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Study on risk factors and associated drug related problems in patients with stroke

Tulsi Bhusal[1], Durga Bista[1*] and Rojeena Koju Shrestha[1]

Abstract

Background The second most common cause of death and disability worldwide is stroke. Drug-related problems (DRPs) can arise during any step of the medication process, whether it involves prescribing, transcribing, dispensing, or administering drugs. The purpose of this study was to assess risk factors and associated DRPs in patients with stroke.

Methods A cross-sectional study was conducted involving patients who had been diagnosed with stroke for 3 months using a purposive sampling technique at Annapurna Hospital. Data on demographics, comorbidities, and medications were collected through patient medical records, medicine Cardex, and nursing notes. DRPs were identified and classified using the Hepler-Strand classification system. Medscape software was used to assess potential drug-drug interactions (pDDIs). Descriptive statistics, chi-square tests, and binary logistic regression were performed.

Results Among the 111 patients, the mean age was 58.72 ± 15.68 years. The majority of strokes were ischemic (68.5%), with the middle cerebral artery being the most commonly affected (24.3%). Males were more commonly affected (76.6%) than females (23.4%). Hypertension was the most prevalent comorbidity (61.3%), followed by diabetes mellitus (27.0%) and hyperlipidemia (21.6%). Hyperlipidemia was significantly associated with risk factors for ischemic stroke. The study found that 91.9% of stroke patients experienced DRPs, with pDDIs being the most common type (91.09%). The severity of pDDIs was predominantly categorized as "monitor closely" (73.2%). The use of more than 10 medications was a significant predictor for high-severity pDDIs.

Conclusion The study concludes that polypharmacy is a significant predictor for high-severity pDDIs, highlighting the need for careful consideration when adding new medications to a patient's therapy. The high rate of pDDIs (91%) emphasizes the critical role of clinical pharmacists in identifying and mitigating these interactions to prevent further drug-related complications in stroke patients. Further research is needed to explore interventions to reduce DRPs.

Clinical trial number Not applicable.

Keywords Stroke, Risk factors, Drug-related problems, Potential drug-drug interactions

*Correspondence:
Durga Bista
durga.bista@ku.edu.np
[1]Department of Pharmacy, School of Science, Kathmandu University, Dhulikhel, Nepal

Background

Stroke is the second leading cause of death and disability worldwide [1]. The World Health Organization has defined stroke as the sudden onset of clinical symptoms indicating a localised (or widespread) disruption of brain function, persisting for over 24 h and resulting in death, without any identifiable cause other than a vascular origin [2]. Stroke events are mainly divided into ischemic and hemorrhagic events. Cerebral ischemia is defined as a reduction in blood flow that can last from several seconds to minutes [3]. Hemorrhagic stroke is an acute neurological injury resulting from bleeding in the head due to intracerebral hemorrhage (bleeding directly into the brain tissue) or subarachnoid hemorrhage (hemorrhage into the cerebrospinal fluid) [4]. Ischemic stroke is relatively common, but hemorrhagic stroke is associated with increased mortality and disability [5]. The incidence of stroke globally increases with age, with 80% of strokes in Western societies involving focal cerebral ischemia and 20% involving cerebral hemorrhage [6].

A systematic review revealed that, over the last forty years, the rate of stroke occurrence has decreased in high-income nations but has increased in low- to middle-income countries [7]. A study from Kathmandu highlighted a rising trend of stroke cases in Nepal, affecting younger individuals and more women [8]. In 2016, stroke was linked to around one million fatalities and 22 million disability-adjusted life-years (DALYs) in South Asia. Specifically, Nepal accounts for nearly 15,000 of these deaths and approximately 330,000 DALYs [9].

Various studies have identified both non-modifiable and modifiable risk factors for stroke. Non-modifiable factors include age, gender, race, ethnicity, and family history. Modifiable factors encompass conditions such as hypertension, atrial fibrillation, dyslipidemia, diabetes, smoking, lack of physical activity, transient ischemic attacks, and other treatable heart disorders that increase the likelihood of experiencing a stroke [10]. A cross-sectional study conducted in Northeast China identified hypertension, dyslipidemia, and smoking as the leading cerebrovascular risk factors [11].

A drug-related problem (DRP) refers to any situation or event related to medication therapy that may hinder or disrupt the achievement of intended health outcomes. Hepler and Strand categorized DRPs into eight distinct types; including untreated medical conditions, low or excessively high dosages, unnecessary medication use, failure to receive necessary drugs, inappropriate drug selection, drug interactions, and adverse drug reactions (ADRs) [12]. A cross-sectional study conducted in Nepal revealed that DRPs were prevalent in 74.2% of patients, total of 106 problems were documented, with unnecessary drug treatment being the most common [13]. A study carried out in Eastern Nepal identified a total of 528 DRPs, with an average of 2.27 ± 0.92 DRPs per patient. Studies on DRPs have been conducted in several countries including India, Pakistan, Indonesia, and China [14]. A prospective interventional study at Jimma University identified 380 drug-related issues primarily concerning treatment efficacy, untreated indications, inappropriate medication therapy, and adverse drug reactions [15]. A study carried out in Norway found that DRPs were common among hospitalized patients, with an average of 2.1 clinically significant DRPs per patient [16]. DRPs are frequently observed in hospitalized patients, with the number of medications, drug interactions, and diagnosed diseases identified as significant risk factors for these issues. Systemic literature reviews identify risk factors, including specific medications, therapeutic categories, and patient-related factors like age and comorbidities as risk factor for DRPs [17]. In Nepal, very few studies have been conducted on DRPs, and specifically, no study has focused on DRPs in stroke patients. This study is the first study to investigate DRPs among stroke patients in Nepal. Thus, to address this gap, this study aimed to identify risk factors and associated DRPs in stroke patients.

