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Association of Pre-Existing Comorbidities with Inpatient Outcomes in Very Elderly Patients Presenting with Primary Intracerebral Hemorrhage

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ABSTRACT

AIM: To explore presenting status and pre-existing comorbidities in very elderly patients and compare the inpatient management outcomes with younger counterparts in intracerebral hemorrhage (ICH).

MATERIAL and METHODS: This ICH database is a retrospective cohort of 814 patients who presented with primary ICH from January 2011 to January 2021. Demographic data, presenting symptoms, pre-existing medical conditions, and imaging findings were recorded. Functional state presented as modified Rankin Scale (MRS) at discharge and inpatient mortality were evaluated.

RESULTS: Our results indicate very elderly patients had significantly higher baseline MRS and comorbidities such as hypertension, hyperlipidemia, and atrial fibrillation at presentation. Similarly, usage of statins, antiplatelets, and anticoagulants was considerably higher in this age group. Very elderly patients were also found to have a higher average volume of hematoma at presentation (p-value 0.0220). Our results indicate that patients with age > 80 have a significantly lower likelihood of having a good clinical mRS score at discharge compared to younger patients (Adjusted OR 0.251, p-value = 0.0026).

CONCLUSION: The present study demonstrates a wide variety of pre-existing factors that correlate with worse outcomes amongst very elderly patients presenting with primary ICH. Given the importance of an aging population as a major healthcare issue in many parts of the world, it is crucial to continue exploring these associations in future research. The findings of this study can be utilized to plan further prospective studies on this topic.

KEYWORDS: Intracerebral hemorrhage, Very elderly, Outcomes

ABBREVIATIONS: ICH: Intracerebral hemorrhage, OR: Odds ratio, GCS: Glasgow Coma Scale, HE: Hematoma expansion, CI: Confidence interval, CT: Computerized tomography, DM: Diabetes mellitus, HTN: Hypertension, HLD: Hyperlipidemia, CAD: Coronary artery disease, CHF: Congestive heart failure, AF: Atrial fibrillation, LOS: Length of stay, GLMMs: Generalized linear mixed effect models

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■ INTRODUCTION

Primary intracerebral hemorrhage (ICH) accounts for 10-15% of all strokes and is associated with high management morbidity and mortality rates (4,12,16,18). While numerous pre-existing comorbidities can put patients at risk for ICH, an increasing age appears to be one of the most remarkable (2,8). Stein et al. proposed a model that predicted a 2.5-fold rise in the proportion of ICH patients over age 80 by the year 2030 (14). As the incidence of ICH increases in the very elderly population (Age $\geq$ 80 years), projected healthcare costs are concomitantly rising (19). Ovbiagele et al. predicted a three-fold increase in the cost of caring for stroke patients over the age of 80 by the year 2030 (10). Patients older than 85 are 10 times more likely to suffer from an ICH than adults aged from 45-54 (11). In addition, adverse outcomes secondary to ICH are more common in the elderly. Predictive models currently suggest that ICH-related adverse events will continue to rise in the near future, which is in part due to an aging population, with increasing rates of anticoagulation use and lack of consensus on the best management strategy for elderly (5).

