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MAJOR ARTICLE

Experience of Treating COVID-19 With Remdesivir and Convalescent Plasma in a Resource-Limited Setting: A Prospective, Observational Study

Janak Koirala,[1,2] Pradip Gyanwali,[1] Robert B. Gerzoff,[3] Saroj Bhattarai,[1] Bipin Nepal,[4] Rekha Manandhar,[5] Runa Jha,[5] Sanjib Sharma,[6] Yuba Raj Sharma,[7] Anup Bastola,[8] Holly Murphy,[9] Subhash Acharya,[10] Prabhat Adhikari,[4] Manita Rajkarnikari,[11] Karishma M. Vaidya,[5] Chhabi L. Panthi,[1] Bihungum Bista,[1] Grishma Giri,[1] Shambhu Aryal,[13] Suman Pant,[1] Akritee Pokharel,[12] Shristi Karki,[1] Sangita Basnet,[2,7] Bhagawan Koirala,[10] and Meghnath Dhimal[1]; for the Nepal COVID-19 Clinical Study Collaborators[a]

[1]Nepal Health Research Council, Kathmandu, Nepal, [2]Division of Infectious Diseases, Southern Illinois University School of Medicine, Springfield, Illinois, USA, [3]Applied Statistical Consulting LLC, Atlanta, Georgia, USA, [4]Grande International Hospital, Kathmandu, Nepal, [5]National Public Health Laboratory, Kathmandu, Nepal, [6]Department of Internal Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal, [7]Department of Internal Medicine, Patan Academy of Health Sciences, Lalitpur, Nepal, [8]Sukraraj Tropical and Communicable Disease Hospital, Kathmandu, Nepal, [9]Saint Joseph Mercy Ann Arbor Hospital, Ann Arbor, Michigan, USA, [10]Department of Internal Medicine, Tribhuvan University Institute of Medicine, Kathmandu, Nepal, [11]Nepal Red Cross, Kathmandu, Nepal, [12]Department of Drug Administration, Kathmandu, Nepal, and [13]Inova Fairfax Hospital, Annandale, Virginia, USA

Background. Convalescent plasma therapy (CPT) and remdesivir (REM) have been approved for investigational use to treat coronavirus disease 2019 (COVID-19) in Nepal.

Methods. In this prospective, multicentered study, we evaluated the safety and outcomes of treatment with CPT and/or REM in 1315 hospitalized COVID-19 patients over 18 years in 31 hospitals across Nepal. REM was administered to patients with moderate, severe, or life-threatening infection. CPT was administered to patients with severe to life-threatening infections who were at high risk for progression or clinical worsening despite REM. Clinical findings and outcomes were recorded until discharge or death.

Results. Patients were classified as having moderate (24.2%), severe (64%), or life-threatening (11.7%) COVID-19 infection. The majority of CPT and CPT + REM recipients had severe to life-threatening infections (CPT 98.3%; CPT + REM 92.1%) and were admitted to the intensive care unit (ICU; CPT 91.8%; CPT + REM 94.6%) compared with those who received REM alone (73.3% and 57.5%, respectively). Of 1083 patients with reported outcomes, 78.4% were discharged and 21.6% died. The discharge rate was 84% for REM (n = 910), 39% for CPT (n = 59), and 54.4% for CPT + REM (n = 114) recipients. In a logistic model comparing death vs discharge and adjusted for age, gender, steroid use, and severity, the predicted margin for discharge was higher for recipients of remdesivir alone (0.82; 95% CI, 0.79–0.84) compared with CPT (0.58; 95% CI, 0.47–0.70) and CPT + REM (0.67; 95% CI, 0.60–0.74) recipients. Adverse events of remdesivir and CPT were reported in <5% of patients.

Conclusions. This study demonstrates a safe rollout of CPT and REM in a resource-limited setting. Remdesivir recipients had less severe infection and better outcomes.

ClinicalTrials.gov identifier. NCT04570982.

Keywords. COVID-19; convalescent plasma; remdesivir.