Methods

Study setting

The study was conducted in a specialized neuro hospital, which primarily manages stroke patients and was selected due to its availability of comprehensive patient records, and accessibility for data collection.

Study design

The research was conducted using a cross-sectional study design for three months from Feb 13 to May 13, 2024 at Annapurna Neurological Institute & Allied Sciences (ANIAS).

Patient selection

The purposive sampling technique was chosen for this study. The study included stroke patients aged 18 and above admitted to the ANIAS ward during the study period, excluding those with transient ischemic attacks. The total number of patients enrolled in this study was 111.

Data collection

Before data collection, approval, and formal permission were obtained from the Institutional Review Committee of ANIAS. Informed consent was obtained from each patient. A data collection form was used to collect patient information including demographic details, laboratory parameters, and treatment charts and types of DRPs as per the needs of the study through a review of patient's medical records, medicine Cardex, and nursing notes. Patients were observed from admission to

discharge. Medscape software was used to check potential drug-drug interactions (pDDI) and categorized into different severity levels like contraindicated, serious, monitored closely, and minor. The identified DRPs were documented and classified using the Hepler-Strand classification system. The CHA_2DS_2VASc and HAS-BLED score were calculated according to the European Society of Cardiology guidelines on the basis of discharge [18]. According to the guideline low risk was identified for CHA_2DS_2VASc score = 0 in men, or 1 in women, high risk for CHA_2DS_2VASc score ≥ 2 in men or ≥ 3 in women, and moderate risk for CHA_2DS_2VASc score 1 in men or 2 in women. For HAS-BLED score ≥ 3 was identified as a high risk of bleeding.

Pretesting the data collection tools

A pilot study was done on 10 patients before the actual data collection. Ten patients were excluded from the study. The required modifications were done after the pilot study. Following the pre-test, only minimal adjustments were made to refine the tools. Physical inactivity and diet were not mentioned in the medical records of patients so these variables were removed from the study. Additionally, the CHA_2DS_2VASc and HAS-BLED scores were added to assess stroke and bleeding risk.

Validity and reliability of the study tools

The Proforma was self-designed and finalized with the help of research supervisors at Kathmandu University, with necessary modifications.

Data analysis and management

After rechecking, incomplete and missing data were excluded. The analysis was conducted using the Statistical Package for Social Sciences (SPSS Version 27). Descriptive statistics were presented using the median and interquartile range for continuous variables that did not follow a normal distribution, while categorical variables were expressed in terms of frequency and percentage. The Chi-square (Fisher-exact) test was employed to assess significant associations. Binary logistic regression (univariate) was used to analyze the risk factor for stroke. To identify predictors for the severity of pDDIs, binary logistic regression was performed using both univariate and multivariate analysis. Variables in the univariate analysis with a p-value less than 0.25 were chosen to be included in the multivariate analysis P-value < 0.05 was considered statistically significant.

Results

Table 1 presents the baseline characteristics of the 111 patients included in the study. The majority of cases were ischemic strokes 68.5% compared to hemorrhagic strokes 31.5%. The median age of stroke patients was

