Received: 9 June 2023 | Accepted: 31 October 2023

DOI: 10.1111/ene.16153

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

A novel risk score predicting 30-day hospital re-admission of patients with acute stroke by machine learning model

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Funding information
The Italian Ministry for University and Research (MUR) under the Program PON

Abstract

Background: The 30-day hospital re-admission rate is a quality measure of hospital care to monitor the efficiency of the healthcare system. The hospital re-admission of acute stroke (AS) patients is often associated with higher mortality rates, greater levels of disability and increased healthcare costs. The aim of our study was to identify predictors of unplanned 30-day hospital re-admissions after discharge of AS patients and define an early re-admission risk score (RRS).

Methods: This observational, retrospective study was performed on AS patients who were discharged between 2014 and 2019. Early re-admission predictors were identified by machine learning models. The performances of these models were assessed by receiver operating characteristic curve analysis.

Results: Of 7599 patients with AS, 3699 patients met the inclusion criteria, and 304 patients (8.22%) were re-admitted within 30 days from discharge. After identifying the predictors of early re-admission by logistic regression analysis, RRS was obtained and consisted of seven variables: hemoglobin level, atrial fibrillation, brain hemorrhage, discharge home, chronic obstructive pulmonary disease, one and more than one hospitalization in the previous year. The cohort of patients was then stratified into three risk categories: low (RRS = 0–1), medium (RRS = 2–3) and high (RRS > 3) with re-admission rates of 5%, 8% and 14%, respectively.

Conclusions: The identification of risk factors for early re-admission after AS and the elaboration of a score to stratify at discharge time the risk of re-admission can provide a tool for clinicians to plan a personalized follow-up and contain healthcare costs.

KEYWORDS
brain hemorrhage, discharge pathways, re-admission, risk score, stroke

INTRODUCTION

The 30-day hospital re-admission rate is an outcome measure which is gaining a crucial role in the assessment of the quality of healthcare systems, since re-admissions overload emergency departments (ED) and account for about half of all hospitalizations [1, 2]. For this reason, commencing October 1, 2012, the US government [3] has planned the Hospital Re-admissions Reduction Program [4], imposing financial penalties for excess hospital re-admissions due to several conditions, including acute stroke (AS).

AS is a leading cause of death, disability and hospitalization, [5] and for stroke survivors the effective management of disability, prevention of foreseeable complications, and discharge to a more suitable setting in the continuity of inpatient and outpatient care are still challenging goals. Several recent studies, investigating the causes and the prevalence of hospital re-admission after stroke [6–11], found that re-admission was often associated with higher mortality rate, greater levels of disability, and increased costs as compared to the initial stroke event. Consequently, the identification of factors that contribute to early re-admission after AS could be useful for reducing health costs and optimizing public resources, through tailor-made management of patients according to the stratification of re-admission risk.

Attempts to detect re-admission predictors in AS patients were often contradictory and sometimes inconclusive [12], considering several factors such as length of hospital stay, National Institutes of Health Stroke Scale (NIHSS), the number of prior hospitalizations, stroke subtypes, hemorrhagic transformation, nosocomial infections, hypertension and any medical complications [13–15].

The aim of our study was to identify predictors of unplanned 30-day hospital re-admissions after discharge of AS patients, to develop a risk stratification score of early re-admission, and to identify patient categories that can be subjected to personalized clinical and instrumental remote monitoring.

METHODS

Study design and population

We conducted a retrospective study, including consecutive adult patients (≥18 years) with a primary diagnosis of AS, who were admitted to Fondazione Policlinico Universitario A. Gemelli, IRCCS-Rome between January 1, 2014 and December 31, 2019. We purposefully chose this timeframe until 2019 to avoid possible biases related to the COVID-19 pandemic period.

Inclusion criteria were: (i) hospitalization for a diagnosis of ischemic stroke or transient ischemic attack according to the International Classification of Diseases, Ninth Revision (ICD-9) codes (ICD-9 433, 434, 435, 436); (ii) intracranial hemorrhage (ICH) or subdural hemorrhage (ICD-9 431, 432); and (3) subarachnoid hemorrhage (SAH) (ICD-9 430).

Exclusion criteria were: (i) hospitalization for planned procedures or in any case not through ED; (ii) any post-traumatic stroke; (iii) inappropriate AS coding; (iv) age ≤18 years; (v) death during hospitalization; and (vi) geo-distance of patient's address from the hospital ≥35 km. The final criterion is defined in the next section.

The study was approved by the Ethics Committee of Fondazione Policlinico A. Gemelli-Rome (Protocol ID No. 3795) and strictly adhered to the observational cohort guidelines.

