

Antibiotic utilization, sensitivity, and cost in the medical intensive care unit of a tertiary care teaching hospital in Nepal

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Nirmal Raj Marasine^{1,2} , Shakti Shrestha³, Sabina Sankhi⁴, Nabina Paudel⁵, Ashish Gautam² and Arjun Poudel⁶

Abstract

Background: High utilization and irrational use of antibiotics in an intensive care unit increases microbial resistance, morbidity, mortality, and costs.

Objective: This study aimed to evaluate the utilization, sensitivity and cost analysis of antibiotics used in the medical intensive care unit of a tertiary care teaching hospital of Nepal.

Methods: A prospective cohort study was conducted on patients admitted to the medical intensive care unit at a tertiary care teaching hospital in central Nepal from July to September 2016. Antibiotic utilization, defined daily dose per 100 bed-days and the cost of antibiotics per patient were calculated. Descriptive statistics were performed using IBM-SPSS 20.0.

Results: A total of 365 antibiotics were prescribed in 157 patients during the study period, with an average of 2.34 prescriptions per patient. Total antibiotic utilization in terms of defined daily dose per 100 bed-days was 49.5. Piperacillin/tazobactam (45.2%) was the most commonly prescribed antibiotic, and meropenem was the most expensive antibiotics (US\$4440.70). The median (interquartile range) cost of antibiotics used per patient was US\$47.67 (US\$63.73). *Escherichia coli*, *Acinetobacter*, and *Pseudomonas* sp. were the common organisms isolated and were found to be resistant to some of the commonly used antibiotics.

Conclusion: This study suggests that the utilization and cost of antibiotics are high in medical intensive care unit of the hospital and *E. coli* was resistant to multiple antibiotics. The findings highlight an urgent need for the implementation of antibiotic stewardship program in order to improve antibiotic utilization in such hospital settings.

Keywords

Antibiotics, cost analysis, drug utilization study, defined daily dose, medical intensive care unit

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Introduction

Antibiotics are the most frequently prescribed medicine in the intensive care unit (ICU).¹ ICUs provide specialized healthcare services to critically ill patients, but evidence suggests a high prevalence of infections in patients admitted to these facilities.² High level of staffing, frequent and extended use of broad-spectrum antibiotics, and exposure of patients to invasive procedures usually make it a susceptible place for infection to the admitted patients.³ Up to 30% patients in the ICU can acquire a nosocomial infection which tends to be 5–10 times superior to non-ICU patients.⁴ Consequently, the antibiotic consumption in the ICU is approximately 10 times higher than the general ward of the hospital, accounting for a significant portion of the total hospital antibiotic consumption and related costs.⁵

In several countries, antibiotic resistance in the ICU setting is emerging as a significant and challenging health problem influencing patient outcomes.^{6–8} Treatment of bacterial infections such as sepsis, intra-abdominal infections, and meningitis

¹Department of Pharmacy, Karnali College of Health Science, Kathmandu, Nepal

²School of Pharmacy, Chitwan Medical College, Bharatpur, Nepal

³School of Pharmacy, University of Queensland, Brisbane, QLD, Australia

⁴Department of Pharmacy, Modern Technical College, Lalitpur, Nepal

⁵School of Pharmacy, Kathmandu University, Dhulikhel, Nepal

⁶School of Clinical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

Corresponding author:

Nirmal Raj Marasine, Department of Pharmacy, Karnali College of Health Science, Gaushala, Kathmandu, 44600, Nepal.

Email: nirmalmarasine@gmail.com



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is becoming difficult as bacteria develop resistance to the antibiotics making the treatment less effective.⁹ Antibiotic resistance leads to longer hospitalization, increased healthcare cost, decreased therapeutic outcome, and eventually increased mortality.^{9,10} For instance, the estimated annual cost of antibiotic resistance in Europe was €9 billion.¹¹ Similarly, death of 25,000 people was reported as a direct consequence of multidrug resistance bacterial infection from the same continent.¹²