Table 1 Baseline characteristics of patients

Baseline Category	Type of stroke		Total	*P* value
	Ischemic *n*=(76) *N* (%)	Hemorrhagic *N*= (35) *n* (%)	(*N* = 111)	
Age of the patients in yrs, Median (IQR)	62 (49–71)	57 (46–70)	60 (49–71)	0.601[a]
18–35	6 (7.9)	4 (11.40)	10 (9.0)	0.74[b]
36–64	37 (48.7)	18 (51.4)	55 (49.5)	
≥ 65+	33 (43.4)	13 (37.1)	46 (41.4)	
Gender				0.92[c]
Male	58 (76.3)	27 (77.1)	85 (76.6)	
Female	18 (23.7)	8 (22.9)	26 (23.4)	
Comorbidities				
Hypertension	44 (57.9)	24 (68.6)	68 (61.3)	1.00[c]
Diabetes	23 (30.3)	7 (20.0)	30 (27.0)	0.25[c]
Atrial Fibrillation	5 (6.6)	0 (0.0)	5 (4.5)	0.17[b]
Hyperlipidemia	21 (27.6)	3 (8.6)	24 (21.6)	**0.02**[c*]
Other Cardiac disease	1 (1.3)	1 (2.9)	2 (1.8)	0.53[b]
Others	19 (25.0)	8 (22.9)	27 (24.3)	0.80[c]
Previous TIA	2 (2.6)	0 (0.0)	2 (1.8)	1.00[b]
Previous Stroke	14 (18.4)	7 (20.0)	21 (18.9)	0.84[c]
Family History of Stroke	7 (9.2)	3 (8.6)	10 (9.0)	0.91[c]
History of Smoking				0.29[b]
Never Smoker	58 (76.3)	31 (88.6)	89 (80.2)	
Current Smoker	14 (18.4)	4 (11.4)	18 (16.2)	
Former Smoker	4 (5.3)	0 (0.0)	4 (3.6)	
Alcohol Consumption				0.92[b]
None	61 (80.3)	28 (80.0)	89 (80.2)	
Occasional	5 (6.6)	3 (8.6)	8 (7.2)	
Mild	1 (1.3)	0 (0.0)	1 (0.9)	
Heavy	5 (6.6)	3 (8.6)	8 (7.2)	
Former Drinker	4 (5.3)	1 (2.9)	5 (4.5)	
Anti-Hypertensive drug				
Calcium Channel Blockers	17 (22.4)	16 (45.7)	33 (29.7)	**0.01**[c*]
Angiotensin Receptor Blocker	21 (27.6)	12 (95.3)	33 (29.7)	**0.01**[b*]
Angiotensin Converting Enzyme Inhibitors	1 (1.3)	0 (0.0)	1 (0.9)	1.00[b]
Diuretics	6 (7.9)	6 (17.2)	12 (10.8)	0.17[b]
Beta-Blockers	11 (15.5)	10 (28.6)	21 (18.9)	0.07[b]
Alpha-Blockers	3 (3.9)	6 (17.1)	9 (8.1)	**0.03**[b*]
Combination Antihypertensive Drug	11 (14.4)	4 (11.5)	15 (13.5)	0.5[b]
Anti-Diabetics				
Insulin	2 (2.6)	0 (0.0)	2 (1.8)	1.00[b]
Biguanides	5 (6.6)	4 (11.4)	9 (8.1)	0.5[b]
Sulfonylureas	4 (5.3)	1 (2.9)	5 (4.5)	1.00[b]
Alpha-Glucosidase Inhibitors	4 (5.2)	0 (0.0)	4 (3.6)	1.00[b]
DPP-4 Inhibitors	1 (1.3)	3 (8.6)	4 (3.6)	0.09[b]
Combination Antidiabetic drug	13 (17.1)	0 (0.0)	13 (11.7)	**0.03**[b*]

Table 1 (continued)

Baseline Category	Type of stroke		Total	*P* value
	Ischemic *n*=(76) *N* (%)	Hemorrhagic *N*= (35) *n* (%)	(*N* = 111)	
HMG-CoA Reductase Inhibitors	73 (96.0)	7 (20.0)	80 (72.0)	**0.00[c]***
Surgical Management	4 (5.3)	6 (17.1)	10 (9.0)	0.07[b]

Notes (*) indicates significant differences in the values between the categories after the respective test at $p < 0.05$. [a]Mann–Whitney U-test, [b]Fischer exact test, [c]Chi-square test of independence

Abbreviations IQR, Inter-quartile range

60 years with an interquartile range of 49–71 years. The most commonly affected age group for stroke patients was 36–64 years (49.5%) followed by the age group above 65 years (41.40%). Males were more commonly affected by strokes (76.6%) compared to females (23.4%). Hypertension was identified as the most prevalent comorbidity in 61.3% of patients, followed by diabetes mellitus 27.0% and hyperlipidemia 21.6%.

The most commonly prescribed anti-hypertensive drugs were calcium channel blockers (CCBs) (29.7%), angiotensin II receptor blockers (ARB) (29.7%), beta-blockers (18.9%), and the least prescribed were angiotensin-converting enzyme Inhibitors (ACE inhibitors) (0.9%). The most commonly prescribed anti-diabetic drugs were biguanides (8.1%), sulfonylureas (4.5%), and the least commonly prescribed were insulin (1.8%).

Table 2 depicts that antiplatelet therapy alone was most commonly prescribed at 60.5% followed by dual antiplatelet therapy (DAPT) at 31.6% in ischemic stroke patients.

Table 3 presents the risk stratification for AF patients based on the CHA_2DS_2VASc and HAS-BLED score. According to the CHA_2DS_2VASc Score, all 5 patients were classified as "High Risk" for stroke. According to HAS-BLED Score, Out of 5 patients, 4 patients were identified as moderate risk of bleeding and 1 patient as high risk of bleeding.

The study shows middle cerebral artery (MCA) infarction (24.3%) was the most common type followed by lacunar infarction (6.3%), posterior cerebral artery (PCA) infarction (1.8%), and PCA with MCA infarction (0.9%) as shown in Fig. 1.

The most prevalent type of hemorrhagic stroke was intracerebral Hemorrhage (ICH) 30.6% followed by subarachnoid Hemorrhage (SAH) 0.9% as shown in Fig. 2 describing various hemorrhagic strokes.