Given the social and healthcare aspects of population aging, it is of paramount importance to determine the underlying risk factors and predictors of poor outcomes of ICH in elderly patients (8). Some risk factors for ICH in the general adult population include smoking, cerebral amyloid angiopathy, drug/alcohol use, and pre-existing comorbidities such as hypertension, diabetes mellitus (DM), heart disease and chronic kidney disease (1,9). In addition, anticoagulation usage is strongly associated with higher mortality and disability rates (5,13). Most, if not all of these risk factors are likely to be more prevalent in older patients and age itself is one of the greatest independent risk factors for spontaneous ICH (9,13). Only a select few studies have evaluated characteristics of ICH patients $\geq$ 80 years old and determined risk factors that were associated with poor ICH outcomes while stratifying by age (6,10,11,14). However, the results from these studies make it difficult to discern whether the poor outcomes in patients $\geq$ 80 years are due to their age or other pre-existing factors. The current literature lacks consensus on the associations and predictive factors of poor outcomes amongst ICH patients $\geq$ 80 years. In addition, the current literature on this topic does not adjust for comorbidities which may be affecting the results that have been observed. The purpose of this study was to compare the characteristics of very elderly ICH patients to younger age groups ICH patients that predict inpatient and discharge outcomes through univariate and multivariate regression analysis. In doing so, we hope to fill the gap that pertains to the current lack of literature on ICH patients over the age of 80. It was hypothesized that elderly patients would have worse outcomes due to more underlying comorbidities and worse clinical presentation at admission. We hypothesized that this effect would persist even after adjusting for comorbidities.

■ MATERIAL and METHODS

We retrospectively reviewed data from January 2011 to January 2021 for 814 consecutive primary ICH encounters admitted with a primary diagnosis of spontaneous ICH. After

removing encounters with multiple admissions, 784 unique patients were included in this study. Demographic characteristics, past medical history, therapeutic interventions, and in-hospital complications were assessed for the entire cohort. For our statistical analysis we created two groups: 1. patients over the age of 80 (defined as the very elderly group) and 2. patients aged 18-79. The primary outcomes of interest were inpatient mortality, mRS at discharge, and hospital length of stay. We categorized all primary outcomes into one of two binary outcomes as either favorable or non-favorable according to the categories described in Figure 1. Multiple prior studies have used similar paradigms when classifying favorable and unfavorable outcomes (7,11,15). An mRS score of 0-2 was classified as favorable outcome and mRS of 3-6 as an unfavorable outcome.

Chi-square tests with exact p-values based on Monte Carlo simulation were utilized to compare gender and race/ethnicity distribution between the two groups. Generalized linear mixed effect models (GLMM) considering patients as random effect were used to examine whether there were significant differences in patient characteristics between the two age groups. Similar univariate analyses were conducted to examine the association between variables and binary clinical outcomes. For continuous outcome, i.e. LOS, linear mixed-effect models (LMMs) were conducted, considering patients as random effect. For binary outcomes, multivariable GLMMs were constructed (termed as Base Models) which adjusted for variables that had significant associations with their respective primary clinical outcome in the univariate analyses. Separate models were constructed for pre-modified mRS, admission mRS, ICH score, and hematoma volume to fit each outcome if these variables were adjusted in the Base Model. Two-way interaction terms between age group and the aforementioned variables were considered in each separate model to examine the possible difference across the levels of the variable in the comparison of the risk of outcome between older and younger groups. For numeric outcome, multivariable LMMs were constructed, following the same process. Participants were treated as the random effect in all GLMMs and LMMs. In GLMMs, an odds ratio (OR) >1 indicated higher risk of outcomes, while

	Favorable Outcome	Non-favorable Outcome
Inpatient Mortality	No	Yes
mRS Discharge	mRS 0-2	mRS 3-6

Figure 1: Binary categorization of primary outcomes as either favorable or non-favorable outcomes. DNR/DNI status was a secondary outcome.

an OR <1 indicated lower risk of outcomes. In LMMs, a difference >0 indicated longer LOS, while a difference <0 indicated shorter LOS. Statistical analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and the significance level was set at 0.05.

RESULTS

Table I highlights the demographic characteristics and primary clinical outcomes comparing the young and elderly patients. Of 814 patients admitted for primary spontaneous ICH, 32.4% were over the age of 80 (N=264). We observed an inpatient mortality rate of 25.57% amongst patients ≥ 80 years old. 93.18% had an mRS at discharge greater than or equal to 3. Hospital length of stay was 3 days shorter in the group ≥ 80 years old for the univariate analysis ($p<0.0001$) but demonstrated no significant difference in the multivariate analysis.