Definitions, data collection and extraction

For each patient admitted through ED, the primary AS diagnosis at discharge, according to ICD-9 codes, was identified as the index event. Hospital re-admission was defined as any unplanned ED access within 30 days from hospital discharge after index diagnosis, with or without hospitalization.

For patients who had several index hospitalizations during a year, each hospitalization was considered separately. Conversely, if an index hospitalization generated multiple re-admissions, only the first re-admission within the 30 days from discharge was defined as the 30-day hospital re-admission.

Geo-distance was defined as the geometrical distance between the coordinates of the patient's home and the coordinates of the hospital address. The patient's address, given by the pair <ZIP code, City> (e.g. 00168, Rome), was translated into geographical coordinates using the OpenStreetMap API for Python [16].

Since our hospital is a regional "hub" for stroke, patients presenting with signs and symptoms of AS can be directly centralized at our hospital, bypassing "spoke" hospitals. Conversely, once these patients are discharged home, the re-admission for causes other than AS may take place in the ED nearest to their residence. Therefore, geo-distance was used as a filter criterion for the cohort definition to avoid bias in assigning a clinically positive outcome ("admission without 30-day re-admission") due to the geographical distance of the patient's address from the hospital.

Details of the retrospective data collection are shown in the supplemental materials (Table S1).

For the goal of the analysis, our research team had access to Data Mart where the variables of interest were stored after standard semi-automated extract, transform and load procedures, which included data quality checks and pseudonymization.

Text mining was used to extract all those variables of interest that were unstructured or partially structured. Most variables extracted through text mining described a patient's previous comorbidities, clinical complications during hospitalization and procedures. The variables of interest were searched by means of a list of words that are commonly used in medical reports to describe each comorbidity/complication/procedure. The categorical variables representing "civil status", "education level" and "discharge destination" had their outcome grouped by feature engineering, as reported in the supplemental materials (Table S2). The numerical variables representing laboratory examinations and the number of admissions within the past year were converted into categorical variables based on the criteria listed in the supplemental materials (Table S3). For laboratory variables, we considered the last examination record within 1 week before discharge.

Statistical analysis

Quantitative variables were expressed by using the following measures: minimum, maximum, range, median and interquartile range (IQR) as appropriate. Categorical variables were summarized as number and percentage (%). Normality of continuous variable distribution was checked using the Shapiro–Wilk test. Numerical variables were then analyzed using the non-parametric Mann–Whitney *U* test while, for categorical variables, Pearson's chi-square test (χ^2) was adopted. A two-tailed p-value <0.05 was considered statistically significant.

In order to use geo-distance as an exclusion criterion, we searched for the optimal geographical exclusion threshold ranging from 5 to 100 km. We filtered our cohort for each distance in this range and applied the Mann–Whitney *U* test on the resulting datasets to assess the statistical dependence between distance and our study outcome. Then, we identified the exclusion threshold as the minimum distance for which the p-value was <0.05. By filtering the patients' cohort for such an exclusion threshold, we could select a cohort of patients for whom the geo-distance does not statistically influence the re-admission outcome ("with 30-day re-admission", "without 30-day re-admission"), given that the p-value was ≥0.05.

Since the goal of the study was to build a score that was able to predict 30-day hospital re-admission for AS discharges, several machine learning predictive models, including logistic regression [17], decision tree [18], random forest [19] and XGBoost [20] were trained and tuned using five-fold cross-validation to investigate their applicability and also had a performance benchmark. The machine learning problem from which we defined our re-admission risk score (RRS) was handled as a binary classification problem where the prediction outcome was "admission with 30-day re-admission" (negative outcome) or "admission without 30-day re-admission" (positive outcome).

The performances of the predictive models were assessed by receiver operating characteristic (ROC) curve analysis in terms of specificity, precision, recall, F1 measure and area under the curve.

As reported by some authors [8], the 30-day re-admission rate for AS and transient ischemic attack is 17.4% (95% CI 12.7%–23.5%), thus the available dataset was imbalanced in class distribution. The synthetic minority oversampling technique (SMOTE) was investigated as a possible solution for increasing prediction performances in the assessed imbalanced classification problem. All the models were trained with both the original imbalanced set and the synthetic set resulting from SMOTE.

Missing values among the dataset were handled according to different criteria. Binary variables related to comorbidities, complications and procedures did not have missing values since our text mining procedure set a variable to zero when the search in the medical records produced no matching. If a laboratory variable was not available within the last week before discharge, it was assumed to be in the normal range. Since the missing values for "hospital distance" were 35% of the dataset size, they were imputed using random samples from its estimated probability density function. Variables with more than 35% of missing values, such as "Admission NIHSS" or "Admission modified Rankin Scale (mRS)", were excluded from the analysis.