The first case of coronavirus disease 2019 (COVID-19) was reported in Nepal on January 23, 2020. After the second case of COVID-19 was detected in a student returning from France in March 2020, Nepal underwent a countrywide lockdown for the next 4 months [1]. This slowed the spread of the virus and allowed time to prepare the hospitals and acquire necessary equipment and therapies before the epidemic was widespread. Following guidelines issued by the US Food and Drug Administration (US FDA) and the European Union Commission Directorate-General for Health and Food Safety, the government of Nepal authorized convalescent plasma treatment (CPT) for investigational use in June 2020. Remdesivir was approved in Nepal as a study drug for COVID-19 in August 2020 in the absence of a legal provision for emergency use authorization (EUA) in Nepal. The Nepal Health Research Council (NHRC) supervised the use of both therapies as investigational agents.

Initial observational and retrospective studies have suggested that CPT may be effective for the treatment of COVID-19 [2, 3]. Compared with matched patients who received standard treatment, a metanalysis showed reduced mortality in CPT-treated

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[a]Study collaborators listed in the Acknowledgments

Correspondence: Janak Koirala, MD, MPH, FACP, FIDSA, Professor of Medicine and Infectious Diseases, Division of Infectious Diseases, Southern Illinois University School of Medicine, PO Box 19636, Springfield, IL 62794-9636, USA (jkoirala@siumed.edu)

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patients [4]. A large multicentered study evaluated and established the safety of CPT in COVID-19 patients [5]. The same group of investigators reported a lower pooled 30-day relative mortality in patients who received CPT with high antibody levels against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6].

The ACTT-1 trial reported a decreased time to recovery in hospitalized patients who received remdesivir for COVID-19 lower respiratory tract infection [7]. Remdesivir was also associated with shorter oxygen and mechanical ventilation use. In another randomized study, a 5-day course of remdesivir was found to be equally effective compared with a 10-day course in COVID-19 patients with pulmonary infiltrates and ≥94% room air oxygen saturation [8].

The objective of this study was to monitor safety and evaluate outcomes in hospitalized patients who received remdesivir, CPT, or both for the treatment of COVID-19 in Nepal.

METHODS

Study Design and Participants

This was a prospective, multicentered, observational study designed to evaluate the safety and outcomes of hospitalized patients with COVID-19 infection in Nepal who were treated with CPT and/or remdesivir. All patients in the 3-month study period from July 30 to October 31, 2020, were included in the study. The government of Nepal authorized CPT for investigational use in June 2020, when the initial study protocol for CPT was prepared. It was amended to add remdesivir in August 2020, when the latter was authorized as a study drug in Nepal. Patients received CPT alone, remdesivir alone, or both treatments either together or sequentially. While the patient was in the study, other antiviral agents were not allowed, but all other drugs necessary for patient management (such as steroids) were permitted. This study was approved by the Ethics Review Board of NHRC and registered with ClinicalTrials.gov (NCT04570982).

After informed consent, patients aged 18 years and older with reverse transcription polymerase chain reaction (RT-PCR)–confirmed COVID-19 were enrolled at NHRC-approved study hospitals. Remdesivir eligibility required the patient to be admitted to a hospital with a moderate, severe, or life-threatening COVID-19 infection as defined by the National Institutes of Health COVID-19 guidelines [9]. To be eligible for CPT, patients had to have COVID-19 infection that was judged by the treating provider to be at high risk of progression to severe or life-threatening disease secondary to age (>65 years), an immunocompromising condition, or comorbidities [9]. Also eligible were patients who progressed to severe or life-threatening infection despite being on remdesivir for 48 hours or longer. Patients aged <18 years and those with any CPT or remdesivir contraindications were excluded.

Study Procedures

Remdesivir was administered intravenously, 200 mg on day 1 followed by 100 mg daily from days 2 to 5, to patients with moderate to severe infections and from days 2 to 10 to patients on a ventilator.

ABO-compatible COVID-19 convalescent plasma was collected from eligible donors who had recovered from PCR-positive COVID-19 infection and were symptom-free for a minimum of 14 days. Donors had to be male or nulliparous females, PCR negative at the time of plasma donation, and willing to sign a donor consent form. Blood from eligible convalescent donors was collected, and plasma was separated and stored following standard procedures [10]. Convalescent plasma (200 mL) was administered intravenously over 2 hours, and patients were monitored for any transfusion-related adverse reactions from 4 hours to 7 days.

