CONTRIBUTION OF MULTIPLE ETIOLOGIC FACTORS TO THE OUTCOME OF PATIENTS WITH INTRACEREBRAL HEMORRHAGE: RESULTS FROM A POPULATION-BASED STUDY

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OBJECTIVES. Ischemic stroke is usually caused by a single etiologic factor whereas for intracerebral hemorrhage (ICH) different etiologic factors may coexist and concur to the development of the bleeding. We aimed to evaluate possible differences in prognosis in patients with single versus multiple etiologic factors contributing to ICH.

MATERIALS AND METHODS. Cases of incident first-ever ICH were recorded over a two-year period (2011-2012) from multiple sources in the district of L'Aquila, central Italy. We attributed etiology according to the SMASH-U (Structural lesion [STRUCT], Medication [MED], Amyloid angiopathy [AA], Systemic/other disease [OTH] , Hypertension [HYPERT], Undetermined [UND]) etiologic classification. Additionally, for each included patient with ICH we considered all the other etiologic factors which may have contributed to the ICH. Patients were followed up to 1 year after the event to ascertain case-fatality rates (CFRs). Predictors of mortality were assessed by Cox regression analysis.

RESULTS. We included 148 patients; overall, according to the SMASH-U classification, 41.2% of cases were due to HYPERT, 27.0% to AA, 9.5% to UND causes, 10.1% to MED, 6.1% to STRUCT, and 6.1% to OTH. After considering possible additional causes, we found a single etiologic factor in 50 (33.8%) patients and multiple factors in 98 (72.8%). HYPERT was the most common additional factor (present in 86.7% of patients with MED and 67.5% of patients with AA) followed by the use of antiplatelets (45.0% of patients with AA, 41.0% with HYPERT) (Table 1). A single factor was common in patients with STRUCT (66.7%), was fairly rare in patients with OTH (44.4%) and HYPERT (33.4%) and uncommon in patients with AA (7.5%) and MED (6.7%) (Table 1). We did not find any difference in mean ICH volume or ICH severity in patients with single versus multiple etiologic factors. CFRs at 30 days and 1 year were also similar in the two groups (Table 2). MED was the single independent predictor of mortality at 30 days (hazard ratio 7.6; 95% confidence interval 1.7-21.4; Table 3) and 1 year (hazard ratio 8.3; 95% confidence interval 1.8-22.3; Table 4) whereas the presence of multiple factors was not.

DISCUSSION. The presence of a single etiologic factor is fairly rare in patients with ICH but the presence of multiple factors is not associated with a worst ICH severity or increased mortality. The use of anticoagulants (mostly vitamin K antagonists) is the only etiologic factor associated with increased risk of death.

CONCLUSIONS. Our data point to the need to improve the prevention of bleeding in patients who take anticoagulants and to develop targeted measures to manage anticoagulant-associated ICH in the acute phase.

	N	Hypertension, n (%)	Other systemic disease, n (%)	Single antiplatelet, n (%)	Double antiplatelet, n (%)	Subtherapeutic anticoagulation, n (%)	Single additional causal factor, n (%)	Two or more additional causal factors, n (%)	Only one cause, n (%)
Structural lesion	9	3 (33.3)	-	-	-	-	3 (33.3)	-	6 (66.7)
Medication	15	13 (86.7)	2 (13.3)	1 (6.7)	-	-	-	14 (93.3)	1 (6.7)
Amyloid angiopathy	40	27 (67.5)	7 (17.5)	18 (45.0)	-	3	20 (50.0)	17 (42.5)	3 (7.5)
Systemic/other disease	9	5 (55.6)	-	1 (11.1)	-	-	4 (44.4)	1 (11.1)	4 (44.4)
Hypertensive angiopathy	61	-	12 (19.7)	25 (41.0)	4 (6.6)	2 (3.3)	31 (50.8)	6 (9.8)	24 (33.4)
Undetermined cause	14	-	1 (7.1)	1 (7.1)	-	-	2 (14.3)	-	12 (85.7)
Total	148	48 (32.4)	22 (14.9)	46 (31.1)	4 (2.7)	5 (3.4)	60 (40.5)	38 (25.7)	50 (33.8)

Table 1

	Additional causal factors (n=98)	No additional causal factors (n=50)	P value
Age, mean±SD	78.4±11.0	70.7±15.6	<0.001
Males, n (%)	52 (53.1)	25 (50.0)	0.724
NIHSS score on admission, median (IQR)	6 (2-10)	5 (2-7.5)	0.275
mRS score at discharge, median (IQR)	3 (2-4)	3 (1.5-4)	0.259
Dead at 30 days, n (%)	45 (45.9)	20 (40.0)	0.493
Dead at 1 year, n (%)	51 (52.0)	23 (46.0)	0.487

Table 2

Predictors of 30-day mortality (Cox)	HR	95% CI	P value
Age, per year	0.997	0.958-1.038	0.884
Male sex	1.695	0.799-3.599	0.169
NIHSS score on admission, per point	1.099	1.049-1.151	<0.001
ICH subtype			
Hypertensive	1 (Ref)	-	-
Structural lesion	0.462	0.062-3.439	0.451
Medication	8.338	1.860-37.381	0.006
Amyloid angiopathy	1.754	0.779-3.951	0.175
Systemic/other disease	3.019	0.764-11.934	0.115
Undetermined cause	5.426	0.589-49.960	0.135
Additional causal factors			
0	1 (Ref)	-	-
1	1.812	0.772-4.252	0.172
2	0.720	0.220-2.355	0.587
3	0.799	0.116-5.525	0.820

Table 3

Predictors of 1-year mortality (Cox)	HR	95% CI	P value
Age, per year	1.004	0.966-1.043	0.851
Male sex	1.480	0.719-3.045	0.287
NIHSS score on admission, per point	1.089	1.042-1.139	<0.001
ICH subtype			
Hypertensive	1 (Ref)	-	-
Structural lesion	0.544	0.076-3.874	0.544
Medication	7.999	1.835-34.865	0.006
Amyloid angiopathy	1.667	0.765-3.632	0.199
Systemic/other disease	5.096	0.559-46.485	0.149
Undetermined cause			
Additional causal factors			
0	1 (Ref)	-	-
1	1.414	0.645-3.100	0.387
2	0.581	0.187-1.808	0.349
3	0.719	0.107-4.833	0.734

Table 4