All machine learning models and the RRS were built on a randomly selected sample of 80% of the cohort and tested on the remaining 20%.

RESULTS

Geo-distance threshold

We found that geo-distance was significantly related to the positive outcome ($p=0.0071$) when the entire dataset was considered. The threshold above which the statistical association between distance and positive outcome became significant was ≥35 km ($p<0.05$). Consequently, patients who lived ≥35 km away from our hospital were excluded from the cohort. Figure S1 represents selection of geo-distance threshold to avoid bias on the positive outcome.

Population analysis

We analyzed a total of 7599 hospital stroke discharges. Of these, 5210 patients with AS were admitted through ED and discharged alive to other community settings. Thirty-five of these patients were excluded for age <18 years, 593 for a concomitant diagnosis of head trauma and 21 for a planned admission. Based on our inclusion criteria, 4561 index events were then eligible for the analysis. Filtering out all eligible stroke patients who lived ≥35 km from the hospital, 3699 index events were finally included in the analysis. A CONSORT

TABLE 1 Characteristics of the study cohort at index hospitalization.

Characteristic	All patients *n* (%) (*n* = 3699)
Age; years [IQR]	74 [63–82]
Male	1945 (52.5)
Hospitalization in the previous year	553 (14.4)
Stroke subtypes	
Acute ischemic stroke	2550 (68.9)
Subarachnoid hemorrhage	257 (6.9)
Intraparenchymal hemorrhage	497 (13.4)
Subdural hemorrhage	337 (9.1)
Comorbidities	
Cardiovascular diseases	515 (13.9)
Atrial fibrillation	1547 (41.8)
Hypertension	1280 (34.6)
Diabetes	981 (26.5)
Hypercholesterolemia	144 (3.9)
COPD	443 (26.5)
Respiratory disease	110 (3)
Oncologic diseases	186 (5)
Endocrinologic and metabolism diseases	219 (5.9)
Neurologic and mental disorders	910 (24.6)
Renal disease	72 (1.4)
Smoking	242 (3.7)
Obesity	46 (1.2)
Outcome	
Hospital length of stay; days [IQR]	9 [6–14]
30-day readmission	304 (8.2)
Discharge settings	
Home	2515 (68)
Other institution of care	1184 (32)
Palliative care	0 (0)
Complications during index-hospitalization	
Sepsis	6 (0.2)
Pneumonia	233 (6.3)
Seizures	133 (3.6)
Urinary tract infections	117 (3.2)
New brain hemorrhage	341 (9.2)
New stroke	0 (0)
Renal disease	52 (1.4)
Ulcer wounds	101 (2.7)
Falls and fractures	66 (1.8)
DVT/pulmonary embolism	57 (1.5)
None; *n* (%)	2768 (74.8)

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; IQR, interquartile range.
Unless stated otherwise, categorical variables are given as number and percentage (%).

TABLE 2 Causes of re-admission.

Re-admission cause	*n* (%) (*n* = 304)
Ischemic stroke	64 (21.1)
Infections	52 (17.1)
Seizures	41 (13.5)
Ischemic heart disease or other cardiac complications	36 (11.8)
Brain hemorrhages	32 (10.5)
Asthenia	13 (4.3)
Headache	12 (3.9)
Metabolic disease	10 (3.3)
Cancer	7 (2.3)
Venous thrombosis or thromboembolism	4 (1.3)
Trauma	3 (1.0)
Other	30 (9.9)

flow diagram, explaining the enrolment process and the number of patients at different times, is shown in Figure S2.

In our study cohort, 2595 (70.1%) patients were affected by ischemic strokes, 504 (13.6%) by ICH, 340 (9.1%) by subdural hemorrhages and 260 (7%) by SAH (Figure S2).

Baseline characteristics of our cohort at index hospitalization are described in Table 1.

30-day re-admission rate and analysis of re-admitted versus non-re-admitted patients

Of the 3699 index hospitalizations, 304 (8.2%) were re-admitted to the ED within 30 days from hospital discharge. Of these, 160 patients (53%) were then hospitalized, while 94 patients (31%) were discharged home, as reported in Figure S3.

The causes of re-admission in our population are summarized in Table 2.

In particular, ischemic stroke was the main cause of re-admission (21.1%), followed by infections (17.1%), seizures (13.5%), ischemic heart disease or other cardiac complications (11.8%) and brain hemorrhages (10.5%).