Donor plasma samples were stored frozen at the blood banks to allow antibody titers to be checked at a later date. The samples were tested at Grande International Hospital, Kathmandu, for total antibody levels (both immunoglobulin [Ig] G and IgM) using the Chemiluminescence Immunoassay Analyzer (CLIA) method using Vitros 5600 (Ortho Clinical Diagnostic). Any result above the signal to cutoff (S/Co) value of ≥1 was considered reactive (VITROS CoV2T Instructions Manual, version 3.2). As per the manufacturer's brochure, an anti-SARS-CoV-2 S/Co ratio of 12 (equivalent to neutralizing antibody titer 1:250) was considered a cutoff for low vs high titers.

Patient data included baseline demographic, clinical, and lab data at enrollment, treatment details, follow-up clinical and lab data during hospital stay, adverse events, and outcomes (death, discharge in good condition, or discharge with disability) at the end of hospitalization. Discharge with disability was defined as presence of complications needing rehabilitation or further treatment after recovery from COVID-19 infection. Additional follow-up data were obtained for patients suspected to have adverse events associated with remdesivir or CPT.

Data Analysis

Patients were divided into 3 treatment groups: CPT alone, remdesivir alone, and CPT plus remdesivir. Baseline information at the time of enrollment, including demographic data, comorbidities, clinical and laboratory findings, and severity of infection, was compared. Study end points included death or discharge of patients in good condition or discharge with disability. All patients who received at least 1 dose of remdesivir or CPT and had an outcome entered into the electronic database were considered for outcome analysis. The 3 treatment groups were evaluated for patient disposition at the end of hospitalization and for durations of hospital stay, ICU stay, and ventilator days. Adverse events associated with convalescent plasma and remdesivir were reported as a proportion of all patients who received each therapy. Given the uncertainties of the pandemic, we had planned to include all patients in the 3-month study period.

To quantify treatment outcomes, we used predicted margins from a logistic regression. The model compared patients with

a hospital discharge with those who died. The model adjusted for age, gender, physician-classified severity, and steroid use. Calculations were carried out using STATA/IC, version 16.1.

Funding Source

This study was funded by the Government of Nepal (GoN), Ministry of Health and Population (MoHP). The GoN/MoHP provided remdesivir and CPT free of cost to all COVID-19 patients during the study period. Neither MoHP nor the provider of the study drugs had any role in the study design, data collection, statistical analysis, interpretation of results, or manuscript preparation. The corresponding author, an independent infectious diseases physician, served as the PI and had independent access to the study data.

Patient Consent

Voluntarily signed written consent forms were obtained from all research participants or their legal guardians. This study was approved by the Ethics Review Board of Nepal Health Research Council.

RESULTS

In the 3-month study period from July to October, 1315 patients from 31 hospitals were enrolled. Their mean age (SD, range) was 55.8 (15.7, 18–99) years, 73.7% were male, and 25.6% were health care workers. Most (71.1%) were from Bagmati Province, which encompasses the Kathmandu Valley, which has the largest population in the country. The most common comorbidities were heart disease (33%), diabetes (29.1%), hypertension (19.1%), and chronic lung disease (11%). Smoking was reported in 12.7% of the patients. Fever (81.5%), shortness of breath (80.3%), and cough (72.3%) were the most common symptoms. At baseline, the mean O2 saturation (SD) was 89.6% (8%). Baseline clinical data including physical examination findings and laboratory results are shown in Table 1. Most patients were assessed to have a severe COVID-19 infection (64%). Moderate and life-threatening infections were reported in 24.2% and 11.7% of patients, respectively.

When the observational study ended on October 31, complete data with outcomes were available for 1083 patients. Outcomes were not available for 209 patients who were still in the hospital at the end of the study or for whom the site investigators had not reported end points. An additional 23 patients were transferred to other non–study facilities before reaching an end point. Among the 1083 patients whose outcomes were reported, 801 (74%) patients were discharged in good condition, 48 (4.4%) were discharged with disability, and 234 (21.6%) died.

Among the 910 patients who received remdesivir alone, 764 (84%) patients recovered and were discharged and 146 (16%) died. The raw survival rates, that is, recovery and discharge from the hospital, were 98.4%, 85.2%, and 29.5% for moderate, severe, and life-threatening COVID-19 infection, respectively (Table 2). Among the remdesivir only recipients, 64.7% and 8.6%, respectively, were classified as having severe and life-threatening infections; 57.5% were admitted to the intensive care unit (ICU), and 26.6% were on a mechanical ventilator. The mean hospital length of stay (LOS) for the remdesivir alone recipients (SD) was 10.7 (5.3) days in the hospital, 7.9 (4.8) days in the ICU, and 4.3 (4.4) days on a ventilator.

