NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | RESEARCH NOTES ISSN: 2576-828X

Clinical and pharmacotherapeutic factors as survival and death predictors in hospitalized post-stroke patients

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Received: 7 September 2022; **Accepted:** 23 February 2023; **Published:** 7 May 2023
Edited by: Kheng Seang Lim (Universiti Malaya, Malaysia)
Reviewed by: Lay Khoon Loo (Hospital Seberang Jaya, Pulau Pinang, Malaysia);
Abdul Hanif Khan Yusof Khan (Universiti Putra Malaysia, Malaysia)
https://doi.org/10.31117/neuroscirn.v6i2.180

Abstract: Stroke is a neurological disease. High mortality and sequelae that cause physical or psychological disability demand greater efforts for adequate therapeutic management. The present study aimed to identify signs, symptoms, comorbidities, and therapeutic agents associated with decreased survival time and increased death risk in hospitalized stroke patients. Medical records of stroke patients hospitalized in 2016 at a Peruvian hospital were included. Post-stroke survival time was determined using the Kaplan-Meier method. A comparison of the mean survival time of ischemic and hemorrhagic stroke patients was carried out with the Mantel-Cox test. In addition, the death risk or hazard ratio (HR) was determined using Cox proportional hazards model. The mean survival time was 34.37 (95% CI, 31.89-36.85) and 16.96 (95% CI, 12.35-21.56) days in post-ischemic and hemorrhagic stroke patients, respectively. Dyspnea, peripheral edema, sensory disorder, diffuse cerebral edema and previous stroke are associated with a decrease in survival time. In addition, multivariate analysis revealed that chronic kidney failure (HR=11.98; 95% CI, 2.33-61.68; p=0,003), dyslipidemia (HR=5.19; 95% CI, 1.65-16.32; p=0.005), previous stroke (HR=1.51; 95% CI, 0.41-5.63; p=0.043), and use of antihemorrhagic (HR=1.12; 95% CI, 0.79-1.59; p=0.002) or antiepileptic drugs (HR=1.08; 95% CI, 0.70-1.68; p=0.016) could be considered as death predictors. Clinical and pharmacotherapeutic factors associated with a decrease in mean survival time and increased death risk in hospitalized stroke patients were identified. These factors should be an alarm sign to provide special and timely medical care that reduces the risk of death in patients.

Keywords: Hemorrhagic Stroke; Ischemic Stroke; Survival Analysis; Proportional Hazards Models; Death Predictors

1.0 INTRODUCTION

Stroke is a neurological emergency with sudden clinical manifestation; it is characterized by a neurological deficit caused by vascular lesions of an ischemic or hemorrhagic type that interrupt the blood supply to the brain (Abbott et al., 2017). This disease is one of the leading causes of morbidity and mortality in the adult population worldwide, which is why it represents a serious public health problem (Saba et al., 2019; Xing et al., 2020). In addition, the appearance of complications and sequelae, such as physical and psychological disability, reduce the quality of life and the functional status of patients (Adoukonou et al., 2020; Grysiewicz et al., 2008; Saber & Saver, 2020). Therefore, this disease demands an early diagnosis and an adequate therapeutic intervention that contributes to a favorable prognosis.

In clinical practice, the prognosis of stroke is carried out by applying scales such as the National Institutes of Health-Stroke Scale (Saber & Saver, 2020), Rankin scale (Rankin, 1957), Barthel-index (Ohura et al., 2017), Glasgow-Coma Scale (Yang et al., 2017), and Simplified Acute Physiology Score (Le Gall, 1993). All these tools consider the patient's clinical condition and signs and symptoms. On the other hand, many studies highlight the importance of comorbidities as risk factors for suffering a stroke (Ahangar et al., 2018; Grysiewicz et al., 2008; Habibi-koolaee et al., 2018; O'Donnell et al., 2016; Xing et al., 2020) and not on how it influences the evolution of the disease. Furthermore, the influence of drugs on the survival time or risk of death of post-stroke patients is unknown. However, therapeutic regimens, comorbidities, and other clinical factors influence the course of the disease. Therefore, they could help predict the survival time or risk of death of hospitalized post-stroke patients. This would allow taking the necessary medical actions in a timely manner to avoid the death of patients.

