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Review Article

The Role of Age in Intracerebral Hemorrhage: An Intricate Relationship

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Abstract

Strokes are one of the leading causes of death in the United States, and intracerebral hemorrhage is the deadliest type of stroke. Age is a strong risk factor for intracerebral hemorrhages and it also affects the body in numerous ways—including changes to the cardiovascular and central nervous systems—that interplay with multiple risk factors. Understanding the role of age in risk and outcomes can guide treatment and future clinical trials. We reviewed the literature for intracerebral hemorrhage risk factors. This review aimed to identify the role of age, as well as characterize the most commonly used age cut-off points in the literature. Current review of the literature suggests the age cut-off for mortality and morbidity vary between 60-80 years of age, with the most common values of 65 or 70 years. In addition to age as a determinant of outcomes, it increases the risk of multiple chronic health conditions and comorbidities including hypertension, diabetes, and treatment with anticoagulants which contribute to the pathology of intracerebral hemorrhages. The interaction of these chronic conditions, age, and intracerebral hemorrhage is evident; however, the exact mechanism and extent of impact remain unclear. The ambiguity of these connections may be further obscured by the current recommendations, individual patient preferences, and literature supported trials of treatment options for aging patients.

Keywords: Intracerebral hemorrhage; Age; Outcome; Predictor and comorbidities

Introduction

In the United States, stroke is the fourth leading cause of death and is one of the leading causes of long-term disability [1,2]. Intracerebral Hemorrhages (ICH) account for approximately 10-15% of all strokes and are considered to have the highest mortality rate [3]. Unlike other types of strokes, ICH does not have an effective treatment, making understanding risks factors and predictors of ICH imperative to proper risk stratification and management. One common risk associated with stroke is advancing age. Hemphill et al. created one of the first widely accepted ICH scores, and in their univariate analysis, individuals aged 80 or older were a significant independent predictor of 30-day mortality, with an odds ratio of 9.55 [4]. Natural and pathological changes that occur with aging carry numerous implications for the body, including changes to the cardiovascular and central nervous systems that interact with many other risk factors for ICH. Although there has been a recent decrease in ICH rates among patients younger than 75, rates have increased in those 75 years or older [5]. Moreover, with the trend of an aging population, there is an increase in incidence rates for many comorbidities that occur with aging, and with the associated increase in incidence rates of stokes, the potential risk of ICH among the elderly is vast. Therefore, it is the aim of this review to characterize and examine age as a predictor of ICH risk and outcomes, and identify significant markers for intervention and treatment.

Effects of Aging

Advanced age is associated with worse clinical outcomes in many conditions. In the case of ICH, this association may be independent or directly related to the pathology of multiple risk factors of stroke, such as hypertension. There are numerous effects of aging on the body, and most significant in the case of ICH, are age related changes of the cerebrovascular system and the aging brain.

The effect of aging on the brain's microvasculature is well-recognized, and includes decreased vascular density, micro embolic brain injury, vessel basement membrane thickening, endothelial dysfunction, and increased blood brain barrier permeability. In addition, cerebral white matter lesions known as leukoaraiosis—characterized by spongiosis, gliosis, demyelination, and capillary degeneration [6]—are seen in the elderly population with vascular risk factors and/or vascular dementia, and are thought to be related to cerebrovascular disease in this population. Systemic conditions such as hypertension and diabetes mellitus may also contribute to these changes of the cerebrovasculature. These structural changes to the brain's vasculature make the parenchyma that it supplies more susceptible to injury, which increases the risk of stroke. Pathology involving further endothelial damage, changes in vessel elasticity, or fluctuations in blood flow and pressure, implicate chronic diseases such as hypertension, atherosclerosis, diabetes, and atrial fibrillation in worsening risks of neurologic injury.

Age-related changes of gross brain volume are also well documented, with an annual loss of volume ranging from 0.2-0.5% [4], especially in regions such as the prefrontal cortex [3], and are thought to be the result of neuronal atrophy. In a study by Gottesman et al., the authors suggested that since the elderly tend to have anatomically

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smaller brains than their younger counterparts, a given stroke volume in the elderly would affect a greater proportion of brain parenchyma, which may be a factor in the poorer neurological outcome [7]. Older populations also have a higher probability of having a history of prior strokes, which could impair their ability to recover from and make them more susceptible to additional injuries [8]. Additionally, several animal studies have shown that white matter vulnerability increases with age and could explain why post-ictus cognitive decline is higher in older populations [9–11].

