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CARRERA PROFESIONAL DE MEDICINA HUMANA**

**“FACTORES DE RIESGO DE COMPLICACIONES
INTRAHOSPITALARIAS EN PACIENTES CON INFARTO
CEREBRAL AGUDO: COHORTE RETROSPECTIVA EN UN
HOSPITAL DE REFERENCIA NACIONAL DE PERÚ”**

Tesis para optar el grado académico de:
MAESTRO EN EPIDEMIOLOGÍA CLÍNICA Y BIOESTADÍSTICA

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Se reúnen para evaluar la tesis titulada: **“Factores de riesgo de complicaciones intrahospitalarias en pacientes con infarto cerebral agudo: Cohorte retrospectiva en un hospital de referencia nacional de Perú”**

Presentada por **Miguel Angel Vences Mijahuanca**
Para optar por el Grado de **Maestro en Epidemiología Clínica y Bioestadística**
Con la asesoría de: **Dra. Leda Yamilee Hurtado Roca**

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INFORME DE REVISIÓN DE ORIGINALIDAD

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Factores de riesgo de complicaciones intrahospitalarias en pacientes con infarto cerebral

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Resumen

Objetivo: Determinar los factores de riesgo para complicaciones intrahospitalarias.

Métodos: Realizamos un estudio de cohorte retrospectivo que incluyó a 192 pacientes con infarto cerebral agudo en un hospital de referencia nacional en Perú de enero a septiembre de 2021. La información demográfica, clínica y paraclínica se registró a partir de las historias clínicas. Se definió como complicación intrahospitalaria todo aquel problema médico durante la estancia hospitalaria sea del tipo infeccioso, neurológico, tromboembólico, inmovilidad o miscelánea. Estimamos los factores de riesgo para presentar alguna complicación intrahospitalaria por medio de riesgo relativo e intervalos de confianza del 95% utilizando modelos de regresión con familia de Poisson y varianza robusta para el modelo bivariado y multivariado, ajustando por edad, sexo y factores de riesgo de ictus. Además, se realizaron análisis secundarios por los tipos de complicaciones intrahospitalarias más frecuentes.

Resultados: Ocurrió al menos una complicación intrahospitalaria en el 32,3% de los pacientes. Las complicaciones más frecuentes fueron infecciosas en un 22,4%, seguidas de un 17,7% de complicaciones neurológicas, siendo mucho menos frecuentes otras complicaciones, como tromboembolismo, inmovilidad y misceláneas. Se reportó una tasa de mortalidad intrahospitalaria del 6.2%. El análisis de regresión mostró que la gravedad del accidente cerebrovascular (RR = 1,76; IC del 95 %: 1,09-2,86) fue un factor de riesgo y la albúmina superior a 3,5 mg/dL (RR=0,53; IC95%: 0,36-0,79) fue un factor protector para la presencia de complicación intrahospitalaria. La Hb (RR=0,86; IC 95%, 0,73-0,99) fue un factor protector para la presencia de complicación neurológica y el antecedente de medicación previa por enfermedad cardiovascular fue un factor de riesgo para presentar complicación infecciosa (RR=2,79; IC 95%, 1,16- 6,71).

Conclusiones: Se observó una baja tasa de mortalidad intrahospitalaria y de complicaciones intrahospitalarias, entre las que destacaron las complicaciones infecciosas y neurológicas. Estos resultados pueden servir como punto de partida para establecer sistemas de atención al ictus que consideren flujos diferenciados considerando la presencia de estos factores en los pacientes con infarto cerebral agudo para la prevención de complicaciones intrahospitalarias.

Abstract

Objective: To determine the risk factors for intrahospital complications.

Methods: We conducted a retrospective cohort study that included 192 patients with acute stroke at a national referral hospital in Peru from January to September 2021. Demographic, clinical, and paraclinical information was recorded from medical records. In-hospital complication was defined as any medical problem during the hospital stay, whether infectious, neurological, thromboembolic, immobility, or miscellaneous. We estimated the risk factors for presenting some in-hospital complication by means of relative risk and 95% confidence intervals using regression models with a Poisson family and robust variance for the bivariate and multivariate model, adjusting for age, sex and risk factors for ictus. In addition, secondary analyzes were performed by the most frequent types of in-hospital complications.

Results: At least one intrahospital complication occurred in 32.3% of the patients. The most frequent complications were infectious in 22.4%, followed by 17.7% neurological complications, other complications such as thromboembolism, immobility and miscellaneous being much less frequent. An in-hospital mortality rate of 6.2% was reported. Regression analysis showed that stroke severity (RR = 1.76; 95% CI: 1.09-2.86) was a risk factor and albumin greater than 3.5 mg/dL (RR = 0.53; 95% CI: 0.36-0.79) was a protective factor for the presence of intrahospital complication. Hb (RR=0.86; 95% CI, 0.73-0.99) was a protective factor for the presence of neurological complications and a history of previous medication for cardiovascular disease was a risk factor for presenting infectious complications (RR=2.79; 95% CI, 1.16-6.71).

Conclusions: A low rate of in-hospital mortality and in-hospital complications were observed, among which infectious and neurological complications stood out. These results can serve as a starting point to establish stroke care systems that consider differentiated flows considering the presence of these factors in patients with acute stroke for the prevention of intrahospital complications.

Versión aprobada para publicar en revista.

Risk factors for in-hospital complications in patients with acute ischemic stroke: retrospective cohort in a national reference hospital in Peru

Abstract

Objective: To describe the clinical and demographic characteristics of patients with acute cerebral infarction treated at a national reference hospital in Peru and determine the risk factors for in-hospital complications.

Methods: We conducted a retrospective cohort study including 192 patients with acute ischemic stroke in a national reference hospital in Peru from January to September 2021. Clinical, demographic and paraclinical information was recorded from medical records. We estimated risk ratios and 95% confidence intervals using regression models with Poisson family and robust variance for the bivariate and multivariate model, adjusting for age, sex and risk factors for stroke.

Results: At least one in-hospital complication occurred in 32.3% of the patients. The most frequent complications were infectious in 22.4%, followed by 17.7% of neurological complications, with other complications, such as thromboembolism, immobility and miscellaneous, being much less frequent. Regression analysis showed that stroke severity (RR=1.76; 95%CI:1.09-2.86) and albumin greater than 3.5 mg/dL (RR=0.53; 95%CI: 0.36-0.79) were independent risk factors for the presence of in-hospital complications.

Conclusions: A high rate of in-hospital complications were observed, among which infectious and neurological complications were the most frequent. Stroke severity was a risk factor and albumin greater than 3.5 mg/dL was a protective factor for the incidence of in-hospital complications. These results can serve as a starting point for establishing stroke care systems that consider differentiated flows for the prevention of in-hospital complications.

Keywords: Stroke, Acute; Ischemic Stroke; Complications; Risk Factors (Source: MeSH).

Introduction

Stroke is one of the leading causes of disability and mortality worldwide [1]. This condition more seriously affects low- and middle-income countries, generating, according to international reports, a high health cost, not only due to hospital expenses but also due to the indirect expenses that it entails in the long term, such as those related to the loss of work of the patient [2],[3],[4].

Previous studies in Europe and Asia have described incidences of in-hospital complications greater than 40% in patients admitted with stroke [5],[6]. In addition, it has been reported that part of the disability and mortality associated with stroke is sustained by the presence of in-hospital complications, many of which could be preventable [6]. Therefore, some measures have been proposed, such as the optimization of comprehensive care protocols and training related to preventive care and timely management of complications for all health personnel involved in the care of patients with stroke [7].

In Latin America, where most countries are low- and middle-income, there may be differences in the rate of in-hospital complications compared to what is reported in other regions. Few studies are available and most provide partial data, reporting only non-neurological complications and their predictive factors [8],[9]. The main objective of this study was to determine the risk factors for in-hospital complications in patients with acute ischemic stroke treated at a national reference hospital in Peru. This article was written following the STROBE guidelines for observational studies [10].

Methods

Design and population

We conducted a retrospective study of a cohort of patients treated at an essential stroke center belonging to the social security system in Lima, Peru. The Edgardo Rebagliati Martins National Hospital is a national reference hospital with resolution capacity for intravenous reperfusion treatment.

The population included all patients over 18 years of age admitted to the emergency department (ED) with a diagnosis of acute ischemic stroke during the period from January 1 to September 30, 2021. The information of the patients enrolled was obtained from the data recorded in the clinical history during hospitalization (from admission to the ED until discharge or death). A diagnosis of acute ischemic stroke was given to patients with acute neurological deficit confirmed by neuroimaging (tomography or cerebral magnetic resonance) and with a maximum stroke-gate time of 72 hours. A total of 215 patients attended the ED with this diagnosis during the study period; of these, we excluded 23 patients diagnosed with COVID-19 at admission or during hospitalization, leaving 192 patients for data analysis.

Variables

In-hospital complications were defined as medical problems arising during hospital stay according to clinical definitions [5],[6]. We made an adaptation of the previously used classification, and the complications were classified as neurological (seizures, recurrent stroke, hemorrhagic transformation, intracranial hypertension and unexplained events), infectious (thoracic, urinary or other infection), thromboembolism (pulmonary and deep vein thrombosis), immobility complications (pressure ulcers and falls) and miscellaneous (not classified in the previous categories). Due to the retrospective design, we did not include pain or psychological complications, because they were not reported in the medical record.

We evaluated demographic variables such as age, sex, level of education, toxic habits (alcohol, smoking and drug use), previous medication for cardiovascular disease as well as the most prevalent pathological antecedents including high blood pressure, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, chronic heart disease, cardiac arrhythmia, autoimmune disease, chronic lung disease, malignant neoplasm, cerebrovascular disease, thyroid disease, obstructive sleep area syndrome, and chronic liver disease. Based on previous comorbidities, the age adjusted Charlson comorbidity index (CCI) [11] was also used.

Regarding clinical variables, the following were determined: baseline status (estimated by the "modified Rankin scale", mRS at admission) [12], vital functions at admission (heart rate, systolic and diastolic blood pressure) and the clinical picture presented in the patient. We recorded the severity of acute ischemic stroke at ED admission and at discharge estimated by the "National Institutes of Health Stroke Scale" (NIHSS) and divided into groups: mild (0-4), moderate (5-15), severe (16-25) and very severe (>25)[13]. We used the etiological classification of the "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) for cerebral infarction [14].

The following laboratory tests were performed at admission (carried out in the first 72 hours of admission): capillary glycemia test, hemoglobin (Hb), leukocytes, neutrophil/lymphocyte ratio (NLR), lactate dehydrogenase (LDH), total protein, albumin, C-reactive protein (CRP) and D-dimers. Imaging

studies were performed to determine the presence of previous vascular lesions, cerebral vascular territory (supratentorial and infratentorial), laterality, leukoaraiosis, microbleeding, early signs of stroke and hemorrhagic transformation. Treatment variables included intravenous reperfusion, surgical treatment, and the type of secondary prevention treatment (single/dual antiplatelet therapy or anticoagulation).

During follow-up, admission to the intermediate care unit, intensive care unit (ICU), functional outcome (good, mRS 0-2 and poor, mRS 3-6) and the destination of the patient (discharge or death) were recorded.

Statistical analysis

The information was recorded and stored anonymously in a database to protect confidentiality and was only accessible by the principal investigator. Subsequently, the database was exported to the STATA v17 program. To summarize the categorical variables, frequencies and percentages were used, while for the quantitative variables, measures of central tendency and dispersion were used depending on the distribution of the data.

To evaluate the associations between in-hospital complications and sociodemographic, clinical, and paraclinical variables, hypothesis tests were performed according to the nature of the independent variables. The Chi-square test was used for categorical variables, while the Student's t test or Mann-Whitney U test was used for quantitative variables.

Finally, the effect size (relative risk and 95% confidence intervals) was estimated by creating Poisson regression models with robust variance. Crude models were constructed in the bivariate analysis considering the following factors: age, sex, history of stroke, baseline status (independent, mRS 0-2 and dependent, mRS 3-5), use of previous medication for cardiovascular disease, presence of previous comorbidity, CCI (low, 0-4 and high, greater than 4), vital functions on admission, clinical picture, severity of stroke (non-severe, 0-10 and severe, greater than 10), length of stay in the ED and laboratory tests (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP, and D-dimer).

The multivariate analysis was adjusted for age, sex and risk factors for stroke (hypertension, diabetes, history of stroke). In addition, a parsimonious model was constructed, performing a nesting model among the variables that were statistically significant in the crude analysis model. The assumption of linearity was evaluated when constructing the models and, additionally, lost data among the variables and collinearity were evaluated in the adjusted models. A statistical significance level of 0.05 was used for all the statistical tests.

Ethical issues

In the present study, only the researchers had access and reviewed the clinical histories, then, there was no direct contact with the patients. The study was carried out in accordance with the Declaration of Helsinki, and the authors ensured anonymity of the patient data included in the study. In addition, the research protocol was approved by the Ethics Committee of the hospital (Letter No. 964 -GRPR - ESSALUD-2021) and the Ethics Committee of the Universidad Científica del Sur (Letter No. 404-CIEI-CIENTÍFICA-2021).

Results

Demographic characteristics of the participants

During the study period, we included 192 patients diagnosed with acute ischemic stroke. The mean age was 71.7 ± 11.9 years, 16.2% of the patients were under 60 years of age, and 64.6% were male. In addition, 74.3% of the patients presented at least one previous comorbidity in the clinical history, and the most frequent was arterial hypertension (67.2%) and diabetes mellitus (30.7%). We found that 36.1% of the patients reported no prior medication for cardiovascular disease, while 57.3% used antihypertensive drugs and 21.4% antiplatelet therapy. Further details of the demographic characteristics of the patients are shown in Table 1.

Clinical characteristics of the study sample

Among the admitted patients, 95.3% had a baseline status of functional independence. The most frequent initial symptoms at admission were limb weakness (75.8%) and dysarthria (49.2%). Disease severity was mild in 26% of the patients, being moderate in 54.2%, severe in 18.2% and very severe in 1.6%. Regarding the etiological classification, 39.1% were reported as long-artery atherosclerosis, 25% cardioembolic, 22.9% lacunar, 2.1% had infrequent causes, and 10.9% had an undetermined etiology. Neuroimaging findings showed that 83.8% corresponded to the supratentorial territory, while the middle cerebral artery was the most reported vascular territory and 31.2% had some degree of leukoaraiosis. With respect to treatment, of the 24 patients (12.5%) admitted within the therapeutic window (stroke-door time of up to 4.5 hours), only 5 patients (2.6%) received acute treatment with recombinant tissue plasminogen activator (rtPA) as prevention strategies. Secondary antiplatelet therapy or anticoagulation was used according to the etiological classification.

In relation to the clinical evolution of the patients, 60 (31.2%) were admitted to an intermediate care unit and 6 (3.1%) to an ICU. The median stay in the ED before admission to a neurological unit was 2 days (interquartile range [IQR], 1-3 days) and the median hospital stay was 15 days (IQR, 10-23 days). As a clinical outcome, a mortality of 6.2% was reported. Regarding functional results, 49.5% of the total number of patients admitted to the study were functionally dependent; the 5 patients who received rtPA were functionally independent. Table 2 shows the clinical and imaging characteristics of the patients studied.

In-hospital complications

During hospitalization, at least one in-hospital complication occurred in 32.3% of patients. Regarding the types of complications, the most frequent were infectious in 22.4% (thoracic 15.1% and urinary 7.3%), followed by 17.7% of neurological complications (recurrent stroke 1.6%, epileptic seizures 1.6%, 5.3% hemorrhagic transformation, intracranial hypertension 3.6% and unexplained events 7.3%), while other complications, such as thromboembolism (deep vein thrombosis 0.5%), immobility (pressure ulcers 5.2%) and miscellaneous (minor bleeding 1%, major bleeding 1.6%, acute renal failure 7.3%, hydroelectrolytic disorder 2.6%) were much less frequent. The coexistence of the 2 most frequent types of complications (neurological and infectious) was reported in 12 patients (6.25%).

When comparing the clinical, demographic and laboratory characteristics of the patients with acute

ischemic stroke presenting in-hospital complications with the group without complications, there were significant differences in age (age difference between complicated versus uncomplicated was 4.52 years; $p=0.013$), the presence of at least one comorbidity (34.9% comorbidity and complication versus 13.0% in not comorbidity and complication; $p=0.035$), high CCI (5 or more have 42.3% with complication; $p=0.008$), previous use of antiarrhythmics ($p=0.001$), severity of stroke according to an NIHSS >10 ($p=0.002$), etiological classification of stroke ($p=0.006$) and in all laboratory tests at admission (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP and D-dimer).

Significant differences were found in the following variables in the exploratory analysis by type of complication in patients with neurological complications: systolic blood pressure at admission (lower systolic blood pressure presented a higher percentage of neurological complications compared to higher 185 mmHg 20.5 vs. 4.0; $p=0.047$), previous use of antiarrhythmics ($p=0.001$), longer ED stay ($p=0.01$), stroke severity according to the NIHSS >10 ($p=0.007$), etiological classification of stroke ($p=0.005$), headache ($p=0.004$), dysarthria ($p=0.011$) and only Hb, leukocyte and CRP values were significant. Regarding infectious complications, significant differences were found in patients with a history of previous medication ($p=0.010$), use of antihypertensive drugs ($p=0.04$), and hypoalbuminemia ($p=0.043$) (Tables 3-5).

Risk factors for in-hospital complications in the bivariate analysis

When evaluating associations with Poisson regression models, a CCI >4 was found to increase the risk of presenting an in-hospital complication by 74% (relative risk [RR]: 1.74; 95% confidence interval [CI]: 1.15 - 2.65). In addition, patients with a NIHSS >10 at admission had a 1.90-fold (95% CI: 1.25 - 2.9) greater risk of presenting an in-hospital complication compared to those with a lower NIHSS. All the laboratory tests presented statistically significant results in the crude analysis (Table 6).

An exploratory analysis was made according to the most frequent types of complications: neurological and infectious. Regarding neurological complications, patients with a NIHSS >10 at admission had a 2.36-fold (95% CI: 1.24 - 4.49) greater risk of presenting a neurological complication compared to those with a lower NIHSS. Hb, leukocyte and CRP values were statistically significant. In the crude analysis of infectious complications, patients with a history of previous medication had a 2.37-fold higher risk (95% CI: 1.16 - 4.83) of presenting some type of infectious complication and albumin levels >3.5 mg/dL was a protective factor, decreasing the risk by 49% (95% CI: 0.28 - 0.94) (Table 7).

Risk factors for in-hospital complications in the multivariate analysis

In the multivariate analysis for in-hospital complications, stroke severity retained the association but decreased in strength from 1.9 to 1.76. (RR=1.76; 95% CI, 1.09-2.86; $p=0.022$) and albumin levels >3.5 mg/dL which went from 0.45 to 0.53 (RR=0.53; 95% CI, 0.36-0.79; $p=0.002$) were maintained after adjusting for age, sex and stroke risk factors (Table 8).

In the exploratory analysis by type of complication, Hb (RR=0.86; 95% CI, 0.73-0.99; $p=0.047$) was a statistically significant protective factor for neurological complications, while in the analysis of infectious complications, all factors except for the history of prior medication for cardiovascular disease lost statistical significance (RR=2.79; 95% CI, 1.16-6.71; $p=0.022$), after adjusting for the confounders

(Table 9).

Discussion

The main objective of this study was to estimate the risk factors for in-hospital complications in patients with acute ischemic stroke hospitalized in a national reference hospital in Peru. As main findings, we found that approximately one in three patients presented in-hospital complications (32.3%) and the severity of the acute ischemic stroke defined by an NIHSS scale > 10 was a risk factor and an albumin level > 3.5 mg/dL was a protective factor for the development of in-hospital complications.

The frequency of in-hospital complications in the present study was lower than that reported by Pandian *et al.* in India (45.9%) and by Langhorne *et al.* in Scotland (85%), although these studies included patients with both ischemic and hemorrhagic stroke. They also considered pain and psychological complications [5],[6]. Our study only included patients with acute ischemic stroke, as we consider that the clinical outcomes of patients with ischemic and hemorrhagic stroke could be heterogeneous [15]. In recent years, there has been a downward trend in the reporting of in-hospital complications, probably due to the optimization of stroke care in the different health systems. Although the highest mortality and disability rates are reported in Latin America and in many low- and middle-income countries [2], in recent years there have been joint efforts to improve this situation in this part of the world [16],[17].

In the present study approximately 1 in 5 patients (22.4%) presented an infectious complication. This is consistent with what has been described in studies conducted in India, Scotland, and Argentina, in which infectious complications were the most frequent, with incidences of 34.4%, 65%, and 20%, respectively [5],[6],[9].

These findings are important, since most of the infectious complications are of the respiratory and urinary tract type, and these can be prevented with adequate education and training of the medical, nursing and technical personnel involved in the care of patients with stroke [18],[19].

In the present study and others, the severity of stroke (NIHSS > 10) has shown to be an important risk factor [6],[8],[9]. This finding can be explained by the fact that the patients with greater stroke severity require different care and greater in-hospital monitoring which may lead to a higher risk of presenting complications during hospitalization. It is therefore important for patients admitted for stroke to be evaluated or admitted early to a stroke or neurological care unit if there is no physical space available in the ED [20],[21]. In the case of our patients, the median stay in the ED was 2 days, which reflects the prompt referral to a neurological care unit.

Another finding in the present study was that albumin levels > 3.5 mg/dL were found to be a protective factor for in-hospital complications. This marker was previously explored by Pandian *et al.* who found an association in the bivariate analysis but without statistical significance in the multivariate analysis [6]. The most plausible explanation is that serum albumin levels are a laboratory sign of the nutritional status of patients, and thus, patients with low albumin levels would have a higher risk of hospital complications and a worse prognosis as seen in similar pathologies [22],[23]. In the exploratory analysis of the risk factors for the most frequent in-hospital complications (neurological and infectious), statistical significance was obtained for Hb as a protective factor for neurological complications, which, unlike previous studies in which the variable of anemia was

considered, we believe Hb values should be analyzed as a numerical variable. Previous articles have shown that the presence of anemia increases the risk of mortality in patients with stroke and is a risk

factor for in-hospital complications [6],[24]. Although the mechanism for this has yet to be defined, it has been postulated that the decrease in oxygen supply in patients with anemia in a state of stress caused by the stroke, which requires an increase in oxygen levels, could predispose these patients to medical complications [6]. The history of prior medication for cardiovascular disease was a risk factor for the presence of infectious complications. This result can be explained in that the history of receiving previous medication is related to the severity of these comorbidities, which could condition the patients to presenting greater susceptibility to infectious processes, such as those reported in the present cohort. Regarding clinical outcomes, the in-hospital mortality in the present study was 6.2%. This value is lower than that reported in previous articles in Peru [25], [26], [27], [28], such as the study carried out by Castañeda *et al.* in which a mortality of 13.6% was reported in patients with acute ischemic stroke admitted to a public hospital of national reference in the period 2000-2009. These findings are consistent with more recent data obtained in other Latin American countries which reported a decrease in hospital mortality due to stroke likely explained by the improvements in the care of these patients in recent years [29],[30].

Our study also showed that almost half of the patients had a poor functional prognosis at discharge. However, the 5 patients who received intravenous reperfusion treatment in the acute stage achieved functional independence. This could be associated with a lower frequency of in-hospital complications; although this effect was not measured in our study, since it has already been shown that intravenous and mechanical reperfusion therapies are cost-effective strategies for reducing mortality, complications, and disability in patients with stroke [31],[32],[33].

This study has some limitations. Since the data were obtained from medical records, some laboratory variables were not available (CGT, LDH, D-dimer), and thus, certain variables could not be included in the multivariate regression models. The study was carried out with the main objective of estimating the risk factors for in-hospital complications, therefore the lack of statistical significance in the analyses of the most frequent types of complications may have been due to a purely statistical and not an epidemiological problem. Likewise, the follow-up period was limited to the time of hospitalization and did not allow analyses of association with the functional prognosis after hospital discharge.

Despite the above limitations, this study has some strengths. A significant number of patients was included because the study was performed in a national reference hospital. In addition, a complete analysis of different risk factors with global complications was carried out and factors were explored according to the most frequent types. Likewise, complete data of most of the variables were available due to adequate registration using the electronic medical record system.

Conclusions

In conclusion, this cohort study reports a high rate of in-hospital complications in patients presenting to the ED with stroke, among which infectious and neurological complications were of note as the most frequent. Stroke severity was a risk factor and albumin levels > 3.5 mg/dL were a protective factor for the incidence of in-hospital complications in patients with acute ischemic stroke. Further studies are needed to confirm these results and develop stroke care systems that consider these markers

to provide deferred care with stricter monitoring and prevention of hospital complications.

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Table 1. Demographic characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Sex		
Female	68	35.4
Male	124	64.6
Age (years)		
30 to 59	31	16.2
60 to 70	50	26
≥71	111	57.8
Baseline status		
Independent (mRS:0-2)	183	95.3
Dependent (mRS:3-5)	9	4.7
Comorbidities		
None	50	25.7
At least 1	142	74.3
Hypertension	129	67.2
Diabetes mellitus	59	30.7
Chronic kidney disease	12	6.3
Chronic coronary disease	14	7.3
Epilepsy	10	5.2
History of previous stroke		
None	154	80.2
Hemorrhagic stroke	2	1
Ischemic stroke	35	18.2
CCI		
0	9	4.7
1 to 2	26	13.5
3 to 4	72	37.5
5 or more	85	44.3
Previous medication		
No	69	36.1
Yes	122	63.9
Antihypertensive	110	57.3
Antiplatelet therapy	41	21.4
Statins	30	15.6
Antiarrhythmics	34	17.7
Warfarin	10	5.2

Abbreviations: mRS: Modified Rankin Scale; CCI: age adjusted Charlson comorbidity index.