The present study aimed to identify the clinical and pharmacotherapeutic factors associated with the increase or decrease in survival time and the risk of death in hospitalized post-stroke patients. Furthermore, it was intended to determine possible predictors of survival and death in these patients.

2.0 MATERIALS AND METHODS

A retrospective study was carried out. The medical records of all patients hospitalized during 2016 (from January 1st to December 31st) at Miguel Angel Mariscal Llerena Hospital in Ayacucho-Peru were evaluated (**Figure 1**). This study considered 97 medical records of patients diagnosed with a stroke, older than 18 years with more than 24 hours of hospitalization, an established therapeutic regimen and a discharge summary. In addition, reports of patients with intracranial hemorrhages due to conditions other than stroke and those referred to other hospitals were excluded.

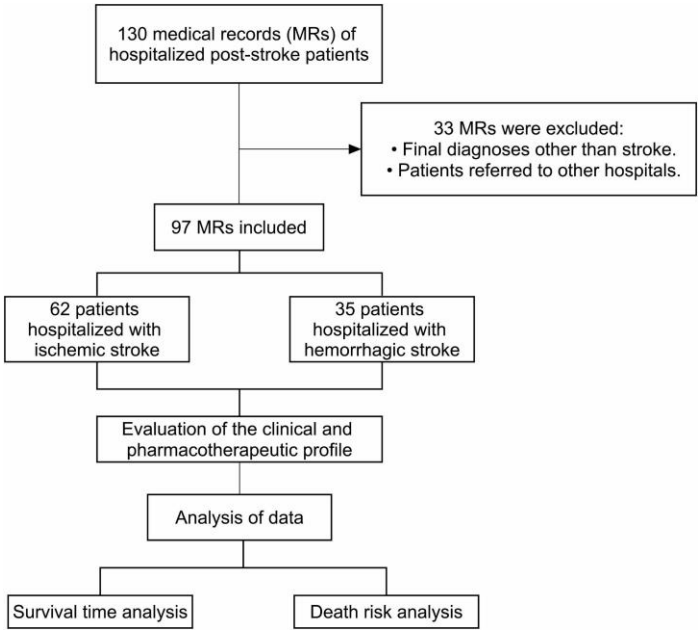

Figure 1: Medical records selection process. The flow chart shows the medical records included in the present study.

In the present study, the clinical factors considered for the survival and risk of death analysis were signs, symptoms, and comorbidities. On the other hand, the pharmacotherapeutic profile was calculated by adding the number of doses of each drug group administered to all patients during their hospitalization, according to the type of stroke. Therefore, the dosage, amount and frequency of drug administration were recorded (Supplementary Table 1). In addition, all drugs were grouped according to the Anatomical Therapeutic and Chemical (ATC) classification. Finally, stroke was categorized as ischemic or hemorrhagic.

2.1 Statistical analysis

Collected data were processed, ordered and coded in a Microsoft Office Excel spreadsheet. Statistical analyses were carried out using SPSS version 23 (IBMCorp.). In all cases, a confidence level of 95% was used.

2.2 Survival analysis

Post-stroke survival time was determined using the Kaplan-Meier method. Because the data in the present

study did not reach the median in all cases (considered as the shortest time when the probability of survival is 50% or less), the mean survival time was used. In addition, the difference between the mean survival time of patients after ischemic and hemorrhagic stroke was determined using the log-rank or Mantel-Cox test. This test made it possible to compare the survival probability of both groups of patients, considering clinical and pharmacotherapeutic factors. Both discharge and death of the patient were censored events.

2.3 Death risk analysis

The risk of death or HR was determined using Cox proportional hazards model, also known as a predictor of death or multivariate hazard rate. This model predicts the risk of death associated with a specific risk factor at a given endpoint (Abd ElHafeez et al., 2021). In other words, it allows the evaluation of the effect of certain factors involved in the patient's risk of death.

2.4 Ethical considerations

The hospital management authorized access to clinical and pharmacotherapeutic data. In addition, the Research Ethics Committee of the National University of Callao granted ethical approval (CARTA 01-CEI-VIRTUAL-2021-VRI-UNAC). The need for informed consent was waived because the data were retrieved and analyzed retrospectively. All data were processed and treated confidentially, following the ethical code formulated by the WHO (Declaration of Helsinki).