Prevalence of Comorbidities

Many common chronic conditions including essential hypertension, coronary artery disease, atrial fibrillation, cardiovascular disease, and diabetes mellitus have a higher prevalence with increasing age [12], and as a result, may confound the attributable risk of age with regards to the odds of having an ICH and the outcomes in patients who survive. Hypertension is a widely identified risk factor for ICH [13–16]—a meta-analysis by Jackson et. al. showed that essential hypertension increases the risk of ICH by approximately two-fold [17], and another study estimated that 83% of ICH patient carry the diagnosis of essential hypertension [18]. Additionally, although atrial fibrillation is primarily a risk factor for cardio embolic stroke [19], this patient population is routinely anti coagulated with agents such as warfarin, which may increase the risk of ICH by two to fivefold in a dose-dependent manner [20–22]. In patients who survive the initial ICH, certain studies have shown that those with other comorbidities, such as diabetes and peripheral vascular disease, have a higher 30-day and 1-year mortality, as well as worse functional outcome [23,24]. Moreover, Pooled data of case-control studies showed that diabetic individuals are 1.3 times more likely than non-diabetics to develop ICH [13]. While diabetes has been identified as a weak risk factor, perhaps the pathogenesis of disease, with both microvascular and macrovascular changes developing over time, increases susceptibility of ICH.

Additionally, a review of the literature indicates other risk factors including alcohol use and smoking historyas potential predictors of ICH [13]. The prevalence of multi morbidity, namely vascular diseases, greatly increases with age and has been found to be present in most people age 65 or older, contributing to higher mortality and reduced functional status, possibly worsening outcomes of ICH [25–28]. In effect, comorbidities likely have varying degrees of influence on the risk of having an ICH and on the functional outcome. However, it is the potential, and likely, culmination of synergy when they act together in the elderly population that could greatly account for the higher incidence and mortality rates seen in this population.

Prognosis

Understanding the independent predictors associated with aging that lead to worse mortality rates and prognoses, such as comorbidities and treatment options, could allow for more effective interventions and reductions in unfavorable outcomes. Factors predicting mortality at 30 days and 1 year include age, cognitive function upon admission, hematoma volume, intra ventricular extension of hematoma, infratentorial location of hematoma, and heart disease [29]. Many of these known risk factors influence each other but after accounting for other variables, age is an independent predictor [30]. Table 1 explores the impact of age on prognosis of ICH morbidity and mortality and characterizes age and ICH outcomes in several well-known studies. Examination of these findings indicates that older age is associated with increased mortality, worse functional outcomes, and decreased long-term survival. As shown in Table 1, the ages most commonly used as a cut-off in the literature range from 60-80 years of age, with the majority being either 65 or 70 years of age.

One study that examined long-term prognosis in survivors after an initial ICH demonstrated that they had persistently increased mortality rates during long-term follow up compared with the general population [31]. They also found that increased age, diabetes mellitus, and anticoagulation therapy at onset of ICH were independent predictors of death among the survivors [31]. Possible explanations for this observation include comorbidities of vascular diseases such as hypertension, atherosclerosis, and cerebral amyloid angiopathy, as discussed above [8,32].

Aging and Other Issues

The weakened physiologic reserve, higher mortality rates, worse healing, worse long-term functional outcomes, and more debilitation with less insult is often seen in comparison to younger cohorts [33]. This reduction in physiologic reserve, the extra capacity of the body's organ systems to overcome challenges, increases the susceptibility of older patients to injury, disease, and loss of function. In Pisani's review article, many of the physiological changes associated with treating elderly populations are elucidated [34]. For instance, as

Table 1: Prognosis of Age in ICH Mortality and Morbidity.

Study	Year	Design	Age	Outcomes	
Kim KD, Change CH, Choi BY, Jung YJ. [28]	2014	Retrospective Cohort	67.87±11.82	Expired	On univariable analysis age was a significant (p=0.007) risk factor of fatality. However, the risk ratio on multivariable analysis was minimal.
			60.63±13.39	Survived	
Tveiten A, Ljostad U, Mygland A, Naess H. [41]	2013	Cross Sectional Study	78.3 mean age	Expired	Mean baseline age was a significant (p=0.001) predictor of long term survival.
			70.8 mean age	Survivors	
			67.3 mean age	Independent functioning	Mean baseline age was a significant (p=0.004) predictor of functional ability in long-term survivors.
			78.3 mean age	Dependent functioning	
Sun W, Pan W, Kranz PG, Hailey CE, Williamson RA, Sun W, Laskowitz DT, James ML. [29]	2013	Retrospective Cohort	Mean 65 Range 52-75	Presence of late neurological deterioration	Younger age was associated with less presence of late neurological deterioration (p=0.281).
			Mean 60 Range 48-71	No presence of later neurological deterioration	
Celikbilek A, Goksel BK, Zararsiz G, Benli S. [16]	2013	Retrospective Cohort	Mean 62.51±14.91 Cut off 65<	Mortality increased with age 65< (p=0.043.)	
				Univariate OR=2.55 at 95% CI for mortality and age over 65 years (p=0.028); multivariate OR=2.85 at 95% CI for mortality and age over 65 years (p=0.035).	
Fogelholm R, Nuutila M, Vuorela AL.[14]	1992	Prospective Cohort	>70	Age >70 years is the only identified factor independently associated with poor functional outcome.	

