In-Hospital and Long-Term Prognosis after Spontaneous Intracerebral Hemorrhage among Young Adults Aged 18-65 Years

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Background: Spontaneous intracerebral hemorrhage (ICH) accounts for 10%-15% of all strokes and has an estimated annual incidence of 5/100,000 in young adults. Limited data on prognosis after ICH in young adults are available. We aimed to identify prognostic predictors after ICH among adults aged 18-65 years. *Methods:* We retrospectively selected all patients with ICH from a prospective single-center registry of adults with first stroke before 65 years between 1997 and 2002. We recorded in-hospital mortality as well as mortality and recurrent stroke after discharge until December 1, 2018. For in-hospital analysis, we compared patients that died in-hospital versus patients discharged alive. For long-term analysis, we compared patients that died in follow-up versus patients still alive. Independent prognostic predictors were identified using multivariate analyses. *Results:* Among 161 patients included, 24 (14.9%) died in-hospital. Among in-hospital survivors, 5-year survival was 92.0%, 10-year survival 78.1%, and 15-year survival 62.0%. After median follow-up of 17 years, 47.4% of patients died, 18 patients had ischemic stroke, and 6 recurrent ICH. Regarding in-hospital prognosis, coma at admission (OR .02 [.00-.11]) was independent predictor for mortality whereas alcoholic habits (OR 12.32 [1.82-83.30]) was independent predictor for survival. An increasing age (OR 1.08 [1.03-1.12]), higher blood glucose levels (OR 1.01 [1.00-1.01]), and hypertension (OR 2.21 [1.22-4.00]) were independent predictors of long-term mortality after ICH. *Conclusions:* Alcoholic habits may influence in-hospital survival after ICH in young adults. Long-term mortality in young adults seems to be lower than in elderly and was predicted by higher blood glucose levels and hypertension.

Key Words: Intracerebral hemorrhage—ICH—stroke—young adults—in-hospital prognosis—long-term prognosis

Background

Spontaneous intracerebral hemorrhage (ICH) accounts for nearly 10%-15% of all strokes.[1] Overall, the annual incidence of ICH is around 25 per 100,000 individuals and is higher among the elderly.[2] Although ICH is less common than ischemic stroke, it is frequently associated to a poor outcome and long-term morbidity.[3,4]

ICH in young adults (18-50 years) has an annual incidence of around 5 per 100,000 individuals.[5] Its in-hospital mortality ranges from 12.5% to 34.1% and 1-month mortality from 8.1% to 26.1%.[5] There are already several observational studies that focused on short-term mortality after ICH in young adults and identified some independent factors associated with early mortality such as female sex, decreased level of consciousness, infratentorial hematoma location, multiple hemorrhages, hyperglycemia, and structural causes of ICH.[6–10]

However, limited data on long-term ICH prognosis in young adults are available. Mortality ranging from 12.5% to 38.9% has been reported in studies with follow-up

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Received May 3, 2019; revision received July 21, 2019; accepted August 11, 2019.

Financial Disclosure: The authors declare no funding.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104350

durations of 6-17 months.[5] Only 2 observational studies reported on longer follow-up periods (median 9.7 years and mean 11.3 years).[11,12] All-cause cumulative mortality was 27.6% at 10 years[12] and 31.4% at 20 years.[11] In addition, little information is available regarding independent predictors of long-term mortality in this setting. Only 1 study identified male sex and diabetes mellitus as predictors of increased long-term mortality after ICH in young adults.[12]

A better understanding of short-term and, most importantly, of long-term prognosis after ICH in young adults is needed.

We aimed to identify predictors of short-term (in-hospital period) and long-term prognosis after spontaneous ICH among young adults aged 18-65 years.

Methods

Patient Selection

We retrospectively analyzed data of all patients admitted with first stroke before 65 years from a prospectively constructed single-center registry from 1997 to 2002. For this study, we included all patients with ICH. We excluded patients without follow-up data. We recorded demographical and clinical characteristics including age, sex, vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, and alcoholic habits), headache and coma at admission. We also analyzed imaging features such as ICH location, intraventricular extension of the hematoma, and brain herniation. Metabolic assessment included admission systolic and diastolic blood pressure, and blood glucose, cholesterol, and triglycerides levels.