Table II highlights patient characteristics for the two groups with p-values to assess significant differences. Medical conditions with a higher prevalence in the elderly group included hypertension (87.1%), hyperlipidemia (60.6%), coronary artery disease (29.8%), atrial fibrillation (32.1%) and cancer (25.9%). Higher rates of medication management, including antiplatelet (59.8%), anticoagulation (29.5%), and statin (46.6%) therapy were observed in the group compared to the younger group (p-values 0.0006, 0.0246 and 0.0105, respectively). A higher prevalence of obesity was noted in younger patients (38.5%, p-value <0.0001). Although no significant differences were noted in hematoma location between the two groups; pa-

tients over 80 years old were much more likely to present with higher ICH scores ($p<0.0001$) and higher hematoma volumes ($p=0.0220$) when compared to the younger group.

Table III demonstrates the base models as a part of the multivariate analysis for each primary outcome (please refer to supplemental tables for details of full model). With regards to primary outcomes, inpatient mortality was not significantly different between the two groups as a part of the univariate analysis. After controlling for mRS on admission, ICH scores, anticoagulation therapy, statin therapy, hematoma volume and history of prior ICH, HLD, CAD, CHF in the multivariate analysis base model, there was again no difference inpatient mortality between the two groups (OR 0.612 95% CI [0.342, 1.095], $p=0.0912$). In the multivariate analysis, patients older than 80 were more likely to have unfavorable mRS scores at discharge per the base model (OR 0.251 95% CI [0.114, 0.556], $p=0.0026$) and when adjusting for both mRS scores prior to admission (OR 0.245 95% CI [0.136, 0.445], $p<0.001$) and at admission.

DISCUSSION

Spontaneous ICH remains a devastating disease with poor outcomes that are disproportionately prevalent amongst patients over age 80 (3,5,15). The prevalence of spontaneous ICH may increase up to 35.2% by the year 2050, a metric that could be accounted for by both an aging population and increasing rates of anticoagulation for comorbid conditions (14). Despite this, there is limited literature comprehensively

Table I: Summary of Demographic Characteristics and Primary Outcomes for the Very Elderly and Younger Patient Groups with p-values Based on Regression Analysis. Chi-Square (χ^2) tests were performed to calculate p-values.

Demographic information (N=784) ^a	n (age 18-79 years)	n (age ≥ 80 years)	p-value (alpha = 0.05)
Median age (years)	67.00±17.00	85.00±7.00	
Sex			
Female	234 (44.40)	137 (53.31)	0.0191
Male	293 (55.60)	120 (46.69)	
Race/Ethnicity			
African American	49 (9.92)	5 (2.02)	0.0003
Asian	17 (3.44)	4 (1.62)	
Hispanic	13 (2.63)	3 (1.21)	
White	415 (84.01)	235 (95.14)	
Clinical outcomes (N=814)	Young patients (n=550)	Very elderly patients (n=264)	
Inpatient mortality	97 (17.67)	67 (25.57)	0.0172
Median hospital length of stay	8.00±14.00	5.00±8.50	<0.0001
mRS discharge 0-2	131 (23.95)	18 (6.82)	<0.0001
mRS discharge 3-6	416 (76.05)	246 (93.18)	

^a784 unique patients were identified in this study of which 28 patients had multiple admissions to the same hospital, thus leading to a total of 814 total encounters. Therefore, we report our demographic data based on the total number of unique patients (N=784) while the remainder of the clinical outcomes and regression data in subsequent tables is based on the number of patient encounters (N=814).

Table II: Characteristics of Very Elderly Group Compared to Young Patient Groups Including Past Medical Conditions, Pre-Existing Medications, and Presenting Clinical Data Based on Generalized Linear Mixed Effect Models (GLMMs). Chi-Square (χ^2) tests were performed to calculate p-values.

