Stroke

TOPICAL REVIEW

Predisposing Factors, Pathologies, and Precipitating Factors Causing Intracerebral Hemorrhage

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ABSTRACT: Most people with spontaneous intracerebral hemorrhage (ICH) have hypertension, which is the strongest modifiable predisposing (risk) factor. However, multiple long-term medical conditions and other known predisposing factors for ICH usually coexist with hypertension, indicating that the causal pathway is multifactorial, and the term hypertensive ICH is oversimplistic. In this review, we integrate the highest quality evidence and our clinical experience in a framework to attribute multiple predisposing factors, underlying pathologies, and precipitating factors as the cause of ICH. In clinical practice, this framework supports physicians to take a holistic approach to treatment and prevention of ICH. In research, this framework shows how existing classification systems for the cause of ICH include underlying macrovascular, microvascular, and other structural pathologies but few predisposing or precipitating factors. Furthermore, this framework can inform the development of a more holistic classification system and expose knowledge gaps, including how predisposing factors lead to underlying pathologies and why only some people with these pathologies experience ICH.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arteriolosclerosis ■ cerebral small vessel diseases ■ hypertension ■ stroke ■ waist-hip ratio

Acute spontaneous (nontraumatic) intracerebral hemorrhage (ICH) causes one-third of strokes and half the deaths and disability due to stroke worldwide.[1] The crude incidence of ICH increased by 43% worldwide between 1990 and 2019, and rates in lower- and middle-income countries are 2× to 4× greater than in high-income countries. Effective prevention strategies and treatments are essential for reducing the burden of this devastating disease.

Specific genetic, environmental, or physiological predisposing (risk) factors may lead to the pathologies that underlie ICH. Prospective cohorts have demonstrated that 15% of ICHs have an underlying macrovascular abnormality, and most of the remainder are attributable to cerebral small vessel diseases (cSVDs) such as arteriolosclerosis, cerebral amyloid angiopathy (CAA), a combination of the 2, or rarer sporadic and genetic subtypes.[2] Although high blood pressure (BP) is the strongest modifiable predisposing factor for ICH,[3] most people with high BP do not develop ICH, suggesting that other factors contribute. The largest case-control study to date found that people with ICH commonly have multiple predisposing factors, including alcohol misuse, high waist-to-hip ratio, reduced physical activity, poor diet, psychosocial factors, and cardiac causes.[4]

In this review, we start by summarizing the highest quality evidence about the many predisposing factors, underlying pathologies, and precipitating factors for

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spontaneous ICH. Next, we describe a holistic approach that physicians can take to recognize and address the many factors contributing to the cause of spontaneous ICH. Finally, we critically appraise how published causal classification systems for ICH have attempted to simplify the complexity of causation and conclude by identifying knowledge gaps and the next steps for research to develop a more inclusive causal classification system for ICH.

PREDISPOSING FACTORS FOR SPONTANEOUS ICH

Predisposing factors determine the development of pathologies that lead to ICH. Although these predisposing factors likely interact, most studies have considered them individually. We conducted a search for systematic reviews and large cohort and case-control studies of predisposing factors for ICH (Supplemental Material), found over 30 putative protective or predisposing factors (Table S1), and listed the predisposing factors with consistent clinical evidence or strong mechanistic support for their association with spontaneous ICH in our framework (Figure).

Demographic Predisposing Factors

In common with other cardiovascular diseases, spontaneous ICH is associated with aging, male sex, and social deprivation (Table S1).[1,5] A combination of genetic, economic, and cultural factors may explain the association with East and South Asian ethnicity.[6] In the United States, people of the Black race and Hispanic ethnicity have higher age-standardized ICH incidence rates.[7] The later age of menopause is a sex-specific predisposing factor.[8]

Genetic Predisposition

Genetic traits may determine some predisposing factors or pathologies underlying ICH. Most knowledge about these traits is derived from populations in Europe and North America, with little information from populations at highest risk in sub-Saharan Africa and South-East Asia. Few epigenetic studies have explored potential