The study investigated the association of risk factors of Ischemic stroke compared to hemorrhagic stroke (Table 4). Among the risk factors, hyperlipidemia was the only one that showed a significant association with ischemic stroke in univariate analysis. Patients with hyperlipidemia were 4.07 times more likely to experience ischemic stroke rather than hemorrhagic stroke (OR = 4.073(1.126–14.733)).

Among the 111 patients, 102 experiencedDRPs (Table 5). A total of 93.4% of those with ischemic stroke and 88.6% of those with hemorrhagic stroke experienced DRPs. A total of 91.9% of stroke patients were affected by DRPs.

The study identified 2 types of DRPs which include (ADRs), and (pDDIs) (Table 6). The study identified that adverse drug reactions (ADRs) occurred in only 1 patient (0.90%). pDDIs were identified in 101 patients (91.09%)). pDDIs were identified as the most prevalent type of DRP in our study. The pDDIs were categorized according to severity as contraindicated, serious, monitored closely, and minor using Medscape software on the basis of discharge medicines.

The study found that the most common severity of pDDI was monitored closely accounting for 73.2% of cases, followed by minor interactions (20.1%), serious interactions (6.29%), and contraindicated interactions (0.52%) as shown in Fig. 3.

The predictors for severity of pDDIs were investigated using binary logistic regression (Table 7). The results showed that hyperlipidemia and the use of more than 10 medicines were significant predictors for high severity of pDDIs in univariate analysis. The use of more than 10 medicines was significant predictors for high severity of pDDIs in multivariate analysis. Patients who took more than 10 drugs were 6.9 times more likely to experience high severity pDDIs than patients who took less than 5 drugs (OR = 6.907 (1.130-42.233), $p = 0.036$)). Other factors age, gender, hypertension, diabetes, heart disease, type of stroke did not show significant association.

Discussion

Stroke represents a significant and increasingly serious issue for global health [1]. Effective management of modifiable risk factors plays a crucial role in reducing stroke incidence. This study is the first to identify DRPs specifically in stroke patients in Nepal.

In the present study, the median age of the patients was 57 years for hemorrhagic strokes and 62 years for ischemic strokes, consistent with the study done in Ethiopia [19]. The age group most frequently affected by stroke was 36–64 years (49.5%) followed by the age group above 65 years (41.40%) in our study. The results obtained in our study differed from the study conducted in Sub-Saharan Africa [20].

Males were more commonly affected by stroke (76.6%) compared to females (23.4%). It closely resembled the findings in the Saudi Arabian study [21]. The study conducted in Nepal indicated that a greater number of males were affected by stroke compared to females [22, 23]. The

Table 2 Anti-thrombotic drugs prescribed for stroke patients on discharge

Anti-thrombotic Drugs	Ischemic stroke
Antiplatelet alone	46 (60.5%)
Dual antiplatelet therapy	24 (31.6%)
Combination therapy (OAC + Aspirin)	1 (1.3%)
Total	76

Abbreviations OAC, Oral Anticoagulants

Table 3 Risk stratification of AF patients ($n=5$)

Category	Subcategory	Frequency (%)
CHA_2DS_2-VASc	High Risk (≥ 2 in men or ≥ 3 in women)	5 (100.0%)
HASBLED	Moderate risk of bleeding	4 (80.0%)
	High Risk of bleeding (≥ 3)	1 (20.0%)
OAC on discharge		1 (20%)

Abbreviations CHA_2DS_2VASC, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism vascular disease, age 65 to 74 years, sex category; HASBLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; OAC, Oral Anticoagulants

majority of the population was found to be male, a trend that is consistent with most other Indian studies [24]. Men experience strokes at a rate that is 1.25 times greater than that of women for the reason that women generally live longer, stroke results in a higher mortality rate among women than men each year [25]. The higher risk in men due to more common habits like smoking and drinking alcohol, along with the lack of protective hormones like estrogen [26].

In our study, hypertension was the most prevalent comorbidity, followed by diabetes mellitus and hyperlipidemia. The findings of present study was almost similar to the study carried out in Pakistan [27].

The most commonly prescribed anti-hypertensive drugs were CCBs (29.7%), and ARBs (29.7%).The finding was similar to the study in Nepal which also showed CCB as the most common antihypertensive drug [25]. Hypertension was prevalent among our patients, leading to antihypertensive drugs being the most commonly prescribed medications. CCBs were chosen more because they can effectively lower high blood pressure and also tend to have fewer side effects compared to other medications [28]. A comprehensive review and meta-analysis demonstrated that CCBs not only effectively reduce the risk of stroke recurrence but also promote the pace of cognitive recovery and achieve better blood pressure management [29].

In the present study, antiplatelet al.one was the most commonly prescribed antithrombotic drug for ischemic stroke patients, particularly for non-cardioembolic stroke. A meta-analysis found that DAPT was beneficial as it lowered the chance of experiencing another stroke but raised the likelihood of bleeding incidents in compared to antiplatelet al.one [30, 31]. Several studies have demonstrated the short term use of DAPT and the use of antiplatelet al.one for long term prevention.