No demographic differences were observed between non-re-admitted and re-admitted patients (Table 3).

Patients affected by subdural hemorrhage, with several hospitalizations in the previous year, discharged home, and undergoing surgery for hematoma evacuation were more frequently re-admitted within 30 days from the hospital discharge ($p = 0.001$, $p < 0.001$, $p = 0.011$ and $p = 0.028$, respectively). Conversely, patients with ischemic stroke, or discharged to another institution of care, were less likely to be re-admitted within 30 days from hospital discharge ($p = 0.039$ and $p = 0.011$, respectively). By evaluating pre-discharge blood tests we found that abnormal values (outside the normal range) of serum creatinine and hemoglobin were more frequent in the

TABLE 3 Differences among patients who were not re-admitted and those who were re-admitted within 30 days.

Characteristic	Non-re-admitted patients *n* (%) (*n* = 3395)	Re-admitted patients *n* (%) (*n* = 304)	*P*-value
Age; years [IQR]	74 [63–82]	75 [66–83]	0.232
Male[a]	1786 (52.6)	159 (52.3)	0.967
Living alone[a]	786 (23.1)	83 (27.3)	0.1189
Hospitalization in the previous year[a]	462 (13.6)	71 (23.3)	<0.001
Hospital length of stay; days [IQR]	9 [6–14]	9 [6–14]	0.69
Index diagnosis			
Ischemic stroke[a]	2398 (69.6)	197 (64.8)	0.039
Brain hemorrhage[a]	997 (29.4)	107 (35.2)	0.039
Brain hemorrhage subtypes[a]			
Intraparenchymal hemorrhage[a]	470 (13.8)	34 (11.1)	0.23
Subarachnoid hemorrhage[a]	231 (6.8)	29 (9.5)	0.095
Subdural hemorrhage[a]	296 (8.7)	44 (14.1)	0.001
Comorbidities			
Cardiovascular diseases[a]	207 (6.1)	23 (7.54)	0.37
Atrial fibrillation[a]	1403 (41.3)	144 (47.2)	0.04
Hypertension[a]	1190 (35)	90 (29.5)	0.06
Diabetes[a]	901 (26.5)	80 (26.2)	0.98
Hypercholesterolemia[a]	136 (4)	8 (2.6)	0.30
COPD[a]	385 (11.3)	58 (19)	0.001
Respiratory disease[a]	99(2.9)	11 (3.6)	0.60
Oncologic disease[a]	170 (5)	16 (5.2)	0.95
Endocrinologic and metabolic disease[a]	196 (5.7)	23 (7.5)	0.25
Neurologic and mental disorder[a]	836 (24.6)	74 (24.2)	0.96
Renal disease[a]	61 (1.8)	11 (3.6)	0.047
Smoking[a]	223 (6.5)	19 (6.2)	0.92
Obesity[a]	39 (1.1)	7 (2.3)	0.14
Discharge settings			
Discharge home[a]	2288 (67.4)	227 (74.7)	0.011
Discharge to other institution of care[a]	1107 (32.6)	77 (25.3)	0.011
Palliative care[a]	0 (0)	0 (0)	–
Procedures			
Thrombolysis[a]	334 (10.1)	25 (8.2)	0.335
Endovascular treatment[a]	210 (6.2)	14 (4.6)	0.326
Hematoma surgical evacuation[a]	310 (9.1)	40 (13.1)	0.028
Decompressive craniectomy[a]	11 (0.3)	1 (0.3)	>0.99
Nasogastric feeding tube[a]	539 (15.9)	45 (14.8)	0.682
Invasive mechanical ventilation[a]	310 (9.1)	26 (8.5)	0.817
Tracheostomy[a]	123 (3.6)	11 (3.6)	>0.99
Urinary catheter[a]	1599 (47.1)	141 (46.3)	0.857
Percutaneous gastrostomy[a]	25 (0.7)	1 (0.3)	0.648
Continuous renal replacement[a]	18 (0.5)	1 (0.3)	0.959
Complications during index-hospitalization			
Sepsis[a]	6 (0.2)	0 (0)	>0.99
Pneumonia[a]	211 (6.2)	22 (7.2)	0.562
Seizures[a]	123 (3.6)	10 (3.3)	0.890

(Continues)

TABLE 3 (Continued)