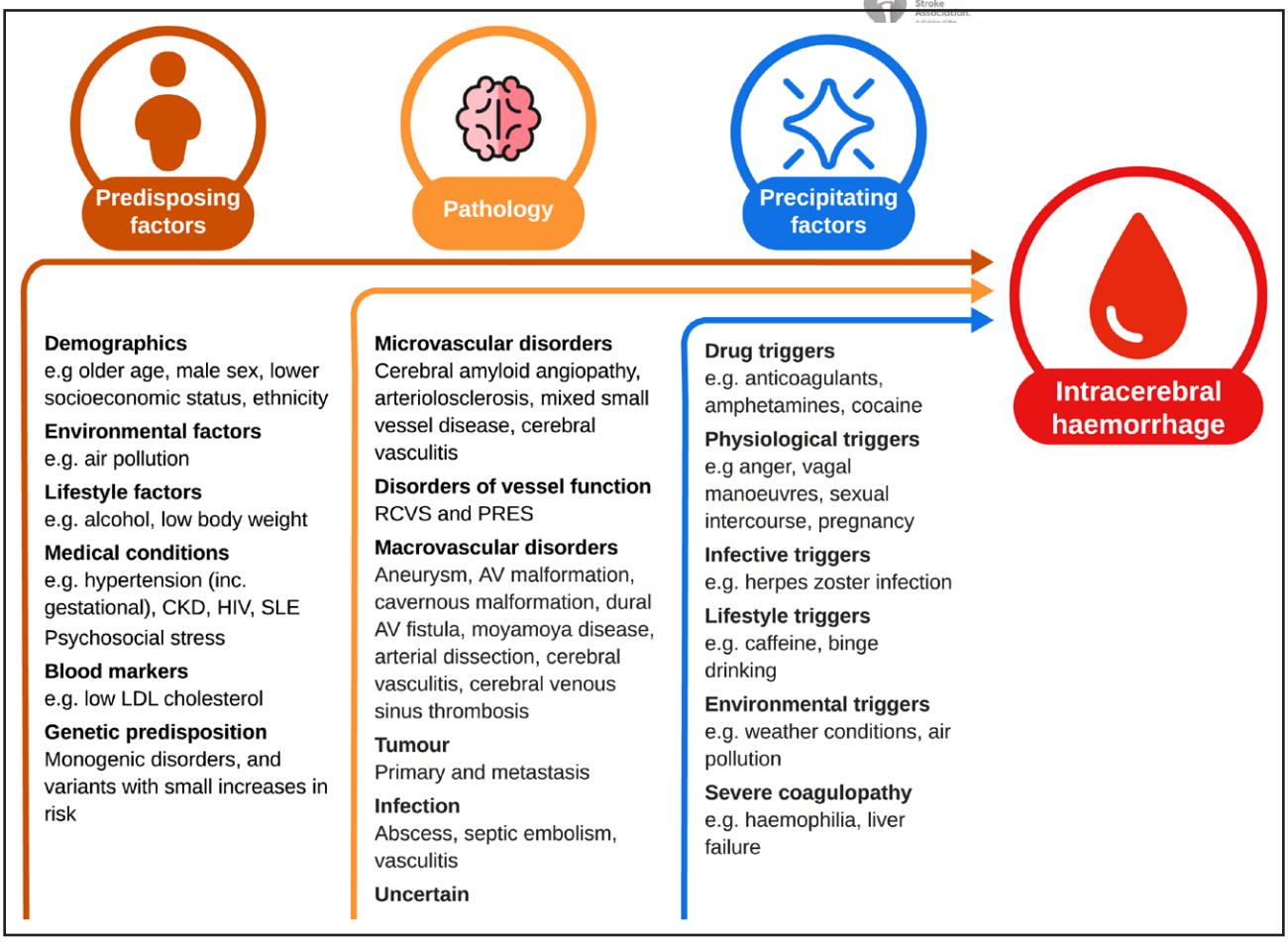

Figure. Predisposing factors, pathologies, and precipitating factors causing intracerebral hemorrhage.
Examples were chosen based on biological plausibility, reliability, consistency, and strength of available evidence (Supplemental Material). LDL indicates low-density lipoprotein; PRES, posterior reversible encephalopathy syndrome; and RCVS, reversible cerebral vasoconstriction syndrome.

interactions between other (eg, environmental) predisposing factors and genetic traits.