All 5 patients in our study were categorized as "High Risk" for stroke, suggesting a need for anticoagulation. Despite high CHA_2DS_2VASc scores, only 1 patient (20%) received oral anticoagulants upon discharge. The reason was unknown because the document was unclear and did not specify any contraindications for prescribing OAC in atrial fibrillation (AF) patients. But the patients received Low molecular weight heparin during hospitalization. HAS-BLED score was calculated excluding labile INR due to lack of data.

Our findings suggest that most of the cases were ischemic which was consistent with previous studies [32–34].

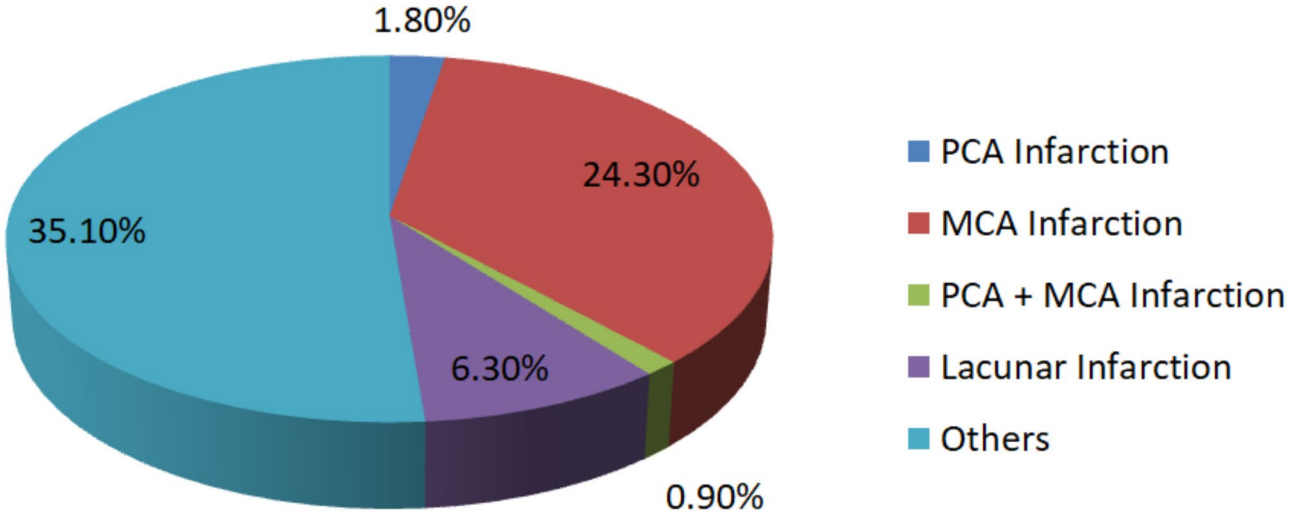

Fig. 1 Type of Ischemic stroke

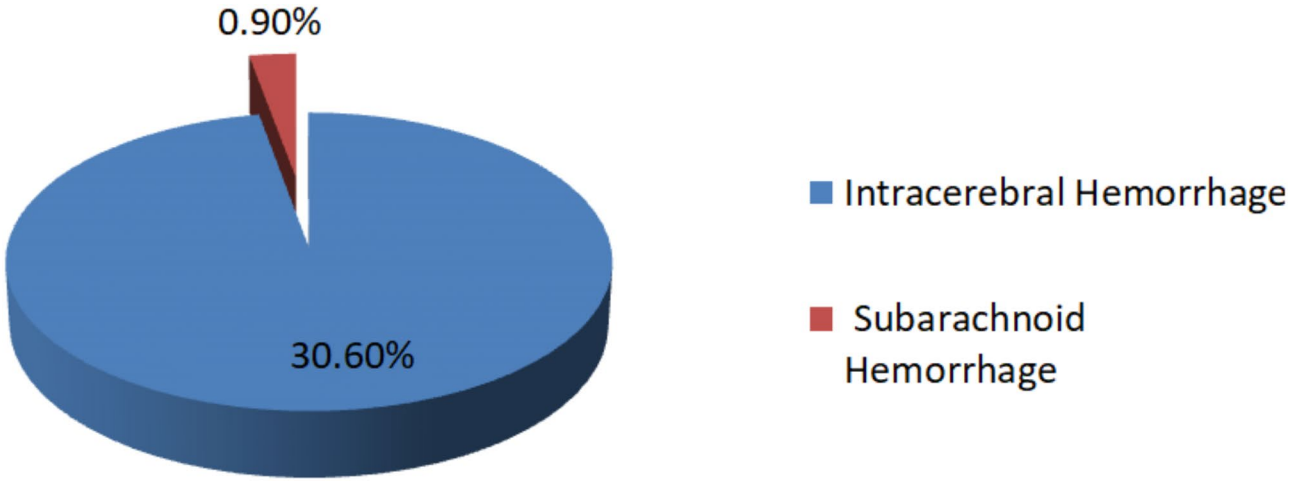

Fig. 2 Type of Hemorrhagic stroke

Table 4 Risk factor of Ischemic stroke compared to Hemorrhagic stroke

Variables		OR (95% CI)	*P* value
Age group	(≤ 65 years)	Reference	
	(≥ 65 years)	1.299(0.571–2.955)	0.533
Gender	Male	Reference	
	Female	1.047(0.405–2.708)	0.924
Hypertension	Yes	0.630(0.270–1.469)	0.285
	No	Reference	
Diabetes	Yes	1.736(0.663–4.543)	0.261
	No	Reference	
Hyperlipidemia	Yes	4.073(1.126–14.733)	**0.032***
	No	Reference	
Heart disease	Yes	2.914(0.337–25.176)	0.331
	No	Reference	
Previous Stroke/TIA	Yes	1.067(0.394–2.885)	0.899
	No	Reference	
Family History	Yes	1.082(0.263–4.459)	0.913
	No	Reference	
Smoking	Yes	1.750(0.531–5.763)	0.357
	No	Reference	
Alcohol	Yes	0.818(0.276–2.425)	0.717
	No	Reference	

Notes (*) indicates odds ratio

Abbreviations OR, Odds Ratio; TIA, Transient Ischemic Attack

Table 5 Drug Related Problems

Drug-Related Problems	Ischemic Stroke	Hemorrhagic Stroke	Total
	71 (93.4%)	31 (88.6%)	102 (91.9%)

Table 6 DRP type (*N* = 102)

DRP type	Frequency (%)
Adverse drug reactions	1 (0.90%)
Potential drug-drug interactions (pDDI)	101(91.0%)