Merely the use of antibiotics does not result in resistance, but it is the misuse, increased use, or irrational use associated with antibiotics that create resistance. Self-medication, antibiotics dispensed by non-qualified personnel, patients not completing the full course of prescribed antibiotics, and inconsistent adherence to the treatment regimen are the major forms of irrational drug use that contributes to the development of resistance toward antibiotics.¹³ Increased antibiotic consumption increases the emergence and spread of resistant organisms. Prescribing antibiotics to treat common conditions such as upper respiratory tract infections and asymptomatic bacteriuria, inadequate knowledge on proper indication and prescribing guidelines, inadequate counseling, and high charge for a physician visit are the common reasons that lead to antibiotic overuse. Likewise, perception of people that antibiotics heal faster than any other medicines and pressure to prescribe antibiotics, and the lack of education about antibiotic resistance in community level adds to its overuse.¹⁴ Rise in the number of resistant organisms leads to an increased consumption of antibiotics as they become insensitive to the usual dose, and thus require a higher dose to treat the same conditions.

Understanding the utilization pattern of antibiotics and their sensitivity toward the microbes can provide an estimate of the burden and effectiveness of antibiotics. However, there is a paucity of data on antibiotic prescription, consumption patterns and cost from ICU setting in Nepal. Therefore, we aimed to explore the antibiotic utilization, sensitivity and cost analysis in patients admitted in ICU of a tertiary care hospital of Central Nepal.

Methods

Study design, site, population, and sample size

A prospective study was conducted in a 17-bed medical intensive care unit (MICU) of Chitwan Medical College Teaching Hospital (CMCTH), Bharatpur, Nepal. CMCTH is a 750-bed tertiary care hospital of central Nepal. The study was conducted between July and September 2016 among patients aged ≥ 18 years, admitted to the MICU and prescribed at least one antibiotic. Patients admitted in department other than MICU were excluded from the study. A total of 157 patients were included during the study period.

Data collection

Data were collected prospectively from the patients' Kardex. Kardex is the prescription and administration record of a patient.¹⁵ Usually in Nepal, Kardex are manually entered and

therefore, to verify the record, we communicated with physician and nurses. All the patients were followed up till their stay in the MICU, which included being shifted to other ward or referred to other centers for further management or discharged by the hospital or discharged on request (DOR) by a patient party or left against medical advice (LAMA) or death. These were considered as outcomes of therapy in this study. Information on demographics (age and sex), clinical characteristics (reason for MICU admission, severity of illness), antibiotic use (indication, total number, generic name, dose, frequency, number of doses per package, number of packaged consumed, and route of administration of antibiotic, utilization of antibiotic), antibiotic cost at the time of the study, antibiotic sensitivity, and length of ICU stay were collected. The severity of illness was assessed using Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Antibiotics were classified using the Anatomical Therapeutic Chemical (ATC) Classification System¹⁶ and their indication was categorized as empirical, prophylaxis and definitive. The utilization of antibiotics in MICU was presented as daily defined dose (DDD) per 100 bed-days, which was calculated using the formula

$$\text{DDD/100 bed-days} = \frac{\text{Number of units administered in a given period} \times 100}{\text{DDD} \times \text{number of days} \times \text{number of beds} \times \text{occupancy index}}$$

The number of beds in MICU was 17 and the occupancy index of 0.82 was calculated as follows

$$\text{Occupancy index} = \frac{\text{Total inpatient service days for a period} \times 100}{\text{Total inpatient bed count} \times \text{number of days in the period}}$$

The cost per unit of antibiotics was obtained from the hospital pharmacy at the time of study to calculate the direct cost of total antibiotics used for each patient. The percentage of antibiotic sensitivity was calculated as number of sensitive cultures out of total sensitivity tests.

Statistical analysis

The data were entered in Microsoft Excel version 13 and analyzed using IBM-SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Data were expressed as mean value and standard deviation (SD) or median and interquartile range (IQR), and mostly descriptive statistics were used. The Kolmogorov–Smirnov test was used to determine the normality of numeric variables.

Ethics

Ethical approval for this study was obtained from the Institutional Review Committee of Chitwan Medical College

Table 1. Demographic and clinical characteristics of patient ($n = 157$).