3.0 RESULTS

3.1 Baseline characteristics

The present study evaluated 130 medical records of hospitalized stroke patients in 2016. Of these, 33 were excluded because the final diagnosis that had caused the symptoms was a disease other than stroke or because the patients were referred to other hospitals. Therefore, the medical records of 97 patients were analyzed. Of which 55 (56.7%) were women, the mean age was 68 years (s.d. 15), and 70% of patients were in an age range between 60 and 90 years. Furthermore, 62 patients (64%) were hospitalized with a diagnosis of ischemic stroke; of these 44 are older than 60 years. There is a high prevalence of this condition in older adults. The maximum length of hospitalization during the observation year was 37 days.

3.2 Survival time

The mean survival time of the patients in both groups (ischemic and hemorrhagic) was 26.76 days (**Table 1**). The highest survival rate was presented by the group of patients with ischemic stroke 58 (59.8%) and had a mean survival time of 34.37 days, while post-hemorrhagic stroke patients had a mean survival time of 16.96 days. In addition, the cumulative survival probability of patients with hemorrhagic stroke was 91.4% at 1 day, 80% at 7 days, 68.3% at 13 days, 54.3% at 24 days, and 0% at 30 days (**Figure 2**).

Table 1. Survival time and hazard ratio according to the type of stroke.

	Ischemic stroke	Hemorrhagic stroke	Total
Survival time			
Mean (95% CI)	34.37 (31.89-36.85)	16.96 (12.35-21.56)	26.76 (22.88-30.63)
Median (95% CI)	-	13.00 (7.37-18.62)	-
p-value	-	0.000	-
Death risk			
HR (95% CI)	0.13 (0.04 - 0.39)	7.49 (2.50 - 22.37)	-
p-value	0.000	0.000	-

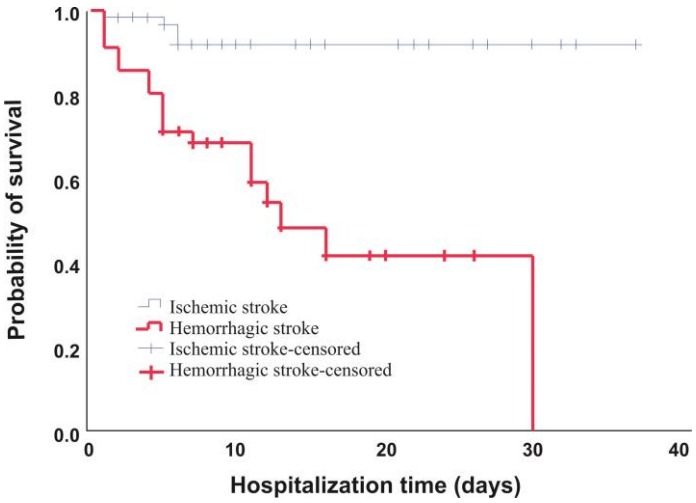

Figure 2: Kaplan-Meyer survival curves for hospitalization time of all patients included in the present study.

Signs and symptoms of patients with the shortest mean survival time were dyspnea, fecal incontinence, peripheral edema, vision disorder and sensory disorder (**Table 2**). The first three even produce a greater decrease in survival time in ischemic stroke patients, while the last one significantly influences hemorrhagic stroke patients ($p<0.05$). However, the number of patients with these conditions is small, making this finding inconclusive.

Table 2. Clinical profile, survival time and hazard ratio according to the clinical characteristics of hospitalized patients.

