Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2016;42:485–492
DOI: 10.1159/000448813

Received: May 2, 2016
Accepted: July 28, 2016
Published online: September 6, 2016

The Effect of Age on Characteristics and Mortality of Intracerebral Hemorrhage in the Oldest-Old

Paola Forti[a] Fabiola Maioli[b] Michele Domenico Spampinato[a]
Carlotta Barbara[d] Valeria Nativio[b] Maura Coveri[b] Marco Zoli[a]
Luigi Simonetti[d] Giuseppe Di Pasquale[c] Gaetano Procaccianti[e]

[a]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, [b]Geriatric Stroke Unit and [c]Cardiology Unit, Medical Department, Maggiore Hospital, [d]Emergency Radiology-Interventional Neuroradiology Unit and [e]Neurology Stroke Unit, Institute of Neurological Sciences of Bologna (IRCCS), Maggiore Hospital, Bologna, Italy

Key Words
Intracerebral hemorrhage · Primary intracerebral hematoma · Stroke in the elderly · Incidence and mortality rates · Cohort study

Abstract
Background: Incidence of acute intracerebral hemorrhage (ICH) increases with age, but there is a lack of information about ICH characteristics in the oldest-old (age ≥85 years). In particular, there is a need for information about hematoma volume, which is included in most clinical scales for prediction of mortality in ICH patients. Many of these scales also assume that, independent of ICH characteristics, the oldest-old have a higher mortality than younger elderly patients (age 65–74 years). However, supporting evidence from cohort studies is limited. We investigated ICH characteristics of oldest-old subjects compared to young (<65 years), young-old (65–74 years) and old-old (75–84 years) subjects. We also investigated whether age is an independent mortality predictor in elderly (age ≥65 years) subjects with acute ICH. ***Methods:*** We retrospectively collected clinical and neuroimaging data of 383 subjects (age 34–104 years) with acute supratentorial primary ICH who were admitted to an Italian Stroke Unit (SU) between October 2007 and December 2014. Measured ICH characteristics included hematoma location, volume and intraventricular extension of hemorrhage on admission CT scan; admission Glasgow Coma Scale ≤8 and hematoma expansion (HE) measured on follow-up CT-scans obtained after 24 h. General linear models and logistic models were used to investigate the association of age with ICH characteristics. These models were adjusted for pre-admission characteristics, hematoma location and time from symptom onset to admission CT scan. Limited to elderly subjects, Cox models were used to investigate the association of age with in-SU and 1-year mortality: the model for in-SU mortality adjusted for pre-admission and ICH admission characteristics and the model for 1-year mortality additionally adjusted for functional status and disposition at SU discharge. ***Results:*** Independent of pre-admission characteristics, hematoma location and time from symptom onset to admission CT-scan, oldest-old subjects had the highest admission hematoma volume ($p < 0.01$). Age was unrelated to all other ICH characteristics including HE. In elderly patients, multivariable adjusted risk of in-SU and 1-year mortality did not vary across age categories. ***Conclusions:*** Oldest-old subjects

KARGER

1015–9770/16/0426–0485$39.50/0

E-Mail karger@karger.com
www.karger.com/ced

Paola Forti
Department of Medical and Surgical Sciences (DIMEC)
University of Bologna
Via Massarenti 9, IT–40138 Bologna (Italy)
E-Mail paola.forti@unibo.it

with acute supratentorial ICH have higher admission hematoma volume than young and young-old subjects but do not differ for other ICH characteristics. When taking into account confounding from ICH characteristics, risk of in-SU and 1-year mortality in elderly subjects with acute supratentorial ICH does not differ across age categories. Our findings question use of age as an independent criterion for stratification of mortality risk in elderly subjects with acute ICH.

Introduction

Age is a major non-modifiable risk factor for spontaneous intracerebral hemorrhage (ICH) [1]. Age-specific risk of ICH [2] is 5-fold higher for elderly (age ≥65 years) compared to young persons (<65 years) and 2-fold higher for oldest-old (≥85 years [3]) compared to young-old (65–74 years) and old-old (74–84 years) [4].

The oldest-old are dissimilar from younger elderly subgroups; they are, by definition, survivors, but their health status and ability to withstand acute stressors is very heterogeneous [4]. Therefore, assumptions based on data from younger age categories can be inappropriate for the oldest-old.