Table 2. Clinical and imaging characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Stroke severity (NIHSS admission)		
I (0 to 4)	50	26
II (5 to 15)	104	54.2
III (16 to 25)	35	18.2
IV (26 or more)	3	1.6
Stroke symptom		
Limb weakness	144	75.8
Dysarthria	94	49.2
Headache	39	20.4
Aphasia	30	15.7
Ataxia	28	14.7
Etiological classification		
Large vessel atherothrombotic	75	39.1
Lacunar	44	22.9
Cardioembolic	48	25
Uncommon causes	4	2.1
Undetermined etiology	21	10.9
Neuroimaging findings		
Cerebral vascular territory		
Infratentorial	31	16.2
Supratentorial	161	83.8
Affected cerebral artery		
MCA	121	63
ACA	3	1.6
PCA	10	5.2
VB	29	15.1
2 or more territories	29	15.1
Imaging laterality		
Left	104	54.2
Right	88	45.8
Leukoaraiosis	59	31.2
Microbleeding	7	3.7
Early signs of stroke	8	4.2
Treatment received		
Thrombolysis	5	2.6
Simple antiplatelet therapy	111	57.8
Dual antiplatelet therapy	7	3.6
Anticoagulation	43	22.4
Statins	141	73.8
Intermediate care unit admission	60	31.2
ICU admission	6	3.1
In-hospital complication	62	32.3
NIHSS at discharge		
I (0 to 4)	52	28.9
II (5 to 15)	101	56.1
III (16 to 25)	26	14.4
IV (26 or more)	1	0.6
NIHSS discharge in patients with thrombolysis		
I (0 to 4)	1	20
II (5 to 15)	4	80
Rankin at discharge		
Independent (mRS:0-2)	85	44.3
Dependent (mRS:3-5)	95	49.5
Death	12	6.2

Abbreviations: MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory; ICU: Intensive Care Unit; mRS: Modified Rankin Scale.

Table 3. Comparison of in-hospital complications and type of complication according to the demographic characteristics of patients with acute ischemic stroke.

variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Age	74.74 (10.7)	70.22 (12.19)	0.013	73.5 (14.4)	71.3 (11.3)	0.407	73.1 (11.3)	71.2 (12.1)	0.373
Sex									
Female	18 (26.5)	50 (73.5)	0.201	14 (20.6)	54 (79.4)	0.439	15 (22.4)	52 (77.6)	0.922
Male	44 (35.5)	80 (64.5)		20 (16.1)	104 (83.9)		27 (21.8)	97 (78.2)	
Stroke history									
No	52 (33.5)	103 (66.5)	0.446	28 (18.1)	127 (81.9)	0.791	36 (23.4)	118 (76.6)	0.345
Yes	10 (27.0)	27 (73.0)		6 (16.2)	31 (83.8)		6 (16.2)	31 (83.8)	
Comorbidities									
No	3 (13.0)	20 (90.0)	0.035	3 (13.0)	20 (87.0)	0.532	3 (13.0)	20 (87.0)	0.269
Yes	59 (34.9)	110 (65.1)		31 (18.3)	138 (81.7)		39 (23.2)	129 (76.8)	
CCI									
0 to 4	26 (24.3)	81 (75.5)	0.008	15 (14.0)	92 (86.0)	0.133	19 (17.8)	88 (82.2)	0.111
5 or more	36 (42.3)	49 (57.7)		19 (22.4)	66 (77.6)		23 (27.4)	61 (72.6)	
Previous medication									
No	21 (30.4)	48 (69.6)	0.653	15 (21.7)	54 (78.3)	0.285	8 (11.8)	60 (88.2)	0.010
Yes	41 (33.6)	81 (66.4)		19 (15.8)	103 (84.4)		34 (27.9)	88 (72.1)	
Antiplatelet therapy									
No	48 (31.8)	103 (68.2)	0.775	27 (17.9)	124 (82.1)	0.904	30 (20.0)	120 (80.0)	0.204
Yes	14 (34.2)	27 (65.8)		7 (17.0)	34 (83.0)		12 (29.3)	29 (70.7)	
Warfarin									
No	57 (31.3)	125 (68.7)	0.219	33 (18.1)	149 (81.9)	0.512	40 (22.1)	141 (77.9)	0.876
Yes	5 (50.0)	5 (50.0)		1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
Statins									
No	52 (32.1)	110 (67.9)	0.894	28 (17.3)	134 (82.7)	0.72	33 (20.5)	128 (79.5)	0.249
Yes	10 (33.3)	20 (66.7)		6 (20.0)	24 (80.0)		9 (30.0)	21 (70.0)	
NOAC									
No	61 (32.5)	127 (67.5)	0.753	32 (17.0)	156 (83.0)	0.087	41 (21.9)	146 (78.1)	0.883
Yes	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)		1 (25.0)	3 (75.0)	
Antihypertensive									
No	28 (34.2)	54 (65.8)	0.635	18 (21.9)	64 (78.1)	0.184	12 (14.8)	69 (85.2)	0.040
Yes	34 (30.9)	76 (69.1)		16 (14.5)	94 (84.5)		30 (27.3)	80 (72.7)	
Anti-arrhythmic									
No	43 (27.2)	115 (72.8)	0.001	21 (13.3)	137 (86.7)	0.001	32 (20.4)	125 (79.6)	0.249
Yes	19 (55.9)	15 (44.1)		13 (38.2)	21 (61.8)		10 (29.4)	24 (70.6)	
Immunosuppressants									
No	60 (32.3)	126 (67.7)	0.956	32 (17.2)	154 (82.8)	0.308	40 (21.6)	145 (78.4)	0.495
Yes	2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)	
Emergency stay*‡	2 (1-3)	2 (1-2)	0.105	2 (1 - 2)	2 (1- 2)	0.010	2 (1- 3)	2 (1 - 2)	0.051

Abbreviations: CCI: age adjusted Charlson comorbidity index; NOAC: Novel oral anticoagulants.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and ‡ Mann-Whitney U test.

Table 4. Comparison of in-hospital complications and type of complication according to the clinical characteristics and imaging findings of patients with acute ischemic stroke.

Variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
SBP (mmHg)									
<=185	50 (31.1)	111 (68.9)	0.095	33 (20.5)	128 (79.5)	0.047	35 (21.9)	125 (78.1)	0.497
>185	12 (48.0)	13 (52.0)		1 (4.0)	24 (96.0)		7 (28.0)	18 (72.0)	
DBP (mmHg)									
<=110	62 (33.5)	123 (66.5)	0.478	34 (18.4)	151 (81.6)	0.635	41 (22.3)	143 (77.7)	0.064
>110	0 (0.0)	1 (100)		0 (0.0)	1(100.0)		1 (100.0)	0 (0.0)	
HR (beats/min)									
<=90	44 (31.2)	97 (68.8)	0.068	25 (17.7)	116 (82.3)	0.832	34 (24.1)	107 (75.9)	0.197
>90	15 (48.4)	16 (51.6)		5 (16.1)	26 (83.9)		4 (13.3)	26 (86.7)	
CGT (mg/dL)									
<=180	22 (33.9)	43 (66.1)	0.167	11 (16.9)	54 (83.1)	0.658	12 (18.5)	53 (81.5)	0.298
>180	1 (11.1)	8 (88.9)		1 (11.1)	8 (88.9)		3 (33.3)	6 (66.7)	
Severity of stroke (NIHSS)									
<=10	25 (23.2)	83 (76.8)	0.002	12 (11.1)	96 (88.9)	0.007	25 (23.2)	83 (76.8)	0.659
>10	37 (44.1)	47 (55.9)		22 (26.2)	62 (73.8)		17 (20.5)	66 (79.5)	
Baseline status									
Independent	60 (32.8)	123 (67.2)	0.508	33 (18.0)	150 (82.0)	0.595	40 (22.0)	142 (78.0)	0.986
Dependent	2 (22.2)	7 (77.8)		1 (11.1)	8 (88.9)		2 (22.2)	7 (77.8)	
Etiological classification									
Large vessel atherothrombotic	23 (30.7)	52 (69.3)	0.006	11 (14.7)	64 (85.3)	0.005	14 (18.7)	61 (81.3)	0.584
Lacunar	7 (15.9)	37 (84.1)		4 (9.1)	40 (90.9)		12 (27.9)	31 (72.1)	
Cardioembolic	23 (47.9)	25 (52.1)		17 (35.4)	31 (64.6)		12 (25.0)	36 (75.0)	
Uncommon causes	3 (75.0)	1 (25.0)		0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	
Undetermined etiology	6 (28.6)	15 (71.4)		2 (9.5)	19 (90.5)		4 (19.1)	17 (80.9)	
Limb weakness									
No	15 (32.6)	31 (67.4)	0.997	11 (23.9)	35 (76.1)	0.221	7 (15.2)	39 (84.8)	0.189
Yes	47 (32.6)	97 (67.4)		23 (16.0)	121 (84.0)		35 (24.5)	108 (75.5)	
Visual deficit									
No	58 (32.9)	118 (67.1)	0.736	31 (17.6)	145 (82.4)	0.720	41 (23.4)	134 (76.6)	0.158
Yes	4 (28.6)	10 (71.4)		3 (21.4)	11 (78.6)		1 (7.1)	13 (92.9)	
Aphasia									
No	50 (31.1)	111 (68.9)	0.337	28 (17.4)	133 (82.6)	0.732	37 (23.0)	124 (77.0)	0.493
Yes	12 (40.0)	18 (60.0)		6 (20.0)	24 (80.0)		5 (17.2)	24 (84.8)	
Headache									
No	52 (34.2)	100 (65.8)	0.308	21 (13.8)	131 (86.2)	0.004	33 (21.9)	118 (78.1)	0.870
Yes	10 (25.6)	29 (74.4)		13 (33.3)	26 (66.7)		9 (23.1)	30 (76.9)	

Epileptic seizures									
No	59 (32.1)	125 (67.9)	0.748	33 (17.9)	151 (82.1)	0.693	42 (23.0)	141 (77.0)	0.125
Yes	3 (37.5)	5 (62.5)		1 (12.5)	7 (87.5)		0 (0.0)	8 (100.0)	
Vertigo									
No	58 (32.9)	118 (67.1)	0.618	31 (17.6)	145 (82.4)	0.817	40 (22.9)	135 (77.1)	0.394
Yes	4 (26.7)	11 (73.3)		3 (20.0)	12 (80.0)		2 (13.3)	13 (86.7)	
Facial paralysis									
No	54 (32.9)	110 (67.1)	0.735	30 (18.3)	134 (81.7)	0.662	35 (21.5)	128 (78.5)	0.605
Yes	8 (29.6)	19 (70.4)		4 (14.8)	23 (85.2)		7 (25.9)	20 (74.1)	
Loss of sensation									
No	61 (34.1)	118 (65.9)	0.065	34 (19.0)	145 (81.0)	0.096	42 (23.6)	136 (76.4)	0.057
Yes	1 (8.3)	11 (91.7)		0 (0.0)	12 (100.0)		0 (0.0)	12 (100.0)	
Unsteady gait									
No	54 (33.1)	109 (66.9)	0.634	28 (17.2)	135 (82.8)	0.587	33 (20.4)	129 (79.6)	0.166
Yes	8 (28.6)	20 (71.4)		6 (21.4)	22 (78.6)		9 (32.1)	19 (67.9)	
Dysarthria									
No	32 (33.0)	65 (67.0)	0.874	24 (24.7)	73 (75.3)	0.011	18 (18.6)	79 (81.4)	0.229
Yes	30 (31.9)	64 (68.1)		10 (10.6)	84 (89.4)		24 (25.8)	69 (74.2)	
Cerebral vascular territory									
Infratentorial	10 (32.3)	21 (67.3)	0.997	3 (9.7)	28 (90.3)	0.201	7 (23.3)	23 (76.7)	0.847
Supratentorial	52 (32.3)	109 (67.3)		31 (19.3)	130 (80.8)		35 (21.7)	126 (78.3)	
Affected cerebral artery									
MCA	41 (33.9)	80 (66.1)	0.892	21 (17.4)	100 (82.6)	0.075	28 (23.3)	92 (76.7)	0.781
ACA	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)		0 (0.0)	3 (100.0)	
PCA	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
VB	7 (24.1)	22 (75.9)		2 (6.9)	27 (93.1)		5 (17.2)	24 (82.8)	
2 or more territories	10 (34.5)	19 (65.5)		6 (20.7)	23 (79.3)		6 (20.7)	23 (79.3)	
Imaging laterality									
Left	35 (33.7)	69 (66.4)	0.661	21 (20.2)	83 (79.8)	0.327	22 (21.2)	82 (78.9)	0.76
Right	27 (30.7)	61 (69.3)		13 (14.8)	75 (85.2)		20 (23.0)	67 (77.0)	
Leukoaraiosis									
No	38 (29.2)	92 (70.8)	0.12	22 (16.9)	108 (83.1)	0.571	30 (23.1)	100 (76.9)	0.717
Yes	24 (40.7)	35 (59.3)		12 (20.3)	47 (79.7)		12 (20.7)	46 (79.3)	

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CGT: capillary glycemia test; MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory.

We used the following statistical tests: chi2 test.

Table 5. Comparison of in-hospital complications and type of complication according to laboratory test results of patients with acute ischemic stroke.

Variable	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Hb (g/dL) †	12.7 (1.8)	13.6 (1.9)	0.003	12.4 (1.9)	13.5 (1.8)	0.035	13.3 (2.1)	13.3 (1.8)	0.946
Leukocytes (cells/μL)									
<5000	7 (50.0)	7 (50.0)	0.001	4 (28.6)	10 (71.4)	0.022	2 (14.3)	12 (85.7)	0.713
5000-12000	41 (27.3)	109 (72.7)		20 (13.3)	130 (86.7)		33 (22.0)	117 (78.0)	
>12000	11 (68.8)	5 (31.3)		6 (37.5)	10 (62.5)		4 (26.7)	11 (73.3)	
NLR									
<3	20 (22.7)	68 (77.3)	0.005	12 (13.6)	76 (86.4)	0.286	18 (20.5)	70 (79.5)	0.671
\geq 3	39 (42.4)	53 (57.6)		18 (19.6)	74 (80.4)		21 (23.1)	70 (76.9)	
LDH (IU/L)									
\leq 350	16 (25.8)	46 (74.2)	0.003	11 (17.7)	51 (82.3)	0.195	13 (21.0)	49 (79.0)	0.624
>350	12 (63.2)	7 (36.8)		6 (31.6)	13 (68.4)		5 (26.3)	14 (73.7)	
Total proteins (g/dL)									
\leq 6	15 (55.6)	12 (44.4)	0.011	6 (22.2)	21 (77.8)	0.549	8 (30.8)	18 (69.2)	0.293
>6	38 (29.9)	89 (70.1)		22 (17.3)	105 (82.7)		27 (21.3)	100 (78.7)	
Albumin (g/dL)									
\leq 3.5	14 (60.9)	9 (39.1)	0.002	6 (26.1)	17 (73.9)	0.192	9 (40.9)	13 (59.1)	0.043
>3.5	33 (27.5)	87 (72.5)		18 (15.0)	102 (85.0)		25 (20.8)	95 (79.2)	
CRP (mg/ dL)									
\leq 2	20 (20.6)	77 (79.4)	<0.001	11 (11.3)	86 (88.7)	0.001	20 (20.6)	77 (79.4)	0.422
>2	29 (63.0)	17 (37.0)		16 (34.8)	30 (65.2)		12 (26.7)	33 (73.3)	
D-dimer (μg/mL)									
\leq 1	6 (20.0)	24 (80.0)	0.012	4 (13.3)	26 (86.7)	0.203	9 (30.0)	21 (70.0)	0.518
>1	21 (48.8)	22 (51.2)		11 (25.6)	32 (74.4)		10 (23.3)	33 (76.7)	

Abbreviations: Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and † Student's t test.

Table 6. Bivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref		
Male	1.34	0.84 - 2.13	0.215
Age			
<=70	Ref.	0.86 - 2.05	0.203
>70	1.33		
Stroke history			
No	Ref.		
Yes	0.81	0.45 - 1.43	0.462
SBP (mmHg) (n=186)			
<=185	Ref.		
>185	1.55	0.97 - 2.47	0.069
HR (beats/min) (n=186)			
<=90	Ref.		
>90	1.55	0.99 - 2.40	0.051
CGT (mg/dL) (n=74)			
<=180	Ref		
>180	0.33	0.49 - 2.18	0.248
Comorbidities			
No	Ref		
Yes	2.68	0.91 - 7.87	0.073
CCI			
0 to 4	Ref		
5 or more	1.74	1.15 - 2.65	0.009
Previous medication			
No	Ref.		
Yes	1.1	0.71 - 1.71	0.656
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.9	1.25 - 2.90	0.003
Baseline status			
Independent	Ref.		
Dependent	1.02	0.81 - 1.29	0.841
Imaging laterality			
Left	Ref		
Right	0.91	0.60 - 1.38	0.662
Hb (g/dL)			
	0.86	0.78 - 0.94	0.001
Leukocytes (cells/μL) (n=180)			
5000-12000	Ref.		
<5000	1.83	1.02 - 3.29	0.044
>12000	2.52	1.65 - 3.84	<0.001
NLR (n=180)			
<3	Ref		
>=3	1.87	1.18 - 2.94	0.007
LDH (IU/L) (n=81)			
<=350	Ref.		
>350	2.45	1.42 - 4.23	0.001
Total Proteins (g/dL) (n=154)			
<=6	Ref.		
>6	0.54	0.35 - 0.83	0.005
Albumin (g/dL) (n=143)			
<=3.5	Ref		
>3.5	0.45	0.29 - 0.70	<0.001
CRP (mg/ dL) (n=143)			
<=2	Ref		
>2	3.06	1.95 - 4.80	<0.001
D-dimer (μg/mL) (n=73)			
<=1	Ref		

>1

2.44

1.12 - 5.35

0.026

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein; CI: confidence interval; RR: relative risk.

Table 7. Bivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref			Ref		
Male	0.78	0.42 - 1.45	0.438	0.97	0.56 - 1.67	0.922
Age						
<=70	Ref.			Ref.		
>70	1.18	0.63 - 2.22	0.61	1.33	0.75 - 2.33	0.327
Stroke history						
No	Ref.			Ref.		
Yes	0.90	0.40 - 2.01	0.793	0.69	0.32 - 1.53	0.363
SBP (mmHg)						
<=185	Ref.			Ref.		
>185	0.20	0.03 - 1.37	<0,001	1.28	0.64 - 2.57	0.487
HR (beat/min)						
<=90	Ref.			Ref.		
>90	0.91	0.38 - 2.19	0.833	0.55	0.21 - 1.45	0.227
CGT (mg/dL)						
<=180	Ref			Ref		
>180	0.66	0.09 - 4.56	0.67	1.81	0.62 - 5.23	0.276
Comorbidities						
No	Ref			Ref		
Yes	1.41	0.47 - 4.25	0.545	1.78	0.60 - 5.31	0.301
CCI						
0 to 4	Ref			Ref		
5 or more	1.59	0.86 - 2.95	0.138	1.54	0.90 - 2.64	0.114
Previous medication						
No	Ref.			Ref.		
Yes	0.72	0.39 - 1.32	0.285	2.37	1.16 - 4.83	0.018
Stroke severity (NIHSS)						
<=10	Ref.			Ref.		
>10	2.36	1.24 - 4.49	0.009	0.88	0.51 - 1.53	0.661
Baseline status						
Independent	Ref.			Ref.		
Dependent	0.61	0.09 - 4.03	0.613	1.01	0.29 - 3.55	0.986
Imaging laterality						
Left	Ref			Ref		
Right	0.73	0.39 - 1.38	0.333	1.09	0.64 - 1.86	0.761
Hb (g/dL)						
0.8	0.70 - 0.91	0.001		0.99	0.85 - 1.17	0.95
Leukocytes (cells/μL)						
5000-12000	Ref.			Ref.		
<5000	2.15	0.85 - 5.41	0.107	0.65	0.17 - 2.43	0.522
>12000	2.81	1.32 - 5.98	0.007	1.21	0.50 - 2.96	0.673
NLR						
<3	Ref			Ref		
>=3	1.43	0.73 - 2.81	0.292	1.13	0.65 - 1.97	0.672
LDH (IU/L)						
<=350	Ref.			Ref.		
>350	1.78	0.76 - 4.19	0.187	1.26	0.51 - 3.09	0.621
Total proteins (g/dL)						
<=6	Ref.			Ref.		
>6	0.78	0.35 - 1.74	0.544	0.69	0.35 - 1.35	0.279
Albumin (g/dL)						
<=3.5	Ref			Ref		
>3.5	0.58	0.26 - 1.30	0.182	0.51	0.28 - 0.94	0.031
CRP (mg/ dL)						
<=2	Ref			Ref		
>2	3.08	1.55 - 6.09	0.001	1.29	0.69 - 2.42	0.419

D-dimer (µg/mL)

<=1	Ref			Ref		
>1	1.92	0.67 - 5.50	0.225	0.78	0.36 - 0.68	0.52

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein. CI: confidence interval; RR: relative risk.

Table 8. Multivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref.		
Male	1.25	0.75 - 2.10	0.393
Age	1.02	0.99 - 1.04	0.086
Hypertension			
No	Ref.		
Yes	0.66	0.40-1.07	0.094
Diabetes			
No	Ref.		
Yes	1.06	0.65-1.72	0.82
Stroke history			
No	Ref.		
Yes	0.93	0.46 - 1.86	0.846
HR (beat/min)			
<=90	Ref.		
>90	1.41	0.88 - 2.27	0.153
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.76	1.09 - 2.86	0.022
NLR			
<3	Ref.		
>=3	1.29	0.8 - 2.08	0.295
Albumin (g/dL)			
<=3.5	Ref.		
>3.5	0.53	0.36 - 0.79	0.002

Multivariate analysis obtained with Poisson regression, parsimonious model. Abbreviations: NLR: neutrophil/lymphocyte ratio; CI: confidence interval; RR: relative risk.

Table 9. Multivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref.			Ref.		
Male	0.88	0.39 - 2.00	0.768	0.89	0.49 - 1.61	0.69
Age	0.99	0.95 - 1.03	0.655	1.01	0.99 - 1.04	0.33
Hypertension						
No	Ref.			Ref.		
Yes	0.88	0.40 - 1.98	0.772	0.97	0.52 - 1.83	0.931
Diabetes						
No	Ref.			Ref.		
Yes	0.76	0.35 - 1.67	0.502	0.95	0.50 - 1.82	0.877
Stroke history						
No	Ref.			Ref.		
Yes	1.14	0.49 - 2.64	0.763	0.67	0.25 - 1.75	0.411
Previous medication						
No				Ref.		
Yes	-			2.79	1.16-6.71	0.022
Stroke severity (NIHSS)						
<=10	Ref.					
>10	1.56	0.72 - 3.40	0.26	-		
Hb (g/dL)	0.86	0.73 - 0.99	0.047	-		
CRP (mg/ dL)						
<=2	Ref.					
>2	2.49	0.97 - 6.38	0.057	-		
Albumin (g/dL)						
<=3.5				Ref.		
>3.5	-			0.67	0.35 - 1.28	0.225

Abbreviations: Hb: hemoglobin; CRP: C-reactive protein.

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Risk factors for in-hospital complications in patients with acute ischemic stroke: retrospective cohort in a national reference hospital in Peru

Abstract

Objective: To describe the clinical and demographic characteristics of patients with acute cerebral infarction treated at a national reference hospital in Peru and determine the risk factors for in-hospital complications.

Methods: We conducted a retrospective cohort study including 192 patients with acute ischemic stroke in a national reference hospital in Peru from January to September 2021. Clinical, demographic and paraclinical information was recorded from medical records. We estimated risk ratios and 95% confidence intervals using regression models with Poisson family and robust variance for the bivariate and multivariate model, adjusting for age, sex and risk factors for stroke.

Results: At least one in-hospital complication occurred in 32.3% of the patients. The most frequent complications were infectious in 22.4%, followed by 17.7% of neurological complications, with other complications, such as thromboembolism, immobility and miscellaneous, being much less frequent. Regression analysis showed that stroke severity (RR=1.76; 95%CI:1.09-2.86) and albumin greater than 3.5 mg/dL (RR=0.53; 95%CI: 0.36-0.79) were independent risk factors for the presence of in-hospital complications.

Conclusions: A high rate of in-hospital complications were observed, among which infectious and neurological complications were the most frequent. Stroke severity was a risk factor and albumin greater than 3.5 mg/dL was a protective factor for the incidence of in-hospital complications. These results can serve as a starting point for establishing stroke care systems that consider differentiated flows for the prevention of in-hospital complications.

Keywords: Stroke, Acute; Ischemic Stroke; Complications; Risk Factors (Source: MeSH).

Introduction

Stroke is one of the leading causes of disability and mortality worldwide ¹. This condition more seriously affects low- and middle-income countries, generating, according to international reports, a high health cost, not only due to hospital expenses but also due to the indirect expenses that it entails in the long term, such as those related to the loss of work of the patient ²⁻⁴.

Previous studies in Europe and Asia have described incidences of in-hospital complications greater than 40% in patients admitted with stroke^{5,6}. In addition, it has been reported that part of the disability and mortality associated with stroke is sustained by the presence of in-hospital complications, many of which could be preventable⁶. Therefore, some measures have been proposed, such as the optimization of comprehensive care protocols and training related to preventive care and timely management of complications for all health personnel involved in the care of patients with stroke ⁷.

In Latin America, where most countries are low- and middle-income, there may be differences in the rate of in-hospital complications compared to what is reported in other regions. Few studies are available and most provide partial data, reporting only non-neurological complications and their predictive factors^{8,9}. The main objective of this study was to determine the risk factors for in-hospital complications in patients with acute ischemic stroke treated at a national reference hospital in Peru. This article was written following the STROBE guidelines for observational studies¹⁰.