Rare monogenic disorders predispose to pathologies that confer a higher risk of ICH, such as CAA via point mutations in the amyloid precursor protein or cystatin C[9] and familial cerebral cavernous malformation via mutations in KRIT1, CCM2, or PDCD10.[10] People with Down syndrome have 3 copies of the amyloid precursor protein gene and high rates of CAA and ICH.[11] Other monogenic variants identified by GWAS studies include APOE, CR1, KCNK17, CETP, STYK1, COL4A2, NOTCH3, 1q22, and 17p12.[12,13] Sickle cell disease is associated with a high risk of both ischemic stroke and ICH, as repeated sickle crises modify cerebral vascaluture.[14]

The complex genetic predisposition to ICH may be best reflected by a polygenic risk score involving 2.6 million variants comprising 21 clinical attributes that determine either predisposing factors (eg, BP, renal function, and lipid profile) or underlying pathology (eg, cSVD).[15]

Modifiable Predisposing Factors

Spontaneous ICH is not an inevitable consequence of aging. Many modifiable predisposing factors have been identified by rigorous large cohort and case-control studies examining multiple factors or systematic reviews of individual predisposing factors (Table S1). Most studies are restricted to high-income countries and sometimes group ICH with subarachnoid hemorrhage (collectively, hemorrhagic stroke) or subdural hemorrhage, which may weaken the strength of identified associations if predisposing factors are not shared by ICH with other intracranial hemorrhages.

Lifestyle exposures that predispose to ICH include high alcohol intake, extremes of weight, unhealthy diet, physical inactivity, and psychosocial stress (including stress at work and home, depression, and stressful life events although the latter might also be a precipitating factor). The data on smoking are unclear: an association was present in a cohort of 1 million women[16] but not in other case-control studies.[4,17] The Global Burden of Disease study is not included in Table S1 because it measures disability-adjusted life years rather than incidence, uses a modeling approach, and reports population attributable fraction rather than risk ratios; it demonstrated a 15.4% (13.2%–17.7%) population attributable fraction for smoking for ICH, with high BP, air pollution, high sodium diet, and kidney dysfunction each contributing >10% of the population attributable fraction.[1]

The leading predisposing comorbidity is hypertension (including gestational hypertension), which has a consistent association in case-control and cohort studies (Table S1), a 56.4% (41.8%–67.7%) population attributable fraction in the Global Burden of Disease study, and a plausible biological mechanism due to the association between hypertension and cSVD.[18] Chronic kidney disease is another prevalent predisposing factor that has been shown to be independent of hypertension in Mendelian randomization analysis.[19] Chronic inflammation (eg, due to systemic lupus erythematosus and rheumatoid arthritis) or infection (eg, HIV) may lead to accelerated atherosclerosis, vasculitis, or vascular remodeling, all of which may increase ICH risk.[20] Prior ischemic stroke is associated with ICH, perhaps due to shared underlying pathology[7]; although this article is generally concerned with first events, people with prior ICH have a high risk of recurrence.[21] The mechanism for the association between migraine and ICH is unclear. Cardiac conditions such as atrial fibrillation may not directly cause pathology related to ICH; the association may be due to anticoagulant therapy precipitating bleeding in people with vascular disease. Lower LDL (low-density lipoprotein) cholesterol has a convincing epidemiological relationship with spontaneous ICH, and Mendelian randomization studies suggest a causal association, which might be mediated via endothelial fragility caused by smooth muscle cell necrosis.[22–24]

Medicines

Several drugs are associated with ICH, but randomized controlled trials are usually too small to detect rare side effects (only 6 intracranial hemorrhages were reported in the 2900 patients in randomized trials comparing warfarin with placebo/open control for atrial fibrillation[25]). Nonetheless, studies have not found large or consistent associations between statin therapy or selective serotonin reuptake inhibitors and ICH.[26,27] Of the NSAIDs, diclofenac and meloxicam may increase risk.[28] Antiplatelet therapy shows a small, nonsignificant association with ICH (rate ratio, 1.32 [0.98–1.54]).[29] Population-based cohorts suggest that the increased incidence of bleeding in people on anticoagulant drugs is highest in the first month after initiation.[30] We hypothesize that oral anticoagulants are not predisposing factors but precipitating factors in people with underlying pathology and predisposing factors.