	Clinical profile, n (%)		Survival time (mean ± 95% CI)			Hazard ratio (± 95% CI)			
Signs and symptoms	**I. S.**	**H. S.**	**I. S.**	**H. S.**	***p*-value**	**Univariate analysis**	***p*-value**	**Multivariate analysis**	***p*-value**
Aphasia	29 (29.9)	8 (8.2)	26.67 (23.13-30.21)	11.12 (5.07-17.18)	0.264	0.96 (0.39-2.38)	0.930	0.84 (0.28-2.53)	0.757
Conscience disorder	21 (21.6)	19 (19.6)	-	-	-	2.03 (0.83-4.95)	0.119	1.35 (0.48-3.77)	0.565
Dysarthria	7 (7.2)	3 (3.1)	29.14 (22.14-36.14)	15.00 (6.99-23.00)	0.936	0.66 (0.15-2.84)	0.574	0.37 (0.04-3.09)	0.357
Dyspnea	5 (5.2)	1 (1.0)	7.66 (4.04-11.28)	12.00 (12.00-12.00)	0.016	3.37 (0.97-11.66)	0.055	-	0.943
Fecal incontinence	2 (2.1)	2 (2.1)	6.00 (6.00-6.00)	6.50 (0.00-14.12)	0.013	5.26 (1.52-18.24)	0.009	4.03 (0.75-21.59)	0.104
Headache	22 (22.7)	13 (13.4)	22.47 (18.83-26.10)	19.66 (12.13-27.19)	0.836	1.27 (0.53-3.03)	0.588	1.31 (0.46-3.76)	0.611
Hemiparesis	35 (36.1)	16 (16.5)	32.08 (30.31-33.85)	12.28 (8.24-16.32)	0.755	0.67 (0.28-1.62)	0.371	0.87 (0.28-2.64)	0.799
Hemiplegia	17 (17.5)	9 (9.3)	18.50 (14.98-22.01)	16.22 (9.38-23.06)	0.535	1.55 (0.62-3.90)	0.351	1.16 (0.40-3.36)	0.780
Paresthesia	17 (17.5)	8 (8.2)	18.54 (15.01-22.07)	14.00 (9.59-18.41)	0.581	1.20 (0.46-3.13)	0.714	0.71 (0.20-2.57)	0.605
Peripheral edema	2 (2.1)	1 (1.0)	3.50 (0.00-8.40)	12.00 (12.00-12.00)	0.003	7.14 (2.06-24.73)	0.002	-	0.921
Sensory disorder	11 (11.3)	4 (4.1)	17.02 (11.38-22.66)	7.00 (0.00-14.20)	0.001	3.03 (1.16-7.94)	0.024	2.42 (0.76-7.70)	0.136
Vision disorder	3 (3.1)	1 (1.0)	8.00 (5.22-10.77)	12.00 (12.00-12.00)	0.140	3.94 (0.71-13.47)	0.132	0.14 (0.01-4.09)	0.257
Vomiting	6 (6.2)	4 (4.1)	27.60 (18.13-37.06)	13.25 (5.12-21.37)	0.423	1.47 (0.49-4.43)	0.492	0.66 (0.12-3.54)	0.629
Comorbidities									
Acute kidney failure	3 (3.1)	2 (2.1)	-	-	-	1.06 (0.14-8.02)	0.954	1.52 (0.15-15.44)	0.721