Methods

Design and population

We conducted a retrospective study of a cohort of patients treated at an essential stroke center belonging to the social security system in Lima, Peru. The Edgardo Rebagliati Martins National Hospital is a national reference hospital with resolution capacity for intravenous reperfusion treatment.

The population included all patients over 18 years of age admitted to the emergency department (ED) with a diagnosis of acute ischemic stroke during the period from January 1 to September 30, 2021. The information of the patients enrolled was obtained from the data recorded in the clinical history during hospitalization (from admission to the ED until discharge or death). A diagnosis of acute ischemic stroke was given to patients with acute neurological deficit confirmed by neuroimaging (tomography or cerebral magnetic resonance) and with a maximum stroke-gate time of 72 hours. A total of 215 patients attended the ED with this diagnosis during the study period; of these, we excluded 23 patients diagnosed with COVID-19 at admission or during hospitalization, leaving 192 patients for data analysis.

Variables

In-hospital complications were defined as medical problems arising during hospital stay according to clinical definitions^{5,6} and were classified as neurological (seizures, recurrent stroke, hemorrhagic transformation, intracranial hypertension and unexplained events), infectious (thoracic, urinary or other infection), thromboembolism (pulmonary and deep vein thrombosis), immobility complications (pressure ulcers and falls) and miscellaneous (not classified in the previous categories).

We evaluated demographic variables such as age, sex, level of education, toxic habits (alcohol, smoking and drug use), previous medication for cardiovascular disease as well as the most prevalent pathological antecedents including high blood pressure, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, chronic heart disease, cardiac arrhythmia, autoimmune disease, chronic lung disease, malignant neoplasm, cerebrovascular disease, thyroid disease, obstructive sleep area syndrome, and chronic liver disease. Based on previous comorbidities, the age adjusted Charlson comorbidity index (CCI)¹¹ was also used.

Regarding clinical variables, the following were determined: baseline status (estimated by the "modified Rankin scale", mRS at admission)¹², vital functions at admission (heart rate, systolic and diastolic blood pressure) and the clinical picture presented in the patient. We recorded the severity of acute ischemic stroke at ED admission and at discharge estimated by the "National Institutes of Health Stroke Scale" (NIHSS) and divided into groups: mild (0-4), moderate (5-15), severe (16-25) and very severe (>25)¹³. We used the etiological classification of the "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) for cerebral infarction¹⁴.

The following laboratory tests were performed at admission (carried out in the first 72 hours of admission): capillary glycemia test, hemoglobin (Hb), leukocytes, neutrophil/lymphocyte ratio (NLR), lactate dehydrogenase (LDH), total protein, albumin, C-reactive protein (CRP) and D-dimers. Imaging studies were performed to determine the presence of previous vascular lesions, cerebral vascular territory (supratentorial and infratentorial), laterality, leukoaraiosis, microbleeding, early signs of stroke and hemorrhagic transformation. Treatment variables included intravenous reperfusion, surgical

treatment, and the type of secondary prevention treatment (single/dual antiplatelet therapy or anticoagulation).

During follow-up, admission to the intermediate care unit, intensive care unit (ICU), functional outcome (good, mRS 0-2 and poor, mRS 3-6) and the destination of the patient (discharge or death) were recorded.

Statistical analysis

The information was recorded and stored anonymously in a database to protect confidentiality and was only accessible by the principal investigator. Subsequently, the database was exported to the STATA v17 program. To summarize the categorical variables, frequencies and percentages were used, while for the quantitative variables, measures of central tendency and dispersion were used depending on the distribution of the data.

To evaluate the associations between in-hospital complications and sociodemographic, clinical, and paraclinical variables, hypothesis tests were performed according to the nature of the independent variables. The Chi-square test was used for categorical variables, while the Student's t test or Mann-Whitney U test was used for quantitative variables.

Finally, the effect size (relative risk and 95% confidence intervals) was estimated by creating Poisson regression models with robust variance. Crude models were constructed in the bivariate analysis considering the following factors: age, sex, history of stroke, baseline status (independent, mRS 0-2 and dependent, mRS 3-5), use of previous medication for cardiovascular disease, presence of previous comorbidity, CCI (low, 0-4 and high, greater than 4), vital functions on admission, clinical picture, severity of stroke (non-severe, 0-10 and severe, greater than 10), length of stay in the ED and laboratory tests (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP, and D-dimer).

The multivariate analysis was adjusted for age, sex and risk factors for stroke (hypertension, diabetes, history of stroke). In addition, a parsimonious model was constructed, performing a nesting model among the variables that were statistically significant in the crude analysis model. The assumption of linearity was evaluated when constructing the models and, additionally, lost data among the variables and collinearity were evaluated in the adjusted models. A statistical significance level of 0.05 was used for all the statistical tests.

Ethical issues

In the present study there was no direct contact with the patients. In addition, only the researchers had access to the clinical history. The research protocol was approved by the Ethics Committee of the hospital (Letter No. 964 -GRPR -ESSALUD-2021) and the Ethics Committee of the Universidad Científica del Sur (Letter No. 404-CIEI-CIENTÍFICA-2021). The study was carried out in accordance with the Declaration of Helsinki, and the authors ensured anonymity of the patient data included in the study.

Results

Demographic characteristics of the participants

During the study period, 192 patients diagnosed with acute ischemic stroke were included. The mean age was 71.7 ± 11.9 years, 16.2% of the patients were under 60 years of age, and 64.6% were male. 74.3% of the patients presented at least one previous comorbidity in the clinical history, the most frequent being arterial hypertension (67.2%) and diabetes mellitus (30.7%). 36.1% of the patients reported no prior medication for cardiovascular disease, while 57.3% used antihypertensive drugs and 21.4% antiplatelet therapy. Further details of the demographic characteristics of the patients are shown in Table 1.

Clinical characteristics of the study sample

Among the admitted patients, 95.3% had a baseline status of functional independence. The most frequent initial symptoms at admission were limb weakness (75.8%) and dysarthria (49.2%). Disease severity was mild in 28.9% of the patients, being moderate in 54.2%, severe in 18.2% and very severe in 1.6%. Regarding the etiological classification, 39.1% were reported as long-artery atherosclerosis, 25% cardioembolic, 22.9% lacunar, 2.1% had infrequent causes, and 10.9% had an undetermined etiology. Neuroimaging findings showed that 83.8% corresponded to the supratentorial territory, while the middle cerebral artery was the most reported vascular territory and 31.2% had some degree of leukoaraiosis.

With respect to treatment, of the 24 patients (12.5%) admitted within the therapeutic window (stroke-door time of up to 4.5 hours), only 5 patients (2.6%) received acute treatment with recombinant tissue plasminogen activator (rtPA) as prevention strategies. Secondary antiplatelet therapy or anticoagulation was used according to the etiological classification.

In relation to the clinical evolution of the patients, 60 (31.2%) were admitted to an intermediate care unit and 6 (3.1%) to an ICU. The median stay in the ED before admission to a neurological unit was 2 days (interquartile range [IQR], 1-3 days) and the median hospital stay was 15 days (IQR, 10-23 days). As a clinical outcome, a mortality of 6.2% was reported. Regarding functional results, 49.5% of the total number of patients admitted to the study were functionally dependent; the 5 patients who received rtPA were functionally independent. Table 2 shows the clinical and imaging characteristics of the patients studied.

In-hospital complications

During hospitalization, at least one in-hospital complication occurred in 32.3% of patients. Regarding the types of complications, the most frequent were infectious in 22.4% (thoracic 15.1% and urinary 7.3%), followed by 17.7% of neurological complications (recurrent stroke 1.6%, epileptic seizures 1.6%, 5.3% hemorrhagic transformation, intracranial hypertension 3.6% and unexplained events 7.3%), while other complications, such as thromboembolism (deep vein thrombosis 0.5%), immobility (pressure ulcers 5.2%) and miscellaneous (minor bleeding 1%, major bleeding 1.6%, acute renal failure 7.3%, hydroelectrolytic disorder 2.6%) were much less frequent. The coexistence of the 2 most frequent types of complications (neurological and infectious) was reported in 12 patients (6.25%).

When comparing the clinical, demographic and laboratory characteristics of the patients with acute ischemic stroke presenting in-hospital complications with the group without complications, there were significant differences in age ($p=0.013$), the presence of at least one comorbidity ($p=0.035$), high CCI ($p=0.008$), previous use of antiarrhythmics ($p=0.001$), severity of stroke according to an NIHSS >10 ($p=0.002$), etiological classification of stroke ($p=0.006$) and in all laboratory tests at admission (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP and D-dimer).

Significant differences were found in the following variables in the exploratory analysis by type of complication in patients with neurological complications: systolic blood pressure at admission ($p=0.047$), previous use of antiarrhythmics ($p=0.001$), longer ED stay ($p=0.01$), stroke severity according to the NIHSS >10 ($p=0.007$), etiological classification of stroke ($p=0.005$), headache ($p=0.004$), dysarthria ($p=0.011$) and only Hb, leukocyte and CRP values were significant. Regarding infectious complications, significant differences were found in patients with a history of previous medication ($p=0.010$), use of antihypertensive drugs ($p=0.04$), and hypoalbuminemia ($p=0.043$) (Tables 3-5).

Risk factors for in-hospital complications in the bivariate analysis

When evaluating associations with Poisson regression models, a CCI >4 was found to increase the risk of presenting an in-hospital complication by 74% (relative risk [RR]: 1.74 95% confidence interval [CI]: 1.15 - 2.65). In addition, patients with a NIHSS >10 at admission had a 1.90-fold (95% CI: 1.25 - 2.9) greater risk of presenting an in-hospital complication compared to those with a lower NIHSS. All the laboratory tests presented statistically significant results in the crude analysis (Table 6).

An exploratory analysis was made according to the most frequent types of complications: neurological and infectious. Regarding neurological complications, patients with a NIHSS >10 at admission had a 2.36-fold (95% CI: 1.24 - 4.49) greater risk of presenting a neurological complication compared to those with a lower NIHSS. Hb, leukocyte and CRP values were statistically significant. In the crude analysis of infectious complications, patients with a history of previous medication had a 2.37-fold higher risk (95% CI: 1.16 - 4.83) of presenting some type of infectious complication and albumin levels >3.5 mg/dL was a protective factor, decreasing the risk by 49% (95% CI: 0.28 - 0.94) (Table 7).

Risk factors for in-hospital complications in the multivariate analysis

In the multivariate analysis for in-hospital complications, stroke severity (RR=1.76; 95% CI, 1.09-2.86; $p=0.022$) and albumin levels >3.5 mg/dL (RR=0.53; 95% CI, 0.36-0.79; $p=0.002$) were maintained after adjusting for age, sex and stroke risk factors (Table 8).

In the exploratory analysis by type of complication, Hb (RR=0.86; 95% CI, 0.73-0.99; $p=0.047$) was a statistically significant protective factor for neurological complications, while in the analysis of infectious complications, all factors except for the history of prior medication for cardiovascular disease lost statistical significance (RR=2.79; 95% CI, 1.16-6.71; $p=0.022$), after adjusting for the confounders (Table 9).

Discussion

The main objective of this study was to estimate the risk factors for in-hospital complications in patients with acute ischemic stroke hospitalized in a national reference hospital in Peru. As main findings, we found that approximately one in three patients presented in-hospital complications (32.3%) and the severity of cerebral infarction defined by an NIHSS scale > 10 was a risk factor and an albumin level > 3.5 mg/dL was a protective factor for the development of in-hospital complications.

The frequency of in-hospital complications in the present study was lower than that reported by Pandian *et al.* in India (45.9%) and by Langhorne *et al.* in Scotland (85%), although these studies included patients with both ischemic and hemorrhagic stroke^{5,6}. Our study only included patients with acute ischemic stroke, as we consider that the clinical outcomes of patients with ischemic and hemorrhagic stroke could be heterogeneous¹⁵.

In recent years, there has been a downward trend in the reporting of in-hospital complications, probably due to the optimization of stroke care in the different health systems. Although the highest mortality and disability rates are reported in Latin America and in many low- and middle-income countries², in recent years there have been joint efforts to improve this situation in this part of the world^{16,17}.

In the present study approximately 1 in 5 patients (22.4%) presented an infectious complication. This is consistent with what has been described in studies conducted in India, Scotland, and Argentina, in which infectious complications were the most frequent, with incidences of 34.4%, 65%, and 20%, respectively^{5,6,9}.

These findings are important, since most of the infectious complications are of the respiratory and urinary tract type, and these can be prevented with adequate education and training of the medical, nursing and technical personnel involved in the care of patients with stroke^{18,19}.

In the present study and others, the severity of stroke (NIHSS > 10) has shown to be an important risk factor^{6,8,9}. This finding can be explained by the fact that the patients with greater stroke severity require different care and greater in-hospital monitoring which may lead to a higher risk of presenting complications during hospitalization. It is therefore important for patients admitted for stroke to be evaluated or admitted early to a stroke or neurological care unit if there is no physical space available in the ED^{20,21}. In the case of our patients, the median stay in the ED was 2 days, which reflects the prompt referral to a neurological care unit.

Another finding in the present study was that albumin levels > 3.5 mg/dL were found to be a protective factor for in-hospital complications. This marker was previously explored by Pandian *et al.* who found an association in the bivariate analysis but without statistical significance in the multivariate analysis⁶. The most plausible explanation is that serum albumin levels are a laboratory sign of the nutritional status of patients, and thus, patients with low albumin levels would have a higher risk of hospital complications and a worse prognosis as seen in similar pathologies^{22,23}.

In the exploratory analysis of the risk factors for the most frequent in-hospital complications (neurological and infectious), statistical significance was obtained for Hb as a protective factor for neurological complications, which, unlike previous studies in which the variable of anemia was considered, we believe Hb values should be analyzed as a numerical variable. Previous articles have shown that the presence of anemia increases the risk of mortality in patients with stroke and is a risk

factor for in-hospital complications^{6,24}. Although the mechanism for this has yet to be defined, it has been postulated that the decrease in oxygen supply in patients with anemia in a state of stress caused by the stroke, which requires an increase in oxygen levels, could predispose these patients to medical complications⁶. The history of prior medication for cardiovascular disease was a risk factor for the presence of infectious complications. This result can be explained in that the history of receiving previous medication is related to the severity of these comorbidities, which could condition the patients to presenting greater susceptibility to infectious processes, such as those reported in the present cohort. Regarding clinical outcomes, the in-hospital mortality in the present study was 6.2%. This value is lower than that reported in previous articles in Peru²⁵⁻²⁸, such as the study carried out by Castañeda *et al.* in which a mortality of 13.6% was reported in patients with acute ischemic stroke admitted to a public hospital of national reference in the period 2000-2009. These findings are consistent with more recent data obtained in other Latin American countries which reported a decrease in hospital mortality due to stroke likely explained by the improvements in the care of these patients in recent years^{29,30}.

Our study also showed that almost half of the patients had a poor functional prognosis at discharge. However, the 5 patients who received intravenous reperfusion treatment in the acute stage achieved functional independence. This could be associated with a lower frequency of in-hospital complications; although this effect was not measured in our study, since it has already been shown that intravenous and mechanical reperfusion therapies are cost-effective strategies for reducing mortality, complications, and disability in patients with stroke³¹⁻³³.

This study has some limitations. Since the data were obtained from medical records, some laboratory variables were not available, and thus, certain variables could not be included in the multivariate regression models. The study was carried out with the main objective of estimating the risk factors for in-hospital complications, therefore the lack of statistical significance in the analyses of the most frequent types of complications may have been due to a purely statistical and not an epidemiological problem. Likewise, the follow-up period was limited to the time of hospitalization and did not allow analyses of association with the functional prognosis after hospital discharge.

Despite the above limitations, this study has some strengths. A significant number of patients was included because the study was performed in a national reference hospital. In addition, a complete analysis of different risk factors with global complications was carried out and factors were explored according to the most frequent types. Likewise, complete data of most of the variables were available due to adequate registration using the electronic medical record system.

Conclusions

In conclusion, this cohort study reports a high rate of in-hospital complications in patients presenting to the ED with stroke, among which infectious and neurological complications were of note as the most frequent. Stroke severity was a risk factor and albumin levels > 3.5 mg/dL were a protective factor for the incidence of in-hospital complications in patients with acute ischemic stroke. Further studies are needed to confirm these results and develop stroke care systems that consider these markers to provide deferred care with stricter monitoring and prevention of hospital complications.

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Table 1. Demographic characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Sex		
Female	68	35.4
Male	124	64.6
Age (years)		
30 to 59	31	16.2
60 to 70	50	26
≥71	111	57.8
Baseline status		
Independent (mRS:0-2)	183	95.3
Dependent (mRS:3-5)	9	4.7
Comorbidities		
None	50	25.7
At least 1	142	74.3
Hypertension	129	67.2
Diabetes mellitus	59	30.7
Chronic kidney disease	12	6.3
Chronic coronary disease	14	7.3
Epilepsy	10	5.2
History of previous stroke		
None	154	80.2
Hemorrhagic stroke	2	1
Ischemic stroke	35	18.2
CCI		
0	9	4.7
1 to 2	26	13.5
3 to 4	72	37.5
5 or more	85	44.3
Previous medication		
No	69	36.1
Yes	122	63.9
Antihypertensive	110	57.3
Antiplatelet therapy	41	21.4
Statins	30	15.6
Antiarrhythmics	34	17.7
Warfarin	10	5.2

Abbreviations: mRS: Modified Rankin Scale; CCI: age adjusted Charlson comorbidity index.

Table 2. Clinical and imaging characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Stroke severity (NIHSS admission)		
I (0 to 4)	50	26
II (5 to 15)	104	54.2
III (16 to 25)	35	18.2
IV (26 or more)	3	1.6
Stroke symptom		
Limb weakness	144	75.8
Dysarthria	94	49.2
Headache	39	20.4
Aphasia	30	15.7
Ataxia	28	14.7
Etiological classification		
Large vessel atherothrombotic	75	39.1
Lacunar	44	22.9
Cardioembolic	48	25
Uncommon causes	4	2.1
Undetermined etiology	21	10.9
Neuroimaging findings		
Cerebral vascular territory		
Infratentorial	31	16.2
Supratentorial	161	83.8
Affected cerebral artery		
MCA	121	63
ACA	3	1.6
PCA	10	5.2
VB	29	15.1
2 or more territories	29	15.1
Imaging laterality		
Left	104	54.2
Right	88	45.8
Leukoaraiosis	59	31.2
Microbleeding	7	3.7
Early signs of stroke	8	4.2
Treatment received		
Thrombolysis	187	97.4
Simple antiplatelet therapy	111	57.8
Dual antiplatelet therapy	7	3.6
Anticoagulation	43	22.4
Statins	141	73.8
Intermediate care unit admission	60	31.2
ICU admission	6	3.1
In-hospital complication	62	32.3
NIHSS at discharge		
I (0 to 4)	52	28.9
II (5 to 15)	101	56.1
III (16 to 25)	26	14.4
IV (26 or more)	1	0.6
NIHSS discharge in patients with thrombolysis		
I (0 to 4)	1	20
II (5 to 15)	4	80
Rankin at discharge		
Independent (mRS:0-2)	85	44.3
Dependent (mRS:3-5)	95	49.5
Death	12	6.2

Abbreviations: MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory; ICU: Intensive Care Unit; mRS: Modified Rankin Scale.

Table 3. Comparison of in-hospital complications and type of complication according to the demographic characteristics of patients with acute ischemic stroke.

variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Age	74.74 (10.7)	70.22 (12.19)	0.013	73.5 (14.4)	71.3 (11.3)	0.407	73.1 (11.3)	71.2 (12.1)	0.373
Sex									
Female	18 (26.5)	50 (73.5)	0.201	14 (20.6)	54 (79.4)	0.439	15 (22.4)	52 (77.6)	0.922
Male	44 (35.5)	80 (64.5)		20 (16.1)	104 (83.9)		27 (21.8)	97 (78.2)	
Stroke history									
No	52 (33.5)	103 (66.5)	0.446	28 (18.1)	127 (81.9)	0.791	36 (23.4)	118 (76.6)	0.345
Yes	10 (27.0)	27 (73.0)		6 (16.2)	31 (83.8)		6 (16.2)	31 (83.8)	
Comorbidities									
No	3 (13.0)	20 (90.0)	0.035	3 (13.0)	20 (87.0)	0.532	3 (13.0)	20 (87.0)	0.269
Yes	59 (34.9)	110 (65.1)		31 (18.3)	138 (81.7)		39 (23.2)	129 (76.8)	
CCI									
0 to 4	26 (24.3)	81 (75.5)	0.008	15 (14.0)	92 (86.0)	0.133	19 (17.8)	88 (82.2)	0.111
5 or more	36 (42.3)	49 (57.7)		19 (22.4)	66 (77.6)		23 (27.4)	61 (72.6)	
Previous medication									
No	21 (30.4)	48 (69.6)	0.653	15 (21.7)	54 (78.3)	0.285	8 (11.8)	60 (88.2)	0.010
Yes	41 (33.6)	81 (66.4)		19 (15.8)	103 (84.4)		34 (27.9)	88 (72.1)	
Antiplatelet therapy									
No	48 (31.8)	103 (68.2)	0.775	27 (17.9)	124 (82.1)	0.904	30 (20.0)	120 (80.0)	0.204
Yes	14 (34.2)	27 (65.8)		7 (17.0)	34 (83.0)		12 (29.3)	29 (70.7)	
Warfarin									
No	57 (31.3)	125 (68.7)	0.219	33 (18.1)	149 (81.9)	0.512	40 (22.1)	141 (77.9)	0.876
Yes	5 (50.0)	5 (50.0)		1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
Statins									
No	52 (32.1)	110 (67.9)	0.894	28 (17.3)	134 (82.7)	0.72	33 (20.5)	128 (79.5)	0.249
Yes	10 (33.3)	20 (66.7)		6 (20.0)	24 (80.0)		9 (30.0)	21 (70.0)	
NOAC									
No	61 (32.5)	127 (67.5)	0.753	32 (17.0)	156 (83.0)	0.087	41 (21.9)	146 (78.1)	0.883
Yes	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)		1 (25.0)	3 (75.0)	
Antihypertensive									
No	28 (34.2)	54 (65.8)	0.635	18 (21.9)	64 (78.1)	0.184	12 (14.8)	69 (85.2)	0.040
Yes	34 (30.9)	76 (69.1)		16 (14.5)	94 (84.5)		30 (27.3)	80 (72.7)	
Anti-arrhythmic									
No	43 (27.2)	115 (72.8)	0.001	21 (13.3)	137 (86.7)	0.001	32 (20.4)	125 (79.6)	0.249
Yes	19 (55.9)	15 (44.1)		13 (38.2)	21 (61.8)		10 (29.4)	24 (70.6)	
Immunosuppressants									
No	60 (32.3)	126 (67.7)	0.956	32 (17.2)	154 (82.8)	0.308	40 (21.6)	145 (78.4)	0.495
Yes	2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)	
Emergency stay*‡	2 (1-3)	2 (1-2)	0.105	2 (1 - 2)	2 (1- 2)	0.010	2 (1- 3)	2 (1 - 2)	0.051

Abbreviations: CCI: age adjusted Charlson comorbidity index; NOAC: Novel oral anticoagulants.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and ‡ Mann-Whitney U test.

Table 4. Comparison of in-hospital complications and type of complication according to the clinical characteristics and imaging findings of patients with acute ischemic stroke.

Variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
SBP (mmHg)									
<=185	50 (31.1)	111 (68.9)	0.095	33 (20.5)	128 (79.5)	0.047	35 (21.9)	125 (78.1)	0.497
>185	12 (48.0)	13 (52.0)		1 (4.0)	24 (96.0)		7 (28.0)	18 (72.0)	
DBP (mmHg)									
<=110	62 (33.5)	123 (66.5)	0.478	34 (18.4)	151 (81.6)	0.635	41 (22.3)	143 (77.7)	0.064
>110	0 (0.0)	1 (100)		0 (0.0)	1(100.0)		1 (100.0)	0 (0.0)	
HR (beats/min)									
<=90	44 (31.2)	97 (68.8)	0.068	25 (17.7)	116 (82.3)	0.832	34 (24.1)	107 (75.9)	0.197
>90	15 (48.4)	16 (51.6)		5 (16.1)	26 (83.9)		4 (13.3)	26 (86.7)	
CGT (mg/dL)									
<=180	22 (33.9)	43 (66.1)	0.167	11 (16.9)	54 (83.1)	0.658	12 (18.5)	53 (81.5)	0.298
>180	1 (11.1)	8 (88.9)		1 (11.1)	8 (88.9)		3 (33.3)	6 (66.7)	
Severity of stroke (NIHSS)									
<=10	25 (23.2)	83 (76.8)	0.002	12 (11.1)	96 (88.9)	0.007	25 (23.2)	83 (76.8)	0.659
>10	37 (44.1)	47 (55.9)		22 (26.2)	62 (73.8)		17 (20.5)	66 (79.5)	
Baseline status									
Independent	60 (32.8)	123 (67.2)	0.508	33 (18.0)	150 (82.0)	0.595	40 (22.0)	142 (78.0)	0.986
Dependent	2 (22.2)	7 (77.8)		1 (11.1)	8 (88.9)		2 (22.2)	7 (77.8)	
Etiological classification									
Large vessel atherothrombotic	23 (30.7)	52 (69.3)	0.006	11 (14.7)	64 (85.3)	0.005	14 (18.7)	61 (81.3)	0.584
Lacunar	7 (15.9)	37 (84.1)		4 (9.1)	40 (90.9)		12 (27.9)	31 (72.1)	
Cardioembolic	23 (47.9)	25 (52.1)		17 (35.4)	31 (64.6)		12 (25.0)	36 (75.0)	
Uncommon causes	3 (75.0)	1 (25.0)		0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	
Undetermined etiology	6 (28.6)	15 (71.4)		2 (9.5)	19 (90.5)		4 (19.1)	17 (80.9)	
Limb weakness									
No	15 (32.6)	31 (67.4)	0.997	11 (23.9)	35 (76.1)	0.221	7 (15.2)	39 (84.8)	0.189
Yes	47 (32.6)	97 (67.4)		23 (16.0)	121 (84.0)		35 (24.5)	108 (75.5)	
Visual deficit									
No	58 (32.9)	118 (67.1)	0.736	31 (17.6)	145 (82.4)	0.720	41 (23.4)	134 (76.6)	0.158
Yes	4 (28.6)	10 (71.4)		3 (21.4)	11 (78.6)		1 (7.1)	13 (92.9)	
Aphasia									
No	50 (31.1)	111 (68.9)	0.337	28 (17.4)	133 (82.6)	0.732	37 (23.0)	124 (77.0)	0.493
Yes	12 (40.0)	18 (60.0)		6 (20.0)	24 (80.0)		5 (17.2)	24 (84.8)	
Headache									
No	52 (34.2)	100 (65.8)	0.308	21 (13.8)	131 (86.2)	0.004	33 (21.9)	118 (78.1)	0.870
Yes	10 (25.6)	29 (74.4)		13 (33.3)	26 (66.7)		9 (23.1)	30 (76.9)	

Epileptic seizures									
No	59 (32.1)	125 (67.9)	0.748	33 (17.9)	151 (82.1)	0.693	42 (23.0)	141 (77.0)	0.125
Yes	3 (37.5)	5 (62.5)		1 (12.5)	7 (87.5)		0 (0.0)	8 (100.0)	
Vertigo									
No	58 (32.9)	118 (67.1)	0.618	31 (17.6)	145 (82.4)	0.817	40 (22.9)	135 (77.1)	0.394
Yes	4 (26.7)	11 (73.3)		3 (20.0)	12 (80.0)		2 (13.3)	13 (86.7)	
Facial paralysis									
No	54 (32.9)	110 (67.1)	0.735	30 (18.3)	134 (81.7)	0.662	35 (21.5)	128 (78.5)	0.605
Yes	8 (29.6)	19 (70.4)		4 (14.8)	23 (85.2)		7 (25.9)	20 (74.1)	
Loss of sensation									
No	61 (34.1)	118 (65.9)	0.065	34 (19.0)	145 (81.0)	0.096	42 (23.6)	136 (76.4)	0.057
Yes	1 (8.3)	11 (91.7)		0 (0.0)	12 (100.0)		0 (0.0)	12 (100.0)	
Unsteady gait									
No	54 (33.1)	109 (66.9)	0.634	28 (17.2)	135 (82.8)	0.587	33 (20.4)	129 (79.6)	0.166
Yes	8 (28.6)	20 (71.4)		6 (21.4)	22 (78.6)		9 (32.1)	19 (67.9)	
Dysarthria									
No	32 (33.0)	65 (67.0)	0.874	24 (24.7)	73 (75.3)	0.011	18 (18.6)	79 (81.4)	0.229
Yes	30 (31.9)	64 (68.1)		10 (10.6)	84 (89.4)		24 (25.8)	69 (74.2)	
Cerebral vascular territory									
Infratentorial	10 (32.3)	21 (67.3)	0.997	3 (9.7)	28 (90.3)	0.201	7 (23.3)	23 (76.7)	0.847
Supratentorial	52 (32.3)	109 (67.3)		31 (19.3)	130 (80.8)		35 (21.7)	126 (78.3)	
Affected cerebral artery									
MCA	41 (33.9)	80 (66.1)	0.892	21 (17.4)	100 (82.6)	0.075	28 (23.3)	92 (76.7)	0.781
ACA	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)		0 (0.0)	3 (100.0)	
PCA	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
VB	7 (24.1)	22 (75.9)		2 (6.9)	27 (93.1)		5 (17.2)	24 (82.8)	
2 or more territories	10 (34.5)	19 (65.5)		6 (20.7)	23 (79.3)		6 (20.7)	23 (79.3)	
Imaging laterality									
Left	35 (33.7)	69 (66.4)	0.661	21 (20.2)	83 (79.8)	0.327	22 (21.2)	82 (78.9)	0.76
Right	27 (30.7)	61 (69.3)		13 (14.8)	75 (85.2)		20 (23.0)	67 (77.0)	
Leukoaraiosis									
No	38 (29.2)	92 (70.8)	0.12	22 (16.9)	108 (83.1)	0.571	30 (23.1)	100 (76.9)	0.717
Yes	24 (40.7)	35 (59.3)		12 (20.3)	47 (79.7)		12 (20.7)	46 (79.3)	

Abbreviations: SBP: systolic blood pressure; DBP: SBP: diastolic blood pressure; HR: heart rate; CGT: capillary glycemia test; MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory.

We used the following statistical tests: chi2 test.

Table 5. Comparison of in-hospital complications and type of complication according to laboratory test results of patients with acute ischemic stroke.

Variable	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Hb (g/dL) †	12.7 (1.8)	13.6 (1.9)	0.003	12.4 (1.9)	13.5 (1.8)	0.035	13.3 (2.1)	13.3 (1.8)	0.946
Leukocytes (cells/μL)									
<5000	7 (50.0)	7 (50.0)	0.001	4 (28.6)	10 (71.4)	0.022	2 (14.3)	12 (85.7)	0.713
5000-12000	41 (27.3)	109 (72.7)		20 (13.3)	130 (86.7)		33 (22.0)	117 (78.0)	
>12000	11 (68.8)	5 (31.3)		6 (37.5)	10 (62.5)		4 (26.7)	11 (73.3)	
NLR									
<3	20 (22.7)	68 (77.3)	0.005	12 (13.6)	76 (86.4)	0.286	18 (20.5)	70 (79.5)	0.671
\geq 3	39 (42.4)	53 (57.6)		18 (19.6)	74 (80.4)		21 (23.1)	70 (76.9)	
LDH (IU/L)									
\leq 350	16 (25.8)	46 (74.2)	0.003	11 (17.7)	51 (82.3)	0.195	13 (21.0)	49 (79.0)	0.624
>350	12 (63.2)	7 (36.8)		6 (31.6)	13 (68.4)		5 (26.3)	14 (73.7)	
Total proteins (g/dL)									
\leq 6	15 (55.6)	12 (44.4)	0.011	6 (22.2)	21 (77.8)	0.549	8 (30.8)	18 (69.2)	0.293
>6	38 (29.9)	89 (70.1)		22 (17.3)	105 (82.7)		27 (21.3)	100 (78.7)	
Albumin (g/dL)									
\leq 3.5	14 (60.9)	9 (39.1)	0.002	6 (26.1)	17 (73.9)	0.192	9 (40.9)	13 (59.1)	0.043
>3.5	33 (27.5)	87 (72.5)		18 (15.0)	102 (85.0)		25 (20.8)	95 (79.2)	
CRP (mg/ dL)									
\leq 2	20 (20.6)	77 (79.4)	<0.001	11 (11.3)	86 (88.7)	0.001	20 (20.6)	77 (79.4)	0.422
>2	29 (63.0)	17 (37.0)		16 (34.8)	30 (65.2)		12 (26.7)	33 (73.3)	
D-dimer (μg/mL)									
\leq 1	6 (20.0)	24 (80.0)	0.012	4 (13.3)	26 (86.7)	0.203	9 (30.0)	21 (70.0)	0.518
>1	21 (48.8)	22 (51.2)		11 (25.6)	32 (74.4)		10 (23.3)	33 (76.7)	

Abbreviations: Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and † Student's t test.

Table 6. Bivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref		
Male	1.34	0.84 - 2.13	0.215
Age			
<=70	Ref.	0.86 - 2.05	0.203
>70	1.33		
Stroke history			
No	Ref.		
Yes	0.81	0.45 - 1.43	0.462
SBP (mmHg) (n=186)			
<=185	Ref.		
>185	1.55	0.97 - 2.47	0.069
HR (beats/min) (n=186)			
<=90	Ref.		
>90	1.55	0.99 - 2.40	0.051
CGT (mg/dL) (n=74)			
<=180	Ref		
>180	0.33	0.49 - 2.18	0.248
Comorbidities			
No	Ref		
Yes	2.68	0.91 - 7.87	0.073
CCI			
0 to 4	Ref		
5 or more	1.74	1.15 - 2.65	0.009
Previous medication			
No	Ref.		
Yes	1.1	0.71 - 1.71	0.656
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.9	1.25 - 2.90	0.003
Baseline status			
Independent	Ref.		
Dependent	1.02	0.81 - 1.29	0.841
Imaging laterality			
Left	Ref		
Right	0.91	0.60 - 1.38	0.662
Hb (g/dL)			
	0.86	0.78 - 0.94	0.001
Leukocytes (cells/μL) (n=180)			
5000-12000	Ref.		
<5000	1.83	1.02 - 3.29	0.044
>12000	2.52	1.65 - 3.84	<0.001
NLR (n=180)			
<3	Ref		
>=3	1.87	1.18 - 2.94	0.007
LDH (IU/L) (n=81)			
<=350	Ref.		
>350	2.45	1.42 - 4.23	0.001
Total Proteins (g/dL) (n=154)			
<=6	Ref.		
>6	0.54	0.35 - 0.83	0.005
Albumin (g/dL) (n=143)			
<=3.5	Ref		
>3.5	0.45	0.29 - 0.70	<0.001
CRP (mg/ dL) (n=143)			
<=2	Ref		
>2	3.06	1.95 - 4.80	<0.001
D-dimer (μg/mL) (n=73)			
<=1	Ref		

>1

2.44

1.12 - 5.35

0.026

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein; CI: confidence interval; RR: relative risk.

Table 7. Bivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref			Ref		
Male	0.78	0.42 - 1.45	0.438	0.97	0.56 - 1.67	0.922
Age						
<=70	Ref.			Ref.		
>70	1.18	0.63 - 2.22	0.61	1.33	0.75 - 2.33	0.327
Stroke history						
No	Ref.			Ref.		
Yes	0.90	0.40 - 2.01	0.793	0.69	0.32 - 1.53	0.363
SBP (mmHg)						
<=185	Ref.			Ref.		
>185	0.20	0.03 - 1.37	<0,001	1.28	0.64 - 2.57	0.487
HR (beat/min)						
<=90	Ref.			Ref.		
>90	0.91	0.38 - 2.19	0.833	0.55	0.21 - 1.45	0.227
CGT (mg/dL)						
<=180	Ref			Ref		
>180	0.66	0.09 - 4.56	0.67	1.81	0.62 - 5.23	0.276
Comorbidities						
No	Ref			Ref		
Yes	1.41	0.47 - 4.25	0.545	1.78	0.60 - 5.31	0.301
CCI						
0 to 4	Ref			Ref		
5 or more	1.59	0.86 - 2.95	0.138	1.54	0.90 - 2.64	0.114
Previous medication						
No	Ref.			Ref.		
Yes	0.72	0.39 - 1.32	0.285	2.37	1.16 - 4.83	0.018
Stroke severity (NIHSS)						
<=10	Ref.			Ref.		
>10	2.36	1.24 - 4.49	0.009	0.88	0.51 - 1.53	0.661
Baseline status						
Independent	Ref.			Ref.		
Dependent	0.61	0.09 - 4.03	0.613	1.01	0.29 - 3.55	0.986
Imaging laterality						
Left	Ref			Ref		
Right	0.73	0.39 - 1.38	0.333	1.09	0.64 - 1.86	0.761
Hb (g/dL)						
0.8	0.70 - 0.91	0.001		0.99	0.85 - 1.17	0.95
Leukocytes (cells/μL)						
5000-12000	Ref.			Ref.		
<5000	2.15	0.85 - 5.41	0.107	0.65	0.17 - 2.43	0.522
>12000	2.81	1.32 - 5.98	0.007	1.21	0.50 - 2.96	0.673
NLR						
<3	Ref			Ref		
>=3	1.43	0.73 - 2.81	0.292	1.13	0.65 - 1.97	0.672
LDH (IU/L)						
<=350	Ref.			Ref.		
>350	1.78	0.76 - 4.19	0.187	1.26	0.51 - 3.09	0.621
Total proteins (g/dL)						
<=6	Ref.			Ref.		
>6	0.78	0.35 - 1.74	0.544	0.69	0.35 - 1.35	0.279
Albumin (g/dL)						
<=3.5	Ref			Ref		
>3.5	0.58	0.26 - 1.30	0.182	0.51	0.28 - 0.94	0.031
CRP (mg/ dL)						
<=2	Ref			Ref		
>2	3.08	1.55 - 6.09	0.001	1.29	0.69 - 2.42	0.419

D-dimer (µg/mL)

<=1	Ref			Ref		
>1	1.92	0.67 - 5.50	0.225	0.78	0.36 - 0.68	0.52

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein. CI: confidence interval; RR: relative risk.

Table 8. Multivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref.		
Male	1.25	0.75 - 2.10	0.393
Age	1.02	0.99 - 1.04	0.086
Hypertension			
No	Ref.		
Yes	0.66	0.40-1.07	0.094
Diabetes			
No	Ref.		
Yes	1.06	0.65-1.72	0.82
Stroke history			
No	Ref.		
Yes	0.93	0.46 - 1.86	0.846
HR (beat/min)			
<=90	Ref.		
>90	1.41	0.88 - 2.27	0.153
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.76	1.09 - 2.86	0.022
NLR			
<3	Ref.		
>=3	1.29	0.8 - 2.08	0.295
Albumin (g/dL)			
<=3.5	Ref.		
>3.5	0.53	0.36 - 0.79	0.002

Abbreviations: NLR: neutrophil/lymphocyte ratio; CI: confidence interval; RR: relative risk.

Table 9. Multivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref.			Ref.		
Male	0.88	0.39 - 2.00	0.768	0.89	0.49 - 1.61	0.69
Age	0.99	0.95 - 1.03	0.655	1.01	0.99 - 1.04	0.33
Hypertension						
No	Ref.			Ref.		
Yes	0.88	0.40 - 1.98	0.772	0.97	0.52 - 1.83	0.931
Diabetes						
No	Ref.			Ref.		
Yes	0.76	0.35 - 1.67	0.502	0.95	0.50 - 1.82	0.877
Stroke history						
No	Ref.			Ref.		
Yes	1.14	0.49 - 2.64	0.763	0.67	0.25 - 1.75	0.411
Previous medication						
No				Ref.		
Yes	-			2.79	1.16-6.71	0.022
Stroke severity (NIHSS)						
<=10	Ref.					
>10	1.56	0.72 - 3.40	0.26	-		
Hb (g/dL)	0.86	0.73 - 0.99	0.047	-		
CRP (mg/ dL)						
<=2	Ref.					
>2	2.49	0.97 - 6.38	0.057	-		
Albumin (g/dL)						
<=3.5				Ref.		
>3.5	-			0.67	0.35 - 1.28	0.225

Abbreviations: Hb: hemoglobin; CRP: C-reactive protein.

Copias de cartas de respuesta a las observaciones de los revisores de la revista.

LETTER

Lima, January 13, 2022

**Editor-in-Chief,
Heliyon**

Through this letter I am raising the observations made to the article:

Manuscript ID: HELIYON-D-22-23749

Article Type: Original Research Article

Section/Category: Medical Sciences

" Risk factors for in-hospital complications in patients with acute ischemic stroke: retrospective cohort in a national reference hospital in Peru " .

RESPONSES TO COMMENTS

No.	Reviewer	Comment	Amendment
1	Reviewer #1	<p>1. Could the manuscript benefit from additional tables or figures, or from improving or removing (some of the) existing ones?</p> <p>Please provide specific suggestions for improvements, removals, or additions of figures or tables. Please number each suggestion so that author(s) can more easily respond.</p> <p>Comment: Yes, authors must give some figures to show how interesting the analysis instead of giving just tables.</p>	The suggestion is accepted and modifications are made in the text, we provide more interesting information on the analysis of the data.
2	Reviewer #1	<p>6. Have the authors clearly emphasized the strengths of their study/theory/methods/argument?</p> <p>Please provide suggestions to the author(s) on how to better emphasize the strengths of their study. Please number each suggestion so that the author(s) can more easily respond.</p> <p>Comment: Yes, but authors need to give more explanation based on figures like increasing or decreasing functions</p>	The suggestion is accepted and the modification is made to the text.
3	Reviewer #1	<p>8. Does the manuscript structure, flow or writing need improving (e.g., the addition of subheadings, shortening of text, reorganization of sections, or moving details from one section to another)?</p> <p>Please provide suggestions to the author(s) on how to improve the manuscript structure and flow. Please number each suggestion so that author(s) can more easily respond.</p> <p>Comment: English must be improved</p>	The language used in the manuscript was improved
4	Reviewer #2	<p>This field is optional. If you have any additional suggestions beyond those relevant to the questions above, please number and list them here.</p>	the authors added a paragraph describing the results of the main risk factors for in-hospital complications and discussing the pathogenesis.

No.	Reviewer	Comment	Amendment
		Comment: please describe types of stroke and pathogenesis provide the rational of the study gender difference should discussed	
5	Reviewer #3	<p>This field is optional. If you have any additional suggestions beyond those relevant to the questions above, please number and list them here.</p> <p>Comment:</p> <ul style="list-style-type: none"> - Please rephrase sentences in pages 10 (lines 57-2) and 11 (4-9) - In the limitation section, please define variables that should be included but that were lacking. 	<ul style="list-style-type: none"> - The sentences in pages 10 and 11 were improved. - In the limitations section, we add the variables that were not included in the multivariate regression models.

We are very grateful for the attention and time.

Respectfully,



Miguel Angel Vences MD (On behalf of the authors)

Versión en español (en caso haya sido aceptada en otro idioma).

Factores de riesgo de complicaciones intrahospitalarias en pacientes con infarto cerebral agudo: Cohorte retrospectiva en un hospital de referencia nacional de Perú

Introducción

El infarto cerebral es una de las enfermedades con el reporte de las mayores tasas de mortalidad y discapacidad a nivel mundial [1]. Estas tasas aumentan en los países de bajos ingresos económicos, muchos de los cuales no cuentan con un sistema organizado de atención de la fase aguda de ictus, generando según reportes internacionales un alto gasto sanitario, no solo por los gastos hospitalarios sino también por los gastos indirectos que conlleva a largo plazo como los relacionados a la pérdida laboral del paciente [2],[3],[4].

Actualmente existe tratamiento para el infarto cerebral que puede reducir la mortalidad y discapacidad; sin embargo, la ventana terapéutica para administrarlo es corta [3]. Existen varias barreras que generan aún más demoras en el inicio de tratamiento para estos pacientes; tales como, el reconocimiento tardío de los síntomas, la demora en el traslado del paciente hacia un hospital especializado, la falta de coordinación entre el sistema prehospitalario y hospitalario, demora en la realización de neuroimagen, la falta de especialistas disponibles (neurólogos, neurólogos vasculares, neuro radiólogos intervencionistas) y la falta de disponibilidad de medicamentos. Todo esto hace que solo un grupo muy pequeño de los pacientes que tienen un infarto cerebral puedan beneficiarse con el tratamiento [4].

Gran parte de la discapacidad y mortalidad asociada al infarto cerebral también es sustentada por la presencia de complicaciones intrahospitalarias en estos pacientes, muchos de los cuales requieren el ingreso a unidades de cuidados intermedios o críticos. Estudios previos en Europa y Asia han descrito incidencias de complicaciones intrahospitalarias superiores al 40% en pacientes ingresados con accidente cerebrovascular [5],[6].

Las complicaciones intrahospitalarias reportadas en los pacientes con infarto cerebral, se infiere que podrían ser evitables en su mayoría si se mejoran los procesos de atención de los pacientes [6]. Así mismo, el monitoreo estricto en la atención aguda de los pacientes con infarto cerebral puede prevenir el desenlace fatal en los pacientes que presenten complicaciones intrahospitalarias. Por ello, se han propuesto algunas medidas, como la optimización de los protocolos de atención integral, la capacitación relacionada con la atención preventiva y el manejo oportuno de las complicaciones para todo el personal de salud involucrado en la atención de pacientes con ictus [7].

En América Latina, donde la mayoría de los países son de ingresos bajos y medios, puede haber diferencias en la tasa de complicaciones intrahospitalarias en comparación con lo que se informa en otras regiones. Garavelli exploró la severidad de infarto cerebral mediante el score de NIHSS como factor predictor de complicaciones no neurológicas del tipo infeccioso, encontrando que un NIHSS mayor o igual a 10 se relacionó con la presencia de complicaciones no neurológicas del tipo infeccioso, quedando muy limitado el estudio a este tipo de complicación intrahospitalaria [8]. Guarnaschelli realizó un estudio en 200 pacientes con enfermedad cerebrovascular, donde identificó un 15.5% de complicaciones infecciosas, concluyendo que los pacientes con puntajes más altos de NIHSS al ingreso fueron los que presentaron mayor porcentaje de complicaciones [9]. No hay estudios disponibles en esta región de Latinoamérica, según la literatura revisada, que aborden de manera más holística las complicaciones intrahospitalarias presentadas en los pacientes con enfermedad cerebrovascular, pues los estudios previamente realizados solo

proporcionaron datos parciales reportando complicaciones no neurológicas y sus factores predictivos [8],[9].

El objetivo principal de este estudio fue determinar los factores de riesgo de complicaciones intrahospitalarias en pacientes con infarto cerebral agudo atendidos en un hospital de referencia nacional en Perú. Este artículo fue escrito siguiendo las pautas STROBE para estudios observacionales [10].

Métodos

Diseño y población

Realizamos un estudio retrospectivo de una cohorte de pacientes atendidos en el Hospital Nacional Edgardo Rebagliati Martins, perteneciente al sistema de seguridad social en Lima, Perú, el cual es una institución de referencia nacional, certificado como centro esencial de ictus, lo que significa que cumple con estándares de calidad de atención en esta dolencia, con capacidad resolutoria para tratamiento de reperfusión intravenosa. La población incluyó a todos los pacientes mayores de 18 años ingresados en el servicio de urgencias (SU) con diagnóstico de infarto cerebral agudo durante el período comprendido entre el 1 de enero y el 30 de septiembre de 2021. La información de los pacientes incluidos se obtuvo de los datos registrados en la historia clínica durante la hospitalización (desde el ingreso en urgencias hasta el alta o fallecimiento). Se dio diagnóstico de infarto cerebral agudo a los pacientes con déficit neurológico agudo confirmado por neuroimagen (tomografía o resonancia magnética cerebral) y con un tiempo puerta de ictus máximo de 72 horas.

Previamente a la ejecución del estudio se estimó en el protocolo de investigación un tamaño muestral mínimo para la estimación de factores de riesgo de complicaciones intrahospitalarias con la calculadora Open Epi versión 3, calculadora de código abierto SSCohort. Estimando a la severidad de ictus (NIHSS >10) como uno de los principales factores de riesgo para complicación intrahospitalaria según antecedente [6], con un porcentaje de complicación intrahospitalaria de 67.4% para los pacientes con ictus severo y 31.4% de complicación intrahospitalaria para quienes no tuvieron un ictus severo, con una razón de no expuestos/expuestos de 1, un nivel de confianza de 95% y potencia de 95% se estimó 50 participantes como mínimo en cada grupo (total de 100).

Respecto a la población final incluida en el estudio, se reportó un total de 215 pacientes que acudieron al SU con este diagnóstico durante el periodo de estudio; de estos, excluimos a 23 pacientes diagnosticados con COVID-19 al ingreso o durante la hospitalización, quedando 192 pacientes para el análisis de datos.

Variables

Se definió como complicación intrahospitalaria, como aquel paciente con la presencia de al menos uno de los siguientes problemas médicos surgidos durante la estancia hospitalaria por infarto cerebral agudo [5],[6]:

- Neurológicos: crisis epiléptica, ictus recurrente, transformación hemorrágica, hipertensión intracraneal o eventos neurológicos inexplicables (definidos como eventos médicos transitorios de sintomatología neurológica sin identificación etiológica).
- Infecciosos: infección localizada a nivel torácico, urinario u otra localización.
- Tromboembólicas: trombosis pulmonar o trombosis venosa profunda.
- Inamovilidad: úlceras por presión o caídas.
- Misceláneas: cualquier problema médico surgido durante estancia hospitalaria no clasificado en las categorías anteriores, sin incluir dolor ni complicaciones psicológicas.

Se evaluaron variables demográficas como edad, sexo, nivel educativo, hábitos tóxicos (alcohol, tabaquismo y consumo de drogas), medicación previa para enfermedades cardiovasculares así como los antecedentes patológicos más prevalentes como hipertensión arterial, diabetes mellitus, dislipidemia, obesidad, enfermedad renal crónica, enfermedad cardíaca crónica, arritmia cardíaca, enfermedad autoinmune, enfermedad pulmonar crónica, neoplasia maligna, enfermedad cerebrovascular, enfermedad tiroidea, síndrome de apnea obstructiva del sueño y enfermedad hepática crónica. Sobre la base de las comorbilidades previas, también se utilizó el índice de comorbilidad de Charlson ajustado por edad (ICC)

[11].

En cuanto a las variables clínicas, se determinaron: estado basal (estimado por la "escala de Rankin modificada", mRS al ingreso) [12], funciones vitales al ingreso (frecuencia cardíaca, presión arterial sistólica y diastólica) y el cuadro clínico presentado en el paciente. Registramos la gravedad del accidente cerebrovascular isquémico agudo al ingreso en urgencias y al alta estimada por la "Escala de accidente cerebrovascular de los Institutos Nacionales de Salud" (NIHSS) y dividida en grupos: leve (0-4), moderado (5-15), severa (16 -25) y muy severa (>25)[13]. Utilizamos la clasificación etiológica del "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) para el infarto cerebral [14].