But the finding contrasted with the study conducted in Nepal which showed hemorrhagic stroke was more prevalent [25]. Research from earlier studies suggests that ischemic stroke is 1.5 to 3 times more prevalent than hemorrhagic stroke in Nepal [35]. Ischemic stroke was more common because it might be due to alterations in the brain's blood flow caused by underlying pathophysiological changes, as well as due to higher incidence of MCA infarction involvement. Ischemic stroke constitutes about 70.87% of stroke cases in Nepal [36].

In our study, the most frequently involved ischemic stroke was the MCA infarction accounting for 24.3% of patients. Several studies reported a higher prevalence of MCA infarction but consistently identified it as the most common ischemic stroke [37–41].

The most common type of hemorrhagic stroke was ICH hemorrhage, observed in 30.6% of patients in our study. A study in Pokhara reported a lower prevalence of ICH in comparison to our study [42]. The finding was consistent with an Ethiopian study [43].

Hyperlipidemia was found significant risk factor for ischemic stroke with OR 4.073 in our study. Similar results were observed in the study in China [11]. A study conducted among Finnish populations found a positive association between total cholesterol levels and the risk of total and ischemic stroke in men, while women showed an inverse association with intracerebral hemorrhagic stroke risk [44]. The relationship between cholesterol levels and stroke is not consistently significant, as multiple stroke subtypes exist, and not all are linked to atherosclerosis [45]. A recent cohort study indicated that the risk of ischemic stroke associated with elevated apoB and non-HDL cholesterol is twice that of elevated LDL cholesterol [46]. A case-control study in India found high cholesterol is a significant risk factor for stroke with an OR 3.76 compared to control [47]. Though there is a well-established connection between hypercholesterolemia

