Co-infection of COVID-19 with Malaria and Dengue -A Hospital based Study in Kathmandu, Nepal

Bajracharya B,[1] Shrestha P,[1] Shrestha D,[1] Karna AK,[1] Mahato RK,[2] Shrestha S,[3] Baral B,[3] Bhandari P,[4] Sah P,[5] Bastola A,[6] Pandey BD[7]

[1]Center for Health and Disease Studies-Nepal, Sankhamul, Kathmandu, Nepal.

[2]Epidemiology and Disease Control Division (EDCD), Department of Health Services, Teku, Kathmandu.

[3]Sukraraj Tropical and Infectious Disease Hospital, Teku, Kathmandu, Nepal.

[4]National Public Health Laboratory, Teku, Nepal.

[5]Sushil Koirala Prakhar Cancer Hospital, Khajura, Banke, Nepal.

[6]Curative Service Division (CSD), Department of Health Services, Ministry of Health and Population.

[7]DEJIMA Infectious Disease Research Alliance (DIDA), Vaccine Research Development Center (VRDC) Nagasaki University, 852-8523 1-12-4 Sakamoto, Nagasaki, Japan

Corresponding Author

Bijay Bajracharya

Center for Health and Disease Studies-Nepal,

Sankhamul, Kathmandu, Nepal.

E-mail: bjbajra@gmail.com

Citation

Bajracharya B, Shrestha P, Shrestha D, Karna AK, Mahato RK, Shrestha S, et al. Co-infection of COVID-19 with Malaria and Dengue -A Hospital-based Study in Kathmandu, Nepal. *Kathmandu Univ Med J*. 2024;87(3):254-9.

ABSTRACT

Background

In tropical countries like Nepal, the COVID-19 pandemic unfolded within a population already grappling with various tropical infectious diseases. Co-infection with malaria and dengue holds clinical significance when managing COVID-19 patients in regions endemic to these diseases.

Objective

To identify malaria and dengue infections in febrile or symptomatic patients suspected of COVID-19 at the Sukraraj Tropical and Infectious Disease Hospital, Kathmandu.

Method

Over two months, a prospective study was conducted on febrile or symptomatic patients suspected of COVID-19 visiting Sukraraj Tropical and Infectious Disease Hospital, Kathmandu. One hundred and twenty-three patients suspected of COVID-19 were tested for SARS-CoV-2 through RT-PCR as well as for malaria and dengue infection using rapid diagnostic test kits.

Result

Out of 123 patients suspected of COVID-19, 64 were confirmed to have COVID-19. No evidence of SARS-CoV-2 and malaria co-infection was found among the 123 tested patients. However, two patients admitted for COVID-19 tested positive for dengue virus infection. The patients with co-infections with dengue or scrub typhus were likely to have a longer hospital stays (OR 2.5; 95% CI: 0.22-29.26), though lacking a significant association.

Conclusion

The two patients diagnosed with dengue virus and SARS-CoV-2 were identified during their hospital visit and both recovered after receiving treatment. Given that COVID-19 patients manifest symptoms resembling many tropical infectious diseases, the study underscores the clinical importance of testing for multiple circulating infections in patients from endemic areas. This approach ensures appropriate and timely management reducing the risk of severity or mortality.

KEY WORDS

Co-infection, COVID-19, Dengue, Malaria, Nepal

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the virus emerged from Wuhan, China in December 2019, and spread globally. SARS-CoV-2 infections can be asymptomatic, causing a mild illness or resulting in severe disease and death. Common symptoms include fever, cough, tiredness, loss of taste or smell, shortness of breath, and headache. As of March 3, 2024, it has infected over 774 million individuals globally and killed more than seven million COVID-19 patients.[1]

The virus spread to the Asia-Pacific region endemic with febrile illnesses including dengue, scrub typhus, typhoid, malaria, and leptospirosis.[2] The most common symptom of these diseases and COVID-19 is fever, and thus pose challenges in the diagnosis and management of COVID-19 in the tropical regions.[3] Several patients of COVID-19 with malaria co-infection have been reported from various countries.[3-6] Outbreaks of dengue amidst ongoing COVID-19 pandemic have been reported from Bangladesh, Brazil, India, Pakistan, Indonesia, Columbia, and Singapore.[7-11] Few studies have reported fatal outcomes among COVID-19 patients with dengue.[12-14]

Therefore, screening for co-circulating infections in febrile patients with fever and without a history of travel to disease endemic areas is inevitable. This study was designed to test for malaria and dengue infections in febrile patients suspected of COVID-19. The study was intended to provide evidence to the stakeholders of the health sector in Nepal to guide them in developing appropriate guidelines for the clinical management of COVID-19 patients.