Se realizaron las siguientes pruebas de laboratorio al ingreso (realizadas en las primeras 72 horas de ingreso): prueba de glucemia capilar (HGT), hemoglobina (Hb), leucocitos, relación neutrófilos/linfocitos (NLR), lactato deshidrogenasa (LDH), proteína total, albúmina, Proteína C reactiva (PCR) y dímero D. Se realizaron estudios de imagen para determinar la presencia de lesiones vasculares previas, territorio vascular cerebral (supratentorial e infratentorial), lateralidad, leucoaraiosis, microsangrado, signos precoces de ictus y transformación hemorrágica. Las variables de tratamiento fueron la reperfusión intravenosa, el tratamiento quirúrgico y el tipo de tratamiento de prevención secundaria (antiagregación plaquetaria única/doble o anticoagulación).

Durante el seguimiento se registró el ingreso a la unidad de cuidados intermedios, unidad de cuidados intensivos (UCI), resultado funcional (bueno, mRS 0-2 y malo, mRS 3-6) y el destino del paciente (alta o muerte).

Análisis estadístico

La información se registró y almacenó de forma anónima en una base de datos para proteger la confidencialidad y solo era accesible para el investigador principal. Posteriormente, la base de datos fue exportada al programa STATA v17. Las variables categóricas fueron resumidas en función de frecuencias y porcentajes, las variables cuantitativas, mediante medidas de tendencia central y dispersión de acuerdo a la distribución de datos.

Para evaluar las asociaciones entre las complicaciones intrahospitalarias y las variables sociodemográficas, clínicas y paraclínicas, se realizaron pruebas de hipótesis. La mayoría de variables se dicotomizaron y se utilizó la prueba de Chi-cuadrado, mientras que para la variable hemoglobina (Hb) se utilizó la prueba t de Student y para la variable estancia en urgencias se usó el test de la U de Mann-Whitney.

Finalmente, se estimó el tamaño del efecto (riesgo relativo e intervalos de confianza del 95 %) mediante la creación de modelos de regresión de Poisson con varianza robusta. Se construyeron modelos crudos en el análisis bivariado considerando los siguientes factores: edad, sexo, antecedente de ictus, estado basal (independiente, mRS 0-2 y dependiente, mRS 3-5), uso de medicación previa para enfermedad cardiovascular, presencia de comorbilidad, ICC (bajo, 0-4 y alto, mayor de 4), funciones vitales al ingreso, cuadro clínico, gravedad del ictus (no grave, 0-10 y grave, mayor de 10), estancia en urgencias y pruebas de laboratorio (Hb, leucocitos, NLR, LDH, proteínas totales, albúmina, PCR y dímero D).

En el análisis multivariado, se construyó un modelo parsimonioso, realizando un modelo de anidamiento entre las variables que resultaron estadísticamente significativas en el modelo de análisis crudo y considerando como variables confusoras a la edad, sexo y factores de riesgo de ictus (hipertensión arterial, diabetes, antecedente de ictus). No se consideró en el análisis multivariado aquellas variables con más del 30% de valores perdidos. Se evaluó en los modelos ajustados, la colinealidad entre las variables de exposición, mediante el método de Belsley; se usó el índice de condición (mayor a 30) y la proporción de descomposición de varianza (superior a 0,5) para asumir colinealidad. Al identificar las variables colineales, se evaluaron individualmente para saber si la exclusión de algunas de ellas disminuía la colinealidad, solucionando así el problema en caso de identificarse. Adicionalmente, se hizo un análisis secundario, para explorar los factores de riesgo de las complicaciones intrahospitalarias más frecuentes. Se utilizó un nivel de significación estadística de 0,05 para todas las pruebas estadísticas.

Consideraciones éticas

En el presente estudio, solo los investigadores tuvieron acceso y revisaron las historias clínicas, entonces, no hubo contacto directo con los pacientes. El estudio se llevó a cabo de acuerdo con la Declaración de Helsinki y los autores aseguraron el anonimato de los datos de los pacientes incluidos en el estudio.

Además, el protocolo de investigación fue aprobado por el Comité de Ética del hospital (Carta N° 964 - GRPR -ESSALUD-2021) y el Comité de Ética de la Universidad Científica del Sur (Carta N° 404-CIEI-CIENTÍFICA-2021).

Resultados

Características demográficas de los participantes

Durante el periodo de estudio se incluyeron 192 pacientes diagnosticados de infarto cerebral agudo. La edad media fue de $71,7 \pm 11,9$ años, el 16,2% de los pacientes eran menores de 60 años y el 64,6% eran hombres. Además, el 74,3% de los pacientes presentaba al menos una comorbilidad previa en la historia clínica, siendo las más frecuentes la hipertensión arterial (67,2%) y la diabetes mellitus (30,7%). Encontramos que el 36,1% de los pacientes no refirió medicación previa para enfermedad cardiovascular, mientras que el 57,3% utilizaba fármacos antihipertensivos y el 21,4% terapia antiplaquetaria. Más detalles de las características demográficas de los pacientes se muestran en la Tabla 1.

Características clínicas de la muestra de estudio

Entre los pacientes ingresados, el 95,3% tenía un estado basal de independencia funcional. Los síntomas iniciales más frecuentes al ingreso fueron debilidad de las extremidades (75,8%) y disartria (49,2%). La gravedad de la enfermedad fue leve en el 26% de los pacientes, moderada en el 54,2%, grave en el 18,2% y muy grave en el 1,6%. En cuanto a la clasificación etiológica, el 39,1% se reportó como aterosclerosis de gran vaso, el 25% cardioembólica, el 22,9% lacunar, el 2,1% de causa poco frecuente y el 10,9% de etiología indeterminada. Los hallazgos de neuroimagen mostraron que el 83,8% correspondía al territorio supratentorial, mientras que la arteria cerebral media fue el territorio vascular más reportado y el 31,2% presentaba algún grado de leucoaraiosis.

Con respecto al tratamiento, de los 24 pacientes (12,5%) ingresados dentro de la ventana terapéutica (tiempo ictus puerta de hasta 4,5 horas), solo 5 pacientes (2,6%) recibieron tratamiento agudo con activador tisular del plasminógeno recombinante (rtPA). Como estrategia de prevención se utilizó antiagregación plaquetaria secundaria o anticoagulación según la clasificación etiológica.

En relación con la evolución clínica de los pacientes, 60 (31,2%) ingresaron en unidad de cuidados intermedios y 6 (3,1%) en UCI. La mediana de estancia en urgencias antes del ingreso en una unidad neurológica fue de 2 días (rango intercuartílico [RIC], 1-3 días) y la mediana de estancia hospitalaria fue de 15 días (RIC, 10-23 días). Como desenlace clínico se reportó una mortalidad del 6,2%. En cuanto a los resultados funcionales, el 49,5% del total de pacientes ingresados en el estudio egresaron con dependencia funcional; los 5 pacientes que recibieron rtPA fueron funcionalmente independientes al egreso. En la tabla 2 se muestran las características clínicas y de imagen de los pacientes estudiados.

Complicaciones intrahospitalarias

Durante la hospitalización ocurrió al menos una complicación intrahospitalaria en el 32,3% de los pacientes. En cuanto a los tipos de complicaciones, las más frecuentes fueron infecciosas en un 22,4% (torácica 15,1% y urinaria 7,3%), seguidas de un 17,7% de complicaciones neurológicas (ictus recurrente 1,6%, crisis epilépticas 1,6%, transformación hemorrágica 5,3%, hipertensión intracraneal 3,6% y eventos inexplicados 7,3%), mientras que otras complicaciones, como tromboembolismo (trombosis venosa profunda 0,5%), inamovilidad (úlceras por presión 5,2%) y misceláneas (hemorragia menor 1%, hemorragia mayor 1,6%, insuficiencia renal aguda 7,3%, trastorno hidroelectrolítico 2,6%) eran mucho menos frecuentes. La coexistencia de los 2 tipos de complicaciones más frecuentes (neurológica e infecciosa) se reportó en 12 pacientes (6,25%).

Al comparar las características clínicas, demográficas y de laboratorio de los pacientes con infarto cerebral agudo que presentaron complicaciones intrahospitalarias con el grupo sin complicaciones, se encontraron diferencias significativas en la edad (diferencia de edad entre complicado versus no complicado fue de 4,52 años; $p=0,013$), la presencia de al menos una comorbilidad (34,9% comorbilidad y complicación versus 13,0% en no comorbilidad y complicación; $p=0,035$), ICC alto (ICC de 5 o mayor; $p=0,008$), uso previo de antiarrítmicos ($p=0,001$), gravedad del ictus según NIHSS >10 ($p=0,002$), aterotrombótico de gran vaso según la clasificación etiológica del ictus ($p=0,006$) y en todas las pruebas de laboratorio al ingreso (Hb, leucocitos, NLR, LDH, proteínas totales, albúmina, PCR y dímero D).

Se encontraron diferencias significativas en las siguientes variables en el análisis exploratorio por tipo de complicación en pacientes con complicaciones neurológicas: presión arterial sistólica al ingreso (la presión arterial sistólica más baja presentó un mayor porcentaje de complicaciones neurológicas en

comparación con la más alta 185 mmHg 20,5 vs 4,0; $p=0,047$), uso previo de antiarrítmicos ($p=0,001$), mayor estancia en urgencias ($p=0,01$), gravedad del ictus según NIHSS >10 ($p=0,007$), aterotrombótico de gran vaso según la clasificación etiológica del ictus ($p=0,005$), cefalea ($p=0,004$), disartria ($p=0,011$) y solo los valores de Hb, leucocitos y PCR fueron significativos. En cuanto a las complicaciones infecciosas, se encontraron diferencias significativas en pacientes con antecedente de medicación previa ($p=0,010$), uso de antihipertensivos ($p=0,04$) e hipoalbuminemia ($p=0,043$) (Tablas 3-5).

Factores de riesgo de complicaciones intrahospitalarias en el modelo de regresión crudo

Al evaluar asociaciones con modelos de regresión de Poisson, se encontró que un ICC > 4 aumenta el riesgo de presentar una complicación intrahospitalaria en un 74% (riesgo relativo [RR]: 1,74; intervalo de confianza [IC] del 95%: 1,15 - 2,65). Además, los pacientes con un NIHSS > 10 al ingreso tenían 1,90 veces (IC 95%: 1,25 - 2,9) más riesgo de presentar una complicación intrahospitalaria en comparación con aquellos con un NIHSS inferior. Todas las pruebas de laboratorio presentaron resultados estadísticamente significativos en el análisis crudo (Cuadro 6).

Se realizó un análisis exploratorio según los tipos de complicaciones más frecuentes: neurológicas e infecciosas. En cuanto a las complicaciones neurológicas, los pacientes con un NIHSS > 10 al ingreso tenían 2,36 veces (IC 95%: 1,24 - 4,49) más riesgo de presentar una complicación neurológica en comparación con aquellos con un NIHSS inferior. Los valores de Hb, leucocitos y PCR fueron estadísticamente significativos. En el análisis crudo de complicaciones infecciosas, los pacientes con antecedentes de medicación previa tenían un riesgo 2,37 veces mayor (IC 95%: 1,16 - 4,83) de presentar algún tipo de complicación infecciosa y niveles de albúmina $> 3,5$ mg/dL fue un factor protector, disminuyendo el riesgo en un 49% (IC 95%: 0,28 - 0,94) (Tabla 7).

Factores de riesgo de complicaciones intrahospitalarias en el modelo de regresión multivariado

En el análisis multivariado, se realizó un modelo parsimonioso realizando un modelo de anidamiento entre las variables que resultaron estadísticamente significativas en el modelo de análisis crudo y considerando como variables confusoras a la edad, sexo y factores de riesgo de ictus (hipertensión arterial, diabetes, antecedente de ictus). Además, se realizó un análisis de colinealidad de las variables antes de ingresar al modelo final, se observó 3 grupos de variables que obtuvieron un índice de condición mayor a 30 y la proporción de descomposición de varianza superior a 0,5. El primer grupo de variables donde se observó colinealidad fueron el recuento de leucocitos, valor de PCR e índice neutrófilo linfocito, decidiendo excluir la variable leucocitos y PCR en el modelo final. También se estimó colinealidad entre las variables índice de comorbilidad de Charlson (ICC) y los factores de riesgo de ictus, excluyendo al ICC. En el grupo de variables nivel de proteína sérica y albúmina también se evidenció colinealidad, excluyendo a proteína sérica del modelo final.

En el modelo multivariado final la gravedad del accidente cerebrovascular mantuvo la asociación, pero disminuyó en intensidad de 1,9 a 1,76. (RR=1,76; IC 95%, 1,09-2,86; $p=0,022$) y se mantuvieron niveles de albúmina $> 3,5$ mg/dL que pasó de 0,45 a 0,53 (RR=0,53; IC 95%, 0,36-0,79; $p=0,002$) tras ajustar por edad, sexo y factores de riesgo de ictus (tabla 8).

En el análisis exploratorio por tipo de complicación neurológica, se hizo también análisis de colinealidad evidenciando colinealidad en dos grupos de variables. En el primer grupo de variables de presión arterial sistólica (PAS) e hipertensión arterial, se excluyó del modelo final a PAS. En el grupo de variables de hemoglobina, PCR y leucocitos, se excluyó la variable de recuento leucocitario.

En el modelo final exploratorio, la Hb (RR=0,86; IC 95%, 0,73- 0,99; $p=0,047$) fue un factor protector estadísticamente significativo para las complicaciones neurológicas, mientras que en el análisis de las complicaciones infecciosas el antecedente de medicación previa por enfermedad cardiovascular fue un factor de riesgo (RR=2,79; IC 95%, 1,16- 6,71; $p=0,022$), tras ajustar por los confusores (Tabla 9).

Discusión

El objetivo principal de este estudio fue estimar los factores de riesgo de complicaciones intrahospitalarias en pacientes con infarto cerebral agudo hospitalizados en un hospital nacional de referencia en Perú. Como principales hallazgos encontramos que aproximadamente uno de cada tres pacientes presentó complicaciones intrahospitalarias (32,3%) y la severidad del ictus isquémico agudo definido por una escala NIHSS > 10 fue factor de riesgo y un nivel de albúmina > 3,5 mg/dL fue un factor protector para el desarrollo de complicaciones intrahospitalarias.

La frecuencia de complicaciones intrahospitalarias en el presente estudio fue menor a la reportada por Pandian et al. en India (45,9%) y por Langhorne et al. en Escocia (85%), aunque estos estudios incluyeron pacientes con accidente cerebrovascular tanto isquémico como hemorrágico. También consideraron el dolor y las complicaciones psicológicas [5],[6]. Nuestro estudio solo incluyó pacientes con infarto cerebral agudo, ya que consideramos que los resultados clínicos de los pacientes con ictus isquémico y hemorrágico podrían ser heterogéneos [15].

En los últimos años se ha observado una tendencia a la baja en la notificación de complicaciones intrahospitalarias, probablemente debido a la optimización de la atención al ictus en los diferentes sistemas sanitarios. Si bien las tasas más altas de mortalidad y discapacidad se reportan en América Latina y en muchos países de ingresos bajos y medianos [2], en los últimos años se han realizado esfuerzos conjuntos para mejorar esta situación en esta parte del mundo [16], [17].

En el presente estudio aproximadamente 1 de cada 5 pacientes (22,4%) presentó una complicación infecciosa. Esto concuerda con lo descrito en estudios realizados en India, Escocia y Argentina, en los que las complicaciones infecciosas fueron las más frecuentes, con incidencias del 34,4%, 65% y 20%, respectivamente [5],[6], [9].

Estos hallazgos son importantes, ya que la mayoría de las complicaciones infecciosas son del tipo respiratorio y del tracto urinario, y estas pueden prevenirse con una adecuada educación y capacitación del personal médico, de enfermería y técnico involucrado en la atención de pacientes con accidente cerebrovascular [18], [19].

En el presente estudio y en otros, la severidad del accidente cerebrovascular (NIHSS > 10) ha demostrado ser un factor de riesgo importante [6],[8],[9]. Este hallazgo puede explicarse por el hecho de que los pacientes con mayor gravedad del ictus requieren cuidados diferentes y mayor seguimiento intrahospitalario, lo que puede conllevar un mayor riesgo de presentar complicaciones durante la hospitalización. Por lo tanto, es importante que los pacientes ingresados por un accidente cerebrovascular sean evaluados o admitidos de manera temprana a una unidad de atención de accidentes cerebrovasculares o neurológica [20],[21]. En el caso de nuestros pacientes, la mediana de estancia en urgencias fue de 2 días, lo que refleja la pronta derivación a una unidad de cuidados neurológicos.

Otro hallazgo en el presente estudio fue que a pesar de haber un 25.5% de datos perdidos (143/192) que podría limitar la interpretación de los resultados de la variable de albúmina > 3,5 mg/dl, esta resultó ser un factor protector para las complicaciones intrahospitalarias. Este marcador fue explorado previamente por Pandian et al. quienes encontraron asociación en el análisis bivariado, pero sin significación estadística en el análisis multivariado [6]. La explicación más plausible es que los niveles de albúmina sérica son un signo de laboratorio del estado nutricional de los pacientes, por lo que los pacientes con niveles bajos de albúmina tendrían un mayor riesgo de complicaciones hospitalarias y un peor pronóstico al igual que en patologías similares [22], [23].

En el análisis exploratorio de los factores de riesgo de las complicaciones intrahospitalarias más frecuentes (neurológicas e infecciosas), se obtuvo significancia estadística para la Hb como factor protector de complicaciones neurológicas. Artículos anteriores han demostrado que la presencia de anemia aumenta el riesgo de mortalidad en pacientes con ictus y es un factor de riesgo de complicaciones intrahospitalarias [6],[24]. Aunque aún no se ha definido el mecanismo, se ha postulado que la disminución del suministro de oxígeno en pacientes con anemia en estado de estrés provocado por el ictus, que requiere un aumento de los niveles de oxígeno, podría predisponer a estos pacientes a complicaciones médicas. [6]. El antecedente de medicación previa para enfermedad cardiovascular fue un factor de riesgo para la presencia de complicaciones infecciosas. Este resultado puede explicarse porque el antecedente de recibir medicación previa se relaciona con la gravedad de estas comorbilidades, lo que podría condicionar a los pacientes a presentar mayor susceptibilidad a procesos

infecciosos, como los reportados en la presente cohorte.

Determinados marcadores laboratoriales han sido considerados previamente como reactantes de fase aguda y se han asociado a peores desenlaces clínicos en infarto cerebral, así como en otras patologías cardiovasculares y neurológicas agudas [25], [26], [27], [28], [29]. En el análisis bivariado nosotros identificamos que el índice neutrófilo/linfocito, PCR, LDH y dímero D se asociaron a la presencia de complicaciones intrahospitalarias, aunque la información fue bastante sugestiva, los hallazgos estuvieron limitados por la información perdida de estos exámenes en algunos de los registros de los pacientes incluidos en el estudio. Se necesitan más estudios para confirmar estos hallazgos, que podrían servir para tomar en cuenta en el flujo de atención de los pacientes con infarto cerebral agudo que presentes estos valores en los exámenes laboratoriales de admisión.

Estudios previos donde se han realizado análisis de los factores de riesgo por complicaciones intrahospitalarias específicas, han evidenciado que la severidad del ictus es un factor de riesgo independiente para la presencia de complicaciones intrahospitalarias tanto de manera específica para complicaciones infecciosas o en el análisis global agrupando a las complicaciones intrahospitalarias en neurológicas y no neurológicas [5], [8], [9]. Así mismo, Pandian realizó un subanálisis de exploración de las complicaciones intrahospitalarias específicas utilizadas en la clasificación, quienes se asociaron de manera independiente con mal pronóstico funcional [5].

En cuanto a los resultados clínicos, la mortalidad hospitalaria en el presente estudio fue del 6,2%. Este valor es inferior al reportado en artículos previos en Perú [30], [31], [32], [33], como el estudio realizado por Castañeda et al. en el que se reportó una mortalidad del 13,6% en pacientes con accidente cerebrovascular isquémico agudo ingresados en un hospital público de referencia nacional en el período 2000-2009. Estos hallazgos son consistentes con datos más recientes obtenidos en otros países de América Latina que reportaron una disminución en la mortalidad hospitalaria por ACV probablemente explicada por las mejoras en la atención de estos pacientes en los últimos años, con la formación de unidades de ictus certificadas, como es el caso del centro donde se realizó nuestro estudio [34],[35]. Así mismo, esto también se puede explicar porque se consideró en el estudio una población bien específica de pacientes con infarto cerebral agudo, excluyendo a los pacientes con hemorragia cerebral o con sintomatología superior a las 72 horas de evolución, que podrían presentar peores desenlaces al ser una población más heterogénea con mayor riesgo de presentar complicaciones tanto intrahospitalarias como a la admisión en el centro hospitalario.

Nuestro estudio también mostró que casi la mitad de los pacientes tenían un mal pronóstico funcional al alta. Sin embargo, los 5 pacientes que recibieron tratamiento de reperfusión intravenosa en la fase aguda lograron la independencia funcional. Esto podría estar asociado a una menor frecuencia de complicaciones intrahospitalarias; aunque este efecto no fue medido en nuestro estudio, ya que se ha demostrado que las terapias de reperfusión intravenosa y mecánica son estrategias costo-efectivas para reducir la mortalidad, las complicaciones y la discapacidad en pacientes con accidente cerebrovascular [36],[37],[38].

Este estudio tiene algunas limitaciones. Dado que los datos se obtuvieron de la historia clínica, algunas variables de laboratorio no estaban disponibles (HGT, LDH, dímero D), por lo que ciertas variables no pudieron incluirse en los modelos de regresión multivariado. Así mismo es preciso mencionar que el modelo multivariado final no pudo contar con la totalidad de los pacientes enrolados, específicamente por la pérdida de información reportada de la variable albúmina. El estudio se realizó con el objetivo principal de estimar los factores de riesgo de complicaciones intrahospitalarias, por lo que la falta de significancia estadística en los análisis de los tipos de complicaciones más frecuentes

puede deberse a un problema puramente estadístico y no epidemiológico. Asimismo, el período de seguimiento se limitó al tiempo de hospitalización y no permitió realizar análisis de asociación con el pronóstico funcional tras el alta hospitalaria.

A pesar de las limitaciones anteriores, este estudio tiene algunas fortalezas. Se incluyó un número importante de pacientes debido a que el estudio se realizó en un hospital de referencia nacional. Además, se realizó un análisis completo de los diferentes factores de riesgo con complicaciones globales y se exploraron los factores según los tipos más frecuentes. Asimismo, se dispuso de datos completos de la mayoría de las variables debido al adecuado registro mediante el sistema de historia clínica electrónica.

Conclusiones

En conclusión, este estudio de cohorte reporta una baja tasa de mortalidad intrahospitalaria y una relativa baja tasa de complicaciones intrahospitalarias, respecto a la evidencia disponible, debido probablemente a la exclusión de los ictus hemorrágicos y a la atención de estos pacientes en un centro con cuidados neurológicos de ictus.

La gravedad del accidente cerebrovascular fue un factor de riesgo y la albúmina superior a 3,5 mg/dL fue un factor protector para la presencia de complicación intrahospitalaria. La hemoglobina fue un factor protector para la presencia de complicación neurológica y el antecedente de medicación previa por enfermedad cardiovascular fue un factor de riesgo para presentar complicación infecciosa.

Estos resultados pueden servir como punto de partida para establecer sistemas de atención de ictus que consideren flujos diferenciados considerando la presencia de estos factores en los pacientes con infarto cerebral agudo, para la prevención de complicaciones intrahospitalarias.

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Tabla 1. Características demográficas de pacientes con infarto cerebral agudo (n=192).

Variables	n	%
Sexo		
Femenino	68	35.4
Masculino	124	64.6
Edad (años)		
30a 59	31	16.2
60 a 70	50	26
≥71	111	57.8
Estado basal		
Independente (mRS:0-2)	183	95.3
Dependente (mRS:3-5)	9	4.7
Comorbilidades		
Ninguna	50	25.7
Al menos 1	142	74.3
Hipertensión arterial	129	67.2
Diabetes mellitus	59	30.7
Enfermedad renal crónica	12	6.3
Enfermedad coronaria crónica	14	7.3
Epilepsia	10	5.2
Historia de ictus previo		
Ninguna	154	80.2
Ictus hemorrágico	2	1
Ictus isquémico	35	18.2
CCI		
0	9	4.7
1 a 2	26	13.5
3 a 4	72	37.5
5 o más	85	44.3
Medicación previa		
No	69	36.1
Si	122	63.9
Antihipertensivo	110	57.3
Antiagregantes	41	21.4
Estatinas	30	15.6
antiarrítmicos	34	17.7
Warfarina	10	5.2

Abreviaciones: mRS: Escala de Rankin modificada; CCI: Índice de Charlson ajustado por edad

Tabla 2. Características clínicas e imagenológicas de pacientes con infarto cerebral agudo (n=192).

Variables	n	%
Severidad de ictus (NIHSS admisión)		
I (0 a 4)	50	26
II (5 a 15)	104	54.2
III (16 a 25)	35	18.2
IV (26 o más)	3	1.6
Síntomas de ictus		
Debilidad de extremidad	144	75.8
Disartria	94	49.2
Cefalea	39	20.4
Afasia	30	15.7
Ataxia	28	14.7
Clasificación etiológica		
Aterotrombótico de gran vaso	75	39.1
Lacunar	44	22.9
cardioembólico	48	25
Causas infrecuentes	4	2.1
etiología no determinada	21	10.9
Hallazgos de neuroimágenes		
Territorio vascular cerebral		
Infratentorial	31	16.2
Supratentorial	161	83.8
Arteria cerebral afectada		
ACM	121	63
ACA	3	1.6
ACP	10	5.2
VB	29	15.1
2 o más territorios	29	15.1
Lateralidad		
Izquierdo	104	54.2
Derecho	88	45.8
Leucoaraiosis	59	31.2
Microsangrado	7	3.7
Signos tempranos de ictus	8	4.2
Tratamiento recibido		
Trombólisis	5	2.6
Terapia antiagregante simple	111	57.8
Terapia antiagregante doble	7	3.6
Anticoagulación	43	22.4
Estatinas	141	73.8
Admisión a unidad de cuidados intermedios	60	31.2
Admisión a UCI	6	3.1
Complicación intrahospitalaria	62	32.3
NIHSS al alta		
I (0 a 4)	52	28.9
II (5 a 15)	101	56.1
III (16 a 25)	26	14.4
IV (26 o más)	1	0.6
NIHSS al alta en pacientes con trombólisis		
I (0 a 4)	1	20
II (5 a 15)	4	80
Rankin al alta		
Independiente (mRS:0-2)	85	44.3
Dependiente (mRS:3-5)	95	49.5
Fallecidos	12	6.2

Abreviaciones: ACM: arteria cerebral media, ACA: arteria cerebral anterior, ACP: arteria cerebral posterior, VB: vertebro basilar; ICU: Unidad de cuidados intensivos ; mRS: Escala de Rankin modificada.