Characteristics	Categories	n (%)
Age ^a	18–94	50.6 (20.18)
Gender	Female	91 (58.0)
Reason for admission	Respiratory illness	34 (21.7)
	Gastrointestinal illness	24 (15.3)
	Renal illness	20 (12.7)
	Poisoning	18 (11.5)
	Reproductive-endocrine illness	12 (7.6)
	Septic shock	15 (9.6)
	Central nervous system illness	11 (7.0)
	Cardiovascular illness	6 (3.8)
	*Others	17 (10.8)
	APACHE II score	0–10
11–20		81 (51.6)
21–30		30 (19.1)
31–40		5 (3.2)
Length of MICU stay (days) ^b	2–16	5 (4)
Outcome of therapy	Death	25 (15.9)
	DOR	20 (12.7)
	LAMA	11 (7.0)
	Shifted to other wards	93 (59.2)
	*Referral	3 (1.9)
	Medical advice	5 (3.2)

IQR: inter quartile range; APACHE II: Acute Physiology and Chronic Health Evaluation II score; MICU: medical intensive care unit; DOR: discharged on request; LAMA: leaving against medical advice.

^aMean (SD) instead of n (%).

^bMedian (IQR) instead of n (%).

*Others: Acute Febrile Index, enteric fever, viral hepatitis, scrub typhus, quadriparesis, pancytopenia, and anemia.

*Referral: patients referred to higher center for further management. APACHE II indicates the severity of illness where the higher score indicates more severity.

Teaching Hospital (CMC/IRC/47). The patients or the caretakers were informed about the details of the study, and their written consent was obtained prior to data collection. The data retrieved were used only for research purpose. There was no any risk involved in the study.

Results

Of the 157 patients admitted in the MICU, 91 (58%) were female. The principal characteristics of the study population have been depicted in Table 1. The mean value (SD) age was 50.60 (20.18) years and majority (51.0%) were older than 50 years. Half of the study patients (81, 51.6%) had an APACHE II score of 11–20. The length of stay ranged from 2 to 16 days, with a median (IQR) = 5 (4). The majority of the patients were shifted to the general wards (59.2%), and the death rate was 15.9%, while only a few (1.9%) were referred to higher centers. Among the total patients, respiratory system-related admission was the common clinical condition

for which an antibiotic was prescribed (31, 21.7%) followed by gastrointestinal 24 (15.3%) and renal illness 20 (12.7%).

A total of 365 antibiotics were prescribed to 157 patients during the period of stay in the MICU (mean \pm SD: 2.32 \pm 0.989, antibiotic per prescription). The majority of patients (72.0%) were on empirical therapy. The majority (73.15%) of prescribed antibiotics were given parenterally. The total cost of antibiotics prescribed in all patients was US\$12,724.34, and the median (IQR) = US\$47.67 (US\$63.73) per patient, as illustrated in Table 2. Total antibiotic consumption based on DDD per 100 bed-days during the study period was 49.43. Utilization pattern, ATC codes, frequency, and DDD/100 bed-days have been shown in Table 3.

The culture and sensitivity test was carried out in 57.3% of the total patients, of which only 113 specimens were sent for testing. From that, total 20 organisms were isolated, out of which sensitivity test was performed only for *Escherichia coli* (*E. coli*) ($n = 10$), *Acinetobacter* ($n = 2$), and *Pseudomonas* sp. ($n = 4$). The antibiotic sensitivity pattern of three organisms showed that almost all isolates were resistant to meropenem (100%). Colistin, amikacin, ceftriaxone, imipenem, nitrofurantoin, and tigecycline showed the highest susceptibility rate (100%) on *E. coli* followed by piperacillin/tazobactam, polymyxin-B (75%), and ceftriaxone and ceftazidime (50%). Similarly, levofloxacin, colistin, ciprofloxacin, and polymyxin-B had the highest susceptibility rate on *Pseudomonas* spp. whereas colistin had the highest susceptibility for *Acinetobacter*, as depicted in Table 4.