Age is usually included as an independent determinant in ICH prognostic scales and oldest-old are often attributed a worse prognosis than younger elderly subgroups based on age alone [5]. Other major ICH determinants include neurological impairment as assessed with the Glasgow Coma Scale (GCS), location and volume of hematoma and intraventricular extension of hemorrhage (IVH) [6, 7]. Hematoma expansion (HE) also influences ICH prognosis and is of interest as a potentially treatable factor [6, 8].

Available data about ICH determinants, however, mostly come from studies that included very few oldest-old and just aggregated them with younger elderly persons [9, 10]. Current knowledge for ICH in the oldest-old is scarce [11–13] and further research is advocated [10].

In this paper, we investigated ICH characteristics of oldest-old subjects and whether, in elderly subjects with acute ICH, age is an independent mortality predictor.

Methods

Patient Selection and Data Collection

Subjects were drawn from an ongoing prospective retrospective cohort study of patients aged ≥18 years with first-episode spontaneous ICH consecutively admitted to the Stroke Unit (SU) of the Maggiore Hospital (Bologna, Italy) since October 2007 [14]. The cohort does not include ICH due to trauma, brain tumor, infections, vascular malformations, vasculitis and hemorrhagic transformation of ischemic stroke. This study included only subjects with supratentorial ICH admitted until December 2014. The Maggiore Hospital Ethics Committee approved the study. All subjects (or their legally authorized representatives) provided written informed consent.

About 99% of the ICH patients admitted to the Maggiore SU (20 beds) are directly referred from the Emergency Department, where they undergo admission CT scan and, if appropriate, early re-coagulation. Patients receive full medical care for at least 2 days [15]. Current Italian laws do not allow formal do-not-resuscitate orders and withdrawal of basic life sustaining treatments (hydratation and nutrition).

Clinical Data

Pre-admission characteristics and admission GCS were documented in the patients' medical records. Pre-admission characteristics included hypertension (history of blood pressure >140/90 mm Hg or current treatment), diabetes mellitus (history, current treatment or glycated hemoglobin ≥6.5% on SU admission [16]), dementia (previous formal diagnosis or presence of standard clinical criteria [17] for at least 6 months before ICH), prestroke modified Ranking Scale (mRS) [18], Charlson Comorbidity Index (CCI) [19] and use of antiplatelets and anticoagulant drugs. The international normalized ratio (INR) measured at the Emergency Department (before eventual anticoagulation reversal) was recorded and stratified according to standard cutoffs [20]. Time from symptom onset to admission CT scan (measured from last seen well for patients with un-witnessed onset) was dichotomized at 6 h [8]. Mortality during SU stay and, for survivors, mRS and disposition at discharge from SU (home, rehabilitation services and definitive institutionalization) were also obtained from medical records. Vital status at 1-year from SU discharge was obtained from the Regional Mortality Registry.

Neuroimaging Analysis

Admission CT scan and the first available follow-up scan (on average 24 h from admission scan; range 4–36 h) were retrospectively reviewed by 2 investigators (M.D.S. and C.B.) assisted by a senior radiologist (L.S.), all blinded to the patient's identity (κ for inter-rater agreement = 0.90). Hematoma location and IVH on admission scans were defined as previously described [21]. Hematoma volume was measured according to the formula of ellipsoids (ABC/2 method) [22]. HE was defined as an increase >33% or absolute increase >6 mm in hematoma volume [8].

Statistical Analyses

Age was analyzed as a categorical variable (<65, 65–74, 75–84 and ≥85 years [3, 4]). Univariate associations were tested using χ^2, Kruskal–Wallis or Mann–Whitney test. Separate general linear models (GLMs) for lobar and deep location were used to test the association of age with admission hematoma volume, analyzed as a continuous dependent variable after square root transformation to approximate normality. Bonferroni multiple comparison test was used for post-hoc pairwise comparisons. Logistic regression was used to test the association of age with location, IVH, admission GCS ≤8 and HE. Choice of covariates was based