Tabla 3. Comparación de complicaciones intrahospitalarias y tipo de complicación según las características demográficas de los pacientes con ictus isquémico agudo.

Variables	Complicación intrahospitalaria			complicación neurológica			complicación infecciosa		
	Si n=62 (%)	No N=130 (%)	P valor	Si n=34 (%)	No N=158 (%)	P valor	Si n=42 (%)	No N=150 (%)	P valor
Edad	74.74 (10.7)	70.22 (12.19)	0.013	73.5 (14.4)	71.3 (11.3)	0.407	73.1 (11.3)	71.2 (12.1)	0.373
Sexo									
Femenino	18 (26.5)	50 (73.5)	0.201	14 (20.6)	54 (79.4)	0.439	15 (22.4)	52 (77.6)	0.922
Masculino	44 (35.5)	80 (64.5)		20 (16.1)	104 (83.9)		27 (21.8)	97 (78.2)	
Historia de ictus									
No	52 (33.5)	103 (66.5)	0.446	28 (18.1)	127 (81.9)	0.791	36 (23.4)	118 (76.6)	0.345
Si	10 (27.0)	27 (73.0)		6 (16.2)	31 (83.8)		6 (16.2)	31 (83.8)	
Comorbilidades									
No	3 (13.0)	20 (90.0)	0.035	3 (13.0)	20 (87.0)	0.532	3 (13.0)	20 (87.0)	0.269
Si	59 (34.9)	110 (65.1)		31 (18.3)	138 (81.7)		39 (23.2)	129 (76.8)	
CCI									
0 a 4	26 (24.3)	81 (75.5)	0.008	15 (14.0)	92 (86.0)	0.133	19 (17.8)	88 (82.2)	0.111
5 o más	36 (42.3)	49 (57.7)		19 (22.4)	66 (77.6)		23 (27.4)	61 (72.6)	
Medicación previa									
No	21 (30.4)	48 (69.6)	0.653	15 (21.7)	54 (78.3)	0.285	8 (11.8)	60 (88.2)	0.010
Si	41 (33.6)	81 (66.4)		19 (15.8)	103 (84.4)		34 (27.9)	88 (72.1)	
Antiagregantes									
No	48 (31.8)	103 (68.2)	0.775	27 (17.9)	124 (82.1)	0.904	30 (20.0)	120 (80.0)	0.204
Sí	14 (34.2)	27 (65.8)		7 (17.0)	34 (83.0)		12 (29.3)	29 (70.7)	
Warfarina									
No	57 (31.3)	125 (68.7)	0.219	33 (18.1)	149 (81.9)	0.512	40 (22.1)	141 (77.9)	0.876
Si	5 (50.0)	5 (50.0)		1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
estatinas									
No	52 (32.1)	110 (67.9)	0.894	28 (17.3)	134 (82.7)	0.72	33 (20.5)	128 (79.5)	0.249
Si	10 (33.3)	20 (66.7)		6 (20.0)	24 (80.0)		9 (30.0)	21 (70.0)	
NOAC									
No	61 (32.5)	127 (67.5)	0.753	32 (17.0)	156 (83.0)	0.087	41 (21.9)	146 (78.1)	0.883
Si	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)		1 (25.0)	3 (75.0)	
Antihipertensivo									
No	28 (34.2)	54 (65.8)	0.635	18 (21.9)	64 (78.1)	0.184	12 (14.8)	69 (85.2)	0.040
Si	34 (30.9)	76 (69.1)		16 (14.5)	94 (84.5)		30 (27.3)	80 (72.7)	
Antiarrítmico									
No	43 (27.2)	115 (72.8)	0.001	21 (13.3)	137 (86.7)	0.001	32 (20.4)	125 (79.6)	0.249
Si	19 (55.9)	15 (44.1)		13 (38.2)	21 (61.8)		10 (29.4)	24 (70.6)	
Inmunosupresores									
No	60 (32.3)	126 (67.7)	0.956	32 (17.2)	154 (82.8)	0.308	40 (21.6)	145 (78.4)	0.495
Si	2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)	
Estancia en urgencias*‡	2 (1-3)	2 (1-2)	0.105	2 (1 - 2)	2 (1- 2)	0.010	2 (1- 3)	2 (1 - 2)	0.051

Abreviaciones: CCI: índice de Charlson ajustado por edad; NOAC: Nuevos anticoagulantes orales

*Mediana (IQR: rango intercuartílico).

Usamos los siguientes test estadísticos: chi2 test and ‡ Mann-Whitney U test.

Tabla 4. Comparación de complicaciones intrahospitalarias y tipo de complicación según las características clínicas y hallazgos imagenológicos de pacientes con ictus isquémico agudo.

Variables	Complicación intrahospitalaria			Complicación neurológica			Complicación infecciosa		
	Si n=62 (%)	No N=130 (%)	P valor	Si n=34 (%)	No N=158 (%)	P valor	Si n=42 (%)	No N=150 (%)	P valor
PAS (mmHg)									
<=185	50 (31.1)	111 (68.9)	0.095	33 (20.5)	128 (79.5)	0.047	35 (21.9)	125 (78.1)	0.497
>185	12 (48.0)	13 (52.0)		1 (4.0)	24 (96.0)		7 (28.0)	18 (72.0)	
PAD (mmHg)									
<=110	62 (33.5)	123 (66.5)	0.478	34 (18.4)	151 (81.6)	0.635	41 (22.3)	143 (77.7)	0.064
>110	0 (0.0)	1 (100)		0 (0.0)	1(100.0)		1 (100.0)	0 (0.0)	
FC (latidos/min)									
<=90	44 (31.2)	97 (68.8)	0.068	25 (17.7)	116 (82.3)	0.832	34 (24.1)	107 (75.9)	0.197
>90	15 (48.4)	16 (51.6)		5 (16.1)	26 (83.9)		4 (13.3)	26 (86.7)	
HGT (mg/dL)									
<=180	22 (33.9)	43 (66.1)	0.167	11 (16.9)	54 (83.1)	0.658	12 (18.5)	53 (81.5)	0.298
>180	1 (11.1)	8 (88.9)		1 (11.1)	8 (88.9)		3 (33.3)	6 (66.7)	
Severidad de ictus (NIHSS)									
<=10	25 (23.2)	83 (76.8)	0.002	12 (11.1)	96 (88.9)	0.007	25 (23.2)	83 (76.8)	0.659
>10	37 (44.1)	47 (55.9)		22 (26.2)	62 (73.8)		17 (20.5)	66 (79.5)	
Estado basal									
Independiente	60 (32.8)	123 (67.2)	0.508	33 (18.0)	150 (82.0)	0.595	40 (22.0)	142 (78.0)	0.986
Dependiente	2 (22.2)	7 (77.8)		1 (11.1)	8 (88.9)		2 (22.2)	7 (77.8)	
Clasificación etiológica									
Aterotrombótico de gran vaso	23 (30.7)	52 (69.3)	0.006	11 (14.7)	64 (85.3)	0.005	14 (18.7)	61 (81.3)	0.584
Lacunar	7 (15.9)	37 (84.1)		4 (9.1)	40 (90.9)		12 (27.9)	31 (72.1)	
cardioembólico	23 (47.9)	25 (52.1)		17 (35.4)	31 (64.6)		12 (25.0)	36 (75.0)	
Causas infrecuentes	3 (75.0)	1 (25.0)		0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	
etiología no determinada	6 (28.6)	15 (71.4)		2 (9.5)	19 (90.5)		4 (19.1)	17 (80.9)	
Debilidad de extremidad									
No	15 (32.6)	31 (67.4)	0.997	11 (23.9)	35 (76.1)	0.221	7 (15.2)	39 (84.8)	0.189
Si	47 (32.6)	97 (67.4)		23 (16.0)	121 (84.0)		35 (24.5)	108 (75.5)	
déficit visual									
No	58 (32.9)	118 (67.1)	0.736	31 (17.6)	145 (82.4)	0.720	41 (23.4)	134 (76.6)	0.158
Si	4 (28.6)	10 (71.4)		3 (21.4)	11 (78.6)		1 (7.1)	13 (92.9)	
Afasia									
No	50 (31.1)	111 (68.9)	0.337	28 (17.4)	133 (82.6)	0.732	37 (23.0)	124 (77.0)	0.493
Si	12 (40.0)	18 (60.0)		6 (20.0)	24 (80.0)		5 (17.2)	24 (84.8)	
Cefalea									
No	52 (34.2)	100 (65.8)	0.308	21 (13.8)	131 (86.2)	0.004	33 (21.9)	118 (78.1)	0.870
Si	10 (25.6)	29 (74.4)		13 (33.3)	26 (66.7)		9 (23.1)	30 (76.9)	

Crisis epiléptica									
No	59 (32.1)	125 (67.9)	0.748	33 (17.9)	151 (82.1)	0.693	42 (23.0)	141 (77.0)	0.125
Si	3 (37.5)	5 (62.5)		1 (12.5)	7 (87.5)		0 (0.0)	8 (100.0)	
vértigo									
No	58 (32.9)	118 (67.1)	0.618	31 (17.6)	145 (82.4)	0.817	40 (22.9)	135 (77.1)	0.394
Si	4 (26.7)	11 (73.3)		3 (20.0)	12 (80.0)		2 (13.3)	13 (86.7)	
parálisis facial									
No	54 (32.9)	110 (67.1)	0.735	30 (18.3)	134 (81.7)	0.662	35 (21.5)	128 (78.5)	0.605
Si	8 (29.6)	19 (70.4)		4 (14.8)	23 (85.2)		7 (25.9)	20 (74.1)	
Pérdida de sensibilidad									
No	61 (34.1)	118 (65.9)	0.065	34 (19.0)	145 (81.0)	0.096	42 (23.6)	136 (76.4)	0.057
Si	1 (8.3)	11 (91.7)		0 (0.0)	12 (100.0)		0 (0.0)	12 (100.0)	
Marcha inestable									
No	54 (33.1)	109 (66.9)	0.634	28 (17.2)	135 (82.8)	0.587	33 (20.4)	129 (79.6)	0.166
Si	8 (28.6)	20 (71.4)		6 (21.4)	22 (78.6)		9 (32.1)	19 (67.9)	
Disartria									
No	32 (33.0)	65 (67.0)	0.874	24 (24.7)	73 (75.3)	0.011	18 (18.6)	79 (81.4)	0.229
Si	30 (31.9)	64 (68.1)		10 (10.6)	84 (89.4)		24 (25.8)	69 (74.2)	
territorio cerebral vascular									
Infratentorial	10 (32.3)	21 (67.3)	0.997	3 (9.7)	28 (90.3)	0.201	7 (23.3)	23 (76.7)	0.847
Supratentorial	52 (32.3)	109 (67.3)		31 (19.3)	130 (80.8)		35 (21.7)	126 (78.3)	
Arteria cerebral afectada									
ACM	41 (33.9)	80 (66.1)	0.892	21 (17.4)	100 (82.6)	0.075	28 (23.3)	92 (76.7)	0.781
ACA	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)		0 (0.0)	3 (100.0)	
ACP	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
VB	7 (24.1)	22 (75.9)		2 (6.9)	27 (93.1)		5 (17.2)	24 (82.8)	
2 o más territorios	10 (34.5)	19 (65.5)		6 (20.7)	23 (79.3)		6 (20.7)	23 (79.3)	
lateralidad imagenológica									
izquierda	35 (33.7)	69 (66.4)	0.661	21 (20.2)	83 (79.8)	0.327	22 (21.2)	82 (78.9)	0.76
Derecha	27 (30.7)	61 (69.3)		13 (14.8)	75 (85.2)		20 (23.0)	67 (77.0)	
Leucoaraiosis									
No	38 (29.2)	92 (70.8)	0.12	22 (16.9)	108 (83.1)	0.571	30 (23.1)	100 (76.9)	0.717
Si	24 (40.7)	35 (59.3)		12 (20.3)	47 (79.7)		12 (20.7)	46 (79.3)	

Abreviaciones: PAS: presión arterial sistólica; PAD: presión arterial diastólica; FC: frecuencia cardiaca; HGT: test de glicemia capilar; ACM: arteria cerebral media, ACA: arteria cerebral anterior, ACP: arteria cerebral posterior, VB: vertebro basilar.
Usamos las siguientes pruebas estadísticas: chi2 test.

Tabla 5. Comparación de complicaciones intrahospitalarias y tipo de complicación según resultados laboratoriales de pacientes con ictus isquémico agudo.

Variable	Complicación intrahospitalaria			Complicación neurológica			Complicación infecciosa		
	Yes n=62 (%)	No n=130 (%)	P valor	Yes n=34 (%)	No n=158 (%)	P valor	Yes n=42 (%)	No n=150 (%)	P valor
Hb (g/dL) †	12.7 (1.8)	13.6 (1.9)	0.003	12.4 (1.9)	13.5 (1.8)	0.035	13.3 (2.1)	13.3 (1.8)	0.946
Leucocitos (cels/μL)									
<5000	7 (50.0)	7 (50.0)	0.001	4 (28.6)	10 (71.4)	0.022	2 (14.3)	12 (85.7)	0.713
5000-12000	41 (27.3)	109 (72.7)		20 (13.3)	130 (86.7)		33 (22.0)	117 (78.0)	
>12000	11 (68.8)	5 (31.3)		6 (37.5)	10 (62.5)		4 (26.7)	11 (73.3)	
NLR									
<3	20 (22.7)	68 (77.3)	0.005	12 (13.6)	76 (86.4)	0.286	18 (20.5)	70 (79.5)	0.671
\geq 3	39 (42.4)	53 (57.6)		18 (19.6)	74 (80.4)		21 (23.1)	70 (76.9)	
LDH (IU/L)									
\leq 350	16 (25.8)	46 (74.2)	0.003	11 (17.7)	51 (82.3)	0.195	13 (21.0)	49 (79.0)	0.624
>350	12 (63.2)	7 (36.8)		6 (31.6)	13 (68.4)		5 (26.3)	14 (73.7)	
proteínas totales (g/dL)									
\leq 6	15 (55.6)	12 (44.4)	0.011	6 (22.2)	21 (77.8)	0.549	8 (30.8)	18 (69.2)	0.293
>6	38 (29.9)	89 (70.1)		22 (17.3)	105 (82.7)		27 (21.3)	100 (78.7)	
Albumina (g/dL)									
\leq 3.5	14 (60.9)	9 (39.1)	0.002	6 (26.1)	17 (73.9)	0.192	9 (40.9)	13 (59.1)	0.043
>3.5	33 (27.5)	87 (72.5)		18 (15.0)	102 (85.0)		25 (20.8)	95 (79.2)	
CRP (mg/ dL)									
\leq 2	20 (20.6)	77 (79.4)	<0.001	11 (11.3)	86 (88.7)	0.001	20 (20.6)	77 (79.4)	0.422
>2	29 (63.0)	17 (37.0)		16 (34.8)	30 (65.2)		12 (26.7)	33 (73.3)	
Dímero D (μg/mL)									
\leq 1	6 (20.0)	24 (80.0)	0.012	4 (13.3)	26 (86.7)	0.203	9 (30.0)	21 (70.0)	0.518
>1	21 (48.8)	22 (51.2)		11 (25.6)	32 (74.4)		10 (23.3)	33 (76.7)	

Abreviaciones: Hb: hemoglobina; NLR: índice neutrófilo/linfocito; LDH: lactato deshidrogenasa; CRP: proteína -C reactiva.

*Mediana (IQR: rango intercuartílico).

Usamos las siguientes pruebas estadísticas: chi2 test y † Student's t test.

Tabla 6. Modelo de regresión cruda de factores de riesgo de complicaciones intrahospitalarias en pacientes con

Variable	RR	95% CI	P valor
ictus isquémico agudo.			
Sexo			
Femenino	Ref		
Masculino	1.34	0.84 - 2.13	0.215
Edad			
<=70	Ref.	0.86 - 2.05	0.203
>70	1.33		
Historia de ictus			
No	Ref.		
Si	0.81	0.45 - 1.43	0.462
PAS (mmHg) (n=186)			
<=185	Ref.		
>185	1.55	0.97 - 2.47	0.069
FC (latidos/min) (n=186)			
<=90	Ref.		
>90	1.55	0.99 - 2.40	0.051
HGT (mg/dL) (n=74)			
<=180	Ref		
>180	0.33	0.49 - 2.18	0.248
Comorbilidades			
No	Ref		
Si	2.68	0.91 - 7.87	0.073
CCI			
0 to 4	Ref		
5 o más	1.74	1.15 - 2.65	0.009
Medicación previa			
No	Ref.		
Si	1.1	0.71 - 1.71	0.656
Severidad de ictus (NIHSS)			
<=10	Ref.		
>10	1.9	1.25 - 2.90	0.003
Estado basal			
Independiente	Ref.		
Dependiente	1.02	0.81 - 1.29	0.841
Lateralidad imagenológica			
Izquierda	Ref		
Derecha	0.91	0.60 - 1.38	0.662
Hb (g/dL)	0.86	0.78 - 0.94	0.001
Leucocitos (cels/μL) (n=180)			
5000-12000	Ref.		
<5000	1.83	1.02 - 3.29	0.044
>12000	2.52	1.65 - 3.84	<0.001
NLR (n=180)			
<3	Ref		
\geq 3	1.87	1.18 - 2.94	0.007
LDH (IU/L) (n=81)			
<=350	Ref.		
>350	2.45	1.42 - 4.23	0.001
proteínas totales (g/dL)(n=154)			
<=6	Ref.		
>6	0.54	0.35 - 0.83	0.005
Albumina (g/dL) (n=143)			
<=3.5	Ref		
>3.5	0.45	0.29 - 0.70	<0.001
CRP (mg/ dL) (n=143)			
<=2	Ref		

>2	3.06	1.95 - 4.80	<0.001
Dímero D (µg/mL) (n=73)			
<=1	Ref		
>1	2.44	1.12 - 5.35	0.026

Abreviaciones: PAS: presión arterial sistólica; FC: frecuencia cardiaca; HGT: test de glicemia capilar; CCI: índice de comorbilidad de Charlson ajustado por edad; Hb: hemoglobina; NLR: índice neutrófilo/linfocito; LDH: lactato deshidrogenasa; CRP: proteína C reactiva; CI: intervalo de confianza; RR: riesgo relativo.

Tabla 7. Modelo de regresión cruda de factores de riesgo de complicaciones neurológicas e infecciosas en pacientes con ictus isquémico agudo.

Variable	complicaciones neurológicas			complicaciones infecciosas		
	RR	95% CI	P valor	RR	95% CI	P valor
Sexo						
Femenino	Ref			Ref		
Masculino	0.78	0.42 - 1.45	0.438	0.97	0.56 - 1.67	0.922
Edad						
<=70	Ref.			Ref.		
>70	1.18	0.63 - 2.22	0.61	1.33	0.75 - 2.33	0.327
Historia de ictus						
No	Ref.			Ref.		
Si	0.90	0.40 - 2.01	0.793	0.69	0.32 - 1.53	0.363
PAS (mmHg)						
<=185	Ref.			Ref.		
>185	0.20	0.03 - 1.37	<0,001	1.28	0.64 - 2.57	0.487
FC (beat/min)						
<=90	Ref.			Ref.		
>90	0.91	0.38 - 2.19	0.833	0.55	0.21 - 1.45	0.227
HGT (mg/dL)						
<=180	Ref			Ref		
>180	0.66	0.09 - 4.56	0.67	1.81	0.62 - 5.23	0.276
Comorbilidades						
No	Ref			Ref		
Si	1.41	0.47 - 4.25	0.545	1.78	0.60 - 5.31	0.301
CCI						
0 a 4	Ref			Ref		
5 o más	1.59	0.86 - 2.95	0.138	1.54	0.90 - 2.64	0.114
Medicación Previa						
No	Ref.			Ref.		
Si	0.72	0.39 - 1.32	0.285	2.37	1.16 - 4.83	0.018
Severidad de ictus (NIHSS)						
<=10	Ref.			Ref.		
>10	2.36	1.24 - 4.49	0.009	0.88	0.51 - 1.53	0.661
Estado basal						
Independiente	Ref.			Ref.		
Dependiente	0.61	0.09 - 4.03	0.613	1.01	0.29 - 3.55	0.986
Lateralidad						
Izquierda	Ref			Ref		
Derecha	0.73	0.39 - 1.38	0.333	1.09	0.64 - 1.86	0.761
Hb (g/dL)						
0.8	0.70 - 0.91	0.001		0.99	0.85 - 1.17	0.95
Leucocitos (cels/μL)						
5000-12000	Ref.			Ref.		
<5000	2.15	0.85 - 5.41	0.107	0.65	0.17 - 2.43	0.522
>12000	2.81	1.32 - 5.98	0.007	1.21	0.50 - 2.96	0.673
NLR						
<3	Ref			Ref		
>=3	1.43	0.73 - 2.81	0.292	1.13	0.65 - 1.97	0.672
LDH (IU/L)						
<=350	Ref.			Ref.		
>350	1.78	0.76 - 4.19	0.187	1.26	0.51 - 3.09	0.621
proteínas totales (g/dL)						
<=6	Ref.			Ref.		
>6	0.78	0.35 - 1.74	0.544	0.69	0.35 - 1.35	0.279
Albumina (g/dL)						
<=3.5	Ref			Ref		
>3.5	0.58	0.26 - 1.30	0.182	0.51	0.28 - 0.94	0.031

CRP (mg/ dL)

<=2	Ref			Ref		
>2	3.08	1.55 - 6.09	0.001	1.29	0.69 - 2.42	0.419

Dímero D (µg/mL)

<=1	Ref			Ref		
>1	1.92	0.67 - 5.50	0.225	0.78	0.36 - 0.68	0.52

Abreviaciones: PAS: presión arterial sistólica; FC: frecuencia cardiaca; HGT: test de glicemia capilar; CCI: índice de Charlson ajustado por edad; Hb: hemoglobina; NLR: índice neutrófilo/linfocito; LDH: lactato deshidrogenasa; CRP: Proteína C-reactiva. CI: intervalo de confianza; RR: riesgo relativo.

Tabla 8. Análisis multivariado de factores de riesgo de complicaciones intrahospitalarias en pacientes con ictus isquémico agudo.

Variable	RR	95% CI	P valor
Sexo			
Femenino	Ref.		
Masculino	1.25	0.75 - 2.10	0.393
Edad	1.02	0.99 - 1.04	0.086
Hipertensión			
No	Ref.		
Si	0.66	0.40-1.07	0.094
Diabetes			
No	Ref.		
Si	1.06	0.65-1.72	0.82
Historia de ictus			
No	Ref.		
Si	0.93	0.46 - 1.86	0.846
FC (lat/min)			
<=90	Ref.		
>90	1.41	0.88 - 2.27	0.153
Severidad de ictus (NIHSS)			
<=10	Ref.		
>10	1.76	1.09 - 2.86	0.022
NLR			
<3	Ref.		
>=3	1.29	0.8 - 2.08	0.295
Albumina (g/dL)			
<=3.5	Ref.		
>3.5	0.53	0.36 - 0.79	0.002

Análisis multivariante obtenido con regresión de Poisson, modelo parsimonioso. Abreviaturas: NLR: relación neutrófilos/linfocitos; IC: intervalo de confianza; RR: riesgo relativo.

Tabla 9. Análisis multivariado de factores de riesgo de complicaciones neurológicas e infecciosas en pacientes con ictus isquémico agudo.

Complicaciones Infecciosas	Complicaciones neurológicas						
	Variable	RR	95% CI	P valor	RR	95% CI	P valor
Sexo							
	Femenino	Ref.			Ref.		
	Masculino	0.88	0.39 - 2.00	0.768	0.89	0.49 - 1.61	0.69
Edad		0.99	0.95 - 1.03	0.655	1.01	0.99 - 1.04	0.33
hipertensión							
	No	Ref.			Ref.		
	Si	0.88	0.40 - 1.98	0.772	0.97	0.52 - 1.83	0.931
Diabetes							
	No	Ref.			Ref.		
	Si	0.76	0.35 - 1.67	0.502	0.95	0.50 - 1.82	0.877
Historia de ictus							
	No	Ref.			Ref.		
	Si	1.14	0.49 - 2.64	0.763	0.67	0.25 - 1.75	0.411
Medicación previa							
	No				Ref.		
	Si	-			2.79	1.16-6.71	0.022
Severidad de ictus (NIHSS)							
	<=10	Ref.					
	>10	1.56	0.72 - 3.40	0.26	-		
Hb (g/dL)		0.86	0.73 - 0.99	0.047	-		
CRP (mg/ dL)							
	<=2	Ref			-		
	>2	2.49	0.97 - 6.38	0.057	-		
Albumina (g/dL)							
	<=3.5				Ref		
	>3.5	-			0.67	0.35 - 1.28	0.225

Ab abreviaciones: Hb: hemoglobina; CRP: Proteína C reactiva.