Outcome Measures

We collected follow-up data from local and national informatic health systems. We recorded data regarding mortality during in-hospital period and mortality after discharge until December 1, 2018. We also recorded modified Rankin Scale (mRS) at discharge and recurrent (hemorrhagic or ischemic) stroke during the follow-up period.

Statistical Analysis

We did 2 separated statistical analyses, one regarding in-hospital prognosis and the other for long-term prognosis. We expressed continuous variables as median (interquartile range, IQR) and categorical variables as numbers (percentage). We performed univariate analyses using the chi-square test or Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. For survival analysis we used Kaplan-Meier curves.

For the in-hospital prognosis analysis, we included all patients with ICH from the registry that met the inclusion criteria. We divided the patients in 2 groups: (1) patients that died during the in-hospital period; and (2) patients that were discharged alive. Demographical and clinical characteristics were compared between the 2 groups using a univariate analysis. Independent prognostic predictors were identified using a logistic regression model adjusted for sex, age, and all variables with P value $<.05$ in the univariate analysis.

For the long-term prognosis analysis, we excluded all patients who died during in-hospital period. We divided the patients in 2 groups: (1) patients that died during the follow-up period; and (2) patients that remained alive. Demographical and clinical characteristics were compared between the 2 groups using a univariate analysis. Independent mortality predictors were identified using a multivariable Cox regression model adjusted for sex, age, and all variables with P value $<.10$ in the univariate analysis.

In addition, we performed a sensitivity analysis comparing patients aged 18-50 years versus patients aged 51-65 years.

We expressed associations as odds ratios (OR) with 95% confidence intervals (CI) or its associated P value. In all analysis, a P value of $<.05$ was considered statistically significant. We used SPSS Statistical Software for Windows (Version 25.0).

Results

Baseline Characteristics

Among 1253 patients with first stroke before 65 years, 205 patients (16.4%) had a spontaneous ICH. From these, we excluded 44 patients due to lack of follow-up data. For this study, we included 161 patients, of which 24 (14.9%) died during in-hospital period.

In the 24 patients that died during in-hospital period, median age was 57 years (IQR 47-61 years), 75.0% (n = 18) were men and 87.5% (n = 21) were white. The most frequent vascular risk factors were hypertension (75.0%, n = 18), alcoholic habits (25.0%, n = 6), smoking (8.3%, n = 2), diabetes mellitus (8.3%, n = 2), and dyslipidemia (4.2%, n = 1). At admission, 75.0% of patients (n = 18) were in coma, and 62.5% (n = 15) had systolic blood pressure (SBP) more than or equal to 190 mm Hg. About 75.0% of patients (n = 18) had basal ganglia ICH, 16.7% (n = 4) had infratentorial ICH, and 12.5% (n = 3) had lobar ICH. Nine patients (37.5%) had intraventricular extension of the hematoma and 16.7% (n = 4) had brain herniation.

Among the 137 in-hospital survivors, median age was 54 years (IQR 48-60), 67.2% (n = 92) were men, and 83.9% (n = 115) were white. The most frequent vascular risk factors were hypertension (70.1%, n = 96), alcoholic habits (54.0%, n = 74), smoking (29.2%, n = 40), dyslipidemia (18.2%, n = 25), and diabetes mellitus (13.9%, n = 19). At admission, 38.0% of patients (n = 52) had headache, 8.0% (n = 11) were in coma, and 69.3% (n = 95) had SBP $\geq$160 mm Hg. About 72.3% of patients (n = 99) had basal ganglia ICH, 15.3% (n = 21) had lobar ICH, and 12.4% (n = 17) had infratentorial ICH. About 50.4% of patients (n = 69) had mRS less than or equal to 2 at discharge.

