time scan statistics for identifying currently active or emerging clusters of COVID-19 at the district level in Nepal, providing results at two distinct time periods of differential intervention attempts- 23 January – 21 July (the end date of nationwide lockdown), and 23 January – 29 November 2020 taking the cutoff date of 21 July. In addition, we investigated biweekly space-time propagation of transmission for locating risk and newly emerged clusters along the timeline. Our results suggest that the travel restriction is the most important non-pharmaceutical intervention against the COVID-19. However, poor implementation of it could not prevent disease transmission in Nepal. In the earlier days, the COVID-19 clusters were developed in western Nepal due to the inflow of infected Nepalese from India. Later, due to the movement of people to the capital city Kathmandu, where medical facilities are concentrated, the cluster was shifted towards the central region. Our findings can be useful for rapidly monitoring evolving space-time patterns of COVID-19 that will enable government and health officials to take appropriate time-sensitive intervention by considering disease's space-time diffusion pathways and potentially prepare for future outbreaks of a highly contagious disease (Masrur *et al.*, 2020).

After the first recorded positive case of COVID-19 on 21 January, there was a lag period of two months for the very next case. However, the cases increased after the third week of March and continued to grow exponentially. The first ascend on the epidemic curve was observed after the third week of April when Nepalese migrants working in India returned home despite nationwide lockdown there. The open border between the countries and the surge of a large number of returnees made it impossible to regulate the movement and manage proper tests and isolation. Therefore, most of the cases were recorded from the districts of Madhesh Province bordering India and that of Sudurpaschim Province, a large number of people from those districts are working in India for a long (Chalise, 2020). Human mobility and control strategy determine the spatial spread of the epidemics (Arimura *et al.*, 2020; Drake *et al.*, 2020; Kraemer *et al.*, 2020; Rader *et al.*, 2020; Zhou *et al.*, 2020). The areas close to the outbreak has a higher risk of contagion, especially in the initial stage of infection (Carteni *et al.*, 2020). Indian cities were severely affected by the COVID-19 since early April (Ray *et al.*, 2020; Tomar & Gupta, 2020) and the inflow of infected but asymptomatic people from those areas without testing increased the cases in particular areas of Nepal. Additionally, those districts of elevated incidences are also characterized by higher population density, lower literacy rates, higher poverty, and in turn preeminent vulnerability to the epidemics (Khanal *et al.*, 2020). Population density is one of the important factors in shaping the spatial pattern of the epidemics as the crowded cities worldwide could experience more prolonged epidemics (Rader *et al.*, 2020). Similar results were observed in China where the population inflow from Wuhan and the strength of economic connection were the main factors affecting the epidemic spread (Xie *et al.*, 2020).

The spatial analysis and predictive modelling of the evolution of the COVID-19 are important to interpret the epidemic phenomenon (Franch-Pardo *et al.*, 2020). Our prospective space-time scanning analysis revealed nine major emerging clusters for the first phase of the study (23 January - 21 July). The most likely cluster, the C1, emerged on 12 June that included 11 districts from Karnali and Sudurpaschim provinces. These districts have higher poverty and a majority of the households have one or more members of the family working as low-skilled manpower in Indian cities like Mumbai, Delhi, and others (Khanal *et al.*, 2020). The first cluster of COVID-19 observed was the consequence of infected returnees from India. Despite the nationwide lockdown imposed and borders sealed, people from India used resumed Indian railway services after the middle of May and returned back Nepal crossing the open border without taking proper precautions and in many cases violating isolation and quarantine protocols of federal and local governments (Chalise, 2020). Clusters 1-5 began on the second week of June and persisted till 21 July that were all associated with the inflow of people from

India. It has signified the importance of social distancing and movement restrictions in containing the epidemic.

The prospective space-time scanning analyses for a wider temporal scale, i.e. from 23 January to – 29 November 2020 revealed seven emerging clusters. The Cluster-4 in the eastern lowland Nepal was the largest cluster encompassing nine districts with a relative risk of 2.11, which is apparently the continuation of the Cluster-3 of the previous time frame i.e. 23 January- 21 July 2020. The Cluster-1 with the highest relative risk of 393.17 included three districts of the capital city Kathmandu valley- Kathmandu, Bhaktapur and Lalitpur. The number of COVID-19 cases was much higher in the Kathmandu district of the valley (MoHP, 2021); however, a high relative risk was not accounted for 23 January- 21 July 2020 due to an enormous base population. When the Government of Nepal lifted the nationwide lockdown on 21 July, people from different districts rushed to the capital city and the number of cases raised abruptly that developed a strong cluster (Cluster-1 for extended period, Figure 4b) with a very high relative risk (393.17). Epidemics in crowded cities disperse rapidly and have larger total attack rates than less populated cities (Rader *et al.*, 2020). To better understand the COVID-19 transmission dynamics, datasets on patient's travel and contact history need to be incorporated (Masrur *et al.*, 2020), however, there is no proper mechanism of tracking in Nepal. Therefore, the Kathmandu valley with more than four million population within 665 km^2 area is under severe risk of COVID-19 outbreak.