Of the 59 patients who received CPT alone, 23 (39%) were discharged and 36 (61%) died. Among the patients who died, 22 had life-threatening and 13 had severe COVID-19 infection. Raw survival rates among patients treated with CPT alone with severe and life-threatening infections were 59.4% and 15.4%, respectively (Table 2). Among the CPT only recipients, 54.2% and 44.1%, respectively, were classified as having severe and life-threatening COVID-19, 91.8% were in an ICU, and 45.9% were on a ventilator. The average LOS for the CPT recipients

Table 1. Baseline Patient Characteristics (n = 1315)

Variables	Values
Age, mean (SD), y	55.8 (15.7)
Gender, %	
Female	26.3
Male	73.4
Comorbidities and risk factors, %	
Heart disease	33
Diabetes	29.1
Hypertension	19.1
Smoking	12.7
Chronic lung disease	11
Immunocompromised[a]	2.8
Major symptoms, %	
Fever	81.5
Cough	72.3
Dyspnea	80.3
Sore throat	15.1
Altered taste or smell	9.5
Diarrhea	8.1
Exam and lab findings, mean (SD)	
Systolic blood pressure, mmHg	123 (17)
Oxygen saturation, %	89.6 (8)
White blood cells, cumm	9.9 (8.9)
Lymphocytes, %	16.9 (10.3)
C-reactive protein, mg/L	86.4 (426)
Alanine aminotransferase, IU/L	59.3 (62.6)
Clinical severity, No. (%)	
Life-threatening	154 (11.7)
Severe	841 (64)
Moderate	318 (24.2)
Treatment groups, No. (%)	
CPT alone	76 (5.7)
Remdesivir alone	1099 (83.5)
CPT and remdesivir	140 (10.6)

Abbreviation: CPT, convalescent plasma therapy.

[a]Included HIV, transplant, cancer.

Table 2. Final Outcomes by Severity and Interventions (n = 1083)

Clinical Severity	Outcome	Intervention Groups			
		CPT, No. (%)	REM, No. (%)	CPT + REM, No. (%)	Total, No. (%)
All patients	Death	36 (61)	146 (16)	52 (45.6)	234 (21.6)
	Discharge	23 (39)	764 (84)	62 (54.4)	849 (78.4)
	Total (100%)	59	910	114	1083
Moderate	Death	1	4 (1.6)	2	7 (2.8)
	Discharge	0	239 (98.4)	7	246 (97.2)
	Total (100%)	1	243	9	253
Severe	Death	13 (40.6)	87 (14.8)	28 (38.9)	128 (18.5)
	Discharge	19 (59.4)	502 (85.2)	44 (61.1)	565 (81.5)
	Total (100%)	32	589	72	693
Life-threatening	Death	22 (84.6)	55 (70.5)	22 (66.7)	99 (72.3)
	Discharge	4 (15.4)	23 (29.5)	11 (33.3)	38 (27.7)
	Total (100%)	26	78	33	137

Abbreviations: CPT, convalescent plasma therapy; REM, remdesivir.

(SD) was 12.4 (6) days in the hospital, 10.2 (5.8) days in the ICU, and 6.8 (5.3) days on a ventilator.

Of the 114 patients treated with both remdesivir and CPT, 62 (54.4%) were discharged and 52 (45.6%) died. Among the patients who died, 22 had life-threatening and 28 had severe COVID-19 infections. Raw survival rates for severe and life-threatening infections were 61.1% and 33.3%, respectively (Table 2). Among the combination CPT and remdesivir recipients, 63.2% and 28.9%, respectively, were classified as having severe and life-threatening COVID-19, 94.6% were admitted to an ICU, and 59.8% were on a ventilator. The average LOS for these patients (SD) was 14 (6.7) days in the hospital, 10.8 (6.3) days in the ICU, and 8.2 (7.4) days on a ventilator.