Interaction of Predisposing Factors

Predisposing factors are likely to interact or be on common causal pathways. In the United States, Black and Hispanic people had a stronger association between hypertension and ICH than White people, but *APOE* allele ε2 or ε4 was only associated with ICH in White people, perhaps due to genetic or sociocultural factors.[7] A prospective cohort study of 19 356 Japanese men found an interaction between alcohol and social support in risk of hemorrhagic stroke.[31] Mediation analysis of a Mendelian randomization study found that 57% of the ICH risk associated with a genetic tendency to obesity was

mediated by type 2 diabetes.[32] However, we could not find any studies of associations or interactions between multiple long-term conditions and ICH incidence. A better understanding of interactions between predisposing factors could allow the identification of high-risk populations and improve preventative strategies.

PATHOLOGIES UNDERLYING SPONTANEOUS ICH

Predisposing factors may mediate their effects by causing or modifying the severity of specific microvascular, macrovascular, hemodynamic, and neoplastic pathologies underlying ICH. Predisposing factors and pathology may interact.

Microvascular Disorders

Most ICH is due to cSVD, which is extremely prevalent in older adults.[33] Imaging features provide evidence of the presence of cSVD and its subtypes. Sporadic cSVD includes arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis[18] and, less often, CAA or rarer microangiopathies. The underlying cause of sporadic CAA is incompletely understood but involves β-amyloid deposition in cortical and leptomeningeal vessel walls, likely due to reduced peptide clearance,[34] leading to lobar ICH in a small proportion of people.[33] Known predisposing factors are age, *APOE* ε4 or ε2 genotype, and iatrogenic causes, including neurosurgical procedures and treatment with human growth hormone.[35,36]

Arteriolosclerosis affects small arteries and arterioles throughout the brain and is associated with hypertension. Specific genetic variants (eg, in the *NOTCH3* gene) are associated with cSVD and increased risk of ICH, particularly in people with other predisposing factors such as hypertension.[13] Modifiable risk factors for cSVD, including obesity and hypertension, may predispose to chronic inflammation leading to remodeling of blood vessels.[37] ICH location is a component of the Boston criteria for CAA, and epidemiological studies suggest different risk factor profiles for lobar ICH compared with nonlobar ICH.[17] Deep ICH (where CAA does not occur) is usually due to arteriolosclerosis and is consequently often attributed to high BP. However, hypertension is associated with ICH in any location (although more prevalent with deep versus lobar ICH), and moderate-severe arteriolosclerosis underlies four-fifths of lobar ICH.[2,17]

Disorders of Blood Vessel Function

Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome have clinical and imaging overlap, suggesting shared pathophysiology. Up to a quarter of people with these syndromes develop ICH. Postmortem examination shows normal blood vessels.[38] Possible mechanisms include failure of cerebral autoregulation, cerebrovascular tone, and endothelial function.[39]

Macrovascular Disorders

Macrovascular abnormalities (aneurysms, arteriovenous malformations, dural arteriovenous fistulae, and cerebral cavernous malformations) are rare in the general population[40] but together account for ≈10% of spontaneous ICH and can often be identified on angiographic imaging. No predisposing factors are known to affect the bleeding risk of arteriovenous malformations or cavernous malformations.[41,42] Intracranial aneurysms occur sporadically; risk factors for rupture include hypertension, age, smoking, previous subarachnoid hemorrhage, aneurysm size and location, and geographic region.[43,44] Mycotic aneurysms and septic arteritis occur secondary to infection, including bacterial endocarditis, dental infection, and cavernous sinus syndrome.[45] Moyamoya disease is rare, although more common in East Asian populations, probably due to genetic differences.[46] Moyamoya syndrome describes the imaging appearance of moyamoya disease secondary to another condition such as sickle cell disease. Cerebral vasculitis is an uncommon cause of ICH that may affect blood vessels of any size depending on the cause. Blood clots can lead to ICH: hemorrhage sometimes follows cerebral venous sinus thrombosis, as pressure builds in upstream vasculature; and arterial occlusion can disrupt vasculature, leading to hemorrhagic transformation of cerebral infarction.[47]

Tumor and Infection

Brain tumors (either primary brain malignancy or metastases) can be highly angiogenic and present with ICH. Infections can cause bleeding either directly or indirectly through abscess formation, septic emboli from remote infection, or vasculitis secondary to, for example, herpes simplex encephalitis.