Table 1. *Univariate analysis of in-hospital mortality in young adults with ICH*

	Overall population 161 (100%)	In-hospital mortality		OR (95% CI)	*P* value
		Present 24 (14.9%)	Absent 137 (85.1%)		
Age (y)	54 (48-60)	57 (47-61)	54 (48-60)	NA	.590
Age 18-50 y	57 (35.4%)	9 (37.5%)	48 (35.0%)	.91 (.43-2.00)	.816
Male gender	110 (68.3%)	18 (75.0%)	92 (67.2%)	.72 (.30-1.70)	.446
White	136 (84.5%)	21 (87.5%)	115 (83.9%)	.78 (.25-2.41)	.657
Risk factors					
Hypertension	114 (70.8%)	18 (75.0%)	96 (70.1%)	.81 (.34-2.00)	.624
Diabetes mellitus type 2	21 (13.0%)	2 (8.3%)	19 (13.9%)	1.65 (.42-6.51)	.359
Dyslipidemia	26 (16.1%)	1 (4.2%)	25 (18.2%)	4.43 (.63-31.37)	.066
Smoking	42 (26.1%)	2 (8.3%)	40 (29.2%)	3.88 (.95-15.81)	**.022**
Alcohol	80 (49.7%)	6 (25.0%)	74 (54.0%)	2.96 (1.24-7.08)	**.009**
Alcohol (g/d)	70.8 (33.2-118.5)	86.4 (43.2-230.4)	69.6 (32.0-117.6)	NA	.387
Headache admission	60 (37.3%)	8 (33.3%)	52 (38.0%)	1.19 (.54-2.61)	.666
Coma admission	29 (18.0%)	18 (75.0%)	11 (8.0%)	.07 (.03-.17)	**<.001**
SBP admission (mm Hg)	180 (150-210)	196 (153-223)	180 (150-200)	NA	.151
SBP ≥160 mm Hg	111 (68.9%)	16 (66.7%)	95 (69.3%)	1.11 (.51-2.42)	.794
SBP ≥190 mm Hg	76 (47.2%)	15 (62.5%)	61 (44.5%)	.54 (.25-1.15)	.104
DBP admission (mm Hg)	100 (88-119)	108 (94-121)	100 (86-116)	NA	.195
Blood glucose admission (mmol/dL)	103 (87-128)	156 (117-197)	100 (86-118)	NA	**<.001**
Cholesterol	208 (180-249)	219 (199-280)	207 (179-248)	NA	.169
Triglycerides	101 (71-149)	94 (50-153)	102 (71-149)	NA	.919
Hematoma location					
Infratentorial	21 (13.0%)	4 (16.7%)	17 (12.4%)	.75 (.28-1.98)	.383
Lobar	24 (14.9%)	3 (12.5%)	21 (15.3%)	1.23 (.40-3.80)	.502
Basal ganglia	117 (72.7%)	18 (75.0%)	99 (72.3%)	.89 (.38-2.09)	.781
Hematoma side, left	74/150 (50.7%)	11/21 (52.4%)	63/129 (48.8%)	1.13 (.51-2.50)	.763
Intraventricular extension	13 (8.1%)	9 (37.5%)	4 (2.9%)	.15 (.08-.27)	**<.001**
Herniation	5/159 (3.1%)	4 (16.7%)	1/135 (0.7%)	.16 (.09-.30)	**.002**

ICH, intracerebral hemorrhage; NA, not applicable; *P* value <.05 in bold.

In-hospital Prognosis

In the univariate analysis, patients that survived in-hospital were more likely to smoke (8.3% versus 29.2%, $P = .022$) and to have alcoholic habits (25.0% versus 54.0%, $P = .009$) than patients who died. On the other hand, coma at admission (75.0% versus 8.0%, $P < .001$), higher blood glucose levels at admission (median 156 mmol/dL versus 100 mmol/dL, $P < .001$), intraventricular extension of hematoma (37.5% versus 16.7%, $P < .001$), and brain herniation (16.7% versus .7%, $P = .002$) were significantly more common in patients that died in-hospital. Table 1 shows the results of univariate analysis of in-hospital prognosis.

In the multivariate analysis, coma at admission [OR .02 (.00-.11), $P < .001$] was an independent predictor for mortality whereas alcoholic habits (OR 12.32 [1.82-83.30], $P = .010$) was an independent predictor for survival during in-hospital period, as shown in Table 2.