Table 1. Pre-admission characteristics of ICH subjects by age category

Characteristics	<65 years (n = 59)	65–74 years (n = 65)	75–84 years (n = 166)	≥85 years (n = 93)	p value
Sex, female	16 (27.1)	23 (35.4)	96 (57.8)	60 (65.5)	<0.001
History of hypertension	32 (54.2)	46 (70.8)	116 (69.9)	69 (74.2)	0.064
Diabetes mellitus	14 (23.7)	18 (27.7)	39 (23.5)	19 (20.4)	0.771
Dementia	4 (6.8)	6 (9.2)	42 (25.3)	28 (30.1)	<0.001
CCI					0.003
0	33 (55.9)	22 (33.8)	53 (31.9)	25 (26.9)	
1	17 (28.8)	19 (29.2)	52 (31.3)	39 (41.9)	
2	4 (6.8)	14 (21.5)	33 (19.9)	20 (21.5)	
≥3	5 (8.5)	10 (15.4)	28 (16.9)	9 (9.7)	
Prestroke mRS					<0.001
0–1	52 (88.1)	57 (87.7)	123 (74.1)	45 (48.4)	
2–3	6 (10.2)	8 (12.3)	33 (19.9)	33 (35.5)	
4–5	1 (1.7)	0 (0.0)	10 (6.0)	15 (16.1)	
Anti-aggregant use	9 (15.3)	28 (43.1)	98 (59.0)	52 (55.9)	<0.001
Anticoagulant use	2 (3.4)	12 (18.5)	32 (19.3)	15 (16.1)	0.035
Admission INR					0.440
<1.2	54 (91.5)	52 (80.0)	131 (78.9)	73 (80.6)	
1.2–2.0	4 (6.8)	6 (9.2)	10 (6.0)	7 (7.5)	
2.1–3.0	1 (1.7)	4 (6.2)	17 (10.2)	8 (8.6)	
>3.0	0 (0.0)	3 (4.6)	8 (4.8)	3 (3.2)	
Time from symptom onset to admission CT scan					
≥6 h	24 (40.7)	31 (47.7)	89 (53.6)	55 (59.1)	0.134
Unwitnessed onset	12 (20.3)	22 (33.8)	69 (41.6)	40 (43.0)	0.017

Data reported as number (%). p value is for univariate comparisons.

upon literature [1, 8] and exploratory univariate analyses. Analyses for volume and location were adjusted for all pre-admission characteristics of table 1 excepting anticoagulant use, due to multicollinearity with INR (model 1). Analyses for volume were additionally adjusted for time to admission CT scan. Analyses for the remaining ICH characteristics were sequentially adjusted for model 1 plus location, volume and, if appropriate, IVH and time to admission CT scan (model 2). The association of age with mortality was investigated using Cox proportional hazards regression sequentially adjusted for models 1 and 2 covariates plus admission GCS. Analyses for 1-year mortality additionally adjusted for mRS and disposition at SU discharge (model 3) [23]. As deaths for age <65 years were too few for analysis (in-SU mortality, n = 2; 1-year mortality, n = 2), Cox regression was restricted to subjects ≥65 years. Lacunar ICH [24] and recourse to intensive care and neurosurgery were also recorded but were too rare for inclusion in multivariable adjusted analyses (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000448813). In additional analyses (data not shown), results did not change when substituting admission INR with reported anticoagulation use and GCS with admission score at the National Institutes of Health Stroke Scale (NIHSS) [25]. NIHSS was not included in this report because of collinearity with GCS. Moreover ICH prognostic scores favor GCS because ICH patients are more likely to have depressed consciousness on initial presentation [5, 15].

Analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, N.Y., USA). Models were tested for interactions. Significance tests were 2-tailed with significance at $p < 0.05$.

Results

Cohort Characteristics

A total of 457 subjects with supratentorial ICH were admitted to the Maggiore SU during the study period; 74 were excluded because of unavailable admission CT scan. The final study cohort included 383 white subjects (lobar ICH, n = 179; deep ICH, n = 204) aged 34–104 years (mean age 77 ± 12 years). Excluded subjects did not differ from study participants for demographic, pre-admission and outcome characteristics (all $p > 0.20$). Univariate analyses of pre-admission characteristics (table 1) showed that subjects of ≥85 years (24.3% of the cohort) were more frequently women, with dementia and high prestroke mRS, and less frequently without comorbidity. Prevalence of anti-aggregant and anticoagulant users also increased with age but only up to age 75–84 years; admis-