METHODS

A cross-sectional study was conducted at Sukraraj Tropical and Infectious Disease Hospital (STIDH) in Kathmandu, Bagmati Province of Nepal from July 3 to September 8, 2021. Informed consent was obtained from either the patients or their family members, and ethical approval was granted by the Nepal Health Research Council (Ref. No.160/2021). All collected information obtained was fully anonymized, used only for this project, and kept confidential.

The study encompassed febrile patients suspected of COVID-19 referred by the attending physicians based on their clinical signs and symptoms. Clinicians gathered information on signs, symptoms, socio-demographics (age, sex), and travel history through a paper-based questionnaire. Patients screened for COVID-19 and suspected of malaria or dengue fever at the time of diagnosis underwent testing for later two diseases. Confirmed COVID-19 patients, with or without co-infections of malaria or dengue were observed for disease progression, hospital stay, disease outcomes, and fatalities until discharge.

SARS-CoV-2 infection confirmation was performed by the hospital by real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay and the result was obtained from patient or hospital record. To confirm co-infection with dengue or malaria, blood samples were collected and subjected to First Response® Malaria Ag P.f./P.v. Card test (WHO Reference Number: PQDx0329-010-00; Premier Medical Corporation Ltd., Mumbai, India) and dengue NS1 + IgM/IgG Combo rapid test (Healgen, Houston, US) following manufacturer's instructions. Dengue combo rapid test kit demonstrated a sensitivity of 95.8% for IgG/IgM and 95.7% for NS1 with a specificity of 99.0% for IgG/IgM and 98.3% for NS1. The First Response® Malaria Ag. P.f./P.v. The card test showed 100% sensitivity and specificity.

Data from the laboratory investigation were entered in an Excel sheet, tabulated, and presented in tables and graphs as counts and percentages. Descriptive and inferential analysis was conducted using SPSS version 22 software. Results obtained from the analysis were reported with a 95% confidence interval.

RESULTS

The study enrolled a total of 123 patients visiting STIDH and the blood samples collected were processed in the laboratory of the same hospital.

Among 123 patients visiting STIDH, 49 (39.8%) were females, and 74 (60.2%) were males. Out of 123 patients, 64 patients (52.03%) were confirmed as SARS-CoV-2 positive. Males (64.1%) were more affected by COVID-19 than females (35.9%). The age of study participants ranged from 12 to 84 years with the mean age 44.56 years (41.66-47.47). The majority of participants belonged to the age group of 31-40. Laboratory screening revealed that 0.8% (1/123) and 3.3% (4/123) of the participants were positive for malaria and dengue respectively. The proportion of dengue (NS1 positive) in suspected COVID-19 patients was only 0.8% (0.0-4.4%). The lone malaria-positive patient was a male in the age group 31-40. Among the four dengue-positive patients, three patients were females, and three belonged to the age group 41-50.

Out of 123 patients visiting STIDH, 64 (52.03%) were confirmed SARS-CoV-2 positive. There were no patients of co-infection with malaria and COVID-19. However, one-non-COVID-19 case tested positive for the presence of *Plasmodium falciparum (Pf)* on the rapid test for malaria. The confirmed patient with the malarial parasite had recently returned from the Central Africa region. Similarly, among two patients who tested positive for SARS-CoV-2 infection, one was positive for (NS1) and the other had dengue virus-specific IgG positive. The two COVID-19-negative patients had a previous dengue virus infection (IgG). The co-infection rate of COVID-19 with dengue was found to be 3.1% (2/64).

Table 1. Socio-demographic characteristics related to COVID-19, malaria and dengue