Table 2. *Multivariate analysis of factors associated to prognosis during in-hospital period*

Factor	OR (95% CI)	*P* value
Male gender	.20 (.03-1.51)	.120
Age (y)	1.00 (.92-1.10)	.931
Smoking	8.00 (.41-156.55)	.171
Alcohol	12.32 (1.82-83.30)	**.010**
Coma admission	.02 (.00-.11)	**<.001**
Blood glucose admission	.07 (1.01-1.00)	.071
Intraventricular extension	1.01 (1.00-1.02)	.613
Herniation	.00 (.00-.00)	.999

P value <.05 in bold.

Survival

Among patients that were discharged alive (n = 137, 85.1%), 1-year survival was 99.3%, 5-year survival was 92.0%, 10-year survival was 78.1%, and 15-year survival was 62.0%. After median follow-up period of 17 years (IQR 11-19 years), 47.4% (n = 65) of patients died. Figure 1 shows the Kaplan-Meier curve of cumulative survival rates.

Stroke Recurrence

During the follow-up of the 137 patients that survived the in-hospital period, 18 patients had ischemic stroke and 6 had recurrent ICH (3 were the cause of death).

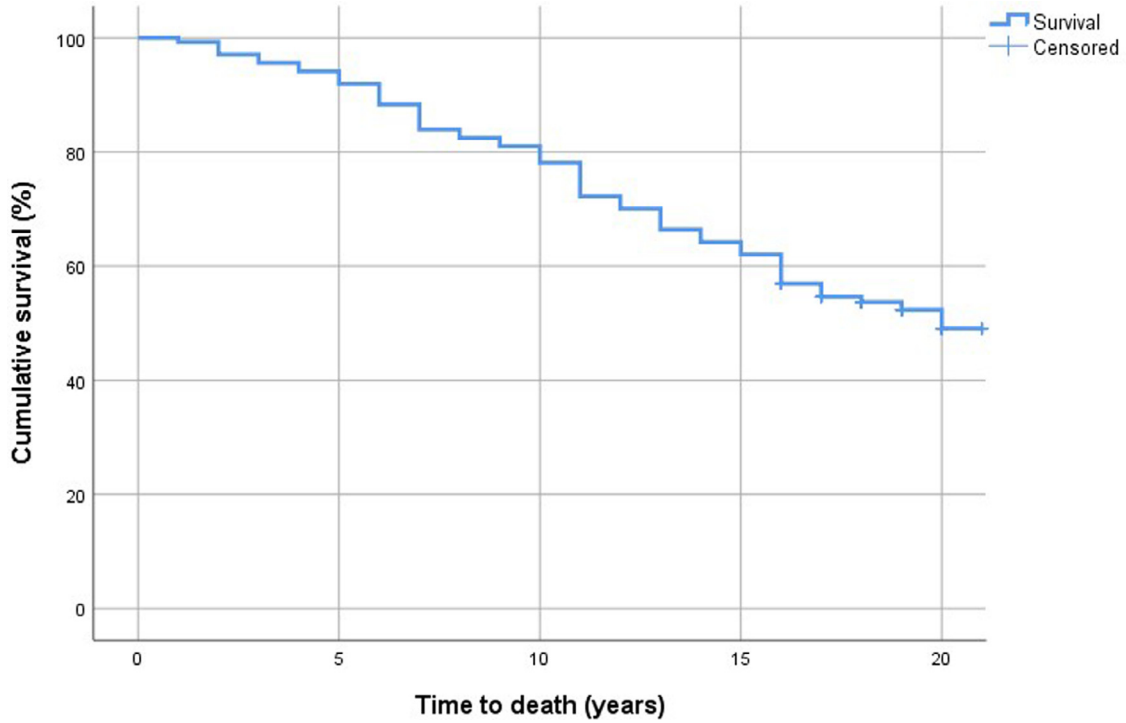

Figure 1. *Kaplan-Meier curve for cumulative survival during the follow-up period of patients discharged alive.*

Long-term Mortality

In the univariate analysis, an increasing age (median 57 years versus 51 years, $P < .001$), diabetes mellitus (20% versus 8.3% $P = .049$), and higher blood glucose levels at admission (median 105 mmol/dL versus 93 mmol/dL $P = .004$) were significantly more common in the group of patients that died during the follow-up period. Instead, headache at admission (29.2% versus 45.8%, $P = .046$) was more likely to be present in patients that survived during the follow-up period. Results of the univariate analysis of long-term mortality are presented in Table 3.

