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BRIEF COMMUNICATION

Expanding Diagnostic Workup for Hypertensive Intracerebral Hemorrhage: a Retrospective LATAM Cerebrovascular Registry Comparison

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On behalf of the RENAMEVASC and LASE investigators. A complete list of the RENAMEVASC and LASE members can be found at the end of the article.

ABSTRACT

Background: The leading cause of spontaneous intracerebral hemorrhage (ICH) is hypertensive arteriolopathy. In addition to age and hypertension history, patients usually present other comorbidities that potentially increase morbimortality. Ancillary studies other than non-contrast computerized tomography (NCCT) may help clarify the diagnosis and increase the detection of potentially modifiable vascular risk factors. Unfortunately, their use is not routinely performed. **Objective:** The study aimed to determine the frequency of ancillary studies performed in patients with hypertensive ICH. **Methods:** We performed a retrospective analysis of three Latin American cerebrovascular registries from academic medical centers, analyzing the results with descriptive statistics focusing on diagnosis and short-term outcomes. **Results:** We analyzed a total of 1,324 patients (mean age 64 years). Hypertension and obesity were the most prevalent risk factors. Only 14% underwent MRI, 10.3% extracranial ultrasonography, and 6.7% echocardiography. Among the three registries, the Latin America Stroke Registry performed more ancillary studies. Most of the patients presented a poor clinical outcome and in-hospital death. **Conclusions:** The use of ancillary studies in the diagnostic workup of ICH was poor in the three registries, and mortality was high. The lack of ancillary studies performed may negatively impact outcomes. (REV INVEST CLIN. 2024;76(5):213-22)

Keywords: Intracerebral hemorrhage. Hypertension. Neuroimaging.

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INTRODUCTION

Intracerebral hemorrhage (ICH) is caused by the rupture of cerebral arteries and the irruption of blood into the brain parenchyma[1]. Although it represents approximately 15% of all strokes, it carries the worst prognosis and long-term quality of life, with a 1-year mortality rate exceeding 50%, resulting in over 2.8 million deaths worldwide[2]. Hypertension is the primary risk factor for ICH, occurring in approximately 60% of cases, especially if it is untreated or irregularly managed[3]. The leading causes of non-traumatic ICH are deep perforating vasculopathy and cerebral amyloid angiopathy (CAA), accounting for 80% of all ICH. The secondary causes are diverse and macrovascular in nature[4-6].

Diagnosing acute ICH requires immediate neuroimaging studies, typically computed tomography (CT) or magnetic resonance imaging (MRI). Due to its accuracy, accessibility, availability, and low cost, non-contrast computed tomography (NCCT) is the reference study, in which ICH can be easily detected as an area of focal hyperdensity[7,8].

Although NCCT is the study of choice, supplementary studies such as MRI, CT angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA) possess a higher diagnostic value not only for hypertensive arteriopathy and CAA but also for other potentially modifiable etiologies. In addition, ancillary studies such as extracranial/intracranial ultrasonography (US), and echocardiography are helpful for risk stratification and secondary prevention strategies[8-13].

Data regarding the frequency of use of ancillary studies is not usually reported worldwide; the limited data corresponds to developed countries, showing an increased performance of supplementary studies[14-18]. Even though developing countries present higher risks of ICH, the use of ancillary studies is substantially reduced and not routinely performed in places such as Latin America (LATAM)[19].

While these ancillary studies cannot replace NCCT as the initial diagnostic tool, they are valuable in elucidating the etiology, particularly in cases where hypertensive ICH is not clearly identified. In addition, they help identify risk factors for recurrence and determine prognosis. In this study, we aimed to determine the frequency of ancillary studies performed among hypertensive ICH patients in three LATAM cerebrovascular registries: Hospital Civil de Guadalajara Fray Antonio Alcalde (HCFAA), Registro Nacional Mexicano de Enfermedad Vascular Cerebral (RENAMEVASC) and Latin-American Stroke Registry (LASE).

METHODS

We analyzed data from three LATAM longitudinal registries of cerebrovascular disease: The HCFAA cohort, a database of a referral hospital center in Western Mexico[20,21]; the RENAMEVASC, a multicenter national registry in Mexico[22], and the LASE registry, a multinational initiative from third-level hospitals across Central and South America[23].