Table 2. ICH admission characteristics by age category

Characteristics	<65 years (n = 59)	65–74 years (n = 65)	75–84 years (n = 166)	≥85 years (n = 93)	p value
Lobar ICH	20 (33.9)	34 (52.3)	76 (45.8)	49 (52.7)	0.107
Unadjusted	1.00	2.14 (1.04–4.42)*	1.65 (0.89–3.06)	2.17 (1.10–4.27)*	
Model 1	1.00	1.78 (0.85–3.76)	1.07 (0.54–2.10)	1.35 (0.65–2.83)	
IVH	17 (28.8)	17 (26.2)	69 (41.6)	46 (49.5)	0.008
Unadjusted	1.00	0.88 (0.40–1.93)	1.76 (0.92–3.34)	2.42 (1.21–4.84)*	
Model 1	1.00	0.81 (0.35–1.85)	1.58 (0.78–3.23)	2.24 (1.03–4.86)*	
Model 2	1.00	0.96 (0.41–2.27)	1.37 (0.65–2.91)	1.38 (0.60–3.21)	
Admission GCS ≤8	4 (6.8)	9 (13.8)	37 (22.3)	26 (28.0)	0.007
Unadjusted	1.00	2.21 (0.64–7.60)	3.94 (1.34–11.60)*	5.34 (1.76–16.21)**	
Model 1	1.00	2.21 (0.62–7.93)	3.12 (0.99–9.85)	4.75 (1.43–15.75)*	
Model 2	1.00	3.90 (0.88–17.33)	2.35 (0.60–9.20)	1.51 (0.34–6.63)	

Data reported as number (%) and OR (95% CI). p value is for univariate comparisons. Model 1 adjusted for pre-admission characteristics; model 2 additionally adjusted for ICH admission characteristics (location, volume and, if appropriate, IVH). p value for significant ORs: * $p < 0.05$, ** $p < 0.01$.

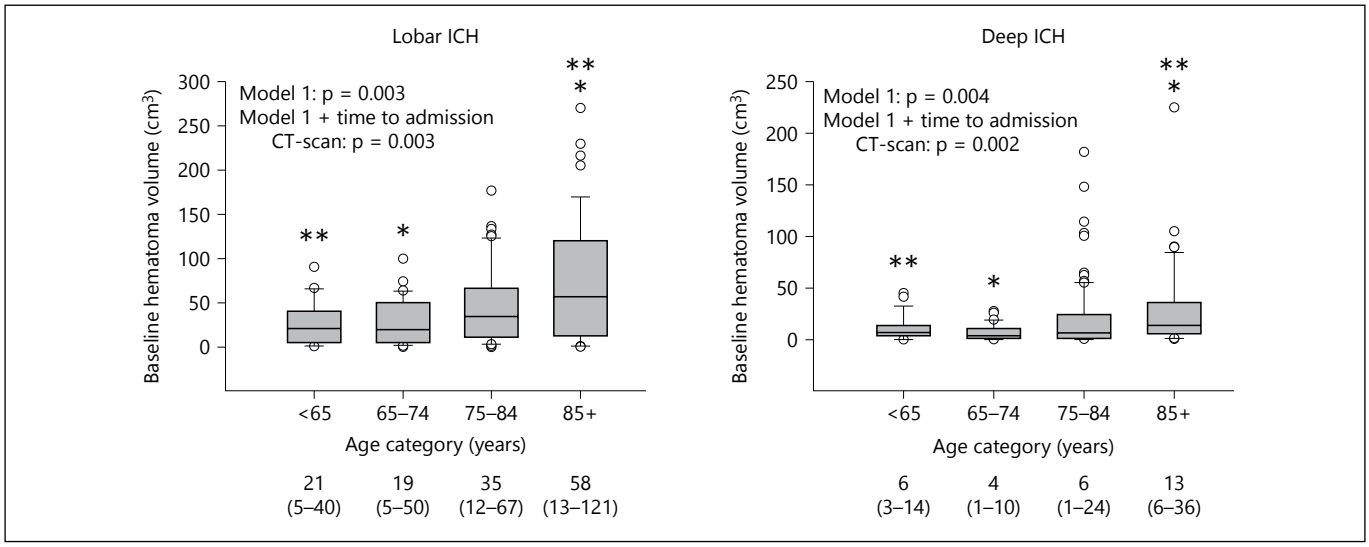

Fig. 1. Box plots of admission hematoma volume by localization of ICH and age categories. Numbers below the box plots are median (IQR). p values are from GLMs adjusted for pre-admission characteristics (model 1) minus or plus time from symptom onset to admission CT scan. Asterisks identify statistically significant post-hoc comparisons (Bonferroni test; * $p < 0.05$, ** $p < 0.01$).

sion INR was unrelated to age. Time to admission CT scan (range 1–48 h) was unrelated to age but un-witnessed onset was more likely in older subjects.