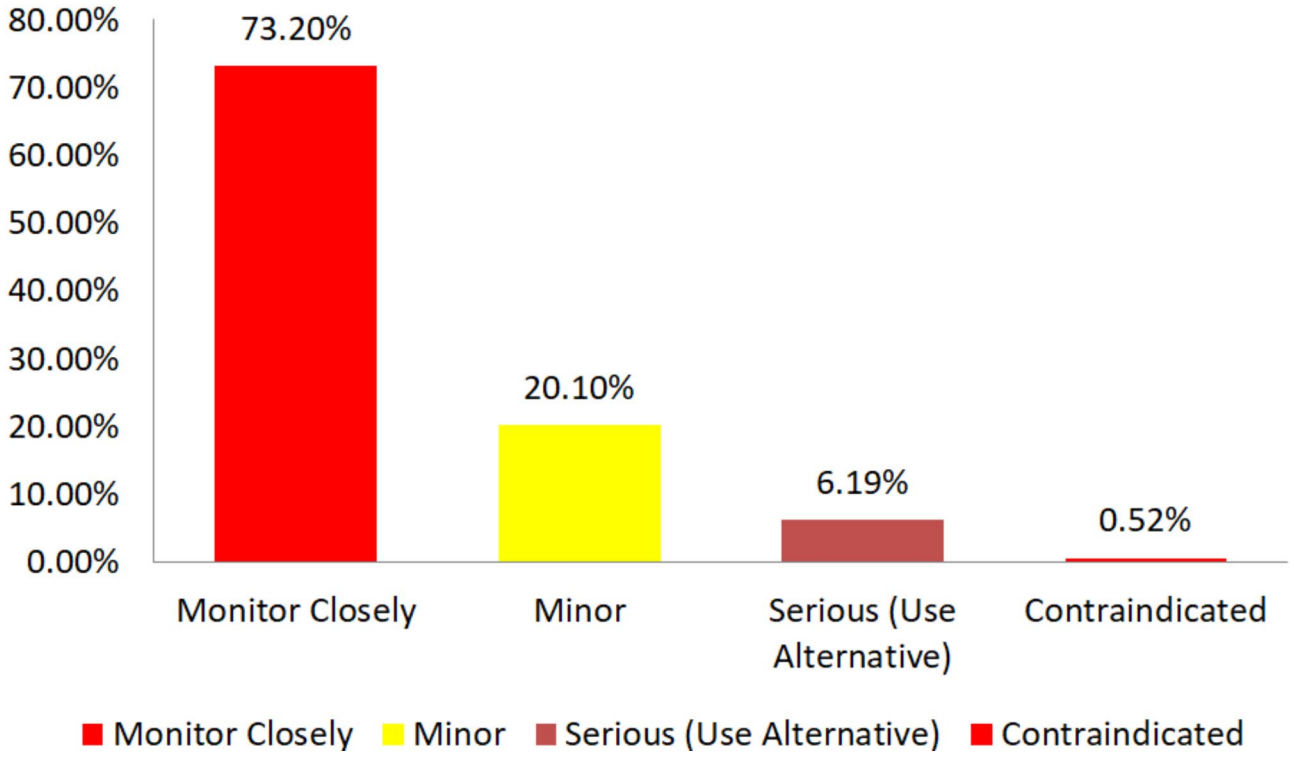

Fig. 3 Potential Drug-Drug interactions

Table 7 Predictors for severity pDDIs

Variable		Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* value
Age group	(≤ 65 years)	1.857(0.606–5.691)	0.279		
	(≥ 65 years)	Reference			
Gender	Male	2.571 (0.548–12.073)	0.231	2.077 (0.382–11.279)	0.397
	Female	Reference			
Hypertension	Yes	0.667 (0.236–1.888)	0.446		
	No	Reference			
Diabetes	Yes	1.150 (0.368–3.593)	0.810		
	No	Reference			
Hyperlipidemia	Yes	3.171(1.056–9.520)	0.040	2.859 (0.798–10.244)	0.107
	No	Reference			
Heart disease	Yes	2.373 (0.421–13.369)	0.327		
	No	Reference			
Type of Stroke	IS	4.057(0.874–18.832)	0.074	3.456 (0.678–17.621)	0.136
	HS	Reference			
Number of medicine	1–5	Reference			
	5–10	1.448(0.28–7.48)	0.658	0.967 (0.165–5.669)	0.970
	> 10	8(1.465–43.677)	0.016	6.907 (1.130- 42.233)	**0.036***

Note (*) indicates odds ratio and adjusted odds ratio with 95% confidence interval is significant at $p < 0.05$

Abbreviations OR, Odd Ratio; IS, Ischemic Stroke; HS, Hemorrhagic Stroke

and various lipoprotein fractions with the severity of carotid atherosclerosis, the relationship between serum cholesterol levels and stroke remains debatable [48]. Elevated LDL cholesterol and reduced HDL cholesterol are associated with an increased risk of ischemic stroke. However, the connection between triglyceride levels and stroke risk is still remaining unclear [49]. High cholesterol levels are known to increase the risk of ischemic stroke though the nature of the relationship may vary across different pathogenic subtypes of ischemic stroke [42]. The inconsistencies in the relationship between cholesterol and stroke across different studies suggest

that future research should focus on detailed lipid profiling and its impact on specific stroke. Other factors were not found significant association with stroke in our study possibly due to the limited sample size.

The study identified 2 types of DRP i.e. (ADRs), and (pDDIs). The present study identified that ADRs occurred in only 1 patient (0.90%) similar to the study conducted in India [50]. But in contrast, a study in Ethiopia reported adverse reaction in 15% of patients [51]. The reason for the low prevalence of ADR in our study might be due to differences in study populations, medication types, and short duration of follow-up.

pDDIs were identified in 101 patients (91.09%)). pDDIs were the most prevalent type of DRPs (91%). These findings aligned with three studies that also highlighted drug-drug interactions as a prevalent issue among DRPs [43, 49, 52]. But the finding contrasted with the study conducted in China which reported treatment safety as the major type of DRP [53, 54]. The prevalence of pDDI was much higher in our study (91.09%) compared to the earlier studies [55, 56]. The reason for the high prevalence of pDDIs in our study might be due to a high number of drugs, the prevalence of comorbidities hypertension, diabetes, and hyperlipidemia, and also due to the inclusion of all severity of interactions. The major pDDIs such as aspirin-diclofenac and diclofenac-enoxaparin can increase bleeding risks, necessitating monitoring of clinical signs and laboratory parameters like PT, aPTT, and INR, while the concurrent use of diclofenac-furosemide and aspirin-furosemide may lead to nephrotoxicity, requiring careful assessment of renal function [57]. A study done in India found that using aspirin and diclofenac together for more than five days led to gastrointestinal bleeding, the physician stop diclofenac, which resolved the issue. Additionally, hypokalemia occurred in patients taking spironolactone with aspirin, and potassium chloride (KCl) injections were given to maintain serum potassium levels [58]. Thus, hospital pharmacists play a critical role in identifying and monitoring pDDIs.