PRECIPITATING FACTORS FOR SPONTANEOUS ICH

A precipitating factor may lead to spontaneous ICH by either causing hemorrhage from a vessel or modifying the severity of subclinical blood leakage. Not every ICH will have an identifiable precipitating factor, many of which are unavoidable, but some are modifiable and have clinical implications, particularly for people with underlying pathology.

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A systematic review without meta-analysis concluded that in adults with hemophilia, severity of disease and hypertension were risk factors for ICH; it is plausible that, particularly in older adults, hypertension may lead to cSVD, and bleeding is precipitated by reduced coagulation function.[48]

There is no obvious mechanism for people on therapeutic doses of antithrombotic therapy to bleed spontaneously in the absence of underlying pathology. However, anticoagulant therapy might precipitate symptomatic ICH in a person with pathology and subclinical ICH (eg, cerebral microhemorrhage),[49,50] supported by population-based studies that demonstrate that the risk of ICH is highest in the first 30 days after starting warfarin.[30] This distinction between precipitating and predisposing factors is important, as ascertaining underlying pathology is important regardless of whether a person is on anticoagulant therapy. Similarly, ICH precipitated by thrombolytics administered for treatment of acute ischemic stroke can be remote from the area of infarction and is associated with underlying pathology of cerebral microbleeds and white matter hyperintensities on brain imaging.[51]

Fluctuations in BP and vascular tone may precipitate ICH. BP increases in the days and weeks before ICH.[52] A population-based cohort study in England found a higher risk of ICH in the first 6 weeks postpartum among women of childbearing age (incidence rate ratio, 3.6 [95% CI, 1.5–8.7]) but not during antepartum or peripartum periods, perhaps related to preeclampsia and gestational hypertension.[53]

Activities that affect BP and vascular tone have been investigated using case-crossover designs, comparing activities over a period immediately before an event, to a period in the past. Anger, heavy exercise, sexual activity, valsalva maneuvers including defecation, cola and coffee consumption, flu-like disease, overeating, playing games, such as mahjong and chess, and death of a partner have all been identified as possible ICH precipitants using this study design.[54–59] However, large odds ratios in some studies suggest recall bias influenced results; in one study, fewer than half of participants recalled having a flu-like illness in the past year, but people in Western Europe average 2.7 upper respiratory tract infections a year.[60] A recent systematic review identified several statistically significant precipitating factors, including antiplatelet, anticoagulant, NSAID, antipsychotic use, anger, cola consumption, and defecation, although the risk estimates were imprecise and included studies that were heterogeneous both statistically and methodologically.[61]

Heavy alcohol intake increases the risk of ICH in the subsequent day and week.[62] Stimulant drugs including cocaine and amphetamines can precipitate ICH and are important to consider in younger populations.[63,64] Changes in environment, including increased air pollution and lower ambient temperature, are associated with small increases in incidence of ICH,[65,66] and risk increases following several viral and bacterial infections.[67–70]

APPLICATION OF A FRAMEWORK FOR THE CAUSE OF SPONTANEOUS ICH

This extensive body of evidence about the many predisposing factors, underlying pathologies, and precipitating factors suggests that there is a complex interplay of these many factors in causing ICH (Figure). The factors listed in the Figure seem to be the most clinically and statistically significant factors according to current evidence (Supplemental Material), and they have implications for clinical practice and future research.

Implications for Clinical Practice

The framework echoes the model of predisposing, precipitating, perpetuating, and protective factors for psychiatric disease and provides a clinically intuitive structure to classify cause, reflecting the complexity seen in clinical practice and epidemiological studies. It does not preclude interactions between predisposing factors, pathologies, and precipitating factors and does not require all categories to explain ICH in one person. Rather, the framework allows a holistic view of each patient, which recognizes that people often have multiple long-term conditions and other predisposing factors for ICH.