Acute myocardial infarction (AMI)	1 (1.0)	2 (2.1)	-	-	-	3.05 (0.71-13.17)	0.135	10.61 (1.52-73.87)	0.107
Arterial hypertension	38 (39.2)	30 (30.9)	-	-	-	5.21 (1.21-22.49)	0.027	2.28 (0.44-11.71)	0.323
Atrial fibrillation with rapid ventricular response	8 (8.2)	0 (0.0)	-	-	-	0.04 (0.00-14.23)	0.283	-	0.970
Chronic kidney failure	2 (2.1)	0 (0.0)	6.00 (6.00-6.00)	16.96 (12.35-21.56)	-	6.73 (1.50-30.11)	0.013	11.98 (2.33-61.68)	0.003
Diffuse cerebral edema	1 (1.0)	1 (1.0)	5.00 (5.00-5.00)	2.00 (2.00-2.00)	0.000	11.76 (2.56-54.01)	0.002	-	-
Dilated cardiomyopathy	3 (3.1)	1 (1.0)	-	-	-	1.34 (0.18-10.03)	0.777	2.41 (0.28-20.62)	0.421
Dyslipidemia	11 (11.3)	8 (8.2)	-	-	-	9.32 (3.64-23.86)	0.000	5.195 (1.65-16.32)	0.005
Hospital-acquired pneumonia	11 (11.3)	9 (9.3)	34.18 (28.91-39.44)	13.75 (5.97-21.52)	0.335	1.56 (0.62-3.89)	0.341	0.89 (0.26-3.08)	0.852
Intracranial hypertension	1 (1.0)	3 (3.1)	-	-	-	4.72 (1.06-20.99)	0.042	1.55 (0.08-30.16)	0.773
Ischemic heart disease	1 (1.0)	0 (0.0)	5.00 (5.00-5.00)	-	-	7.72 (0.99-59.86)	0.050	0.847 (0.08-8.44)	0.887
Mellitus diabetes	17 (17.5)	20 (20.6)	25.00 (21.26-28.73)	14.54 (9.13-9.94)	0.225	3.70 (1.49-9.21)	0.005	2.550 (0.92-7.05)	0.071
Metabolic alkalosis	3 (3.1)	1 (1.0)	-	-	-	0.73 (0.10-5.52)	0.759	0.098 (0.01-1.29)	0.077
Multiple organ dysfunction syndrome	1 (1.0)	1 (1.0)	-	-	-	2.21 (0.29-16.63)	0.442	4.32 (0.41-46.01)	0.226
Obesity	3 (3.1)	0 (0.0)	8.50 (5.03-11.96)	-	-	2.17 (0.29-16.36)	0.453	0.71 (0.08-6.08)	0.757
Previous stroke	7 (7.2)	4 (4.1)	9.57 (3.09-16.05)	8.00 (4.39-11.60)	0.009	3.72(1.34-10.38)	0.012	1.51 (0.41-5.63)	0.043
Sepsis	3 (3.1)	2 (2.1)	-	-	-	1.87 (0.42-8.22)	0.407	6.50 (1.16-36.36)	0.533
Transient ischemic attack (TIA)	7 (7.2)	0 (0.0)	-	-	-	-	-	-	-
Urinary tract infections	6 (6.2)	3 (3.1)	-	-	-	0.86 (0.20-3.71)	0.840	0.78 (0.16-3.84)	0.755