Characteristics	N(%)	COVID-19		Malaria		Dengue	
		Positive	Negative	Positive	Negative	Positive	Negative
Gender							
Female	49 (39.8)	23 (35.9)	26 (44.1)	-	49 (40.2)	3 (75)	46 (38.6)
Male	74 (60.2)	41 (64.1)	33 (55.9)	1	73 (59.8)	1(25)	73(61.3)
Total	**123**	**64 (52.03)**	**59 (47.9)**	**1 (0.8)**	**122 (99.2)**	**4 (3.3)**	**119 (96.7)**
Age group (yrs)							
11-20	4(3.3)	1(25)	3(75)	-	4 (100)	-	4 (100)
21-30	23(18.7)	11(47.8)	12 (52.2)	-	23 (100)	-	23 (100)
31-40	**31(25.2)**	16(51.6)	15 (48.4)	**1(3.2)**	30 (96.8)	-	31(100)
41-50	24(19.5)	11(45.8)	13 (54.2)	-	24 (100)	**3(12.5)**	21(87.5)
51-60	22(17.8)	12(54.5)	10 (45.5)	-	22 (100)	**1(4.5)**	21 (95.5)
61-70	9 (7.3)	6 (66.7)	3 (33.3)	-	9 (100)	-	9 (100)
71-80	7 (5.7)	4(6.3)	3 (42.9)	-	7 (100)	-	7 (100)
81-90	3(2.4)	3(100)	-	-	3 (100)	-	3 (100)
Total	**123**	**64**	**59**	**1**	**122**	**4**	**119**

Table 2. Co-infection between COVID-19 and Dengue

Dengue		COVID-19	
	N (%)	Positive (%)	Negative (%)
Overall	123	64 (52.03)	59 (47.9)
Dengue-specific result			
NS1 Positive	**1 (25)**	**1 (100)**	0
IgG Positive	**3 (75)**	**1 (33.3)**	**2 (66.7)**
IgM Positive	0	0	0
Negative	119 (96.7)	62 (52.1)	57 (47.9)

Table 3. Outcome of Co-infection of Dengue with COVID-19

	COVID-19 test result	Dengue test result	Signs and symptoms	Outcome of co-infection of dengue with COVID-19
Patient 1	Positive	Dengue IgG positive	Fever, headache, and shortness of breath	Discharged after 10 days of hospital stay
Patient 2	Positive	Dengue NS1 positive	Fever, nausea, and body aches	Discharged after 10 days of hospital stay

A 49-year-old female patient, among 64 individuals testing positive for both COVID-19 and dengue IgG antibodies presented with fever, headache, and shortness of breath (SOB) upon hospital admission. Following admission to the intensive care unit (ICU), her condition improved, and she was transferred to the special cabin after three days. After a ten-day hospital stay, she demonstrated improvement and was subsequently discharged.

Another patient, a 59-year-old female with a confirmed case of COVID-19, positive patient exhibited symptoms such as a fever, nausea, and body aches and was also revealed to have the dengue NS1 antigen positive. She was admitted to the hospital's general ward with an oxygen supplement. After a 10-day hospital stay, her condition was stable, and she was also discharged.

Table 4. Laboratory findings of patients with COVID-19 and dengue co-infection

Laboratory findings	Patient 1	Patient 2	Reference value
Total leucocyte count	8700	9800	4000-11000
Neutrophils	**83**	**93**	40-75
Lymphocytes	**15**	**05**	20-45
Eosinophils	00	00	1-6
Monocytes	02	02	2-10
Basophils	00	00	0-1
Platelet	275	229	150-400
D-dimer	**9.68**	**0.64**	0-0.5
Alkaline phosphatase	50	**140**	Male: 53-128; Female: 42-98 Child: 54-369
SGPT	23	17	Up to 42
SGOT	**42**	27	Up to 37
S ferritin	**272.11**	**234**	Male: 30-400, Female: 13-150

The laboratory findings of both co-infected patients of COVID-19 with dengue showed neutrophilia, lymphocytopenia, elevated transaminases, and elevated serum ferritin. Additionally, the D-dimer values were also elevated in both cases.

Along with co-infection of dengue, malaria, and COVID-19, we also investigated other common infectious diseases prevalent in Nepal. During our study , some interesting findings emerged. Besides malaria and dengue, the Scrub typhus IgM antibody test was found positive in two

Table 5. Cases of infections other than malaria and dengue

COVID-19 test	Count of patients	Scrub typhus IgM positive	Leptospira IgG positive	Brucella antibody positive
Positive	64	2	0	0
Negative	59	12	2	1
Total	**123**	**14**	**2**	**1**

COVID-19-positive patients and twelve COVID-19-negative patients. The proportion of scrub typhus in suspected COVID-19 patients was 11.4% (6.4-18.4%) which was higher as compared to that of dengue and malaria. Unfortunately, one COVID-19 patient with scrub typhus had a fatal outcome. Similarly, the Leptospira-specific IgG antibody and Brucella-specific antibody test were also confirmed in two and one COVID-19-negative patients, respectively.