This framework encourages attribution of all of the potential causes that exist in one patient (eg, an octogenarian man, of lower socioeconomic status, exposed to high ambient air pollution, suffering psychosocial stress following a recent bereavement, with prior alcohol misuse, and a history of hypertension and atrial fibrillation for which he has been taking oral anticoagulation, who experiences lobar ICH with mixed CAA and deep perforating arteriopathy cSVD biomarkers on magnetic resonance imaging). The recognition and explanation of these multiple factors by physicians avoid a focus on one predisposing factor (eg, hypertension) that disregards others (eg, alcohol misuse), treats multiple underlying pathologies equally, and identifies all precipitating factors rather than just one (eg, anticoagulation). This explanation avoids value judgments about attribution and provides multiple modifiable approaches to the prevention of future major adverse cardiovascular events for patients.

Implications for Research

Several classification systems for the cause of ICH have been proposed, aiming to stratify patients by survival, target treatment, or phenotype for clinical research (Table 1).[71–74] However, none of these systems encompasses the spectrum of predisposing factors for ICH, nor reflects the complexity of their combination with

Table 1. Published Causal Classification Systems for Intracerebral Hemorrhage

Classification system		Includes ≥1 predisposing factor	Includes ≥1 pathology	Includes ≥1 precipitating factor	Can allocate multiple causes
SMASH-U[71]	Structural vascular lesions Medication Amyloid angiopathy Systemic disease Hypertension, Undetermined	•	•	•	–
H-ATOMIC[72]	Hypertension Cerebral amyloid angiopathy Tumor Oral anticoagulants Vascular malformation Infrequent causes Cryptogenic	•	•	•	•
CLAS-ICH[73]	Arteriolosclerosis Cerebral amyloid angiopathy Mixed SVD Other rare forms of SVD Secondary causes (macrovascular causes, tumor, and other rare causes)	–	•	–	•
CADMUS*[74]	CAA Deep Perforator Arteriopathy Mixed CAA-DPA Undetermined SVD	–	•	–	•

CAA indicates cerebral amyloid angiopathy; cSVD, cerebral small vessel disease; DPA, deep perforator arteriopathy; ICH, intracerebral hemorrhage; and SVD, small vessel disease.

*For ICH due to cSVD.

underlying pathologies and predisposing factors on the causal pathway that is seen in most patients in clinical practice.

SMASH-U assigns a single category from a group of predisposing factors, precipitating factors, and pathological findings but does not allow allocation of multiple causes.[71] In SMASH-U, hemorrhage location primarily determines underlying cSVD pathology (CAA or hypertension), a method now superseded by computed tomography and magnetic resonance imaging–based criteria for CAA. The categories were defined by the authors of this article and are associated with long-term survival. SMASH-U has since been modified with the addition of posterior reversible encephalopathy syndrome/reversible cerebral vasoconstriction syndrome for young adults.[75] However, SMASH-U does not include several predisposing factors (such as alcohol, chronic kidney disease, or HIV), pathologies (such as cerebral vasculitis), and precipitating factors (such as infection and pregnancy).

H-ATOMIC is similar to SMASH-U but allows for attribution of multiple causes, with a degree of certainty (definite, probable, or possible) for each.[72] The category definitions in H-ATOMIC are complex and, for hypertension, include raised BP in the 6 hours after ICH, a physiological response seen in three-quarters of patients.[76] The system has been applied to patients in clinical practice: in a cohort of 439 people with ICH, most were attributed a cause, and only 2% were classified as cryptogenic. However, H-ATOMIC does not include several predisposing factors (such as chronic kidney disease and HIV) and precipitating factors (such as pregnancy) and classifies alcohol as an infrequent cause despite the high prevalence of its use and its association with ICH.

For both H-ATOMIC and SMASH-U, it is not clear how the list of causes or the criteria for ascertaining those causes was derived. H-ATOMIC and SMASH-U both include hypertension, a clear predisposing factor, but not other factors with consistent evidence and biological plausibility, such as alcohol use (perhaps due to the lack of primary studies when these classification systems were designed). H-ATOMIC and SMASH-U include oral anticoagulation, which is unlikely to be the sole cause. Despite their similarities, in a head-to-head comparison, SMASH-U and H-ATOMIC classified one-third of patients differently, usually because >1 potential cause was present.[77]

Two other classification systems, CLAS-ICH and CADMUS, are restricted to classifying ICH attributed to cSVD on the basis of computed tomography and magnetic resonance imaging features, respectively, and can be used to identify CAA, non-CAA, and mixed cSVD on imaging.[73,74] These systems build on the pathologically validated Boston criteria for CAA on magnetic resonance imaging and the Edinburgh criteria for CAA on computed tomography. CLAS-ICH and CADMUS have demonstrated reproducibility among different raters and cohorts and allow for multiple underlying pathologies, but neither incorporates predisposing factors to these pathologies or precipitating factors, providing only one dimension of the cause of a person's ICH.