Steroid use was reported for only 576 patients, and 516 of these had recorded outcomes. Of the 227 patients who received steroids in addition to antiviral therapy (remdesivir, CPT, or both), 210 (92.5%) survived, compared with 229 (79.2%) of the 289 who did not receive steroids (odds ratio, 3.2; 95% CI, 1.8–5.7).

The mean LOS after treatment initiation was shorter for remdesivir recipients (9.4 days; 95% CI, 9–9.7 days) compared with CPT (11.2 days; 95% CI, 8.9–13.5 days) and CPT plus remdesivir recipients (11.7 days; 95% CI, 10.4–13.1 days).

Donor plasma SARS-CoV-2 total antibody levels were measured for 86 (40%) CPT recipients, 41 of whom had documented outcomes. The median total antibody levels in donor plasma (interquartile range) were higher among the recipients who were discharged alive (240 [0.1–410.25]) compared with those who died (49 [0.06–289]), but the difference was not statistically significant ($P > .05$).

In an unadjusted logistic model predicting discharge in good condition or with a disability vs death, the predicted margins for the discharge of a patient in good condition or with a disability were higher among patients who received remdesivir alone (0.79; 95% CI, 0.76–0.82) compared with those who received CPT alone (0.39; 95% CI, 0.27–0.51) or CPT plus remdesivir (0.51; 95% CI, 0.42–0.60). In a model adjusted for age, gender, steroid use, and severity, the predicted margin for recovery and discharge remained higher for remdesivir alone (0.82; 95% CI, 0.79–0.84) compared with CPT alone (0.58; 95% CI, 0.47–0.70) or CPT plus remdesivir (0.67; 95% CI, 0.60–0.74) (Table 3).

Adverse events were reported in 34 (4.5%) patients who received remdesivir. The most common adverse events included elevated liver enzymes (alanine aminotransferase or alanine transaminase [ALT] >5 times above the normal limit) in 2.7% and a rise in serum creatinine in 1% of patients. Both returned to normal ranges after stopping remdesivir. Adverse reactions to CPT were reported in 10 (4.6%) patients and included fever and rash. None of the deaths were attributed to the adverse events related to the treatment. All adverse events reversed after stopping treatment.

DISCUSSION

We have presented an overview of COVID-19 management with rollout of remdesivir and CPT under a research protocol in a low/middle-income country. Despite limited resources, the

Table 3. Outcomes by Treatment Group: Model Predicted Margins Unadjusted and Adjusted for Severity; Controlled for Age and Gender (n = 1083)

Outcome	Interventions	Unadjusted Predicted Margin (95% CI)	Adjusted Predicted Margin[a] (95% CI)
Death	CPT	0.61 (0.49–0.73)	0.42 (0.30–0.53)
Discharge	CPT	0.39 (0.27–0.51)	0.58 (0.47–0.70)
Death	REM	0.16 (0.14–0.19)	0.18 (0.16–0.21)
Discharge	REM	0.84 (0.81–0.86)	0.82 (0.79–0.84)
Death	CPT + REM	0.44 (0.35–0.52)	0.33 (0.26–0.40)
Discharge	CPT + REM	0.56 (0.48–0.65)	0.67 (0.60–0.74)

Abbreviations: CI, confidence interval; CPT, convalescent plasma therapy; REM, remdesivir.
[a]Adjusted for age, gender, and severity.

Government of Nepal provided treatment of COVID-19 free of cost in 31 hospitals nationwide. We performed a descriptive analysis of the cohort in this observational study. This intervention provided rapid access to new treatments when there was a lack of effective therapy to treat COVID-19. Additional benefit was the expansion of clinical research training to >150 health care workers in 31 sites throughout the country.

We describe the clinical characteristics, treatment pattern, and outcomes for patients treated with remdesivir alone, remdesivir plus CPT, and CPT alone in this low-resource setting. The majority of the patients were older, male, and had comorbidities. A quarter of the patients were health care workers. These demographic findings are comparable to the experiences shared by other investigators [11, 12]. This is the first published study describing advanced and organized treatment of hospitalized COVID-19 patients in this country.

The overall survival rate was 78.4% in our study. Patients who received remdesivir alone had better outcomes compared with those who received CPT alone or CPT and remdesivir. This may be due to the fact that, as compared with those who received remdesivir alone, a larger proportion of patients who received CPT alone or CPT and remdesivir had more severe or life-threatening COVID-19 infection, were admitted to the ICU, and were on mechanical ventilation. In contrast, a relatively larger proportion of remdesivir alone recipients (26.7%) had moderate COVID-19 infection compared with the CPT recipients (2%–8%). Though we adjusted for severity, age, gender, and steroids, we recognize that biases limit any conclusions we may draw.