In the multivariate analysis, an increasing age (OR 1.08 [1.03-1.12], $P = .001$), higher blood glucose levels (OR 1.01 [1.00-1.01], p =.032), and hypertension (OR 2.21 [1.22-4.00], $P = .009$) were independent predictors of long-term mortality after ICH, as shown in Table 4 and Figure 2.

Sensitivity Analysis

We compared characteristics between the group of patients aged 18-50 years and the group of patients aged 51-65 years that survived the in-hospital period. Among the 48 patients (35.0%) aged 18-50 years, median age was 45 years (IQR 41-48 years), 66.7% (n = 32) were men, and 72.9% (n = 35) were white. About 62.5% of patients (n = 30) presented with headache at admission, 58.3% (n = 28) had SBP more than or equal to 160 mm Hg, 64.6% (n = 31) had basal ganglia ICH, and 47.9% (n = 23) had mRS less than or equal to 2 at discharge. Details are presented in supplemental Table 1.

In the univariate analysis, being white (72.9% versus 89.8%, $P = .010$), having SBP more than or equal to 160 mm Hg (58.3% versus 75.3%, $P = .040$), and higher blood glucose levels (median 89 mmol/dL versus 103 mmol/dL, $P = .012$) were significantly more common in the group of patients aged 51-65 years. In contrast, headache at admission (62.5% versus 24.7%, $P < .001$) was more likely to be present in patients aged 18-50 years.

Discussion

In this consecutive single-center cohort of 161 ICH patients aged 18-65 years, in-hospital mortality was 14.9% and cumulative mortality 17 years after ICH onset was 47.4%. Regarding in-hospital prognosis, coma at admission was an independent predictor for mortality whereas alcoholic habits were an independent predictor for survival. An increasing age, higher blood glucose levels, and hypertension were independent predictors of long-term mortality after ICH.

Considering the results of previous observational studies on prognostic predictors after ICH,[13] the association of previous alcoholic consumption with in-hospital survival in our cohort was unexpected. However, other observational studies had already reported similar results.[14,15] One found a numerically, non-significant, higher number of patients with alcoholic habits among 30-day survivors after ICH.[15] In another study, patients who consumed alcohol were found to have a lower mortality rate and a higher functional recovery rate after ICH.[14] In fact, this