ICH Admission Characteristics

Admission hematoma volume was higher for lobar (median (interquartile range, IQR), 30 (8–66) cm^3) than deep ICH (8 (2–20) cm^3, univariate $p < 0.001$). Regardless of location, volume increased across age categories (univariate $p < 0.001$) and the association was confirmed in multivariable GLMs even when adjusting for time to admission CT scan (fig. 1). Significant post-hoc comparisons were found for age ≥85 years compared to age <65 and 65–74 years but not compared to age 75–84 years, due to the increasing scattering of volume values.

According to logistic regression (table 2), occurrence of lobar ICH was higher for age 65–74 and ≥85 years com-

Table 3. Hematoma expansion by age category in subjects with ICH

Characteristics	<65 years (n = 51)	65–74 years (n = 57)	75–84 years (n = 139)	≥85 years (n = 77)	p value
Hematoma expansion	8 (15.7)	10 (17.5)	34 (25.4)	29 (37.7)	0.014
Time from symptom onset to admission CT scan					
≥6 hours	20 (39.2)	27 (47.4)	78 (56.1)	49 (63.6)	0.035
Unwitnessed onset	9 (17.6)	18 (31.6)	59 (42.4)	36 (46.8)	0.003
Unadjusted	1.00	1.14 (0.41–3.16)	1.74 (0.74–4.06)	3.25 (1.34–7.86)**	
Model 1	1.00	0.92 (0.31–2.70)	1.36 (0.53–3.54)	2.95 (1.09–8.00)*	
Model 2	1.00	1.70 (0.47–6.14)	1.62 (0.51–5.09)	3.86 (1.14–13.09)*	
Model 2 plus time from symptom onset to admission CT scan	1.00	1.01 (0.33–3.09)	1.25 (0.47–3.32)	2.41 (0.84–6.92)	

Data reported as number (%) and OR (95% CI). p value is for univariate comparisons. Model 1 adjusted for pre-admission characteristics; model 2 additionally adjusted for ICH admission characteristics (location, volume, intraventricular extension of hemorrhage). p value for significant ORs: * $p < 0.05$, ** $p < 0.01$.

pared to <65 years and occurrence of IVH and GCS ≤8 was higher for age ≥85 years compared to <65 years in unadjusted models, but all associations disappeared in multivariable models.

Hematoma Expansion

Follow-up CT scans were available for 84.6% of subjects (148 lobar and 176 deep ICH) and overall HE occurrence was 25% (n = 81). Subjects without follow-up CT scan (death before scan, n = 30; neurosurgery before scan, n = 10; unknown reason, n = 19) did not differ by age but had higher prestroke mRS and CCI, lower admission GCS and higher admission volume (univariate $p > 0.05$ for all). As shown in table 3, age had univariate associations with HE, time to admission CT scan and un-witnessed onset; in logistic regression, risk of HE was higher for age ≥85 years compared to <65 years in unadjusted analyses and model 1, but not in model 2.

Mortality

Among subjects ≥65 years (n = 324, mean age 81 ± 7 years), overall in-SU mortality rate was 25.9% (n = 84) for a median length of SU stay of 9 days (range 1–53 days). Age was associated with in-SU mortality in univariate analyses, and in Cox regression, risk was higher for age ≥85 years compared to age 65–74 years in both unadjusted analyses and model 1, but not in model 2 (table 4, top). Among subjects alive at SU discharge (n = 240, mean age 80 ± 7 years), overall 1-year mortality rate was 30.8% (n = 74) for a median follow-up time of 286 days, and age had univariate associations with discharge mRS, institutionalization and 1-year mortality (table 4, middle). In Cox regression (table 4, bottom), 1-year mortality risk was higher for age 65–74 and ≥85 years compared to age 65–74 years in unadjusted analyses as well as in models 1 and 2, but not in model 3. In Cox models limited to subjects with follow-up CT, results did not change after additional adjustment for HE and time to admission CT scan (data not shown).

Discussion

This retrospective analysis of a single-center SU cohort shows that oldest-old subjects with acute ICH have higher admission hematoma volume than young and young-old subjects. The association is independent of pre-admission characteristics, hematoma location and time from symptom onset to admission CT scan. This study also shows that age is unrelated to other ICH characteristics including HE. Moreover, in elderly subjects with acute ICH, increasing age is not an independent mortality predictor.