Abbreviations: CI: Confidence Interval; OR: Odds ratio

individuals age, their ability to respond to sympathetic stimulation declines, leading to failure of compensatory mechanisms such as increased maximal heart rate, ejection fraction and cardiac output. This puts them at an increased risk for vascular complications. A decrease in pulmonary function up to 50% can also be seen with older patients. Likewise, the kidneys also experience declining function due to the fact that approximately 40% of the nephrons become sclerotic between the ages of 25 and 85. Furthermore, renal blood flow decreases by half and the glomerular filtration rate declines to about 45% by the time an individual reaches 80 years of age. Medications will also have a different physiological effect. Hepatic blood flow diminishes by 30% between the ages of 30 and 75, and this alters the absorption, distribution, metabolism and excretion of medication. These factors culminate in age-related decline of organ system functions that cause an increased vulnerability to sepsis, changes in pharmodynamics, and cognitive decline [34], all of which are contributing to disproportionate rates of complications, extended inpatient hospitalizations, and intensive care unit admissions in older cohorts compared to their younger counterparts. While a determined age at which these changes occur most frequently is still uncertain, the literature suggests that age does impact certain complication rates during inpatient hospitalizations after stroke [35].

A self-fulfilling prophecy

Hospital management may also play a role in the differences in mortality and outcome between older and younger patients. Elderly patients tend to have more end-of-life care plans, including Do Not Resuscitate (DNR) orders, advanced care plans, and living wills. While studies indicate that there is not a difference in complication rates between elderly patients with ICH and younger ones [20], often times studies exclude patients over certain ages, which may skew the data.

As a result, it is possible that the nuances in management of ICH could be providing a selection bias, in that elderly patients with worse outcomes are less likely to receive intervention due to premeditated goals of care [36]. A recent study showed that patients who were treated more aggressively and transferred to specialist centers had better outcomes, yet interestingly it was younger patients that had higher transfer rates [37]. In this study, the odds of a patient being transferred decreased by 50% for every 10 year increase in age. After adjusting for prognostic factors, which included age, the authors stated that neurosurgical care remained strongly associated with a lower hazard of death while a DNR was associated with a higher hazard of death.

The role of DNRs in the mortality and morbidity of elderly patients is controversial. Some studies suggest that a DNR order could negatively impact the management and care [38], others have not found any such association [39]. Moreover, patients holding DNR orders tend to be associated with more severe strokes and increased age, which lead to higher mortality rates. These factors make it difficult to distinguish whether the findings are due to the stroke or a selection bias that precipitates withholding treatment options [40].

Elderly patients are also less likely to undergo surgical treatment, perhaps due to established end-of-life preferences or recommendations for treatment. Preliminary results, from the minimally invasive surgery and recombinant tissue-type plasminogen activator in ICH evacuation phase II (MISTIE II) trial, demonstrated that clot evacuation and treatment were effective in reduction of Perihematoma Edema (PHE) [41]. However, the MISTIE II trial, did not include patients older than 75, making it difficult to extrapolate the data for older populations. Nevertheless, the role of PHE in ICH is important in regards to secondary neuronal injuries and has been implicated in worsening outcomes for patients with larger edema volume [42]; therefore the potential surgical treatment to improve outcomes is important in this population. While there are a myriad of factors involved in making a decision regarding treatment with surgical intervention for an individual, the decision to withhold this treatment in an elderly individual may be shifting the odds towards an unfavorable outcome.

Conclusion

Aging carries numerous implications for the body, including changes to the cardiovascular system and central nervous system that interplay with multiple risk factors for ICH. Understanding the role of age in risk and outcomes of ICH can directly improve the planning of clinical trials and patient care. Identification of most commonly used age cut-off points in the literature can direct clinical practice. As assessed in this review, the literature suggests the age cut-off for mortality and morbidity to occur within the range of 60-80 years of age, with the most commonly used value of 65 or 70 years. Additionally, age increases the risk of multiple chronic health conditions and comorbidities, including hypertension, hypercholesterolemia, diabetes, and atrial fibrillation, which contribute to the pathology of ICH. These effects could also be exacerbated if the elderly populations have had these comorbidities for a longer period of time. The age-related interplay of these chronic conditions are highly likely to influence the risk of ICH, however, the mechanisms of interactions, extent of impact, and direction of causality are still uncertain.

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