Discussion

This study evaluated the utilization, sensitivity and cost analysis of antibiotics used in the MICU of a tertiary care teaching hospital of Nepal over 2 months. The study revealed that the utilization of antibiotics was considerably high in this setting and a number of such antibiotics were resistant to the isolated strains of microorganism. This study also showed that there was a high variation in the cost of these utilized antibiotics. The median hospital stay was 5 days with median APACHE II score of 17% and 15.9% mortality rate. APACHE II is measured during the first 24 h of ICU admission and objectively quantifies the severity of disease.¹⁷

The findings of the antibiotic utilization suggested that almost half of the MICU patients received one DDD of an antibiotic every day (DDD/100 bed-days was \sim 50). This was comparatively lower than a study conducted in a similar setting in Western Nepal (Manipal Teaching Hospital, Pokhara, Nepal) for 4 months, where the utilization was 118.2/100 bed-days.⁶ However, this study was conducted in Central Nepal for only 2 months. Furthermore, there is a paucity of evidence from Nepal on antibiotic utilization. A study from Turkey reported a significant reduction in antibiotic utilization from 93.6 to 63.1 DDD/100 patient-days in 1 year (2011–2012), where the absolute change was 30.2 DDD/100 bed-days.¹⁸ The finding of this study showed that 365

Table 2. Antibiotic use and cost in MICU.

Characteristics	Categories	n (%)
Indication of antibiotic therapy	Empirical	113 (72.0)
	Definitive	15 (9.6)
	Prophylaxis	29 (18.5)
Number of antibiotics used	One	29 (18.5)
	Two	72 (45.9)
	Three	38 (24.2)
	Four	12 (7.6)
	Five or more	6 (3.8)
Route of administration	Parenteral	267 (73.15)
	Oral	98 (26.36)
Direct antibiotic cost ^a	US\$4.14–US\$679.00	US\$47.67 (US\$63.73)

^aMedian (IQR) instead of n (%); 1US\$ = Nepalese rupees (NRs) 108.54.

There were 128 patients on empirical therapy at the initiation of the treatment and 15 of them switched to the definitive therapy.

Table 3. Utilization of antibiotics in the MICU (n = 157).

Name of antibiotic	ATC code	Number of prescriptions	Percentage	DDD (g)	DDD/100 bed-days
Piperacillin/tazobactam	J01CR05	71	45.2	14	7.79
Ceftriaxone	J01DD04	54	34.4	2	6.14
Metronidazole	J01XD01	45	28.7	1.5	5.12
Doxycycline	J01AA02	38	24.2	0.1	8.65
Azithromycin	J01FA10	32	20.4	0.3	6.07
Meropenem	J01DH02	28	17.8	2	4.78
Levofloxacin	J01MA12	25	15.9	0.5	2.84
Cefotaxime	J01DD01	15	9.6	4	1.28
Amikacin	J01GB06	13	8.3	1	1.11
Amoxicillin/clavulanate	J01CR02	12	7.6	3	1.69
Clindamycin	J01FF01	8	5.1	1.8	0.91
Imipenem/cilastatin	J01DH51	6	3.8	2	0.34
Linezolid	J01XX08	4	2.5	1.2	0.45
Ciprofloxacin(P)	J01MA02	2	1.27	0.5	0.18
Ciprofloxacin(O)	J01MA02	2	1.27	1	0.22
Vancomycin	J01XA01	3	1.9	2	0.34
Flucloxacillin	J01CF05	3	1.9	2	0.34
Ampicillin	J01CA01	3	1.9	2	0.51
Cefuroxime	J01DC02	2	1.3	0.5	0.45
Colistin	J01XB01	2	1.3	3MU	0.22
Total antibiotic consumption					49.43

ATC: Anatomical Therapeutic Chemical classification; DDD: defined daily dose; P: parenteral; O: oral.

antibiotics were prescribed during the study period, that is, an average of two antibiotics per patient. These data are comparable to that reported in the literature from varying geographic regions and types of patients, which showed it ranged from 1.73 to 5.1.^{6,19–21} We also found that the DDD/100 bed-days for the six most frequently prescribed antibiotics were 8.7 (doxycycline), 7.8 (piperacillin/tazobactam), 6.2 (ceftriaxone), 6.1 (azithromycin), 5.1 (metronidazole), and 4.8 (meropenem). In a study in Western Nepal, in a similar setting, the utilization of penicillin, fluoroquinolones, second-generation cephalosporins, and third-generation

cephalosporins were 55.1, 5.34, 0.82, and 13.74 DDD/100 bed-days, respectively.⁶ In a similar study from India, the five most utilized antimicrobial agents were third-generation cephalosporins (18.48), meropenem (16.47), levofloxacin (15.97), metronidazole (14.65), and ceftriaxone (13.42).²² The acquisition of infection during nosocomial stay, presence of multiple comorbidities, high rate of invasive procedure, and presence of risk factors for infection due to multiple drug resistant pathogens favor high utilization of antibiotics in MICU.^{3,4} In this study, antibiotics use was empirical in 70% of the patients and definitive in 9.6% of them. Among