Only 3 previous investigations compared ICH admission characteristics and mortality of oldest-old to those of younger patients [11–13]; results are conflicting and only in-hospital mortality was investigated (online suppl. table 2 for a detailed summary). The only investigation providing volumetric data is a case–control study of hypertensive patients [12]; oldest-old did not differ from younger patients for hematoma volume but had higher IVH occurrence.

Table 4. Mortality and discharge characteristics by age category in elderly subjects with ICH

	65–74 years	75–84 years	≥85 years	p value
All elderly subjects, n	65	166	93	
In-SU mortality	9 (13.8)	43 (25.9)	32 (34.4)	0.015
Unadjusted	1.00	1.85 (0.90–3.81)	2.68 (1.27–5.62)**	
Model 1	1.00	1.85 (0.88–3.87)	3.04 (1.39–6.63)**	
Model 2	1.00	1.69 (0.79–3.65)	1.55 (0.68–3.55)	
Elderly subjects alive at SU discharge, n	56	123	61	
Discharge mRS				0.001
0–1	50 (89.3)	92 (74.8)	29 (47.5)	
2–3	6 (10.7)	26 (21.1)	22 (36.1)	
4–5	0 (0.0)	5 (4.1)	10 (16.4)	
Discharge disposition				0.054
Home	18 (32.1)	29 (23.6)	15 (24.6)	
Rehabilitation	30 (53.6)	67 (54.5)	24 (39.3)	
Institutionalization	8 (14.3)	27 (22.0)	22 (36.1)	
1-Year mortality	8 (14.3)	39 (31.7)	27 (44.3)	0.002
Unadjusted	1.00	2.64 (1.23–5.66)*	3.76 (1.71–8.28)**	
Model 1	1.00	2.31 (1.05–5.09)*	2.75 (1.19–6.34)*	
Model 2	1.00	2.26 (1.00–5.10)*	2.98 (1.27–7.01)*	
Model 3	1.00	2.31 (0.96–5.57)	2.13 (0.84–5.44)	

Data reported as number (%) and HR (95% CI). p value is for univariate comparisons. Model 1 adjusted for pre-admission characteristics; model 2 additionally adjusted for ICH admission characteristics (location, admission volume, intraventricular extension of hemorrhage and GCS ≤8); model 3 additionally adjusted for mRS and disposition at SU discharge. p value for significant HRs: * $p < 0.05$, ** $p < 0.01$.

Current knowledge about age and ICH volume is scant and contrasting. Of 2 small studies, one reported a positive association in lobar but not in deep ICH [26] whereas the other reported no association [27]. A large study, conversely, reported an inverse association between age and volume in deep ICH [28].

Our findings for admission hematoma volume in the oldest-old are consistent with existing knowledge on the role of aging on brain architecture and neuroinflammation. Documented age-related alterations of brain architecture include damage of the blood–brain barrier, white-matter lesions and cerebral amyloid angiopathy (CAA), which is often associated to cortical superficial siderosis [29, 30]. These alterations may weaken brain architecture and favor physical disruption from local bleeding. Brain atrophy may also contribute to a larger hematoma volume on presentation because of a less effective tamponade effect [9, 26]. Additional damage might derive from an excess of local neuroinflammatory response due to dysregulation of aging microglia [31] possibly through acceleration in the formation of brain edema [32]. We actually observed a wide range of values for admission hematoma volume in oldest-old subjects and data dispersion was already noticeable for the old-old. This finding agrees with consolidated evidence that aging is associated with a growing heterogeneity in the ability of organs and tissues to withstand acute stressors [4].

Our data for hematoma location are consistent with previous evidence that the trend for increasing occurrence of lobar ICH in older patients is actually explained by other age-related characteristics such as use of antithrombotic drugs and CAA [2]. In our study, oldest-old subjects also had higher occurrence of admission IVH and GCS ≤8, but these associations were mostly explained by differences in hematoma location and volume.