The median hospital stay for COVID-19-positive patients was eight days. We observed that the individuals with co-infections with dengue or scrub typhus were likely to have a longer hospital stays (OR 2.5; 95% CI: 0.22-29.26), though lacking a significant association. Similarly, the co-infection either with dengue or scrub typhus, as well as sex and age, were not found to be significant predictors of poor outcomes or death in COVID-19 patients with respective OR as 0.14 (95% CI: 0.01-1.9), 0.42 (95% CI: 0.04-4) and 0.98 (95% CI: 0.93-1.03).

DISCUSSION

The COVID-19 pandemic is exerting immense pressure on the healthcare and management systems in nearly every country of the world. As of January 10, 2024, Nepal has reported over 10,03,450 cases and approximately 12,031 deaths.[15] In tropical countries like Nepal, various endemic vector-borne diseases such as malaria, dengue, scrub typhus, and leptospirosis persist alongside the ongoing spread of COVID-19. Amidst this crisis scenario, health services face disruptions due to travel restrictions; health facilities primarily focus on COVID-19 management. Many individuals refrain from seeking care in health facilities due to fear, stigma, and lack of knowledge. Febrile cases suspected of COVID-19 with recent travel history are advised to undergo testing for dengue and malaria. These diseases may manifest independently or concurrently with COVID-19. This study represents the first attempt to our knowledge, to assess the co-infection between COVID-19 and malaria/dengue in Nepal.

In tropical, subtropical, and temperate regions, no prior efforts have been made to elucidate the co-infection conditions between COVID-19 and malaria/dengue. Given the shared symptoms and travel history both significant for COVID-19 and malaria, diagnosing co-infection may pose a challenge. COVID-19 patients and those with malaria/dengue exhibit similar clinical symptoms (e.g., fever, chills, headache, fatigue, and myalgia) and laboratory parameters

Table 6. Relation between co-infection and hospital stay

		Hospital stays up to median hospital stay	Hospital stays greater than median hospital stay	Total
Co-infection	No	33	28	**61**
	Yes	1	2	**3**
Total		**34**	**30**	**64**

(e.g., leukopenia, lymphopenia, thrombocytopenia, and elevated transaminases) that can be alike.[7]

Nepal experienced a total of six waves of COVID-19, ranging from small to large. The COVID-19 positivity rate observed in this study was 52.03%, making higher incidence. This elevation can be attributed to the study being conducted during the second wave of COVID-19 in a specialized hospital dedicated to COVID-19 in Kathmandu, Nepal. Nevertheless, the high SARS-CoV-2 positivity rate recorded in this limited population group merely reflects the current situation. Given that this is a preliminary study with a limited sample size, not fully representative of Nepal's entire population, further research with a larger sample size is advisable. Out of the 64 patients who tested positive for COVID-19, 41 were males and 23 were females. Males exhibited a higher frequency of COVID-19 infection compared to females. This discrepancy may be attributed to males engaging in outdoor activities, visiting shops and markets, as well as participating in social gatherings and public events.

The age group 31–40 accounted for most COVID-19 patients (51.6%), followed by the 51–60 age group. Among male COVID-19 patients, a higher prevalence was observed in the age groups of 21 to 30, followed by the 31 to 40 age group. Similarly, the age groups 31–40 and 41–50 showed the highest proportion of female COVID-19 patients. Due to the COVID-19 outbreak and the enforcement of severe lockdown, children and the elderly are constrained to stay at home. This restriction could explain the higher infection rate among young and middle-aged individuals compared to children and the elderly. Similar findings were reported in studies conducted by other countries.[16-18]

The study identified a malaria infection rate of only 0.8% (1/123) and a dengue infection rate of 3.2% (4/123) while the co-infection rate of COVID-19 with dengue was found to be 3.1%. In contrast, Sebastiao et al. reported a higher infection rate of 13% for malaria and 27% for dengue which significantly surpassed our study. However, the overall co-infection rate between COVID-19 and vector-borne diseases (VBD) was 11.4%.[19]

In a similar study in India, the incidence of co-infection of COVID-19 with malaria and/or dengue was found to be 1.4%.[20] The absence of COVID-19 and malaria co-infection in our study is unsurprising, as all COVID-19 patients tested negative for malaria. This outcome is predictable, given the study's limitation to the STIDH of Bagmati province which

has a lower prevalence/incidence of malaria. Additionally, the country's mobility was constrained due to the COVID-19 pandemic and a stringent lockdown, which negatively impacted individual migration. Due to time and budget restrictions, the study could only be conducted at STIDH, one of the renowned tertiary hospitals in the nation with a consistent influx of patients from all across the nation. It is recommended that healthcare professionals include malaria screening alongside COVID-19 testing.[6]