Patient characteristics	Young patients (n=550)	Very elderly patients (n=264)	p-value
	n (%)	n (%)	
Hypertension	148 (18.59)	114 (21.39)	0.0093
Hyperlipidemia	361 (45.99)	259 (49.24)	0.0165
Diabetes	575 (73.16)	378 (71.73)	0.2196
Coronary artery disease	612 (77.18)	428 (80.60)	0.0037
Congestive heart failure	715 (90.16)	481 (90.58)	0.5855
History of previous intracranial hemorrhage	703 (88.65)	468 (87.97)	0.4161
Atrial fibrillation	616 (77.78)	438 (82.64)	0.0001
Cancer	627 (79.27)	433 (81.85)	0.0190
BMI	519 (67.49)	324 (61.48)	<.0001
Medications			
Statin	491 (60.32)	350 (63.64)	0.0105
Anticoagulant	593 (75.93)	411 (78.59)	0.0246
Antiplatelet	409 (50.25)	303 (55.09)	0.0006
Presenting clinical data			
Hematoma location			
Deep supratentorial	233 (43.47)	97 (37.74)	0.0846
Lobar	266 (49.63)	149 (57.98)	
Other	37 (6.90)	11 (4.28)	
Median hematoma volume	11.50±34.00	14.33±42.95	0.0220
ICH score			
0	172 (31.27)	0 (0)	<0.0001
1	161 (29.27)	83 (31.56)	
2	114 (20.73)	73 (27.76)	
3	77 (14.00)	61 (23.19)	
4	26 (4.73)	29 (11.03)	
5	0 (0)	17 (6.46)	

assessing the factors that affect outcomes of ICH in elderly patients. Our findings indicate that patients age 80 and above had higher hematoma volumes, more cardiovascular comorbidities, and higher rates of anticoagulation. After performing a univariate analysis that elucidated statistically significant differences in primary outcomes between several patient characteristics, we conducted a multivariate analysis (Table III) that controlled for these characteristics when comparing to younger patients. Our multivariate analysis demonstrated that patients over the age of 80 were more likely to have worse mRS scores at discharge. Although very elderly patients demonstrated higher inpatient mortality rates on univariate analysis, the multivariate analysis showed no significant differences in

inpatient mortality between the two groups. Preclinical studies have proposed several pathophysiological mechanisms that may account for poor ICH outcomes in older adults. These include progressive parenchymal degeneration that is more subject to mass effect of hematomas, vascular dysfunction secondary to stiffening, hardening and sclerotic changes in vessels, and the deleterious effects of underlying inflammatory processes due to both non-vascular and cerebrovascular diseases (17).

While the reasons for poor recovery from ICH continue to be investigated in preclinical models, there is a rising need for clinical studies to better understand possible associations that may explain the underlying pathophysiology. In doing

Table III: Odds Ratio with 95% CIs for Binary Outcomes by Age Group Based on GLMMs with Multivariate Analysis. Chi-Square (χ^2) tests were performed to calculate the adjusted odds ratios and p-values.

Outcome: Inpatient Mortality²				
Model	Variable	Comparison	Adjusted OR (95% CI)	p-value
Base model	Age	≥80 vs <80	0.612 (0.342, 1.095)	0.0912
Controlled for: MRS at admission, ICH score, HLD, CAD, CHF, History of Previous ICH, Obesity (BMI>30), statin use, anticoagulant use and hematoma volume	Hematoma volume	(Unit = 1 mm ³)	1.003 (0.998, 1.009)	0.2227
	ICH score	3-6 vs 0-2	7.613 (4.233, 13.690)	<0.0001
	Age * ICH score	(≥3 vs <3 [Age≥80])	10.215 (4.519, 23.092)	<0.0001
Outcome: Favorable MRS at discharge⁴				
Base model	Age	≥80 vs <80	0.251 (0.114, 0.556)	0.0026
Controlled for: pre-modified mRS, mRS at admission, ICH score, surgical intervention, HTN, DM, CAD, CHF, AF, statin use, anticoagulant use and hematoma volume	Pre-modified MRS	3-6 vs 0-2	0.060 (0.006, 0.558)	0.0177
	Hematoma volume	Unit = 1 mm ³	0.996 (0.985, 1.006)	0.3608
	ICH score	3-6 vs 0-2	0.093 (0.018, 0.477)	0.0081