Characteristic	Non-re-admitted patients *n* (%) (*n* = 3395)	Re-admitted patients *n* (%) (*n* = 304)	*P*-value
Urinary tract infections[a]	105 (3.1)	12 (3.9)	0.519
New brain hemorrhage[a]	315 (9.2)	26 (8.6)	0.752
New stroke[a]	0 (0)	0 (0)	-
Renal disease[a]	47 (1.3)	5 (1.6)	0.908
Ulcer wounds[a]	90 (2.7)	11 (3.6)	0.419
Fall and fractures[a]	56 (1.6)	10 (3.2)	0.065
DVT/pulmonary embolism[a]	50 (1.5)	7 (2.3)	0.378
None[a]	2546 (75.0)	222 (73.3)	0.492
Laboratory parameters			
Blood urea nitrogen[a]	542 (15.9)	57 (18.7)	.2S7
Serum albumin[a]	670 (19.7)	66 (21.6)	0.452
C-reactive protein[a]	699 (20.6)	63 (20.7)	>0.99
Serum creatinine[a]	607 (17.9)	69 (22.6)	0.045
Fibrinogen[a]	575 (16.9)	52 (17.1)	>0.99
Hemoglobin[a]	917 (27.0)	101 (33.1)	0.024
White blood cells[a]	505 (14.9)	52 (17.1)	0.338
Erythrocyte sedimentation rate[a]	227 (6.7)	24 (7.9)	0.494

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; IQR, interquartile range.
Unless stated otherwise, categorical variables are given as number and percentage (%).
[a]Pearson's chi-squared test.

re-admitted patients ($p=0.045$ and $p=0.024$, respectively) (Table 3). Moreover, we evaluated the differences in demographic and clinical factors among patients who required hospitalization after re-admission through ED and those who did not require a further hospitalization (Table 4). As expected, patients who required hospitalization after ED re-admission were older, required hospitalization in the previous year, had a significantly longer hospital stay during index hospitalization, and suffered from a recurrence of stroke or infections. Patients who were not hospitalized after ED re-admission had mainly access to ED for headache, epilepsy or asthenia.

Predictive model development and performance analysis

All the variables that reached statistical significance by univariate analysis were then considered for multivariate analysis showing that one or more admissions in the previous year, chronic obstructive pulmonary disease (COPD) and discharge home were significantly associated with an increased risk of re-admission for AS patients (Table S4 and Figure 1). Among machine learning models considered for building RRS [17–20], the logistic regression analysis had the best trade-off between ease of interpretation and prediction performances (Tables S5 and S6).

Tables S5 and S6 show model performances with the original imbalanced and SMOTE-adjusted dataset, resulting from five-fold cross-validation. For each cross-validation run, the classification threshold was selected using the Youden's index criterion.

Early re-admission risk score

By stepwise selection, seven variables were included in the logistic regression analysis to build RRS: hemoglobin level, atrial fibrillation, brain hemorrhage, discharge home, one hospitalization in the previous year, COPD, and more than one hospitalization in the previous year (Table S7).

Each resulting feature's score was defined by its logistic regression coefficient after normalization to what was considered as the one-point increase (+1 increase). We decided to associate the +1 increase with the variable whose coefficient was closest to the coefficient midrange. Given that our coefficient range and midrange are respectively [0.2362–0.7910] and 0.2774, we selected the coefficient related to the index diagnosis of brain hemorrhage as the +1 increase. The final RRS resulted from the sum of the rounded, normalized model coefficients, and it could range between 0 and 9 (Table 5).

Based on the RRS, the study cohort was then stratified into three groups: low (RSS = 0–1), medium (RSS = 2–3) and high re-admission risk (RSS > 3) groups with re-admission rates of 5%, 8% and 14%, respectively (Figure S4).

DISCUSSION

In this study, we report a 30-day re-admission rate of 8.2%, which is in line with the percentages observed in recent studies where it ranged between 6.7% and 15.1% [6, 7, 21–26]. These small

TABLE 4 Differences among patients who required hospitalization after re-admission through emergency department and those who did not.