During the nationwide lockdown imposed by the federal government of Nepal, all public places remained shut down and strictly followed government directives. Many local municipal governments also efficiently implemented the closure, isolation, tracking and quarantine; those which failed to do so experienced initial community outbreaks. Therefore, till June 2020, community-level transmission was localized in few districts such as Udaypur, Parsa, and Banke (Figure 6). However, since July, many districts of Lumbini and Sudurpaschim provinces have experienced a high relative risk. The major reason behind such was the unpreparedness of the federal government (Thakur *et al.*, 2020) which failed to seal the southern border that imported hundreds of COVID-19 positive people from India, and could not properly test, track and isolate the individuals rescued from the Arabian countries. The nationwide lockdown was lifted on 21 July without any plan and predictions on the prospective outbreaks or waves. Chatterjee et al. (Chatterjee *et al.*, 2020) predicted that relaxation of containment measures before the arrival of the peak infection may result in a threefold rise at the peak, which seems valid in the context of Nepal. Another important shortcoming was the use of less reliable and inefficient antibody-based diagnosis (the rapid diagnostic tools) (Bisoffi *et al.*, 2020; Ghaffari *et al.*, 2020) emphasized in place of the antigen-based RT-PCR. By the end of November, densely populated Kathmandu valley had the largest number of COVID-19 patients having thousands of cases diagnosed every day and dozens of deaths. The centralization of the health facilities in the capital city Kathmandu caused people to move into it for the diagnosis and treatment of diseases including COVID-19. It is an established fact that people having compromised immunity due to pulmonary and cardiovascular disorders are highly prone to COVID-19 infection (Fang *et al.*, 2020; Zheng *et al.*, 2020). A large number of old-age people visiting hospitals for medical checkups were found positive to the COVID-19 and many were diagnosed positive only after death. Restrictions on mobility substantially limit COVID-19 spread (Glaeser *et al.*, 2020); failure on mobility management caused OVID-19 hotspots in many districts of Nepal including Kathmandu and other megacities like Biratnagar, Nepalgunj, Bharatpur, etc. Densely populated areas having inadequate health care systems and poor socio-economic infrastructure experience higher severity if strong restrictions are not implemented (Siam *et al.*, 2021). Inefficient and inadequate intervention against the epidemic has resulted in a strong cluster within the Kathmandu valley and Bharatpur where medical facilities are centralized but becoming short to contain the COVID-19. Therefore, together with medical care, non-pharmaceutical interventions such as travel restrictions, tracking and isolation are inevitable.

This study, for the first time, explored active and emerging clusters of COVID-19 in Nepal using prospective space-time scanning. Those disease clusters were examined in the light of the effectiveness of the nonpharmaceutical interventions and it identified the movement restriction the most important strategy to curb the transmission of SARS-CoV-2. However, there were some limitations associated with this study that should be taken into consideration while interpreting our results. For instance, underreporting of the disease in the absence of effective surveillance, monitoring and diagnosis might have caused a situation beyond the true condition of the COVID-19. The timeframe for this study was between January and November 2020 only which did not include the cases of the second major wave of the disease in Nepal. This study was conducted at the district level only due to the data availability at that spatial extent. It could give even better insight if the data were available at a fine resolution of the local administrative units. Despite those limitations, the findings of this research could be valuable to the health authorities within Nepal and beyond to better allocate resources and improve interventions on the pandemic for containing it efficiently.

CONCLUSIONS

The epidemic spread rate in Nepal has an evident spatial variation. Districts of Sudurpaschim and Madhesh provinces bordering India experienced rapid transmission of the COVID-19 when the Nepalese migrants returned home in May/June. The unmanaged population inflow from India crossing the sealed border had significant effects on the epidemic spread rate. The cities where medical facilities are concentrated, such as the capital city Kathmandu and Bharatpur Metropolitan City became the highest-risk active clusters since August. It is important to detect emerging clusters that would reveal more updated space-time transmission dynamics of COVID-19 to better allocate resources and improve decision-making as the outbreaks continue to grow. The purposive and time-bound movement restriction appears to be the most important non-pharmaceutical intervention against the COVID-19 for resource-scarce countries with limited health care facilities.

ACKNOWLEDGEMENTS

We thank Ministry of Health and Population, Government of Nepal for providing the valuable data on COVID-19 in Nepal.

AUTHOR CONTRIBUTIONS

BKA and LK conceptualized the study. BKA, LK, SKA, SP, BKN and BKP collected and processed data. BKA and LK analyzed the data and prepared the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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