Age is not currently considered a HE determinant [8] but data for oldest-old are lacking. In our study, oldest-old had the highest incidence of HE, but the association was mainly mediated by time to admission CT scan. The latter is an acknowledged major determinant of HE [8]. However, our finding must be considered with caution because, in our study, onset time for older ICH cases was more likely to be estimated from last time seen well rather than actually witnessed. This association might result from age-related social features such as living alone or with other elderly relatives. Moreover, elderly persons

have low awareness of potential stroke symptoms and are less likely to promptly call for emergency services [33]. ICH-related mortality risk is known to be higher for the elderly compared to that of young people [2]. However, evidence that age per se is associated with a further dose-response increase of ICH mortality from age 65 onwards is mostly based on cohorts lacking information about ICH volumetric characteristics [2, 34]. All the same, several ICH prognostic scales attribute additional risk points to oldest-old persons compared to young-old and old-old persons regardless of other admission characteristics [5]. Our data question this use of age for ICH risk stratification of elderly subjects by showing that, when ICH-related and discharge characteristics are taken into account, mortality risk, both during SU stay and at 1-year, does not actually differ across young-old, old-old and oldest-old subjects.

The major strengths of this study include the sample size, availability of volumetric data and lack of bias from formal orders for withdrawal of care. Our study also has important limitations. First, we performed a retrospective analysis of prospectively collected data and had no control on timing of CT scans. Second, precision of estimation for ICH onset time decreased with age. Third, other unmeasured characteristics may influence HE (e.g., APOE genotype [8], malnutrition, hyperglycemia, admission blood pressure [8, 35, 36]) and ICH outcome (e.g., hematoma sedimentation level [37]). Third, the ABC/2 method may be less accurate than the semi-automated techniques [6, 8]. Finally, the study was underpowered for estimation of mortality in those <65 years.

In conclusion, this study shows that oldest-old ICH subjects with acute ICH have higher admission hematoma volume but age is unrelated to other ICH characteristics including HE. The study also suggests that age per se should not be used for stratification of mortality risk in elderly subjects with acute ICH.

Acknowledgment

This work was supported by the Basic Oriented Research Grant RFO2012 from the University of Bologna.

Disclosure Statement

The authors report no conflicts of interest.

References

1 Ikram MA, Wieberdink RG, Koudstaal PJ: International epidemiology of intracerebral hemorrhage. Curr Atheroscler Rep 2012;14:300–306.
2 van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ: Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010;9:167–176.
3 Suzman R, Riley MW: Introducing the 'oldest old'. Milbank Mem Fund Q Health Soc 1985;63:177–186.
4 Baltes PB, Smith J: New frontiers in the future of aging: from successful aging of the young old to the dilemmas of the fourth age. Gerontology 2003;49:123–135.
5 Hwang BY, Appelboom G, Kellner CP, Carpenter AM, Kellner MA, Gigante PR, Sander Connolly E: Clinical grading scales in intracerebral hemorrhage. Neurocrit Care 2010;13:141–151.
6 LoPresti MA, Bruce SS, Camacho E, Kunchala S, Dubois BG, Bruce E, Appelboom G, Connolly ES: Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. J Neurol Sci 2014;345:3–7.
7 Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. Lancet 2009;373:1632–1644.
8 Brouwers HB, Greenberg SM: Hematoma expansion following acute intracerebral hemorrhage. Cerebrovasc Dis 2013;35:195–201.
9 Camacho E, LoPresti MA, Bruce S, Lin D, Abraham M, Appelboom G, Taylor B, McDowell M, DuBois B, Sathe M, Sander Connolly E: The role of age in intracerebral hemorrhages. J Clin Neurosci 2015;22:1867–1870.
10 Steiner T, Petersson J, Al-Shahi Salman R, Christensen H, Cordonnier C, Csiba L, Harnof S, Krieger D, Mendelow D, Molina C, Montaner J, Overgaard K, Roine RO, Schmutzhard E, Tatlisumak T, Toni D, Stapf C: European research priorities for intracerebral haemorrhage. Cerebrovasc Dis 2011;32:409–419.
11 Arboix A, Vall-Llosera A, García-Eroles L, Massons J, Oliveres M, Targa C: Clinical features and functional outcome of intracerebral hemorrhage in patients aged 85 and older. J Am Geriatr Soc 2002;50:449–454.
12 Chiquete E, Ruiz-Sandoval MC, Alvarez-Palazuelos LE, Padilla-Martínez JJ, González-Cornejo S, Ruiz-Sandoval JL: Hypertensive intracerebral hemorrhage in the very elderly. Cerebrovasc Dis 2007;24:196–201.
13 Stein M, Misselwitz B, Hamann GF, Scharbrodt W, Schummer DI, Oertel MF: Intracerebral hemorrhage in the very old: future demographic trends of an aging population. Stroke 2012;43:1126–1128.
14 Forti P, Maioli F, Arnone G, Nativio V, Zagnoni S, Riva L, Pedone C, Pirazzoli GL, Coveri M, Zoli M, Di Pasquale G, Procaccianti G: Mortality after admission to stroke unit for intracerebral hemorrhage: effect of age 80 and older and multimorbidity. J Am Geriatr Soc 2015;63:812–813.
15 Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American heart association/American stroke association. Stroke 2015;46:2032–2060.
16 American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36(suppl 1):S67–S74.
17 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®. American Psychiatric Publishing, 2000.