Characteristic	ED re-admitted patients with hospitalization *n* (%) (*n* = 160)	ED re-admitted patients without hospitalization *n* (%) (*n* = 144)	*P*-value
Age; years [IQR]	77.00 [69.00–85.00]	72.00 [57.75–80.00]	<0.001
Male[a]	74 (51.39)	85 (53.12)	0.851
Living alone[a]	36 (25)	47 (29.38)	0.468
Hospitalization in the previous year[a]	24 (16.67)	47 (29.38)	0.013
Hospital length of stay during index hospital admission; days [IQR]	10.00 [6.00–15.00]	8.00 [5.00–13.00]	0.038
Index diagnosis during index hospital admission			
Ischemic stroke[a]	89 (61.81)	99 (61.88)	>0.999
Brain hemorrhage[a]	50 (34.73)	55 (34.38)	>0.999
Brain hemorrhage subtypes[a]			
Intraparenchymal hemorrhage[a]	17 (11.81)	17 (10.62)	0.886
Subarachnoid hemorrhage[a]	17 (11.81)	11 (6.88)	0.199
Subdural hemorrhage[a]	16 (11.11)	27 (16.88)	0.202
Comorbidities during index hospital admission			
Cardiovascular diseases[a]			
Atrial fibrillation[a]	57 (39.58)	87 (54.38)	0.014
Hypertension[a]	43 (29.86)	47 (29.38)	>0.999
Diabetes[a]	31 (21.53)	49 (30.62)	0.095
Hypercholesterolemia[a]	4 (2.78)	4 (2.5)	>0.999
COPD[a]	21 (14.58)	37 (23.12)	0.081
Respiratory disease[a]	2 (1.39)	9 (5.62)	0.095
Oncologic disease[a]	6 (4.17)	10 (6.25)	0.579
Endocrinologic and metabolic disease[a]	13 (9.03)	10 (6.25)	0.486
Neurologic and mental disorder[a]	30 (20.83)	44 (27.5)	0.223
Renal disease[a]	3 (2.08)	8 (5)	0.293
Smoking[a]	14 (9.72)	5 (3.12)	0.033
Obesity[a]	4 (2.78)	3 (1.88)	0.888
Discharge settings after index hospital admission			
Discharge home[a]	114 (79.17)	113 (70.62)	0.115
Discharge to other institution of care[a]	30 (20.83)	47 (29.38)	0.115
Palliative care[a]	–	–	–
Procedures performed during index hospital admission			
Thrombolysis[a]	12 (8.33)	13 (8.12)	>0.999
Endovascular treatment[a]	4 (2.78)	10 (6.25)	0.243
Hematoma surgical evacuation[a]	15 (10.42)	25 (15.62)	0.241
Decompressive craniectomy[a]	0 (0)	1 (0.62)	0.319
Nasogastric feeding tube[a]	15 (10.42)	30 (18.75)	0.06
Invasive mechanical ventilation[a]	12 (8.33)	14 (8.75)	>0.999
Tracheostomy[a]	7 (4.86)	4 (2.5)	0.428
Urinary catheter[a]	57 (39.58)	84 (52.5)	0.032
Percutaneous gastrostomy[a]	1 (0.69)	0 (0)	0.319
Continuous renal replacement[a]	0 (0)	1 (0.62)	0.319
Causes of ED re-admission			
Ischemic stroke[a]	46 (28.75)	18 (12.5)	<0.001

(Continues)

TABLE 4 (Continued)

Characteristic	ED re-admitted patients with hospitalization *n* (%) (*n* = 160)	ED re-admitted patients without hospitalization *n* (%) (*n* = 144)	*P*-value
Infection[a]	42 (26.25)	10 (6.94)	<0.001
Seizures[a]	13 (8.13)	28 (19.44)	0.0040
Ischemic heart disease or other cardiac complications[a]	13 (8.13)	23 (15.97)	0.035
Brain hemorrhages[a]	23 (14.38)	9 (6.25)	0.021
Asthenia[a]	2 (1.25)	11 (7.46)	0.007
Headache[a]	0 (0)	12 (8.33)	<0.001
Metabolic disease[a]	6 (3.75)	4 (2.78)	0.636
Cancer[a]	4 (2.5)	3 (2.08)	0.059
Venous thrombosis or thromboembolism[a]	2 (1.25)	2 (1.39)	0.915
Trauma[a]	1 (0.63)	2 (1.39)	0.505
Other[a]	20 (13.89)	10 (6.25)	0.029

Abbreviations: ED, emergency department; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
Unless stated otherwise, categorical variables are given as number and percentage (%).
[a]Pearson's chi-squared test.