Our study found that the most common severity of pDDI was monitored closely, followed by minor interactions, serious interactions, and contraindicated interactions. Our study identified a contraindicated interaction between apixaban and dexamethasone as per Medscape software. Despite Food and Drug Administration advice against combining apixaban with CYP3A4 inducers, the ARISTOTLE trial and a nested case-control study found no significant impact on apixaban effectiveness or safety, nor an increased risk of thromboembolic events with concomitant use of dexamethasone [59]. So, it implies that despite the theoretical concerns, the actual clinical risk might be lower than expected.

A study conducted in Pakistan showed monitor closely as the most prevalent type of drug interactions similar to our study [60]. Other studies identified that moderate interaction was the most common type of drug interaction [61–63].

Using multivariate logistic regression, it was found that polypharmacy (more than 10 medicines) polypharmacy was significant predictors for high severity of pDDIs in the present study. Studies conducted in India and Sudan also identified a number of prescribed drugs as predictors for drug-drug interaction [64, 65]. Numerous studies have indicated that polypharmacy has been associated with a higher risk of pDDI [66]. Other factors were not significant predictors of high-severity pDDIs in our study, possibly due to the limited sample size.

Based on the finding that hyperlipidemia is a significant risk factor for ischemic stroke, it is recommended that clinicians should prioritize routine monitoring of lipid profiles in stroke patients. The importance of rigorous lipid monitoring and optimization of lipid-lowering therapy should be prioritized in ischemic stroke management. The high prevalence of pDDIs as the most common DRP highlights careful medication review and deprescribing in managing stroke patient, particularly for those on multiple medications. The "monitor closely" classification for most pDDIs highlights the need for vigilant oversight of stroke patients' medication regimens to prevent adverse effects and enhance treatment outcomes.

The study has several limitations. The drug-drug interactions were only potential and classified based on severity using a single software, Medscape. The exclusive use of medscape for drug interaction analysis is recognised as a potential limitation, as differences in drug interaction classification may exist across various databases. Hence, it is recommended to use additional tools such as Lexicomp, Micromedex, and UpToDate to identify PDDIs. The patient history was limited, and since patients were only followed from admission to discharge, any drug-related problems that might have occurred after discharge were not captured. Some patients were excluded due to incomplete records which may have influenced the representativeness of the results. The study had a limited sample size, and the duration was short. The limited sample size may introduce selection bias so, should be interpreted with caution. It was a non-interventional study. The study was conducted at a single hospital, so the results should be interpreted carefully, as they may not be relevant to other hospital settings. Therefore, further multicenter studies involving larger and more diverse populations are necessary to validate the relevance of these findings in different clinical environments.

Conclusion

From these findings, we can conclude that polypharmacy as significant predictor of high-severity pDDIs so emphasizing the need for careful consideration when

adding any new medication. Each additional drug should be introduced with particular caution to minimize the risk of severe interactions. The high rate of pDDIs (91%) highlights the significance of clinical pharmacists in identifying these problems, which can help prevent further drug-related complications in patients. Healthcare professionals should be actively encouraged to utilize software tools for detecting pDDIs. To mitigate such pDDIs, it is recommended to assess alternative detection tools and propose strategies if they are unavailable. Additionally, implementing hospital protocols for checking drug interactions before prescribing and raising awareness among medical and nursing staff about monitoring patients on polypharmacy will enhance patient management and safety. It is crucial to encourage clinicians to conduct thorough medication reviews, monitor for drug interactions, implementing standardized protocols for medication management can help mitigate risks associated with DRPs. Future research could benefit from longitudinal studies to track the progression of DRPs among stroke patients over time. Additionally, prospective interventional studies with larger sample sizes should be conducted to further investigate drug-related problems among stroke patients. The clinical pharmacist might play a vital role as a possible intervention to reduce DRPs.

Abbreviations

ADR	Adverse Drug Reactions
ANIAS	Annapurna Neurological Institute and Allied Science
CCB	Calcium Channel Blockers
DRP	Drug Related Problem
DAPT	Dual Antiplatelet Therapy
ICH	Intracerebral Hemorrhage
MCA	Middle Cerebral Artery
PDDI	Potential Drug-Drug Interaction
SAH	Subarachnoid Hemorrhage

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Author contributions
(1) Tulsi Bhusal originally conceptualized the study, did data collection, analyzed and wrote the main manuscript. (2) Durga Bista contributed as a supervisor to refine the study proposal, helped during analysis, reviewed the manuscript and provided final approval. (3) Rojeena Koju Shrestha supervised the work and reviewed the final manuscript.

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Data availability
Data is provided within the manuscript and supplementary information files.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Institutional Review Committee of Annapurna Hospital, Kathmandu with approval reference number IRC-ANIAS-114-2023/2024 before carrying out the study. All patients were given written informed consent. Patient information was kept confidential throughout the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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