Table 3. *Univariate analysis of long-term mortality in young adults with ICH*

	Overall population 137 (100%)	Cumulative mortality		OR (95% CI)	*P* value
		Present 65 (47.4%)	Absent 72 (52.6%)		
Age (y)	54 (48-60)	57 (52-62)	51 (44-58)	NA	**<.001**
Male gender	92 (67.2%)	44 (67.7%)	48 (66.7%)	.98 (.67-1.42)	.898
White	115 (83.9%)	58 (89.2%)	57 (79.2%)	.63 (.33-1.19)	.109
Risk factors					
Hypertension	96 (70.1%)	41 (63.1%)	55 (57.3%)	1.37 (.97-1.94)	.089
Diabetes mellitus type 2	19 (13.9%)	13 (20%)	6 (8.3%)	.64 (.45-.93)	**.049**
Dyslipidemia	25 (18.2%)	15 (23.1%)	10 (13.9%)	.74 (.51-1.09)	.164
Smoking	40 (29.2%)	21 (32.3%)	19 (26.4%)	.86 (.60-1.25)	.447
Alcohol	74 (54%)	39 (60%)	35 (48.6%)	.78 (.54-1.13)	.182
Headache admission	52 (38%)	19 (29.2%)	33 (45.8%)	1.48 (1.00-2.23)	**.046**
Coma admission	11 (8%)	6 (9.2%)	5 (6.9%)	.86 (.49-1.52)	.623
SBP admission (mm Hg)	180 (150-200)	180 (151-210)	180 (150-200)	NA	.630
SBP > 160 mm Hg	95 (69.3%)	45 (69.2%)	50 (69.4%)	1.01 (.69-1.47)	.978
SBP > 190 mm Hg	61 (44.5%)	28 (43.1%)	33 (45.8%)	1.06 (.74-1.52)	.746
DBP admission (mm Hg)	100 (86-116)	100 (87-120)	100 (82-113)	NA	.691
Blood glucose admission (mmol/dL)	100 (86-118)	105 (90-148)	93 (85-113)	NA	**.004**
Cholesterol	207 (179-248)	209 (186-249)	203 (174-246)	NA	.321
Triglycerides	102 (71-149)	116 (81-167)	96 (68-128)	NA	.051
Hematoma location					
Infratentorial	17 (12.4%)	10 (15.4%)	7 (9.7%)	.78 (.50-1.21)	.315
Lobar	21 (15.3%)	7 (10.8%)	14 (19.4%)	1.50 (.80-2.82)	.159
Basal ganglia	99 (72.3%)	48 (73.8%)	51 (70.8%)	.92 (.61-1.39)	.694
Hematoma side, left	63/129 (48.8%)	29/61 (47.5%)	34/68 (50.0%)	.95 (.66-1.37)	.780
Intraventricular extension	4 (2.9%)	3 (4.6%)	1 (1.4%)	.62 (.34-1.13)	.272
Herniation	1 (0.7%)	1 (1.6%)	0 (0%)	NA	.474
mRS ≤2 discharge	69 (50.4%)	29 (44.6%)	40 (55.6%)	1.26 (.88-1.80)	.201
Recurrent hematoma	6 (4.4%)	5 (7.7%)	1 (1.4%)	.55 (.37-.82)	.072
Ischemic stroke	18 (13.1%)	10 (15.4%)	8 (11.1%)	.83 (.53-1.31)	.460

ICH, intracerebral hemorrhage; NA, not applicable; *P* value <.05 in bold.

study reported that previous alcohol consumption was an independent predictor of functional recovery after ICH.[14] One possible explanation may be the alcohol-related cerebral atrophy effect on ICH outcome. Several studies reported on alcohol-related cerebral atrophy[16,17] and 1 observational study identified cerebral atrophy as an independent predictor of survival after ICH.[18] Unfortunately, we could not provide this conclusion from our results since we lack data regarding cerebral and ICH volumes. Further research is needed concerning alcoholic habits' influence on ICH outcome.

Table 4. *Multivariate analysis of factors associated with long-term mortality in young patients with ICH*

Factor	OR (95% CI)	*P* value
Male gender	1.38 (.74-2.59)	.313
Age (y)	1.08 (1.03-1.12)	**.001**
Diabetes	1.06 (.44-2.56)	.894
Hypertension	2.21 (1.22-4.00)	**.009**
Headache admission	1.68 (.87-3.23)	.120
Blood glucose admission	1.01 (1.00-1.01)	**.032**
Triglycerides	1.00 (1.00-1.01)	.093
Recurrent hematoma	.57 (.19-1.74)	.323

ICH, intracerebral hemorrhage; *P* value <.05 in bold.

Although there are several observational studies regarding long-term prognosis after ICH in older populations,[19,20] only 2 reported on long-term ICH prognosis in young adults.[11,12] We report a cumulative mortality 17 years after ICH onset of 47.4%, which is higher than other observational studies that stated an all-cause cumulative mortality of 27.6% at 10 years[12] and 31.4% at 20 years.[11] This could probably be explained by the higher median age of our study that included patients aged 18-65 years, when other studies only included patients with less than 50 years. In fact, in our sensitivity analysis comparing patients aged 18-50 years versus patients aged 51-65 years, the cumulative mortality at 17 years of the first group (29.2%) was in line with those previous observational studies.[11,12]

Koivunen et al[12] identified male sex and diabetes mellitus as predictors of increased long-term mortality after ICH in young adults. In our analysis, higher blood glucose levels were also independently associated to