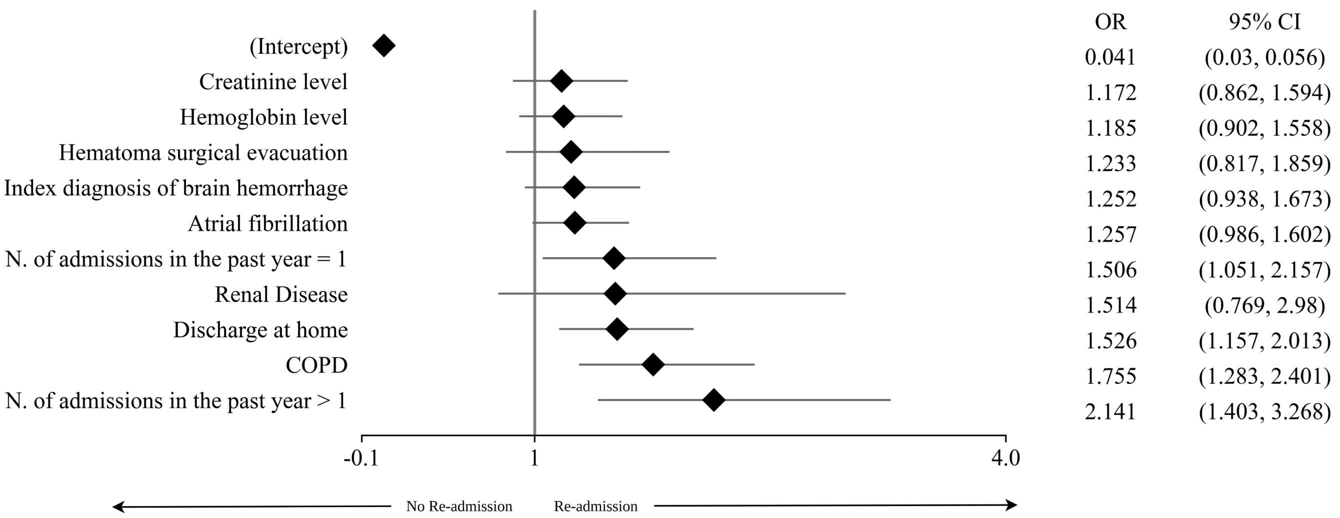

FIGURE 1 Forest plot of multivariate regression analysis evaluating 30-day re-admission predictors. CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

TABLE 5 Re-admission risk score (RRS) definition by logistic regression analysis.

Feature	OR	Lower 95% CI	Upper 95% CI	*P*-value	Coefficient	Normalized coefficient	Score
Hemoglobin level[a]	1.27	0.98	1.64	0.072	0.23	0.81	+1
Atrial fibrillation	1.27	1.00	1.62	0.051	0.24	0.82	+1
Index diagnosis of brain hemorrhage	1.34	1.04	1.72	0.024	0.29	1	+1
Discharge home	1.53	1.16	2.01	0.003	0.42	1.45	+1
Number of admissions in the past year = 1	1.54	1.08	2.20	0.018	0.43	1.48	+1
COPD	1.77	1.30	2.42	<0.001	0.57	1.96	+2
Number of admissions in the past year >1	2.21	1.45	3.36	<0.001	0.79	2.71	+3

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.
[a]Cutoff <12 g/dL (female) and < 13 g/dL (male).

differences between the studies could be due to the dissimilar follow-up times as well as the different subtypes, severity and treatments of strokes. Moreover, the 30-day re-admission rate observed in our stroke cohort was lower than the rates reported in other conditions such as heart failure, pneumonia and all-cause hospitalizations [27, 28]. This is probably due to the different discharge settings of various population, with stroke patients who are more likely to be discharged from hospitals to inpatient rehabilitation or long-term care facilities rather than home. Indeed, by univariate and multivariate analysis, we identified discharge home as a predictor of early re-admission, regardless of marital status and level of education, suggesting that patients who are directly discharged home have limited access to information, health and community support services. These data, also confirmed by other recent studies [28], suggest that home interventions in support to stroke patients could prevent early hospital re-admissions and improve their adherence to the therapeutic plan and satisfaction with the received care [29, 30]. Indeed, patients who were discharged home represented most of the patients who required ED access without hospitalization, mainly due to minor symptoms. If these symptoms could be identified early and corrected, we assume that these patients might avoid ED re-admission. In addition to discharge home, we identified a higher frequency of brain hemorrhage and surgical evacuation as predictors of early re-admission. This increased risk may be due both to the different clinical management between surgical and neurological sub-intensive ward and to the worse prognosis of surgical hemorrhagic stroke, which is associated with higher prevalence of secondary seizures. Not surprisingly, in our study, seizure was the third highest cause of re-admission, involving more than 12% of re-admitted patients, in agreement with other studies where central nervous system diseases, such as epilepsy and re-stroke, are the most frequent causes of re-admission [11, 28].

Moreover, evaluating comorbidities and complications during hospitalization, renal disease and COPD have been identified as predictors of early re-admission in our patient cohort. These predictors were also identified in a large cohort of ischemic stroke patients where both COPD and renal disease were found to be predictors of unplanned 30-day readmission [31]. In other two studies, conducted on populations of hospitalized patients, using different machine learning algorithms, CODP or the drugs frequently used in COPD treatment appear among the risk factors for hospital re-admission [32, 33].