Table 4. Antibiotic sensitivity in commonly isolated organisms from the MICU.

	Micro-organism isolated (% sensitivity = number of cultures sensitive/number tested)		
	<i>E. coli</i> (n = 10)	<i>Acinetobacter</i> (n = 2)	<i>Pseudomonas</i> spp. (n = 4)
Ceftriaxone	50	50	66.66
Piperacillin/tazobactam	75	NT	25
Meropenem	0	0	0
Imipenem	100	NT	0
Cefotaxime	25	0	50
Levofloxacin	40	NT	100
Amikacin	100	50	66.66
Colistin	100	100	100
Ciprofloxacin	0	0	40
Cefepime	75	50	0
Nitrofurantoin	100	NT	NT
Tigecycline	100	0	50
Polymyxin-B	75	NT	100
Ceftazidime	50	0	50
Cotrimoxazole	25	0	NT

NT: not tested.

empirically used antibiotics, piperacillin/tazobactam comprised of the major proportion. This may be defined on the basis of disease condition of patients admitted in MICU, where the prevalence of patients with respiratory illness was higher in this study. Likewise, delay in obtaining antibiotic sensitivity reports, and possibility of false-negative results might be other reason to undertake empirical therapy to manage the condition of admitted patients. Antibiotics were used prophylactically in 18.5% of the patients in this study, which is higher than that obtained in other study from South Africa.²³

Studies have shown that antibiotics are used as a prophylaxis in several countries. Data from Western European countries suggested that 71% of all patients were receiving antibiotics as prophylaxis or treatment in ICUs.²⁴ A single-centered prospective study in Belgium found 42% were prescribed prophylaxis²⁵ while a nationwide, single-day survey in 52 ICUs of Japan showed 34% of the prescriptions were prophylaxis intravenous (IV) antibiotics.²⁶ In the context of Nepal, the prophylactic use of antibiotic in MICU is not explicitly stated in the literature, but international guidelines on initial antibiotic selection are generally applied in the ICUs of Nepal and empiric choices are made for serious ICU-related infections. However, evidence suggest that patients in ICU are more prone to nosocomial infection, so antibiotics could have been used prophylactically for the prevention of infection from *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Clostridioides difficile*, and so on.

This study revealed *E. coli* as the most frequent isolate that demonstrated multidrug resistance to several antibiotics, whereas a study from Indonesia reported *P. aeruginosa* as the most common pathogen from specimen in ICU.²⁷ We observed a high level of resistance to meropenem (100%),

ciprofloxacin (100%), cefotaxime (75%), cotrimoxazole (75%), and levofloxacin (60%) against the most common isolate *E. coli*. Similar finding was reported by a study conducted in the capital city of Nepal, where *E. coli* was found highly resistant (>75%) to ampicillin, cefotaxime, cefepime, ciprofloxacin, and levofloxacin.²⁸ Colistin, amikacin, and ceftriaxone demonstrated most sensitivity to most of the isolates in this study. In contrast to this, meropenem was found to be the most sensitive antibiotic against all bacterial isolates from ICU admitted patients in studies conducted in Central and Eastern Nepal.^{29,30}