The HCFAA cohort included 540 consecutive adult patients with spontaneous ICH hospitalized between 1999 and 2007, where the main objective was to characterize the clinical, radiological, therapeutic, and functional outcomes at hospital discharge. The RENAMEVASC registry (2002-2004) was a hospital-based observational study designed and conducted by the Mexican Association of Cerebrovascular Disease (AMEVASC) to improve stroke knowledge and raise awareness in the community, where investigators from 25 referral hospitals of 14 Mexican federal states recruited 2000 stroke patients, and 564 (28.2%) of whom corresponded to ICH. In the LASE registry (2012-2017), 19 centers across Central and South America compiled data on demographics, vascular risk factors, clinical stroke description, ancillary tests, and functional outcomes at short-term follow-up of patients. A total of 4788 patients were included (1229 patients from nine Mexican centers), and 495 patients (10.3%) corresponded to ICH. A detailed description of the registries has been published elsewhere[20-23]. For the present analysis, the cohorts were grouped into decades: the first decade of this century included HCFAA and RENAMEVASC, and the second decade included LASE.

We collected data on patients diagnosed with spontaneous ICH, selecting only patients with hypertensive ICH > 18 years. We recorded and analyzed different risk factors such as hypertension, obesity, diabetes, smoking, ischemic heart disease, and cardiac arrhythmias.

Table 1. Baseline characteristics of three Latin American hypertensive intracerebral hemorrhage registries

	Total (n = 1324)	HCFAA (n = 441)	RENAMEVASC (n = 396)	LASE (n = 487)	p-value
Inclusion period	1999-2017	1999-2007	2002-2004	2012-2017	-
Age [years, mean (SD)]	64.7 (14.9)	66.99 (13.9)	65.27 (13.4)	62.31 (16.4)	< 0.001
Female gender, n (%)	620 (47)	215 (48.8)	190 (48.0)	215 (44.1)	0.321
Cardiovascular risk factor					
History of hypertension, n (%)	1048 (79.2)	389 (88.2)	332 (83.8)	327 (67.1)	< 0.001
Obesity, n (%)	379 (34.9)	196 (44.4)	134 (34.1)	49 (19.5)	< 0.001
Diabetes, n (%)	290 (21.9)	87 (19.7)	89 (22.5)	114 (23.4)	0.379
Smoking, n (%)	260 (19.7)	84 (19.0)	93 (23.6)	83 (17.0)	0.047
Ischemic heart disease, n (%)	59 (4.5)	6 (1.4)	30 (7.6)	23 (4.7)	< 0.001
Any cardiac arrhythmia, n (%)	22 (1.7)	5 (1.1)	7 (1.8)	10 (2.1)	0.538
ICH location					
Deep, n (%)	886 (68.3)	348 (78.9)	265 (66.9)	273 (59.2)	< 0.001
Lobar, n (%)	272 (21.0)	49 (11.1)	84 (21.3)	139 (30.2)	< 0.001
Infratentorial ICH, n (%)	125 (9.6)	43 (9.8)	33 (8.4)	49 (10.6)	0.536
Intraventricular irruption, n (%)	533 (41.9)	243 (55.1)	172 (48.6)	118 (24.7)	< 0.001
ICH diagnostic workup					
CT, n (%)	1303 (98.4)	436 (98.9)	394 (99.5)	473 (97.1)	0.013
MRI, n (%)	185 (14.0)	22 (5.0)	11 (2.8)	152 (31.2)	< 0.001
DSA, n (%)	81 (6.1)	28 (6.3)	13 (3.3)	40 (8.2)	0.010
Cardiovascular workup					
Extracranial US, n (%)	137 (10.3)	2 (0.5)	11 (2.8)	124 (25.5)	< 0.001
TTE, n (%)	89 (6.7)	7 (1.6)	12 (3.0)	70 (14.4)	< 0.001
Functional outcome at hospital discharge					
Good outcome (mRs 0-2), n (%)	277 (22.2)	63 (14.3)	52 (13.1)	162 (39.7)	< 0.001
Poor outcome (mRs 3-5), (%)	563 (45.2)	150 (34.0)	222 (56.1)	191 (46.8)	< 0.001
In-hospital mortality, n (%)	405 (32.5)	228 (51.7)	122 (30.8)	55 (13.5)	< 0.001
Length of stay					
In-hospital stay [days, mean (SD)]	11.57 (11.91)	11.57 (12.11)	13.08 (13.19)	10.04 (9.95)	0.002

HCFAA: Hospital Civil Fray Antonio Alcalde; RENAMEVASC: Registro Nacional Mexicano de Enfermedad Vascular Cerebral; LASE: Latin-American Stroke Registry.