Based on machine learning methods, we defined a seven-items RRS and stratified our cohort of AS patients into three risk classes in which high re-admission risk (RSS >3) patients are three times more likely to have early re-admission than the low-risk group (RSS <2). The low-risk group had a 39% lower re-admission incidence than the generic re-admission rate (8.21%) according to the results calculated for our cohort. In contrast, the high-risk group had a 70% higher re-admission incidence than the generic rate. The medium-risk group had a rate of re-admission comparable to the generic rate.

To our knowledge, our study is the first attempt to define a specific 30-day RRS for AS inpatients. Nonspecific screening tools, such as the LACE index [34], hospital score [35] and 8Ps [36], have sometimes been used for re-admission risk stratification in patients with acute cerebrovascular disease. In particular, in a recent study carried out in patients with ischemic stroke, subjects in the high LACE+ index category had a significantly greater unplanned 30-day re-admission risk after stroke as compared to lower LACE+ risk groups [34].

However, given the variability of resources, patient demographics and case mix, the use of generic and non-specific risk stratification tools for re-admission in patients with such a specific disease as stroke would require the adjustment of risk prediction models for disease-related factors.

LIMITATIONS

Limitations include the retrospective nature and the monocentric design of the study. Indeed, the study population was obtained from a single academic care center, hence it may not be representative of population samples and may not be appropriate for evaluating the outcomes in other hospital settings.

Furthermore, by considering the relatively high recall and specificity, the model performed reasonably well in predicting the negative outcomes. However, due to the low precision, the model was less reliable for predicting the positive outcomes. This may suggest the need for further research, accounting for larger sample size, to increase the performance of the model and better refine the RRS score for implementation in clinical practice. In particular, larger models will allow selection of clusters of patients and account for unexplored variables (i.e., frailty).

Another limitation of this study is the exclusion of NIHSS score among the predictors of re-admission, due to the high number of missing values. Unfortunately, in our dataset this variable was not well sourced or collected. Furthermore, we were unable to extend the study into stroke subgroups (e.g., ischemic stroke, ICH or transient ischemic attack). Further studies will be necessary, on a larger sample size, to obtain a complete analysis in each stroke subgroup.

Lastly, regarding laboratory variables, we only considered the values within the last week before discharge. In an advanced version of our RSS, we might include trends of laboratory examinations over time to account for the patients' time-dependent conditions.

CONCLUSIONS

The identification of risk factors that contribute to early re-admission after AS and the stratification, through a specific seven-items RRS, of AS patients at discharge time can provide a tool that enables clinicians to plan personalized follow-ups.

The 30-day risk assessment of discharge failure could be effective in the future to support clinical discharge pathways for patients with AS. However, its use in different subpopulations of patients and countries should be further demonstrated.

AUTHOR CONTRIBUTIONS

Study concept and design: Giovanna Mercurio, Giovanni Frisullo. Acquisition of data: Benedetta Gottardelli, Jacopo Lenkowicz, Simone Bellavia, Irene Scala, Pierandrea Rizzo. Analysis and interpretation of data: Giovanna Mercurio, Giovanni Frisullo, Benedetta Gottardelli, Jacopo Lenkowicz, Anna Benedetta Del Signore, Simone Bellavia, Irene Scala, Pierandrea Rizzo. Drafting of the manuscript: Giovanna Mercurio, Giovanni Frisullo, Benedetta Gottardelli, Jacopo Lenkowicz, Stefano Patarnello, Antonio Giulio de Belvis, Riccardo Maviglia, Maria Grazia Bocci, Alessandro Olivi, Francesco Franceschi, Andrea Urbani, Massimo Antonelli, Paolo Calabresi, Vincenzo Valentini. Critical revision of the manuscript for important intellectual content: Antonio Giulio de Belvis, Stefano Patarnello, Alessandro Olivi, Francesco Franceschi, Andrea Urbani, Massimo Antonelli, Paolo Calabresi, Vincenzo Valentini. Study supervision: Giovanna Mercurio. All authors read and approved the final manuscript.

FUNDING INFORMATION

This study received partial funding from the Italian Ministry for University and Research (MUR) under the Program PON Research and Innovation supporting the development of the artificial intelligence platform Gemelli Generator at Fondazione Policlinico Universitario A. Gemelli IRCCS.

CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mercurio G, Gottardelli B, Lenkowicz J, et al. A novel risk score predicting 30-day hospital re-admission of patients with acute stroke by machine learning model. *Eur J Neurol*. 2024;31:e16153. doi:10.1111/ene.16153