ANEXOS

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Risk factors for in-hospital complications in patients with acute ischemic stroke:
Retrospective cohort in a national reference hospital in Peru

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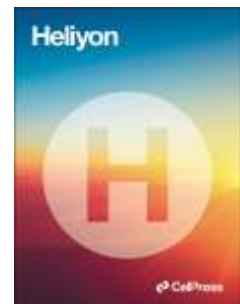
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Risk factors for in-hospital complications in patients with acute ischemic stroke: retrospective cohort in a national reference hospital in Peru

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Abstract

Objective: To describe the clinical and demographic characteristics of patients with acute cerebral infarction treated at a national reference hospital in Peru and determine the risk factors for in-hospital complications.

Methods: We conducted a retrospective cohort study including 192 patients with acute ischemic stroke in a national reference hospital in Peru from January to September 2021. Clinical, demographic and paraclinical information was recorded from medical records. We estimated risk ratios and 95% confidence intervals using regression models with Poisson family and robust variance for the bivariate and multivariate model, adjusting for age, sex and risk factors for stroke.

Results: At least one in-hospital complication occurred in 32.3% of the patients. The most frequent complications were infectious in 22.4%, followed by 17.7% of neurological complications, with other complications, such as thromboembolism, immobility and miscellaneous, being much less frequent. Regression analysis showed that stroke severity (RR=1.76; 95%CI:1.09-2.86) and albumin greater than 3.5 mg/dL (RR=0.53; 95%CI: 0.36-0.79) were independent risk factors for the presence of in-hospital complications.

Conclusions: A high rate of in-hospital complications were observed, among which infectious and neurological complications were the most frequent. Stroke severity was a risk factor and albumin greater than 3.5 mg/dL was a protective factor for the incidence of in-hospital complications. These results can serve as a starting point for establishing stroke care systems that consider differentiated flows for the prevention of in-hospital complications.

Keywords: Stroke, Acute; Ischemic Stroke; Complications; Risk Factors (Source: MeSH).

Introduction

Stroke is one of the leading causes of disability and mortality worldwide [1]. This condition more seriously affects low- and middle-income countries, generating, according to international reports, a high health cost, not only due to hospital expenses but also due to the indirect expenses that it entails in the long term, such as those related to the loss of work of the patient [2],[3],[4].

Previous studies in Europe and Asia have described incidences of in-hospital complications greater than 40% in patients admitted with stroke [5],[6]. In addition, it has been reported that part of the disability and mortality associated with stroke is sustained by the presence of in-hospital complications, many of which could be preventable [6]. Therefore, some measures have been proposed, such as the optimization of comprehensive care protocols and training related to preventive care and timely management of complications for all health personnel involved in the care of patients with stroke [7].

In Latin America, where most countries are low- and middle-income, there may be differences in the rate of in-hospital complications compared to what is reported in other regions. Few studies are available and most provide partial data, reporting only non-neurological complications and their predictive factors [8],[9]. The main objective of this study was to determine the risk factors for in-hospital complications in patients with acute ischemic stroke treated at a national reference hospital in Peru. This article was written following the STROBE guidelines for observational studies [10].

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Methods

Design and population

We conducted a retrospective study of a cohort of patients treated at an essential stroke center belonging to the social security system in Lima, Peru. The Edgardo Rebagliati Martins National Hospital is a national reference hospital with resolution capacity for intravenous reperfusion treatment.

The population included all patients over 18 years of age admitted to the emergency department (ED) with a diagnosis of acute ischemic stroke during the period from January 1 to September 30, 2021. The information of the patients enrolled was obtained from the data recorded in the clinical history during hospitalization (from admission to the ED until discharge or death). A diagnosis of acute ischemic stroke was given to patients with acute neurological deficit confirmed by neuroimaging (tomography or cerebral magnetic resonance) and with a maximum stroke-gatetime of 72 hours. A total of 215 patients attended the ED with this diagnosis during the study period; of these, we excluded 23 patients diagnosed with COVID-19 at admission or during hospitalization, leaving 192 patients for data analysis.

Variables

In-hospital complications were defined as medical problems arising during hospital stay according to clinical definitions [5],[6]. We made an adaptation of the previously used classification, and the complications were classified as neurological (seizures, recurrent stroke, hemorrhagic transformation, intracranial hypertension and unexplained events), infectious (thoracic, urinary or other infection), thromboembolism (pulmonary and deep vein thrombosis), immobility complications (pressure ulcers and falls) and miscellaneous (not classified in the previous categories). Due to the retrospective design, we did not include pain or psychological complications, because they were not reported in the medical record.

We evaluated demographic variables such as age, sex, level of education, toxic habits (alcohol, smoking and drug use), previous medication for cardiovascular disease as well as the most prevalent pathological antecedents including high blood pressure, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, chronic heart disease, cardiac arrhythmia, autoimmune disease, chronic lung disease, malignant neoplasm, cerebrovascular disease, thyroid disease, obstructive sleep area syndrome, and chronic liver disease. Based on previous comorbidities, the age adjusted Charlson comorbidity index (CCI) [11] was also used.

Regarding clinical variables, the following were determined: baseline status (estimated by the "modified Rankin scale", mRS at admission) [12], vital functions at admission (heart rate, systolic and diastolic blood pressure) and the clinical picture presented in the patient. We recorded the severity of acute ischemic stroke at ED admission and at discharge estimated by the "National Institutes of Health Stroke Scale" (NIHSS) and divided into groups: mild (0-4), moderate (5-15), severe (16-25) and very severe (>25)[13]. We used the etiological classification of the "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) for cerebral infarction [14].

The following laboratory tests were performed at admission (carried out in the first 72 hours of

admission): capillary glycemia test, hemoglobin (Hb), leukocytes, neutrophil/lymphocyte ratio (NLR), lactate dehydrogenase (LDH), total protein, albumin, C-reactive protein (CRP) and D-dimers. Imaging studies were performed to determine the presence of previous vascular lesions, cerebral vascular territory (supratentorial and infratentorial), laterality, leukoariosis, microbleeding, early signs of stroke and hemorrhagic transformation. Treatment variables included intravenous reperfusion, surgical treatment, and the type of secondary prevention treatment (single/dual antiplatelet therapy or anticoagulation).

During follow-up, admission to the intermediate care unit, intensive care unit (ICU), functional outcome (good, mRS 0-2 and poor, mRS 3-6) and the destination of the patient (discharge or death) were recorded.

Statistical analysis

The information was recorded and stored anonymously in a database to protect confidentiality and was only accessible by the principal investigator. Subsequently, the database was exported to the STATA v17 program. To summarize the categorical variables, frequencies and percentages were used, while for the quantitative variables, measures of central tendency and dispersion were used depending on the distribution of the data.

To evaluate the associations between in-hospital complications and sociodemographic, clinical, and paraclinical variables, hypothesis tests were performed according to the nature of the independent variables. The Chi-square test was used for categorical variables, while the Student's t test or Mann-Whitney U test was used for quantitative variables.

Finally, the effect size (relative risk and 95% confidence intervals) was estimated by creating Poisson regression models with robust variance. Crude models were constructed in the bivariate analysis considering the following factors: age, sex, history of stroke, baseline status (independent, mRS 0-2 and dependent, mRS 3-5), use of previous medication for cardiovascular disease, presence of previous comorbidity, CCI (low, 0-4 and high, greater than 4), vital functions on admission, clinical picture, severity of stroke (non-severe, 0-10 and severe, greater than 10), length of stay in the ED and laboratory tests (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP, and D-dimer).

The multivariate analysis was adjusted for age, sex and risk factors for stroke (hypertension, diabetes, history of stroke). In addition, a parsimonious model was constructed, performing a nesting model among the variables that were statistically significant in the crude analysis model. The assumption of linearity was evaluated when constructing the models and, additionally, lost data among the variables and collinearity were evaluated in the adjusted models. A statistical significance level of 0.05 was used for all the statistical tests.

Ethical issues

In the present study, only the researchers had access and reviewed the clinical histories, then, there was no direct contact with the patients. The study was carried out in accordance with the Declaration of Helsinki, and the authors ensured anonymity of the patient data included in the

study. In addition, the research protocol was approved by the Ethics Committee of the hospital (Letter No. 964 -GRPR -ESSALUD-2021) and the Ethics Committee of the Universidad Científica del Sur (Letter No. 404-CIEI-CIENTÍFICA-2021).

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Results

Demographic characteristics of the participants

During the study period, we included 192 patients diagnosed with acute ischemic stroke. The mean age was 71.7 ± 11.9 years, 16.2% of the patients were under 60 years of age, and 64.6% were male. In addition, 74.3% of the patients presented at least one previous comorbidity in the clinical history, and the most frequent was arterial hypertension (67.2%) and diabetes mellitus (30.7%). We found that 36.1% of the patients reported no prior medication for cardiovascular disease, while 57.3% used antihypertensive drugs and 21.4% antiplatelet therapy. Further details of the demographic characteristics of the patients are shown in Table 1.

Clinical characteristics of the study sample

Among the admitted patients, 95.3% had a baseline status of functional independence. The most frequent initial symptoms at admission were limb weakness (75.8%) and dysarthria (49.2%). Disease severity was mild in 26% of the patients, being moderate in 54.2%, severe in 18.2% and very severe in 1.6%. Regarding the etiological classification, 39.1% were reported as long-artery atherosclerosis, 25% cardioembolic, 22.9% lacunar, 2.1% had infrequent causes, and 10.9% had an undetermined etiology. Neuroimaging findings showed that 83.8% corresponded to the supratentorial territory, while the middle cerebral artery was the most reported vascular territory and 31.2% had some degree of leukoaraiosis.

With respect to treatment, of the 24 patients (12.5%) admitted within the therapeutic window (stroke-door time of up to 4.5 hours), only 5 patients (2.6%) received acute treatment with recombinant tissue plasminogen activator (rtPA) as prevention strategies. Secondary antiplatelet therapy or anticoagulation was used according to the etiological classification.

In relation to the clinical evolution of the patients, 60 (31.2%) were admitted to an intermediate care unit and 6 (3.1%) to an ICU. The median stay in the ED before admission to a neurological unit was 2 days (interquartile range [IQR], 1-3 days) and the median hospital stay was 15 days (IQR, 10-23 days). As a clinical outcome, a mortality of 6.2% was reported. Regarding functional results, 49.5% of the total number of patients admitted to the study were functionally dependent; the 5 patients who received rtPA were functionally independent. Table 2 shows the clinical and imaging characteristics of the patients studied.

In-hospital complications

During hospitalization, at least one in-hospital complication occurred in 32.3% of patients. Regarding the types of complications, the most frequent were infectious in 22.4% (thoracic 15.1% and urinary 7.3%), followed by 17.7% of neurological complications (recurrent stroke 1.6%, epileptic seizures 1.6%, 5.3% hemorrhagic transformation, intracranial hypertension 3.6% and unexplained events 7.3%), while other complications, such as thromboembolism (deep vein thrombosis 0.5%), immobility (pressure ulcers 5.2%) and miscellaneous (minor bleeding 1%, major bleeding 1.6%, acute renal failure 7.3%, hydroelectrolytic disorder 2.6%) were much less frequent. The coexistence of the 2 most frequent types of complications (neurological and

infectious) was reported in 12 patients (6.25%).

When comparing the clinical, demographic and laboratory characteristics of the patients with acute ischemic stroke presenting in-hospital complications with the group without complications, there were significant differences in age (age difference between complicated versus uncomplicated was 4.52 years; $p=0.013$), the presence of at least one comorbidity (34.9% comorbidity and complication versus 13.0% in not comorbidity and complication; $p=0.035$), high CCI (5 or more have 42.3% with complication; $p=0.008$), previous use of antiarrhythmics ($p=0.001$), severity of stroke according to an NIHSS >10 ($p=0.002$), etiological classification of stroke ($p=0.006$) and in all laboratory tests at admission (Hb, leukocytes, NLR, LDH, total protein, albumin, CRP and D-dimer).

Significant differences were found in the following variables in the exploratory analysis by type of complication in patients with neurological complications: systolic blood pressure at admission (lower systolic blood pressure presented a higher percentage of neurological complications compared to higher 185 mmHg 20.5 vs. 4.0; $p=0.047$), previous use of antiarrhythmics ($p=0.001$), longer ED stay ($p=0.01$), stroke severity according to the NIHSS >10 ($p=0.007$), etiological classification of stroke ($p=0.005$), headache ($p=0.004$), dysarthria ($p=0.011$) and only Hb, leukocyte and CRP values were significant. Regarding infectious complications, significant differences were found in patients with a history of previous medication ($p=0.010$), use of antihypertensive drugs ($p=0.04$), and hypoalbuminemia ($p=0.043$) (Tables 3-5).

Risk factors for in-hospital complications in the bivariate analysis

When evaluating associations with Poisson regression models, a CCI > 4 was found to increase the risk of presenting an in-hospital complication by 74% (relative risk [RR]: 1.74; 95% confidence interval [CI]: 1.15 - 2.65). In addition, patients with a NIHSS > 10 at admission had a 1.90-fold (95% CI: 1.25 - 2.9) greater risk of presenting an in-hospital complication compared to those with a lower NIHSS. All the laboratory tests presented statistically significant results in the crude analysis (Table 6).

An exploratory analysis was made according to the most frequent types of complications: neurological and infectious. Regarding neurological complications, patients with a NIHSS > 10 at admission had a 2.36-fold (95% CI: 1.24 - 4.49) greater risk of presenting a neurological complication compared to those with a lower NIHSS. Hb, leukocyte and CRP values were statistically significant. In the crude analysis of infectious complications, patients with a history of previous medication had a 2.37-fold higher risk (95% CI: 1.16 - 4.83) of presenting some type of infectious complication and albumin levels > 3.5 mg/dL was a protective factor, decreasing the risk by 49% (95% CI: 0.28 - 0.94) (Table 7).

Risk factors for in-hospital complications in the multivariate analysis

In the multivariate analysis for in-hospital complications, stroke severity retained the association but decreased in strength from 1.9 to 1.76. (RR=1.76; 95% CI, 1.09-2.86; $p=0.022$) and albumin levels > 3.5 mg/dL which went from 0.45 to 0.53 (RR=0.53; 95% CI, 0.36-0.79; $p=0.002$) were

maintained after adjusting for age, sex and stroke risk factors (Table 8).

In the exploratory analysis by type of complication, Hb (RR=0.86; 95% CI, 0.73-0.99; p=0.047) was a statistically significant protective factor for neurological complications, while in the analysis of infectious complications, all factors except for the history of prior medication for cardiovascular disease lost statistical significance (RR=2.79; 95% CI, 1.16-6.71; p=0.022), after adjusting for the confounders (Table 9).

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proof

Discussion

The main objective of this study was to estimate the risk factors for in-hospital complications in patients with acute ischemic stroke hospitalized in a national reference hospital in Peru. As main findings, we found that approximately one in three patients presented in-hospital complications (32.3%) and the severity of the acute ischemic stroke defined by an NIHSS scale > 10 was a risk factor and an albumin level > 3.5 mg/dL was a protective factor for the development of in-hospital complications.

The frequency of in-hospital complications in the present study was lower than that reported by Pandian *et al.* in India (45.9%) and by Langhorne *et al.* in Scotland (85%), although these studies included patients with both ischemic and hemorrhagic stroke. They also considered pain and psychological complications [5],[6]. Our study only included patients with acute ischemic stroke, as we consider that the clinical outcomes of patients with ischemic and hemorrhagic stroke could be heterogeneous [15].

In recent years, there has been a downward trend in the reporting of in-hospital complications, probably due to the optimization of stroke care in the different health systems. Although the highest mortality and disability rates are reported in Latin America and in many low- and middle-income countries [2], in recent years there have been joint efforts to improve this situation in this part of the world [16],[17].

In the present study approximately 1 in 5 patients (22.4%) presented an infectious complication. This is consistent with what has been described in studies conducted in India, Scotland, and Argentina, in which infectious complications were the most frequent, with incidences of 34.4%, 65%, and 20%, respectively [5],[6],[9].

These findings are important, since most of the infectious complications are of the respiratory and urinary tract type, and these can be prevented with adequate education and training of the medical, nursing and technical personnel involved in the care of patients with stroke [18],[19].

In the present study and others, the severity of stroke (NIHSS > 10) has shown to be an important risk factor [6],[8],[9]. This finding can be explained by the fact that the patients with greater stroke severity require different care and greater in-hospital monitoring which may lead to a higher risk of presenting complications during hospitalization. It is therefore important for patients admitted for stroke to be evaluated or admitted early to a stroke or neurological care unit if there is no physical space available in the ED [20],[21]. In the case of our patients, the median stay in the ED was 2 days, which reflects the prompt referral to a neurological care unit.

Another finding in the present study was that albumin levels > 3.5 mg/dL were found to be a protective factor for in-hospital complications. This marker was previously explored by Pandian *et al.* who found an association in the bivariate analysis but without statistical significance in the multivariate analysis [6]. The most plausible explanation is that serum albumin levels are a laboratory sign of the nutritional status of patients, and thus, patients with low albumin levels would have a higher risk of hospital complications and a worse prognosis as seen in similar pathologies [22],[23].

In the exploratory analysis of the risk factors for the most frequent in-hospital complications

(neurological and infectious), statistical significance was obtained for Hb as a protective factor for neurological complications, which, unlike previous studies in which the variable of anemia was considered, we believe Hb values should be analyzed as a numerical variable. Previous articles have shown that the presence of anemia increases the risk of mortality in patients with stroke and is a risk factor for in-hospital complications [6],[24]. Although the mechanism for this has yet to be defined, it has been postulated that the decrease in oxygen supply in patients with anemia in a state of stress caused by the stroke, which requires an increase in oxygen levels, could predispose these patients to medical complications [6]. The history of prior medication for cardiovascular disease was a risk factor for the presence of infectious complications. This result can be explained in that the history of receiving previous medication is related to the severity of these comorbidities, which could condition the patients to presenting greater susceptibility to infectious processes, such as those reported in the present cohort.

Regarding clinical outcomes, the in-hospital mortality in the present study was 6.2%. This value is lower than that reported in previous articles in Peru [25], [26], [27], [28], such as the study carried out by Castañeda *et al.* in which a mortality of 13.6% was reported in patients with acute ischemic stroke admitted to a public hospital of national reference in the period 2000-2009. These findings are consistent with more recent data obtained in other Latin American countries which reported a decrease in hospital mortality due to stroke likely explained by the improvements in the care of these patients in recent years [29],[30].

Our study also showed that almost half of the patients had a poor functional prognosis at discharge. However, the 5 patients who received intravenous reperfusion treatment in the acute stage achieved functional independence. This could be associated with a lower frequency of in-hospital complications; although this effect was not measured in our study, since it has already been shown that intravenous and mechanical reperfusion therapies are cost-effective strategies for reducing mortality, complications, and disability in patients with stroke [31],[32],[33].

This study has some limitations. Since the data were obtained from medical records, some laboratory variables were not available (CGT, LDH, D-dimer), and thus, certain variables could not be included in the multivariate regression models. The study was carried out with the main objective of estimating the risk factors for in-hospital complications, therefore the lack of statistical significance in the analyses of the most frequent types of complications may have been due to a purely statistical and not an epidemiological problem. Likewise, the follow-up period was limited to the time of hospitalization and did not allow analyses of association with the functional prognosis after hospital discharge.

Despite the above limitations, this study has some strengths. A significant number of patients was included because the study was performed in a national reference hospital. In addition, a complete analysis of different risk factors with global complications was carried out and factors were explored according to the most frequent types. Likewise, complete data of most of the variables were available due to adequate registration using the electronic medical record system.

Conclusions

In conclusion, this cohort study reports a high rate of in-hospital complications in patients presenting to the ED with stroke, among which infectious and neurological complications were of note as the most frequent. Stroke severity was a risk factor and albumin levels > 3.5 mg/dL were a protective factor for the incidence of in-hospital complications in patients with acute ischemic stroke. Further studies are needed to confirm these results and develop stroke care systems that consider these markers to provide deferred care with stricter monitoring and prevention of hospital complications.

PRODUCTION NOTES:

Author contribution statement:

Miguel A. Vences: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis data; Wrote the paper. </p>

Virgilio E. Failoc-Rojas: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis data; Wrote the paper. </p>

Diego Urrunaga-Pastor: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. </p>

Yamilée Hurtado-Roca: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis data; Wrote the paper. </p>

Data availability statement:

Data will be made available on request.

Declaration of interest's statement:

The authors declare no conflict of interest.

Additional information:

No additional information is available for this paper.

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Table 1. Demographic characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Sex		
Female	68	35.4
Male	124	64.6
Age (years)		
30 to 59	31	16.2
60 to 70	50	26
≥71	111	57.8
Baseline status		
Independent (mRS:0-2)	183	95.3
Dependent (mRS:3-5)	9	4.7
Comorbidities		
None	50	25.7
At least 1	142	74.3
Hypertension	129	67.2
Diabetes mellitus	59	30.7
Chronic kidney disease	12	6.3
Chronic coronary disease	14	7.3
Epilepsy	10	5.2
History of previous stroke		
None	154	80.2
Hemorrhagic stroke	2	1
Ischemic stroke	35	18.2
CCI		
0	9	4.7
1 to 2	26	13.5
3 to 4	72	37.5
5 or more	85	44.3
Previous medication		
No	69	36.1
Yes	122	63.9
Antihypertensive	110	57.3
Antiplatelet therapy	41	21.4
Statins	30	15.6
Antiarrhythmics	34	17.7
Warfarin	10	5.2

Abbreviations: mRS: Modified Rankin Scale; CCI: age adjusted Charlson comorbidity index.

Table 2. Clinical and imaging characteristics of patients with acute ischemic stroke (n=192).

Variables	n	%
Stroke severity (NIHSS admission)		
I (0 to 4)	50	26
II (5 to 15)	104	54.2
III (16 to 25)	35	18.2
IV (26 or more)	3	1.6
Stroke symptom		
Limb weakness	144	75.8
Dysarthria	94	49.2
Headache	39	20.4
Aphasia	30	15.7
Ataxia	28	14.7
Etiological classification		
Large vessel atherothrombotic	75	39.1
Lacunar	44	22.9
Cardioembolic	48	25
Uncommon causes	4	2.1
Undetermined etiology	21	10.9
Neuroimaging findings		
Cerebral vascular territory		
Infratentorial	31	16.2
Supratentorial	161	83.8
Affected cerebral artery		
MCA	121	63
ACA	3	1.6
PCA	10	5.2
VB	29	15.1
2 or more territories	29	15.1
Imaging laterality		
Left	104	54.2
Right	88	45.8
Leukoaraiosis	59	31.2
Microbleeding	7	3.7
Early signs of stroke	8	4.2
Treatment received		
Thrombolysis	5	2.6
Simple antiplatelet therapy	111	57.8
Dual antiplatelet therapy	7	3.6
Anticoagulation	43	22.4
Statins	141	73.8
Intermediate care unit admission	60	31.2
ICU admission	6	3.1
In-hospital complication	62	32.3
NIHSS at discharge		
I (0 to 4)	52	28.9
II (5 to 15)	101	56.1
III (16 to 25)	26	14.4
IV (26 or more)	1	0.6
NIHSS discharge in patients with thrombolysis		
I (0 to 4)	1	20
II (5 to 15)	4	80
Rankin at discharge		
Independent (mRS:0-2)	85	44.3
Dependent (mRS:3-5)	95	49.5
Death	12	6.2

Abbreviations: MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory; ICU: Intensive Care Unit; mRS: Modified Rankin Scale.

Table 3. Comparison of in-hospital complications and type of complication according to the demographic characteristics of patients with acute ischemic stroke.

Variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Age	74.74 (10.7)	70.22 (12.19)	0.013	73.5 (14.4)	71.3 (11.3)	0.407	73.1 (11.3)	71.2 (12.1)	0.373
Sex									
Female	18 (26.5)	50 (73.5)	0.201	14 (20.6)	54 (79.4)	0.439	15 (22.4)	52 (77.6)	0.922
Male	44 (35.5)	80 (64.5)		20 (16.1)	104 (83.9)		27 (21.8)	97 (78.2)	
Stroke history									
No	52 (33.5)	103 (66.5)	0.446	28 (18.1)	127 (81.9)	0.791	36 (23.4)	118 (76.6)	0.345
Yes	10 (27.0)	27 (73.0)		6 (16.2)	31 (83.8)		6 (16.2)	31 (83.8)	
Comorbidities									
No	3 (13.0)	20 (90.0)	0.035	3 (13.0)	20 (87.0)	0.532	3 (13.0)	20 (87.0)	0.269
Yes	59 (34.9)	110 (65.1)		31 (18.3)	138 (81.7)		39 (23.2)	129 (76.8)	
CCI									
0 to 4	26 (24.3)	81 (75.5)	0.008	15 (14.0)	92 (86.0)	0.133	19 (17.8)	88 (82.2)	0.111
5 or more	36 (42.3)	49 (57.7)		19 (22.4)	66 (77.6)		23 (27.4)	61 (72.6)	
Previous medication									
No	21 (30.4)	48 (69.6)	0.653	15 (21.7)	54 (78.3)	0.285	8 (11.8)	60 (88.2)	0.010
Yes	41 (33.6)	81 (66.4)		19 (15.8)	103 (84.4)		34 (27.9)	88 (72.1)	
Antiplatelet therapy									
No	48 (31.8)	103 (68.2)	0.775	27 (17.9)	124 (82.1)	0.904	30 (20.0)	120 (80.0)	0.204
Yes	14 (34.2)	27 (65.8)		7 (17.0)	34 (83.0)		12 (29.3)	29 (70.7)	
Warfarin									
No	57 (31.3)	125 (68.7)	0.219	33 (18.1)	149 (81.9)	0.512	40 (22.1)	141 (77.9)	0.876
Yes	5 (50.0)	5 (50.0)		1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
Statins									
No	52 (32.1)	110 (67.9)	0.894	28 (17.3)	134 (82.7)	0.72	33 (20.5)	128 (79.5)	0.249
Yes	10 (33.3)	20 (66.7)		6 (20.0)	24 (80.0)		9 (30.0)	21 (70.0)	
NOAC									
No	61 (32.5)	127 (67.5)	0.753	32 (17.0)	156 (83.0)	0.087	41 (21.9)	146 (78.1)	0.883
Yes	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)		1 (25.0)	3 (75.0)	
Antihypertensive									
No	28 (34.2)	54 (65.8)	0.635	18 (21.9)	64 (78.1)	0.184	12 (14.8)	69 (85.2)	0.040
Yes	34 (30.9)	76 (69.1)		16 (14.5)	94 (84.5)		30 (27.3)	80 (72.7)	
Anti-arrhythmic									
No	43 (27.2)	115 (72.8)	0.001	21 (13.3)	137 (86.7)	0.001	32 (20.4)	125 (79.6)	0.249
Yes	19 (55.9)	15 (44.1)		13 (38.2)	21 (61.8)		10 (29.4)	24 (70.6)	
Immunosuppressants									
No	60 (32.3)	126 (67.7)	0.956	32 (17.2)	154 (82.8)	0.308	40 (21.6)	145 (78.4)	0.495
Yes	2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)		2 (33.3)	4 (66.7)	
Emergency stay*‡	2 (1-3)	2 (1-2)	0.105	2 (1 - 2)	2 (1 - 2)	0.010	2 (1 - 3)	2 (1 - 2)	0.051

Abbreviations: CCI: age adjusted Charlson comorbidity index; NOAC: Novel oral anticoagulants.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and ‡ Mann-Whitney U test.