Ischemic stroke (IS); Hemorrhagic Stroke (HS); Confidence Interval (CI); Occurrence number (n).

Table 3. Pharmacotherapeutic profile, survival time and hazard ratio according to the clinical characteristics of hospitalized patients.

ATC		Pharmacotherapeutic profile, n (%)		Survival time (mean ± 95% CI)			Hazard ratio (± 95% CI)			
		I. S.	H. S.	I. S.	H. S.	*p*-value	Univariate analysis	*p*-value	Multivariate analysis	*p*-value
B05X	i.v. solution additives	351 (6.78)	153 (2.96)	34.52 (31.81-37.23)	18.47 (12.27-24.67)	0.299	0.95 (0.89-1.03)	0.212	1.12 (0.92-1.37)	0.086
C01	Cardiac therapy	43 (0.83)	25 (0.48)	32.57 (24.54-40.61)	14.00 (5.34-22.66)	0.727	0.96 (0.81-1.12)	0.579	1.41 (0.82-2.42)	0.257
C02	Antihypertensives	413 (7.98)	329 (6.36)	30.56 (27.92-33.19)	14.84 (10.99-18.69)	0.568	0.96(0.92-1.02)	0.175	0.92 (0.79-1.06)	0.006
C03*	Diuretics	112 (2.16)	132 (2.55)	29.05 (2.13-24.88)	15.77 (2.68-10.51)	-	1.13 (0.98-1.29)	0.084	1.82 (1.18-2.79)	0.272
C10	Lipid-modifying agents	388 (7.49)	58 (1.12)	35.34 (33.09-37.59)	15.14 (10.77-19.51)	0.225	0.88 (0.79-0.98)	0.027	1.17 (0.89-1.54)	0.596
B01	Antithrombotic agents	540 (10.43)	33 (0.64)	34.79 (32.37-37.22)	11.00 (8.34-13.66)	0.714	0.83 (0.72-0.95)	0.008	0.53 (0.36-.79)	0.208
B02	Antihemorrhagic	15 (0.29)	2 (0.04)	27.40 (17.58-37.22)	30.00 (30.00-30.00)	0.620	1.24 (0.87-1.76)	0.237	1.12 (0.79-1.59)	0.002
A02	Medications for acid-related disorders	521 (10.06)	237 (4.58)	34.37 (31.89-36.85)	17.43 (12.67-22.19)	-	0.82 (0.74-0.92)	0.001	0.62 (0.41-.93)	0.242
A03	Drugs for functional gastrointestinal disorder	29 (0.56)	15 (0.29)	-	-	-	0.22 (0.00-613.38)	0.772	1.36 (0.84-2.20)	0.810
A06	Laxatives	43 (0.83)	34 (0.66)	33.90 (28.14-39.66)	12.55 (8.89-16.21)	0.881	1.09 (0.89-1.33)	0.383	0.95 (0.65-1.39)	0.002
A10	Drugs used in diabetes	26 (0.50)	11 (0.21)	-	-	-	1.11 (0.84-1.48)	0.466	1.49 (0.76-2.91)	0.511
R03	Drugs for obstructive airways diseases	99 (1.91)	21 (0.41)	32.19 (27.16-37.24)	17.89 (12.99-22.79)	0.835	0.98 (0.92-1.06)	0.682	1.33 (0.99-1.77)	0.080
R05	Cough and cold preparations	75 (1.45)	6 (0.12)	-	-	-	0.62 (0.30-1.26)	0.187	0.22 (0.04-1.19)	0.880
R06	Systemic antihistamines	20 (0.39)	6 (0.12)	29.44 (22.87-36.02)	12.50 (11.81-13.19)	0.953	0.62 (0.22-1.73)	0.364	1.06 (0.48-2.38)	0.021
H02	Systemic corticosteroids	60 (1.16)	26 (0.50)	34.42 (29.56-39.26)	10.70 (6.12-15.28)	0.355	0.99 (0.86-1.13)	0.873	0.91 (0.54-1.51)	0.052
J01	Systemic antibacterials	479 (9.25)	298 (5.76)	-	-	-	0.98 (0.94-1.03)	0.409	1.26 (1.05-1.50)	0.703
J02	Antimycotics for systemic use	11 (0.21)	3 (0.06)	-	-	-	0.89 (0.52-1.51)	0.656	0.93 (0.13-6.75)	0.013
M01A	Nonsteroidal anti-inflammatory and antirheumatic products	10 (0.19)	41 (0.79)	6.33 (2.07-10.60)	16.50 (12.14-20.86	0.198	0.99 (0.78-1.26)	0.924	0.73 (0.45-1.19)	0.943
M03	Muscle relaxants	3 (0.06)	11 (0.21)	-	-	-	1.06 (0.69-1.63)	0.793	1.45 (0.60-3.47)	0.213
N02A	Opioid analgesics	15 (0.29)	88 (1.70)	28.00 (17.46-38.54)	13.08 (5.68-20.49)	0.044	1.08 (0.99-1.16)	0.072	0.67 (0.49-.93)	0.002
N02B	Other analgesics and antipyretics	45 (0.87)	61 (1.18)	33.12 (26.02-40.23)	17.82 (12.96-22.67)	0.239	0.99 (0.86 -1.16)	0.960	0.43 (0.25-.73)	0.209
N03	Antiepileptics	47 (0.91)	46 (0.89)	-	-	-	1.04 (0.91-1.19)	0.567	1.08 (0.70-1.68)	0.016
N05	Psycholeptics	32 (0.62)	31 (0.60)	-	-	-	1.13 (0.96-1.33)	0.135	1.92 (1.26-2.92)	0.717
N06	Psychoanaleptics	130 (2.51)	3 (0.06)	28.50 (25.65-31.35)	11.00 (11.00-11.00)	0.967	0.83 (0.64-1.08)	0.164	1.14 (0.69-1.87)	0.248

*Anatomical Therapeutic and Chemical classification (ATC); Ischemic stroke (IS); Hemorrhagic Stroke (HS); Confidence Interval (CI); Occurrence number (n). * Also drugs that cause osmotic diuresis (ATC, B05BC).*

Twenty-one comorbidities were identified, the most frequent being arterial hypertension, diabetes, dyslipidemia, and hospital-acquired pneumonia (**Table 2**). In addition, it was determined that diffuse cerebral edema, ischemic heart disease, obesity and previous stroke are concomitant diseases in patients with a shorter survival time. Of these, diffuse cerebral edema and previous stroke significantly influence the survival time of hemorrhagic stroke patients ($p<0.05$).