This study showed that the average cost of antibiotics utilized in the MICU per person was US\$47.67, but it varied from US\$4 to US\$679. The most frequently prescribed antibiotics were the combination of piperacillin and tazobactam (45.2%), and meropenem was the most expensive antibiotics of all (US\$4440.70). A study in India reported that patients spent about US\$3506.26 on total antibiotic cost or US\$32.58 per patient, the combination of piperacillin and tazobactam being the most expensive antibiotics.²⁰ Similarly, the previous study from Western Nepal reported an average expenditure of US\$25.1 ± 16.2 on the drugs prescribed in ICU and US\$28.83 per patient cost of antimicrobial agents.⁶ On the contrary, comparisons of antibiotic utilization costs globally could be often deceptive due to the immense alteration of drug prices globally. Overuse of expensive antibiotics such as meropenem and piperacillin/tazobactam in this study depicts extra cost for patients. Different factors may be attributed to the antibiotic use pattern in this study, such as lack of proper drug use policies, lack of appropriate protocols, guidelines, and formulary books. Furthermore, inappropriate monitoring and evaluation of antibiotic use, microbial resistance, lack of continued medical education,

and lack of clinical pharmacologists or clinical pharmacist are the other associated factors that may cause over- and misuse of antibiotics in hospitals.³¹

In this study, the majority of the antibiotics were prescribed for parenteral use, which was comparable to previous studies in Western Nepal and India.^{6,20} MICU provides medical services to severely ill patients who are often unable to take medicines orally. In such condition, parenteral preparations overcome the problems associated with oral administration, providing rapid onset of action, better bioavailability, and speedy symptomatic relief. Besides their advantage, they are associated with more complications, are less patient convenient, and more expensive than oral preparations leading to increase in overall healthcare cost to patients.³² Conversion of IV antibiotics to oral could benefit the patients by increasing the possibility of earlier discharge from hospital, eliminating adverse events associated with IV therapy, reducing the risk of acquiring a hospital infection, increasing patient comfort and mobility, and lowering the cost of daily antibacterial use.^{33,34}

There are a number of limitations to this study. We explored the antibiotic utilization pattern over a period of 2 months; hence, the influence of seasonal variations on disease pattern and antibiotics utilization could not be considered. Not all the antibiotics were tested for sensitivity; therefore, the sensitivity prevalence may be higher than those reported in this study. There were also cases which were not discharged, rather LAMA or DOR or shifted to other wards, and a clear outcome in these patients could not be known. Similarly, a power analysis and sample size calculation was also not performed in the study. Likewise, the total healthcare cost of the individual patient was outside the scope of this study, and therefore, we were only able to calculate the cost for antibiotics use. Moreover, the overuse of antibiotics could give rise to the risk of developing *Clostridioides difficile* infection, but whether this was true remains beyond the scope of this study. But this could be considered as a potential area to explore as a future study. Finally, the clinical microbiology part of the study could have been strengthened. Despite these limitations, this study provides an insight into the antibiotic use in ICU and the cost associated with it. The findings might be beneficial for policy formulation of antibiotics in Nepal.

Conclusion

This study suggests that the utilization of antibiotics and their cost in MICU of Central Nepal is high. *E. coli* was the most common isolate that demonstrated resistance toward multiple antibiotics that could pose a challenging issue in the therapeutic outcome of patients in the MICU. These findings highlight an urgent need for standard guidelines, protocols, educational intervention, surveillance, and antibiotic stewardship program in this setting. It also urges for the rational

use of antibiotics and their subsequent pharmacoeconomic evaluation.

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Author contributions

N.R.M. contributed to the conceptualization. N.R.M. contributed to the data curation. N.R.M., S.S. (Shakti Shrestha), and S.S. (Sabina Sankhi) contributed to the formal analysis. The funding acquisition is nil. N.R.M. contributed to the methodology. N.R.M. contributed to the project administration. N.R.M., S.S. (Shakti Shrestha), S.S. (Sabina Sankhi), and A.G. contributed to the visualization. N.R.M. and S.S. (Sabina Sankhi) contributed to the writing—original draft. N.R.M., S.S. (Shakti Shrestha), S.S. (Sabina Sankhi), N.P., and A.P. contributed to the writing—review and editing. A.G. contributed to the supervision.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the Institutional Review Committee of Chitwan Medical College Teaching Hospital (CMC/IRC/47).

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Informed consent

The patients or the caretakers were informed about the details of the study, and their written consent was obtained prior to data collection.

ORCID iD

Nirmal Raj Marasine  <https://orcid.org/0000-0003-4353-382X>

Data availability

The raw data used to support the findings of this study are made available from the corresponding author upon reasonable request.

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