A limitation of our work is the lack of complete data on steroid use. At the outset of this protocol, data supporting dexamethasone use in patients with COVID-19 requiring supplemental oxygen were not yet available. At the time our study was implemented, this had not yet become standard of care [9, 13]. However, among those reporting steroid use, patients who received steroids in addition to antiviral therapy had a higher survival rate, similar to findings from other studies [14, 15].

The death rate among remdesivir recipients in the World Health Organization Solidarity trial was 12.5%, compared with 16% in our study [16]. Only 9.3% of the remdesivir recipients in the Solidarity trial were on mechanical ventilators, compared with 26.6% in our study. This demonstrates that our cohort treated with remdesivir was different and had higher disease severity.

Remdesivir recipients with moderate COVID-19 who were hospitalized with pneumonia but did not require oxygen had a mortality of 1.6%. This is comparable to other studies showing 1%–2% mortality among moderate COVID-19 patients who received remdesivir [8].

Hospital LOS from admission as well as after initiation of study interventions was shorter for remdesivir recipients compared with the patients who received CPT with or without remdesivir. In addition to a higher severity of infection among patients who received CPT, this difference is also attributable to the clinical practice of using remdesivir as the first-line therapy in hospitalized patients and the addition of CPT only after the patient's clinical condition continued to deteriorate. As there was limited availability of apheresis and a lack of plasma banking, it took 1–2 days to find a matching donor, and plasma from a donor was used for only 1 patient.

Recent data have suggested that the role of convalescent plasma is earlier, particularly within 72 hours of disease onset [17]. Studies have shown a benefit limited to the recipients of convalescent plasma with high antibody levels [18, 19]. Although our data were limited by a small number of reported antibody titers, patients with higher donor plasma total antibody titers tended to have better outcomes. A lack of outcome data on all patients and a lack of follow-up data after discharge were the other limitations of this study.

Both remdesivir and CPT were well tolerated, with adverse events reported in <5% of the patients. The most common remdesivir-associated adverse event was elevated liver enzymes (2.7% patients), which improved after cessation of the drug. This is comparable to the 2%–3% of patients with a rise in ALT reported in other studies [7, 8, 20]. The adverse events reported for CPT (4.6%) in our study were less than the 6.9% of 20 000 convalescent plasma recipients reported in the expanded access study by the Mayo Clinic [21]. These safety data reinforce our efforts to rapidly expand new therapies to settings like ours through a research mechanism. This is particularly useful during a pandemic when proven therapies are not available.

This is the first national-level, multicentered clinical study of COVID-19 treatment conducted in Nepal. We studied 2 therapeutic agents that had received EUA in other countries. Given the rapidity of the study design for the treatment of COVID-19 and other challenges imposed by the pandemic, our experience is encouraging and thought-provoking. Similar to studies in other countries, a control group without treatment was not considered ethical, limiting interpretation of outcomes. Here we provide the first published data on the treatment of COVID-19 in Nepal, including demographics of hospitalized patients and outcomes. More importantly, through this research mechanism we were able to safely introduce therapies where proven interventions were lacking for a highly virulent infection. An added benefit was the opportunity to provide clinical research training to Nepal's health care workers. This intervention is a cornerstone for similar large-scale research initiatives in the future.

This multicentered study conducted in a real-world setting demonstrates an effective, rapid, and safe rollout of new therapies amidst a pandemic in a resource-limited setting. The most important aspect of our work may be the capacity-building for this type of clinical care and research in Nepal. This study is a proof of concept that effective national clinical research may be

safely and effectively conducted during a pandemic in Nepal. As we optimize our research capacity beyond this proof of concept, we anticipate greater opportunities for patients to benefit from new strategies to address the COVID-19 pandemic and infectious diseases in general.