Regarding pharmacotherapy, the use of 24 drug groups classified according to ATC was evidenced (**Table 3**). Of these, the most widely used were antithrombotic agents, drugs for acid-related disorders, antibiotics, antihypertensives, lipid modifying agents, intravenous additive solutions (specifically potassium chloride), psychoanalytic, diuretics, and drugs for obstructive airway diseases. Furthermore, opioid analgesics were found to influence differently ($p<0.05$) in both types of stroke patients.

3.3 Death risk

During the observation period (hospitalization time in 2016), the death of 21 (21.6%) patients was evidenced, of whom 17 had hemorrhagic strokes. Cumulative mortality was four (19%) on the first day and 15 (71.4%) on the first fifteen days of hospitalization. The death risk in hemorrhagic stroke patients was significantly higher (HR=7.49) than in ischemic stroke patients (**Table 1**).

Univariate analysis showed that the signs and symptoms that produce a significant death risk ($p<0.05$) are sensory disorder, fecal incontinence, and peripheral edema (**Table 2**). In addition, it was observed that the comorbidities that increase the death risk are diabetes mellitus, previous stroke, intracranial hypertension, arterial hypertension, chronic renal failure, dyslipidemia and diffuse cerebral edema. Likewise, a significant reduction in death risk was evidenced with the use of lipid-modifying agents, antithrombotic agents, and drugs for acid-related disorders (**Table 3**).

On the other hand, multivariate analysis shows and confirms the significant influence ($p<0.05$) of chronic renal failure, dyslipidemia, and previous stroke as factors that increase the death risk; as well as the use of antihemorrhagic and antiepileptic drugs. However, the use of opioids, antifungals, antihypertensives and laxatives influenced the reduction of death risk in the patients (**Table 3**).

4.0 DISCUSSION

Tools available to assess the prognosis of stroke fundamentally consider the patient's clinical background (Quinn et al., 2017; Saber & Saver, 2020). However, the present study demonstrates the influence of both clinical factors and the therapeutic regimen on survival time and death risk in hospitalized stroke patients. Therefore, they could be considered survival or death predictors after a stroke episode.

The present study corroborates the high prevalence of ischemic stroke in patients older than 60 years, as reported by other studies (Grysiewicz et al., 2008; Roy-O'Reilly & McCullough, 2018). In addition, it was observed that, of all hospitalized patients, almost two-thirds were diagnosed with ischemic stroke, a finding similar to that reported by Habibi-koolaee et al. (2018).

Regarding survival time, it is known that hospitalization of stroke patients favors their survival because they receive timely medical care (Alvarez-Sabín et al., 2011). However, data from the present study show zero probability of survival if the hospital length of stay is prolonged up to 30 days. This fact is due to medical complications that appear in the patients, a finding also reported by Abdo et al. (2019). These medical complications are mainly due to the presence of other concomitant diseases, which are frequent conditions in older adults (Radisauskas et al., 2019). Among the comorbidities that negatively influence survival time are diffuse cerebral edema, ischemic heart disease, obesity, and previous stroke. In addition to being considered stroke risk factors (Xing et al., 2020), these diseases become predictors of a shorter survival time in post-stroke patients.

Furthermore, special care must be taken with hemorrhagic stroke patients because they have greater brain damage and a low probability of survival (Cruz-Cruz et al., 2019). The prognosis of these patients is worse, especially if they also suffer from a sensory disorder, diffuse cerebral edema or previously had a stroke, because they are associated with a shorter survival time. It is worth mentioning that a comprehensive study of the influence of opioids on the clinical evolution of stroke patients is necessary to explain the significant difference ($p<0.05$) between the survival time of patients after hemorrhagic and ischemic stroke. However, this phenomenon could be due to the possible neuroprotective effect of opioids through the δ-opioid receptors (DOR) reported by Feng et al. (2009). Furthermore, the vasodilatory effect of opioids reported by Şahin et al. (2005) would make it possible to

redistribute and restore adequate blood flow, a situation that favors during and after the episode of ischemic and hemorrhagic stroke.