1: P-values were from generalized linear mixed effect models with patients' ID as random effect.

so, necessary modifications in the healthcare system can be made to manage the long-term care for elderly ICH patients. In this study of 814 ICH patients, 32.4% were older than the age of 80. For reference, the INTERACT2 trial, one of the largest landmark studies assessing ICH outcomes in 2794 patients, was comprised of 19.9% of patients over the age of 75 (11). Another large trial of 3448 ICH patients had 34% of patients over the age of 80 (14). Our patient population in Suffolk County includes 18.2% of patients over the age of 65, which may account for why the proportion of elderly patients in this cohort is much higher in comparison to some other studies (3). ICH patients ≥ 80 years in this study were also more likely to be of female sex which is in line with Forman et al.'s study where 149 of 220 (68%) elderly ICH patients were female (6). mRS scores both at baseline ($p=0.0005$) and on admission ($p=0.0438$) were more likely to be greater than 3 amongst patients ≥ 80 years.

Our findings also demonstrate that the only comorbidity with a higher prevalence in the younger group was obesity. This is a trend that was also seen in a study by Yang et al. (18). Similarly, our findings demonstrated that hypertension (87.1%), hyperlipidemia (60.6%), coronary artery disease (29.8%), atrial fibrillation (32.1%) and cancer (25.9%) all had a significantly higher prevalence in patients ≥ 80 years included. The prevalence of these comorbidities in this ICH cohort is significantly higher than both nationwide prevalence rates amongst healthy adults as well as the prevalence rates reported in multiple cohort studies of elderly ICH patients (3,7,19). This may be accounted for by the fact that our institution primarily serves a suburban, Caucasian population with high rates of access to healthcare insurance and medications needed to manage these comorbidities.

Moreover, we also observed a disproportionately higher number of Caucasian patients amongst the group ≥ 80 years in comparison to the younger group (95.1% vs. 84.0%). In gen-

eral, optimal medical management allows adults to live longer with cardiovascular disease and other comorbidities. Since Caucasian patients in our population are more likely to have access to better health insurance and medical management, this may explain why patients ≥ 80 years are predominantly white. In addition, this could also account for why many comorbidities were more prevalent amongst ICH patients ≥ 80 years when compared to their younger counterparts.

Although medical management of comorbidities is crucial for improving longevity, one must consider that the presence of cardiovascular disease, malignancy and other comorbidities in the acute setting for an ICH patient is also more likely to predict poor outcomes. In our multivariate analysis for each primary outcome, we controlled for the comorbidities noted to have a statistically significant difference for primary outcomes in the univariate analysis. We believe that the significant differences in mortality were eliminated on multivariate analysis for several reasons. The most important reason likely pertains to differences in comorbidities that were not accounted for in the univariate analysis. Conditions such as CHF, poorly managed atrial fibrillation or HTN can all be associated with worse outcomes among ICH patients (16). When these conditions are accounted for, mortality rates end up being similar between these groups. In addition, the presence of these conditions usually makes these patients poor surgical candidates, and they will often receive less aggressive treatment than patients who are more healthy.

In order to gain a better understanding of the associations seen in both our study and the current literature, longitudinal prospective cohort studies and randomized controlled trials will be needed to further explore associations. As the prevalence of ICH rises in the aging population, so too will the demand for patient beds in long-term care facilities, as many elderly patients do not have family members at home to care for them long-term (12). The trends in our study further stress the

importance of the future healthcare system allocating more financial resources towards long-term healthcare facilities. In contrast, favorable discharge outcomes rates were significantly higher amongst the younger cohort in this study ($p < 0.0001$) which may be due in part to decreased disability or a higher likelihood of having a family member care for them post-discharge. Notably, the higher prevalence of favorable outcomes was seen even after controlling for important covariates in the multivariate analysis. A relatively favorable prognosis amongst the younger cohort may also explain why these patients had a significantly longer hospital LOS compared to very elderly patients on univariate analysis ($p < 0.0001$).