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Author contributions. Nepal COVID-19 Clinical Study Collaborators: Core Investigators, study design, study conduction, data monitoring, interpretation, manuscript writing—Janak Koirala (PI), Pradip Gyanwali (Co-PI), Meghnath Dhimal, Saroj Bhattarai, Bipin Nepal, Rekha Manandhar. Study design, lab protocol, supervision—Runa Jha, Manita Rajkarnikar, Karishma Malla Vaidya. Data collection, study conduction, data monitoring—Chhabi Panthi, Bihungum Bista, Grishma Giri, Suman Pant, Akritee Pokharel, Shristi Karki. Lead statistician—Robert B. Gerzoff. Study design, manuscript writing, editing—Holly Murphy, Shambhu Aryal, Sangita Basnet, Bhagawan Koirala. Clinical investigators core group, protocol writing, study design—Sanjib Sharma, Yuba Raj Sharma, Anup Bastola, Prabhat Adhikari, Subhash Acharya.

Nepal COVID-19 clinical study collaborators: clinical site investigators. Armed Police Force Hospital (Kathmandu): Roshan Kumar Jha, Anil Shrestha. Alka Hospital (Lalitpur): Ashesh Dhungana, Shreejana Shrestha. B&B Hospital (Lalitpur): Sarita Pandey, Sangita Shakya, Philip S. Ranjit. Bhaktapur Hospital (Bhaktapur): Sunil Dhungel, Devendra Bhattarai, Sumitra Gautam. Bharatpur Hospital (Bharatpur): Pramod Poudel, Kalyan Sapkota. Bheri Hospital (Nepalgunj): Khagendra J. Shah, Rajesh K. Mandal, Rajan Pandey. Bhim Hospital (Siddharthanagar): Sumit Prajapati, Arif Hussain, Shakuntala Gupta. BP Koirala Institute of Health Sciences (Dharan): Roshan Chhetri, Krishna Pokharel, Kala Thapa. Chitwan Medical College (Bharatpur): Shital Adhikari, Gopendra P. Deo, Basanta Gauli. College of Medical Sciences (Bharatpur): Pukar Ghimire, Bishnu Regmi. Kathmandu University School of Medical Sciences (Kathmandu): Ram B. Gurung, Rajeev Shrestha, Dipesh Tamrakar. Grande International Hospital (Kathmandu): Sushil Khanal, Upasana Acharya. HAMS Hospital (Kathmandu): Suhail Sapkota, Reema Shrestha. KIST Medical College (Kathmandu): Milesh J. Sijapati, Smriti Koirala, Suraj Bajracharya. Koshi Provincial Hospital (Biratnagar): Deepak Sigdel, Den P. Acharya. Lumbini Provincial Corona Hospital (Butwal): Sudarshan Chhetri, Prashanta Acharya, Hari P. Panthi. Nepal Academy of Medical Sciences, Bir Hospital (Kathmandu): Ashesh Dhungana, Achyut R. Karki. Narayani Hospital (Birgunj): Ram K. Singh, Uday N. Singh, Rakesh Tiwari. National Medical College (Kathmandu): Asraf Hussain, Rupesh Shah, Parwez A. Ansari. Nepal Mediciti Hospital (Lalitpur): Diptesh Aryal, Sanjit K. Shrestha, Kanchan Koirala. Nepal Police Hospital (Kathmandu): Kiran Kumar KC, Bidur P. Acharya. Nepalgunj Medical College (Nepalgunj): Shyam BK, Sumit Pandey. Norvic International Hospital (Kathmandu): Suraj K. Gupta, Deepa Shakya, Yunima Sapkota, Anju Adhikari. Om Hospital and Research Center (Kathmandu): Bishwanath Koirala, Bipin Karki. Patan Academy of Health Sciences (Lalitpur): Yuba R. Sharma, Bimal K. Pandey. Pokhara Academy of Health Sciences (Pokhara): Buddhi S. Lamichhane, Sanjay Shrestha. Seti Provincial Hospital (Dhangadi): Sher B. Kamar, Ashok Chaudhary, Jagdish Joshi. Shahid Gangalal National Heart Centre (Kathmandu): Kunjang Sherpa, Reeju Manandhar. Shree Birendra Hospital (Kathmandu): Chiranjibi Pant, Rinku Joshi. Sukraraj Tropical and Infectious Disease Hospital (Kathmandu): Anup Bastola, Bimal S. Chalise. Tribhuvan University Institute of Medicine (Kathmandu): Santa K. Das, Pramesh S. Shrestha.

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