On the other hand, the in-hospital mortality rate was 21.6%; a similar finding was reported by Fekadu et al. (2019). In addition, it was observed that almost 80% of all the deceased were post-hemorrhagic stroke patients. In other words, a high death risk was evidenced in these patients, as can be deduced from the Cox proportional hazards analysis. This finding agrees with what was stated by Grysiewicz et al. (2008), who concluded that hemorrhagic stroke is less frequent, but there is a greater probability of death.

Factors associated with the increased death risk of patients evaluated in the present study were identified, which were classified into signs, comorbidities and pharmacotherapeutic agents. Regarding the signs, peripheral edema is related to other comorbidities that can aggravate the clinical picture of the patients, for which special attention to its presence is already suggested (Cho & Yang, 2018). In addition, some studies indicate that sensory disorder and fecal incontinence are associated with the age of the patients and this is a stroke risk factor (Jacob & Kostev, 2020; Sayedahmed & Alkhair, 2021). However, the present study showed that the presence of these signs during the hospitalization time of stroke patients produces a high death risk. Regarding comorbidities, chronic kidney failure and dyslipidemia could also be death predictors. The latter has already been reported as a concomitant disease associated with an increased death risk (Gaynor et al., 2018). In addition, if the hospitalized patient had previously had a stroke, there is a significant risk of a fatal outcome; this finding was also reported by Heuschmann (2004).

Finally, the present study shows for the first time that the use of antihemorrhagic and antiepileptic drugs is associated with an increased risk of death in hospitalized post-stroke patients. Regarding the use of antihemorrhagics, the main drug was phytomenadione. In addition, **Table 3** shows that the majority of patients who used this drug were ischemic stroke patients. The medical records show it was mainly administered to treat excessive anticoagulation. As reported in the literature, phytomenadione is an adequate drug to treat cases of over-anticoagulation (DeZee et al., 2006; Mahtani et al., 2014). However, in stroke patients, it could increase the risk of death. Likewise, it was found that antithrombotics, lipid-modifying agents, drugs for acid-related disorders, antihypertensives, opioids, antifungals and laxatives decrease the death risk.

As can be seen, both the clinical picture and the pharmacotherapeutic regimen influence the stroke prognosis; thus, they can help to predict the disease outcome. Furthermore, the present study proposes possible predictors of death that would suggest taking specific medical actions in a timely manner and reducing the risk of death in hospitalized patients with stroke. However, studies involving a larger patient population are needed.

5.0 CONCLUSIONS

In summary, stroke is one of the public health problems of difficult clinical management due to the complications, sequelae, and high mortality that it produces. Therefore, it demands greater efforts for adequate therapeutic management. In the present study, clinical and pharmacotherapeutic factors associated with a decrease in the mean survival time and the increased death risk in hospitalized stroke patients were identified. Thus, it was evidenced that dyspnea, peripheral edema, sensory disorder, diffuse cerebral edema and previous stroke could be considered predictors of decreased survival time. In addition, chronic kidney failure, dyslipidemia, previous stroke, and the use of antihemorrhagic or antiepileptic drugs could be considered death predictors. Therefore, any of these factors should be an alarm sign to provide special and timely medical care that reduces the risk of death in patients. However, to be considered as a strategy for the therapeutic management of stroke, studies involving a larger population of patients is required.

Data availability: The datasets used in the present study are available from the corresponding author upon reasonable request.

Acknowledgements: The authors would like to thank the staff of the statistics unit of Miguel Angel Mariscal Llerena Hospital for their contribution in identifying the medical records.

Author Contributions: NVC. and ZD were responsible for the concept and design of the study. JKR and NVC contributed to the drafting of the manuscript. NVC, ZD, YC and JA collected the data. JKR, NVC, ZD, YC and JA analyzed the data. All authors read the manuscript and approved the final version.

Conflicts of Interest: The authors declare that there is no conflict of interest.

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