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All 4 classification systems attempt to provide simple, practical approaches but do not reflect the number and variety of predisposing factors seen in patients in clinical practice, who usually have multiple long-term conditions (only H-ATOMIC applies to all ICH and allows multiple causes), and none reflects the complexity of their combination with underlying pathologies and precipitating factors on the causal pathway that is seen in most patients in clinical practice. Although reductionist approaches simplify statistical analysis, multivariable approaches and mediation analyses could dissect the multitude of factors contributing to the cause of ICH. The danger of simplifying attribution of cause is that these classification systems could lead to unintended cognitive biases in clinical practice, resulting in modifiable factors being overlooked.

Future Directions and Conclusions

The framework suggests questions for future research into interactions between predisposing factors, precipitating factors, and pathology (Table 2). Answering these questions may require innovative research methods. ICH is a relatively common condition where research is hampered by difficulties in recruiting frail and unwell participants. Along with traditional approaches, identifying causal pathways to ICH with animal models and randomized controlled trials, artificial intelligence techniques applied to large-scale, detailed data sets describing the many factors contributing to the cause of ICH could assist with prediction and stratification of those at risk. Combining artificial intelligence with causal inference techniques may produce the most clinically useful results for both prediction and treatment of ICH.[78] Artificial intelligence analysis of brain imaging at scale can be linked to other population health data to enhance understanding of how risk factors are associated with underlying pathology and identify populations for more detailed cohort and interventional studies.[79] Within these large data sets, clustering techniques such as latent class analysis could be used to align predisposing factors to underlying pathology (including markers of macrovascular and microvascular diseases, and anatomic location) and stratify based on prognosis.[80,81] The conceptual approach and analytical techniques can incorporate new discoveries and guide further research into the mechanism of ICH and its prevention, prognosis, and treatment. Ultimately, research should aim to produce a model where people with ICH can be given personalized prevention and treatment depending on their underlying predisposing factors and pathology, which could be translated to clinical practice.

Although our framework is inclusive and exposes knowledge gaps (specifically the interplay between predisposing factors, pathologies, and precipitating factors), it also has some limitations. First, our framework is not conveniently reductionist. Second, although there is extensive primary research on individual predisposing factors (Supplemental Material), residual confounding may affect these, and uncertainties remain around the interactions between predisposing factors that are common in the general population. Third, we do not know how the many genetic factors, lifestyle factors, and medical conditions interact to lead to underlying pathology and precipitate ICH or how having multiple long-term conditions or particular combinations of conditions affects risk.

Ultimately, future research could use this framework to derive and validate a more inclusive system for classifying the cause of ICH and test its association with prognosis or modification of interventions' effects in clinical trials to add clinical utility by personalizing approaches to investigation, acute treatment, prevention of complications, and secondary prevention.

Table 2. Questions for Future Research

How do common predisposing factors such as alcohol consumption, smoking, diabetes, and body weight interact to affect the risk of intracerebral hemorrhage?
How do predisposing factors lead to, and interact with, underlying pathology, and which predisposing factors are associated with which pathologies?
How does having multiple long-term conditions, and combinations of medical conditions, affect the risk of intracerebral hemorrhage?
What precipitating factors lead some people with underlying pathologies to develop intracerebral hemorrhage, while others do not?
How do pathologies such as arteriolosclerosis and cerebral amyloid angiopathy interact to alter the risk of intracerebral hemorrhage?
Can modification of predisposing and precipitating factors reduce the risk of intracerebral hemorrhage?

ARTICLE INFORMATION

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Supplemental Material

Search Strategies and Study Selection Criteria
Table S1
References 83–110

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