Table 4. Comparison of in-hospital complications and type of complication according to the clinical characteristics and imaging findings of patients with acute ischemic stroke.

Variables	In-hospital complication			Neurological complication			Infectious complication		
	Yes	No	P value	Yes	No	P value	Yes	No	P value
	n=62 (%)	n (%)		n=34 (%)	n (%)		n=42 (%)	n (%)	
SBP (mmHg)									
<=185	50 (31.1)	111 (68.9)	0.095	33 (20.5)	128 (79.5)	0.047	35 (21.9)	125 (78.1)	0.497
>185	12 (48.0)	13 (52.0)		1 (4.0)	24 (96.0)		7 (28.0)	18 (72.0)	
DBP (mmHg)									
<=110	62 (33.5)	123 (66.5)	0.478	34 (18.4)	151 (81.6)	0.635	41 (22.3)	143 (77.7)	0.064
>110	0 (0.0)	1 (100)		0 (0.0)	1(100.0)		1 (100.0)	0 (0.0)	
HR (beats/min)									
<=90	44 (31.2)	97 (68.8)	0.068	25 (17.7)	116 (82.3)	0.832	34 (24.1)	107 (75.9)	0.197
>90	15 (48.4)	16 (51.6)		5 (16.1)	26 (83.9)		4 (13.3)	26 (86.7)	
CGT (mg/dL)									
<=180	22 (33.9)	43 (66.1)	0.167	11 (16.9)	54 (83.1)	0.658	12 (18.5)	53 (81.5)	0.298
>180	1 (11.1)	8 (88.9)		1 (11.1)	8 (88.9)		3 (33.3)	6 (66.7)	
Severity of stroke (NIHSS)									
<=10	25 (23.2)	83 (76.8)	0.002	12 (11.1)	96 (88.9)	0.007	25 (23.2)	83 (76.8)	0.659
>10	37 (44.1)	47 (55.9)		22 (26.2)	62 (73.8)		17 (20.5)	66 (79.5)	
Baseline status									
Independent	60 (32.8)	123 (67.2)	0.508	33 (18.0)	150 (82.0)	0.595	40 (22.0)	142 (78.0)	0.986
Dependent	2 (22.2)	7 (77.8)		1 (11.1)	8 (88.9)		2 (22.2)	7 (77.8)	
Etiological classification									
Large vessel atherothrombotic	23 (30.7)	52 (69.3)	0.006	11 (14.7)	64 (85.3)	0.005	14 (18.7)	61 (81.3)	0.584
Lacunar	7 (15.9)	37 (84.1)		4 (9.1)	40 (90.9)		12 (27.9)	31 (72.1)	
Cardioembolic	23 (47.9)	25 (52.1)		17 (35.4)	31 (64.6)		12 (25.0)	36 (75.0)	
Uncommon causes	3 (75.0)	1 (25.0)		0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	
Undetermined etiology	6 (28.6)	15 (71.4)		2 (9.5)	19 (90.5)		4 (19.1)	17 (80.9)	
Limb weakness									
No	15 (32.6)	31 (67.4)	0.997	11 (23.9)	35 (76.1)	0.221	7 (15.2)	39 (84.8)	0.189
Yes	47 (32.6)	97 (67.4)		23 (16.0)	121 (84.0)		35 (24.5)	108 (75.5)	
Visual deficit									
No	58 (32.9)	118 (67.1)	0.736	31 (17.6)	145 (82.4)	0.720	41 (23.4)	134 (76.6)	0.158
Yes	4 (28.6)	10 (71.4)		3 (21.4)	11 (78.6)		1 (7.1)	13 (92.9)	
Aphasia									
No	50 (31.1)	111 (68.9)	0.337	28 (17.4)	133 (82.6)	0.732	37 (23.0)	124 (77.0)	0.493
Yes	12 (40.0)	18 (60.0)		6 (20.0)	24 (80.0)		5 (17.2)	24 (84.8)	
Headache									
No	52 (34.2)	100 (65.8)	0.308	21 (13.8)	131 (86.2)	0.004	33 (21.9)	118 (78.1)	0.870
Yes	10 (25.6)	29 (74.4)		13 (33.3)	26 (66.7)		9 (23.1)	30 (76.9)	

Epileptic seizures									
No	59 (32.1)	125 (67.9)	0.748	33 (17.9)	151 (82.1)	0.693	42 (23.0)	141 (77.0)	0.125
Yes	3 (37.5)	5 (62.5)		1 (12.5)	7 (87.5)		0 (0.0)	8 (100.0)	
Vertigo									
No	58 (32.9)	118 (67.1)	0.618	31 (17.6)	145 (82.4)	0.817	40 (22.9)	135 (77.1)	0.394
Yes	4 (26.7)	11 (73.3)		3 (20.0)	12 (80.0)		2 (13.3)	13 (86.7)	
Facial paralysis									
No	54 (32.9)	110 (67.1)	0.735	30 (18.3)	134 (81.7)	0.662	35 (21.5)	128 (78.5)	0.605
Yes	8 (29.6)	19 (70.4)		4 (14.8)	23 (85.2)		7 (25.9)	20 (74.1)	
Loss of sensation									
No	61 (34.1)	118 (65.9)	0.065	34 (19.0)	145 (81.0)	0.096	42 (23.6)	136 (76.4)	0.057
Yes	1 (8.3)	11 (91.7)		0 (0.0)	12 (100.0)		0 (0.0)	12 (100.0)	
Unsteady gait									
No	54 (33.1)	109 (66.9)	0.634	28 (17.2)	135 (82.8)	0.587	33 (20.4)	129 (79.6)	0.166
Yes	8 (28.6)	20 (71.4)		6 (21.4)	22 (78.6)		9 (32.1)	19 (67.9)	
Dysarthria									
No	32 (33.0)	65 (67.0)	0.874	24 (24.7)	73 (75.3)	0.011	18 (18.6)	79 (81.4)	0.229
Yes	30 (31.9)	64 (68.1)		10 (10.6)	84 (89.4)		24 (25.8)	69 (74.2)	
Cerebral vascular territory									
Infratentorial	10 (32.3)	21 (67.3)	0.997	3 (9.7)	28 (90.3)	0.201	7 (23.3)	23 (76.7)	0.847
Supratentorial	52 (32.3)	109 (67.3)		31 (19.3)	130 (80.8)		35 (21.7)	126 (78.3)	
Affected cerebral artery									
MCA	41 (33.9)	80 (66.1)	0.892	21 (17.4)	100 (82.6)	0.075	28 (23.3)	92 (76.7)	0.781
ACA	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)		0 (0.0)	3 (100.0)	
PCA	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
VB	7 (24.1)	22 (75.9)		2 (6.9)	27 (93.1)		5 (17.2)	24 (82.8)	
2 or more territories	10 (34.5)	19 (65.5)		6 (20.7)	23 (79.3)		6 (20.7)	23 (79.3)	
Imaging laterality									
Left	35 (33.7)	69 (66.4)	0.661	21 (20.2)	83 (79.8)	0.327	22 (21.2)	82 (78.9)	0.76
Right	27 (30.7)	61 (69.3)		13 (14.8)	75 (85.2)		20 (23.0)	67 (77.0)	
Leukoaraiosis									
No	38 (29.2)	92 (70.8)	0.12	22 (16.9)	108 (83.1)	0.571	30 (23.1)	100 (76.9)	0.717
Yes	24 (40.7)	35 (59.3)		12 (20.3)	47 (79.7)		12 (20.7)	46 (79.3)	

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CGT: capillary glycemia test; MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar territory.

We used the following statistical tests: chi2 test.

Table 5. C
ischemic stroke.

Variable	In-hospital complication			Neurological complication			Infectious complication		
	Yes n=62 (%)	No n (%)	P value	Yes n=34 (%)	No n (%)	P value	Yes n=42 (%)	No n (%)	P value
Hb (g/dL) †	12.7 (1.8)	13.6 (1.9)	0.003	12.4 (1.9)	13.5 (1.8)	0.035	13.3 (2.1)	13.3 (1.8)	0.946
Leukocytes (cells/μL)									
<5000	7 (50.0)	7 (50.0)	0.001	4 (28.6)	10 (71.4)	0.022	2 (14.3)	12 (85.7)	0.713
5000-12000	41 (27.3)	109 (72.7)		20 (13.3)	130 (86.7)		33 (22.0)	117 (78.0)	
>12000	11 (68.8)	5 (31.3)		6 (37.5)	10 (62.5)		4 (26.7)	11 (73.3)	
NLR									
<3	20 (22.7)	68 (77.3)	0.005	12 (13.6)	76 (86.4)	0.286	18 (20.5)	70 (79.5)	0.671
\geq 3	39 (42.4)	53 (57.6)		18 (19.6)	74 (80.4)		21 (23.1)	70 (76.9)	
LDH (IU/L)									
\leq 350	16 (25.8)	46 (74.2)	0.003	11 (17.7)	51 (82.3)	0.195	13 (21.0)	49 (79.0)	0.624
>350	12 (63.2)	7 (36.8)		6 (31.6)	13 (68.4)		5 (26.3)	14 (73.7)	
Total proteins (g/dL)									
\leq 6	15 (55.6)	12 (44.4)	0.011	6 (22.2)	21 (77.8)	0.549	8 (30.8)	18 (69.2)	0.293
>6	38 (29.9)	89 (70.1)		22 (17.3)	105 (82.7)		27 (21.3)	100 (78.7)	
Albumin (g/dL)									
\leq 3.5	14 (60.9)	9 (39.1)	0.002	6 (26.1)	17 (73.9)	0.192	9 (40.9)	13 (59.1)	0.043
>3.5	33 (27.5)	87 (72.5)		18 (15.0)	102 (85.0)		25 (20.8)	95 (79.2)	
CRP (mg/ dL)									
\leq 2	20 (20.6)	77 (79.4)	<0.001	11 (11.3)	86 (88.7)	0.001	20 (20.6)	77 (79.4)	0.422
>2	29 (63.0)	17 (37.0)		16 (34.8)	30 (65.2)		12 (26.7)	33 (73.3)	
D-dimer (μg/mL)									
\leq 1	6 (20.0)	24 (80.0)	0.012	4 (13.3)	26 (86.7)	0.203	9 (30.0)	21 (70.0)	0.518
>1	21 (48.8)	22 (51.2)		11 (25.6)	32 (74.4)		10 (23.3)	33 (76.7)	

Abbreviations: Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein.

*Median (IQR: interquartile range).

We used the following statistical tests: chi2 test and † Student's t test.

Table 6. Bivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref		
Male	1.34	0.84 - 2.13	0.215
Age			
<=70	Ref.	0.86 - 2.05	0.203
>70	1.33		
Stroke history			
No	Ref.		
Yes	0.81	0.45 - 1.43	0.462
SBP (mmHg) (n=186)			
<=185	Ref.		
>185	1.55	0.97 - 2.47	0.069
HR (beats/min) (n=186)			
<=90	Ref.		
>90	1.55	0.99 - 2.40	0.051
CGT (mg/dL) (n=74)			
<=180	Ref		
>180	0.33	0.49 - 2.18	0.248
Comorbidities			
No	Ref		
Yes	2.68	0.91 - 7.87	0.073
CCI			
0 to 4	Ref		
5 or more	1.74	1.15 - 2.65	0.009
Previous medication			
No	Ref.		
Yes	1.1	0.71 - 1.71	0.656
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.9	1.25 - 2.90	0.003
Baseline status			
Independent	Ref.		
Dependent	1.02	0.81 - 1.29	0.841
Imaging laterality			
Left	Ref		
Right	0.91	0.60 - 1.38	0.662
Hb (g/dL)			
	0.86	0.78 - 0.94	0.001
Leukocytes (cells/μL) (n=180)			
5000-12000	Ref.		
<5000	1.83	1.02 - 3.29	0.044
>12000	2.52	1.65 - 3.84	<0.001
NLR (n=180)			
<3	Ref		
>=3	1.87	1.18 - 2.94	0.007
LDH (IU/L) (n=81)			
<=350	Ref.		
>350	2.45	1.42 - 4.23	0.001
Total Proteins (g/dL) (n=154)			
<=6	Ref.		
>6	0.54	0.35 - 0.83	0.005
Albumin (g/dL) (n=143)			
<=3.5	Ref		
>3.5	0.45	0.29 - 0.70	<0.001
CRP (mg/ dL) (n=143)			
<=2	Ref		
>2	3.06	1.95 - 4.80	<0.001
D-dimer (μg/mL) (n=73)			
<=1	Ref		

>1

2.44

1.12 - 5.35

0.026

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein; CI: confidence interval; RR: relative risk.

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Table 7. Bivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref			Ref		
Male	0.78	0.42 - 1.45	0.438	0.97	0.56 - 1.67	0.922
Age						
<=70	Ref.			Ref.		
>70	1.18	0.63 - 2.22	0.61	1.33	0.75 - 2.33	0.327
Stroke history						
No	Ref.			Ref.		
Yes	0.90	0.40 - 2.01	0.793	0.69	0.32 - 1.53	0.363
SBP (mmHg)						
<=185	Ref.			Ref.		
>185	0.20	0.03 - 1.37	<0,001	1.28	0.64 - 2.57	0.487
HR (beat/min)						
<=90	Ref.			Ref.		
>90	0.91	0.38 - 2.19	0.833	0.55	0.21 - 1.45	0.227
CGT (mg/dL)						
<=180	Ref			Ref		
>180	0.66	0.09 - 4.56	0.67	1.81	0.62 - 5.23	0.276
Comorbidities						
No	Ref			Ref		
Yes	1.41	0.47 - 4.25	0.545	1.78	0.60 - 5.31	0.301
CCI						
0 to 4	Ref			Ref		
5 or more	1.59	0.86 - 2.95	0.138	1.54	0.90 - 2.64	0.114
Previous medication						
No	Ref.			Ref.		
Yes	0.72	0.39 - 1.32	0.285	2.37	1.16 - 4.83	0.018
Stroke severity (NIHSS)						
<=10	Ref.			Ref.		
>10	2.36	1.24 - 4.49	0.009	0.88	0.51 - 1.53	0.661
Baseline status						
Independent	Ref.			Ref.		
Dependent	0.61	0.09 - 4.03	0.613	1.01	0.29 - 3.55	0.986
Imaging laterality						
Left	Ref			Ref		
Right	0.73	0.39 - 1.38	0.333	1.09	0.64 - 1.86	0.761
Hb (g/dL)						
0.8	0.70 - 0.91	0.001		0.99	0.85 - 1.17	0.95
Leukocytes (cells/μL)						
5000-12000	Ref.			Ref.		
<5000	2.15	0.85 - 5.41	0.107	0.65	0.17 - 2.43	0.522
>12000	2.81	1.32 - 5.98	0.007	1.21	0.50 - 2.96	0.673
NLR						
<3	Ref			Ref		
\geq 3	1.43	0.73 - 2.81	0.292	1.13	0.65 - 1.97	0.672
LDH (IU/L)						
<=350	Ref.			Ref.		
>350	1.78	0.76 - 4.19	0.187	1.26	0.51 - 3.09	0.621
Total proteins (g/dL)						
<=6	Ref.			Ref.		
>6	0.78	0.35 - 1.74	0.544	0.69	0.35 - 1.35	0.279
Albumin (g/dL)						
<=3.5	Ref			Ref		
>3.5	0.58	0.26 - 1.30	0.182	0.51	0.28 - 0.94	0.031
CRP (mg/ dL)						
<=2	Ref			Ref		
>2	3.08	1.55 - 6.09	0.001	1.29	0.69 - 2.42	0.419

D-dimer ($\mu\text{g/mL}$)

≤ 1	Ref			Ref		
> 1	1.92	0.67 - 5.50	0.225	0.78	0.36 - 0.68	0.52

Abbreviations: SBP: systolic blood pressure; HR: heart rate; CGT: capillary glycemia test; CCI: age adjusted Charlson comorbidity index; Hb: hemoglobin; NLR: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein. CI: confidence interval; RR: relative risk.

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Table 8. Multivariate analysis of risk factors for in-hospital complications in patients with acute ischemic stroke.

Variable	RR	95% CI	P value
Sex			
Female	Ref.		
Male	1.25	0.75 - 2.10	0.393
Age	1.02	0.99 - 1.04	0.086
Hypertension			
No	Ref.		
Yes	0.66	0.40-1.07	0.094
Diabetes			
No	Ref.		
Yes	1.06	0.65-1.72	0.82
Stroke history			
No	Ref.		
Yes	0.93	0.46 - 1.86	0.846
HR (beat/min)			
<=90	Ref.		
>90	1.41	0.88 - 2.27	0.153
Stroke severity (NIHSS)			
<=10	Ref.		
>10	1.76	1.09 - 2.86	0.022
NLR			
<3	Ref.		
>=3	1.29	0.8 - 2.08	0.295
Albumin (g/dL)			
<=3.5	Ref.		
>3.5	0.53	0.36 - 0.79	0.002

Multivariate analysis obtained with Poisson regression, parsimonious model. Abbreviations: NLR: neutrophil/lymphocyte ratio; CI: confidence interval; RR: relative risk.

Table 9. Multivariate analysis of risk factors for neurological and infectious complications in patients with acute ischemic stroke.

Variable	Neurological complications			Infectious complications		
	RR	95% CI	P value	RR	95% CI	P value
Sex						
Female	Ref.			Ref.		
Male	0.88	0.39 - 2.00	0.768	0.89	0.49 - 1.61	0.69
Age	0.99	0.95 - 1.03	0.655	1.01	0.99 - 1.04	0.33
Hypertension						
No	Ref.			Ref.		
Yes	0.88	0.40 - 1.98	0.772	0.97	0.52 - 1.83	0.931
Diabetes						
No	Ref.			Ref.		
Yes	0.76	0.35 - 1.67	0.502	0.95	0.50 - 1.82	0.877
Stroke history						
No	Ref.			Ref.		
Yes	1.14	0.49 - 2.64	0.763	0.67	0.25 - 1.75	0.411
Previous medication						
No				Ref.		
Yes	-			2.79	1.16-6.71	0.022
Stroke severity (NIHSS)						
<=10	Ref.					
>10	1.56	0.72 - 3.40	0.26	-		
Hb (g/dL)	0.86	0.73 - 0.99	0.047	-		
CRP (mg/ dL)						
<=2	Ref.					
>2	2.49	0.97 - 6.38	0.057	-		
Aldumin (g/dL)						
<=3.5				Ref.		
>3.5	-			0.67	0.35 - 1.28	0.225

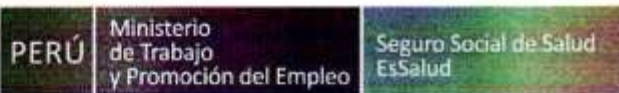
Abbreviations: Hb: hemoglobin; CRP: C-reactive protein.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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"Año del Bicentenario del Perú: 200 años de Independencia"
"Decenio de la Igualdad de oportunidades para mujeres y hombres"

CARTA N° **964** -GRPR-ESSALUD-2021

Lima, **01 DIC 2021**

Señor Médico Residente
MIGUEL ÁNGEL VENCES MIJAHUANCA
Investigador Principal
Presente.-

Asunto: **APROBACIÓN DE PROYECTO DE INVESTIGACIÓN**

De mi consideración:

La presente tiene el objeto dar respuesta a su solicitud de Aprobación y Autorización de Ejecución del Estudio Observacional titulado: "**PROYECTO CICAR: ESTUDIO DE COHORTE EN PACIENTES HOSPITALIZADOS POR INFARTO CEREBRAL AGUDO EN EL HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS**".

Al respecto, manifestarle que el presente proyecto ha sido evaluado y aprobado por el Comité Institucional de Ética en Investigación del Hospital Nacional Edgardo Rebagliati Martins, el cual vela por el cumplimiento de las directrices metodológicas y éticas correspondientes, incluyendo las buenas prácticas clínicas, los principios de protección de los sujetos de investigación contenidos en la declaración de Helsinki, y con los deberes y responsabilidades estipulado en las normas legales e institucionales vigentes.



En ese sentido, la Gerencia de la Red Prestacional Rebagliati, manifiesta su **Aprobación y Autoriza la Ejecución** del presente proyecto de investigación en el Hospital Nacional Edgardo Rebagliati Martins.

Cabe señalar que, una vez ejecutado y concluido el proyecto, deberá presentar el **Informe Final**, a la Oficina de Investigación y Docencia, para conocimiento y fines correspondientes.

Sin otro en particular, quedo de usted.

Atentamente.

ESSALUD
RED PRESTACIONAL REBAGLIATI
Dr. Juan Santillana Callirgos
CMP 11616
GERENTE

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832	2021	271



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COMITÉ DE ÉTICA DEL HOSPITAL NACIONAL
EDGARDO REBAGLIATI MARTINS

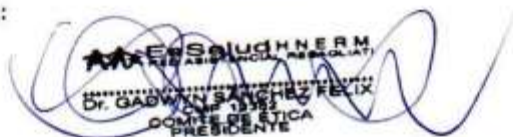
CERTIFICADO DE CALIFICACIÓN ÉTICA


El Comité de Ética del Hospital Nacional Edgardo Rebagliati Martins, en la sesión realizada el día 07 de octubre de 2021, ha acordado aprobar el Proyecto de investigación titulado "Proyecto Cicar: Estudio de Cohorte en Pacientes Hospitalizados por Infarto Cerebral Agudo en el Hospital Nacional Edgardo Rebagliati Martins", presentado por el **Mr. Miguel Ángel Vences Mijahuanca**, como Investigador Principal

El investigador deberá hacer llegar al Comité de Ética un informe de avance del estudio en forma anual.

FECHA: 01 de noviembre de 2021

FIRMA :




 HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS
 Dr. GADWIN SANCHEZ FELIX
 C.O.P. 15382
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COMITÉ INSTITUCIONAL DE ÉTICA EN INVESTIGACIÓN



CONSTANCIA N° 404-CIEI-CIENTÍFICA-2021

El presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) da constancia que el proyecto de Investigación, cuyos datos se registran a continuación, ha sido aprobado por el CIEI-CIENTÍFICA.

Código de registro: 762-2021-POSSO
 Título: Estudio de cohorte en pacientes hospitalizados por infarto cerebral agudo en el Hospital Nacional Edgardo Rebagliati Martins
 Investigador(a): Miguel Angel Vences Mijahuanca

La aprobación del proyecto de investigación implica que el documento presentado a evaluación cumple con los lineamientos de Universidad en materia de investigación y ética, los cuales se sustentan en la normativa internacional vigente. Adicionalmente, en el contexto de la pandemia de enfermedad por COVID-19, le recomendamos cumplir con las normas publicadas por el estado peruano (accesos, medidas de bioseguridad, etc.) y tener los permisos de las instituciones en las que realizará el estudio antes de ejecutarlo.

En tal sentido, esta aprobación carecerá de valor si es que el proyecto de Investigación arriba indicado es modificado de cualquier forma. Toda enmienda, añadido, eliminación o eventualidad (eventos adversos, etc.) posterior a la fecha de aprobación debe ser reportado al CIEI-CIENTÍFICA.

La vigencia de la aprobación de este documento es de dieciocho (18) meses (hasta el 16 de mayo del 2023), periodo en el que puede desarrollarse el proyecto. Cualquier trámite para su renovación deberá ser enviado antes del término de la vigencia de este documento, debiendo suspenderse todo desarrollo hasta que la renovación sea aprobada. La presente aprobación será ratificada en la sesión del CIEI más próxima.

Villa El Salvador, 17 de noviembre de 2021



 Mg. Pulton Paul Rivera Albinagorta
 Presidente
 Comité Institucional de Ética en Investigación



RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 685 - DACMH-DAFCS-U. CIENTIFICA-2021

Lima, 17 de noviembre del 2021

VISTO:

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de investigación titulado: "ESTUDIO DE COHORTE EN PACIENTES HOSPITALIZADOS POR INFARTO CEREBRAL AGUDO EN EL HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS".

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el Grado de Maestro.

Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

SE RESUELVE:

ART. 1º Aprobar, en vías de regularización e inscribir el proyecto de tesis titulado ESTUDIO DE COHORTE EN PACIENTES HOSPITALIZADOS POR INFARTO CEREBRAL AGUDO EN EL HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS", presentado por el alumno MIGUEL ANGEL VENCES MIJAHUANCA con N° de registro: 762-2021-POSSO.

ART. 2º Nombrar la Docente Leda Yamilee Hurtado Roca, como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.


Mg. JORDI GRAU MONGE
 Director Académico (e)
 Carrera de Medicina Humana



c.c. Archivo