Co-infections of COVID-19 and dengue have been reported in various countries including Bangladesh, Brazil, India, Pakistan, Indonesia, Columbia, France, Saudia Arabia, and Singapore.[7-14] In our study, two patients who tested positive for COVID-19 also exhibited positivity for the dengue NS1 antigen and dengue IgG antibody. These patients were females aged 49 and 59 years. Previous research has identified co-infections in adults aged 18-69 years with COVID-19 and dengue.[7,11,13,14] A case report of detailing the co-infection of COVID-19 and malaria as well as dengue in a 21-year-old male with a history of travel to Mumbai two months ago was previously published in Nepal.[21]

The patient positive for dengue IgG experienced a fever, headache, and shortness of breath. The patient with positive dengue NS1 had symptoms including fever, nausea, and body aches. Fever was a common symptom shared by both co-infected patients. The key laboratory findings for both patients included neutrophilia, lymphocytopenia, elevated transaminases, and increased serum ferritin, promoting clinicians to conduct immediate dengue testing. Similar laboratory findings have been reported in other studies.[22,23]

In our study, both co-infected patients received a timely diagnosis and recovered successfully with proper treatment, without any complications aligning with the findings of other studies.[7,8,11,23] In contrast, two co-infected cases in Saudi Arabia had unfavorable outcomes attributed to poor prognosis and diagnosis.[12] Owing to a study conducted by Pandey et al. the double burden of COVID-19 and dengue has elevated the risk of heightened severity, more severe cases, and fatalities in Nepal.[24] Additionally, the potential misinterpretation of these viral infections could lead to delayed or inappropriate treatment and inefficient resource allocation.[23] In this era of the pandemic, clinicians in endemic areas must be aware of diagnostic challenges and remain vigilant for co-infections involving COVID-19, dengue, and other tropical pathogens.[25-27]

Throughout the study, several noteworthy findings emerged. Alongside cases of Malaria and Dengue, two COVID-19-positive patients were hospitalized exhibited positive scrub typhus IgM antibody tests, and twelve COVID-19-negative who were also diagnosed with scrub typhus infections. Unfortunately, an 84-year-old COVID-19-positive patient with pneumonia and scrub typhus experienced a fatal outcome. Similarly, two COVID-19-negative patients tested positive for Leptospira IgG antibodies, while another COVID-19-negative patient tested positive for Brucella antibodies.

A case report detailing the co-infection of COVID-19 and scrub typhus in a young patient with a history of dry cough and dyspnea at night was previously published in Nepal.[28] Likewise, another case report highlighted the co-infection of COVID-19 and scrub typhus in 70-year-old Indian lady.[29] In many disease-endemic countries like Nepal, scrub typhus may easily be overshadowed by COVID-19 due to its similar clinical manifestations.[30]

The study suggested that the COVID-19 patients with extended hospital stays were likely to have dengue or scrub typhus simultaneously with OR 2.5 (95% CI: 0.22-29.26) although the association lacks significance. Similarly, factors such as age, sex, and co-infection with either dengue or scrub typhus were not identified as significant predictors of the poor outcome or death of the COVID-19 infection with respective OR as 0.14 (95% CI: 0.01-1.9), 0.42 (95% CI: 0.04-4) and 0.98 (95% CI: 0.93-1.03). This lack of significance can be attributed to the study's short duration, small population, and confinement to a single institution.

Despite providing valuable insights, our results have several limitations. This is a preliminary study conducted with a small size population over a short period, rendering it non-representative of the entire country's population. Therefore, further studies encompassing a larger and more diverse population are imperative.

CONCLUSION

The two patients co-infected with the dengue virus and SARS-CoV-2 were diagnosed during their hospital visit and they both recovered after receiving treatment. The study observed co-infection with the dengue virus in COVID-19 patients. Given that COVID-19 patients exhibit symptoms similar to those of various tropical infectious diseases, the study emphasized the clinical significance of conducting tests for multiple circulating infections in patients from endemic areas. This approach is crucial for ensuring appropriate and timely management to prevent severity or mortality.

ACKNOWLEDGEMENTS

We are grateful to all the participants of this study as well as the staff of Sukraraj Tropical and Infectious Disease Hospital, where the study was carried out for their kind cooperation and support. This work was partially funded by NHRC provincial grant (2077/78).

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