While clinical trials are still being conducted, meta-analyses of the current data suggest that these interventions may be associated with lower rates of complications while still offering a mortality benefit. However, the majority of these studies have been conducted in patients under the age of 70, and therefore additional studies will be needed to assess their efficacy in very elderly patients (20). Notable strengths of our study include the population size for which ICH was evaluated in older patients. Because ICH is often fatal in older patients, few studies have adequately assessed functional outcomes and long-term mortality in the very elderly. Our series included 264 patients over the age of 80, of which 74.4% were safely discharged. Our results demonstrate that ICH is not always fatal in older populations and that aggressive medical management and surgical interventions may still be used even if the prognosis seems poor. Another important strength of this study is the consideration given to baseline functional status prior to ICH. By utilizing pre-admission mRS, we discerned an effect for functional ability post ICH that took how functional patients were before admission. This is important in an elderly population that is more likely to have worse mRS scores at baseline.

It is important to consider functional reserve and DNR/DNI status when interpreting our results. Patients who are full code with better baseline functionality at admission are more likely to recover from ICH if it is treated promptly before the deleterious consequences take place. Because patients over the age of 80 are more likely to have DNR/DNI orders, and have less functionality, this indirectly affects their hospital course when admitted for ICH. Clinicians should be aware of this when taking care of these patients so that aggressive measures can still be pursued when indicated.

Limitations

This study has a few limitations. Firstly, the suburban patient population served by this hospital is more affluent with a greater access to health insurance in comparison to many of the ICH populations studied in the current literature (11). Our cohort was not very diverse as 87.7% of patients evaluated in this study were of Caucasian race. Therefore, these results may not be easily generalizable to more diverse populations with minority ethnic groups. Additionally, the results also cannot be generalized to populations with ICH who come from lower socioeconomic backgrounds with have limited access to healthcare and poor management of chronic comorbidities.

The second limitation of this study is the lack of long-term follow-up. While mRS scores at discharge were obtained, traditional 3-month, 6-month and one year follow-up scores were not obtained as this data was not available for many of these patients who either

CONCLUSION

In this study, clinical outcomes at discharge were remarkably poorer amongst very elderly patients when compared to their younger counterparts including higher rates of mortality, more discharges to hospice care and rehabilitation as well as unfavorable discharge mRS scores. The results of our study emphasize an increasing need of the healthcare system to facilitate more resources towards long-term care facilities that will inevitably be needed to care for ICH patients with disability. In addition, this study reported a higher prevalence of comorbidities in our patient population in comparison to previous ICH studies which may account for why ICH management in these patients is becoming increasingly complex and costly. Differences in the prevalence of these comorbidities between different ICH populations may have a role in explaining variations in mortality rates and functional outcomes. Longitudinal studies will be needed to further assess the impact of long-term medical management of these outcomes on ICH mortality rates. Altogether, the poor functional outcomes seen in this study, in conjunction with many similar findings in the current literature, further emphasize the need to improve management options for ICH patients over the age of 80.

Declarations

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Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

Ethics approval and consent to participate: This study was approved by Stony Brook Medicine Institutional Review Board (IRB:2021-00449). As this was a retrospective study no patient consent was needed.

AUTHORSHIP CONTRIBUTION

Study conception and design: RD, MJ, KG

Data collection: SS, KG, RM, MJ, CW

Analysis and interpretation of results: XZ

Draft manuscript preparation: KG, RM, RD

Critical revision of the article: RD

Other (study supervision, fundings, materials, etc...): RD

All authors (KG, MJ, XZ, RM, SS, CW, RD) reviewed the results and approved the final version of the manuscript.

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