18 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
19 Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
20 Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP, Woo D: Warfarin use leads to larger intracerebral hematomas. Neurology 2008;71:1084–1089.
21 Falcone GJ, Biffi A, Brouwers HB, Anderson CD, Battey TW, Ayres AM, Vashkevich A, Schwab K, Rost NS, Goldstein JN, Viswanathan A, Greenberg SM, Rosand J: Predictors of hematoma volume in deep and lobar supratentorial intracerebral hemorrhage. JAMA Neurol 2013;70:988–994.
22 Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304–1305.
23 van Almenkerk S, Smalbrugge M, Depla MF, Eefsting JA, Hertogh CM: What predicts a poor outcome in older stroke survivors? A systematic review of the literature. Disabil Rehabil 2013;35:1774–1782.
24 Arboix A, García-Eroles L, Massons J, Oliveres M, Targa C: Hemorrhagic lacunar stroke. Cerebrovasc Dis 2000;10:229–234.
25 Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, et al: Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
26 Kuramatsu JB, Sauer R, Mauer C, Lücking H, Kloska SP, Kiphuth IC, Staykov D, Köhrmann M, Huttner HB: Correlation of age and haematoma volume in patients with spontaneous lobar intracerebral haemorrhage. J Neurol Neurosurg Psychiatry 2011;82:144–149.
27 Wasay M, Yousuf A, Lal D, Awan S: Predictors of the intracerebral hemorrhage volume in hypertensive patients. Cerebrovasc Dis Extra 2011;1:1–5.
28 Falcone GJ, Brouwers HB, Biffi A, Anderson CD, Battey TW, Ayres AM, Vashkevich A, Schwab KM, Rost NS, Goldstein JN, Viswanathan A, Greenberg SM, Rosand J: Warfarin and statins are associated with hematoma volume in primary infratentorial intracerebral hemorrhage. Neurocrit Care 2014;21:192–199.
29 Vasilevko V, Passos GF, Quiring D, Head E, Kim RC, Fisher M, Cribbs DH: Aging and cerebrovascular dysfunction: contribution of hypertension, cerebral amyloid angiopathy, and immunotherapy. Ann N Y Acad Sci 2010;1207:58–70.
30 Charidimou A, Ni J, Martinez-Ramirez S, Vashkevich A, Ayres A, Rosa nd J, Gurol EM, Greenberg SM, Viswanathan A: Cortical superficial siderosis in Memory Clinic patients: further evidence for underlying cerebral amyloid angiopathy. Cerebrovasc Dis 2016;41:156–162.
31 Wang J: Preclinical and clinical research on inflammation after intracerebral hemorrhage. Prog Neurobiol 2010;92:463–477.
32 Zheng H, Chen C, Zhang J, Hu Z: Mechanism and therapy of brain edema after intracerebral hemorrhage. Cerebrovasc Dis 2016;42:155–169.
33 Caruso D, Perez Akly M, Costantini PD, Fridman S, Esnaola MM: Do elderly patients call 911 when presented with clinical scenarios suggestive of acute stroke? A cross-sectional study. Cerebrovasc Dis 2015;39:87–93.
34 Weimar C, Benemann J, Diener HC: Development and validation of the Essen intracerebral haemorrhage score. J Neurol Neurosurg Psychiatry 2006;77:601–605.
35 Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, Skolnick BE, Davis SM: Determinants of intracerebral hemorrhage growth: an exploratory analysis. Stroke 2007;38:1072–1075.
36 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T: Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 1997;28:2370–2375.
37 Sato S, Delcourt C, Zhang S, Arima H, Heeley E, Zheng D, Al-Shahi Salman R, Stapf C, Tzourio C, Robinson T, Lindley RI, Chalmers J, Anderson CS: Determinants and prognostic significance of hematoma sedimentation levels in acute intracerebral hemorrhage. Cerebrovasc Dis 2016;41:80–86.