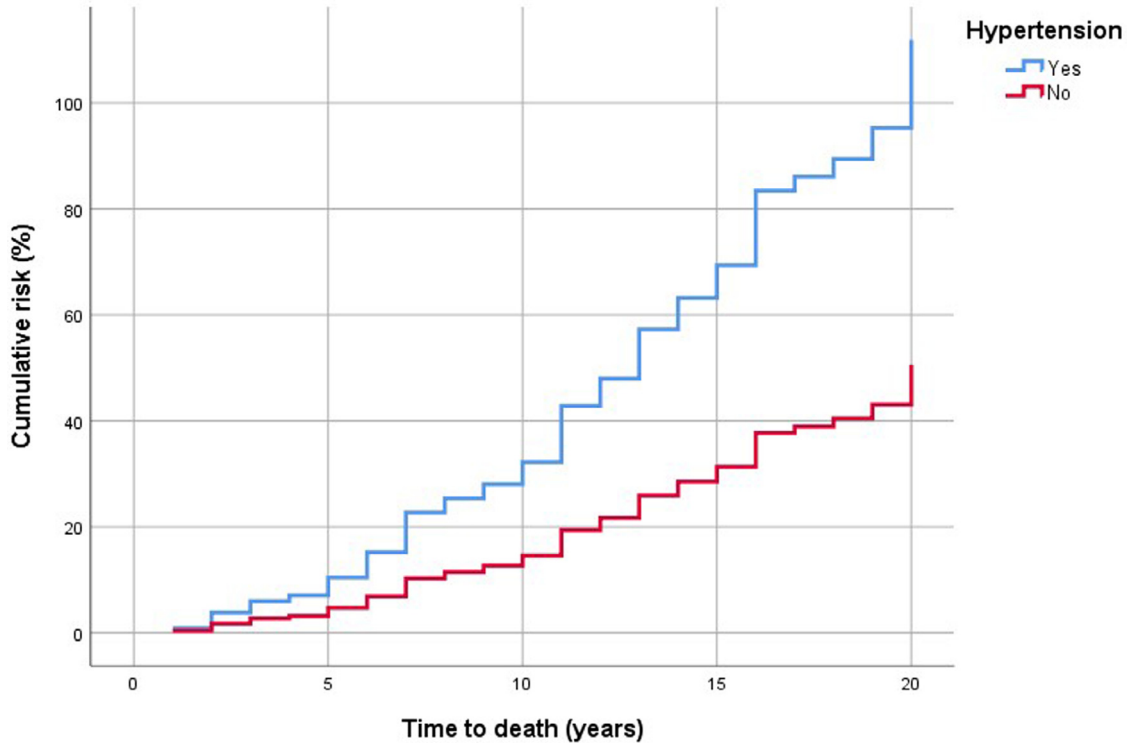

Figure 2. *Kaplan-Meier curves showing the influence of hypertension in long-term mortality after ICH. ICH, intracerebral hemorrhage.*

long-term mortality after ICH. Additionally, hypertension was also an independent predictor of long-term mortality after ICH. Diabetes mellitus and hypertension are common vascular risk factors frequently associated to both ischemic and hemorrhagic stroke.[21] They share some similar pathophysiological pathways[22] contributing to deleterious effects on the microvasculature, resulting in hematoma expansion and impaired neuroregeneration, probably leading to poorer outcomes.

We reported one of the longest follow-up studies after ICH in young adults so far, collecting data from a prospectively constructed hospital-based registry. However, our study has some limitations. The main limitation of this study is the lack of data regarding cerebral and ICH volumes as well as concerning specific etiological aspects. Secondly, this was a single-center observational study with a relatively small sample size. Thirdly, since it was a retrospective follow-up study, we could not account for long-term functional outcome neither risk of post-ICH dementia or epilepsy. In addition, data on recurrent stroke were based on new hospital admissions or information from national heath platforms during the follow-up period, with the risk of missing some patients. Therefore, these results should be interpreted with caution.

Conclusion

In this consecutive single-center cohort of ICH patients aged 18-65 years, in-hospital mortality was 14.9% and cumulative mortality 17 years after ICH onset was 47.4%. Previous alcoholic habits may influence in-hospital survival after ICH in young adults. Long-term mortality in young adults seems to be lower than in elderly and was predicted by higher blood glucose levels and hypertension.

Declaration of Competing Interest

The authors declare no conflict of interest regarding this article.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104350.

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