We collected ICH location data (deep, lobar, infratentorial, and intraventricular). Later, we extracted data regarding ancillary studies used for diagnostic workup, including NCCT, MRI, DSA, extracranial US, and transthoracic echocardiography (TTE).

The outcome was recorded at hospital discharge and classified as good prognosis (Modified Rankin Scale [mRS] 0-2), poor prognosis (mRS 3-5), and death (mRS 6), in addition to the length of in-hospital stay in days. Regarding ethical statements, the Institutional Ethics Committee approved all the stroke data sets according to international and local research regulations.

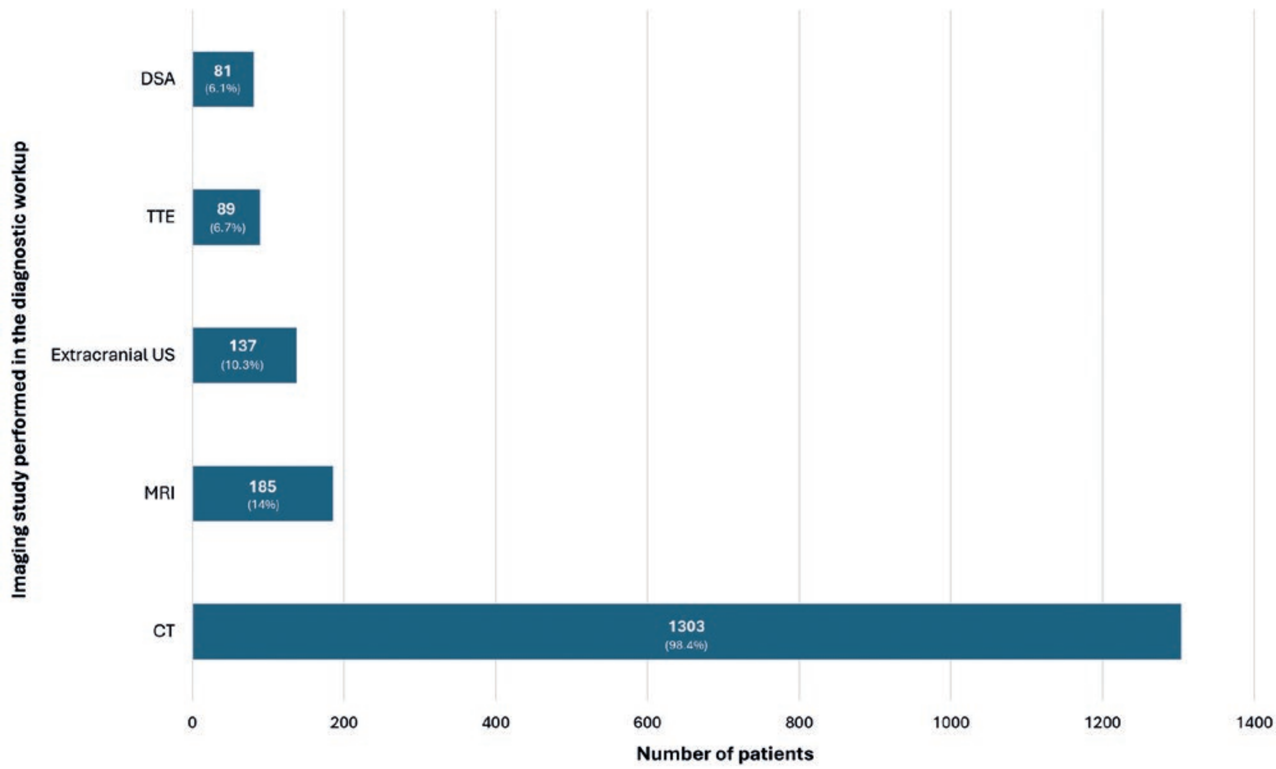
Statistical analysis

Demographic data are summarized descriptively using proportions, mean, or median (if non-normal distribution). The baseline characteristics of the cohorts were compared using Student's t-test for continuous variables or Pearson's X^2 for categorical variables. All p values were considered significant if $p < 0.05$. This statistical analysis was performed with R version 4.1.0 (The R Foundation for Statistical Computing). The collected data were analyzed and presented in percentages and frequencies.

RESULTS

We analyzed a total of 1,324 patients with hypertensive ICH from the three Latin American cohorts. The overall mean age was 64.7 years (47% were female). The LASE cohort included the youngest patients (mean age 62.31 years, $p \leq 0.001$). The principal risk factors among the three registries were hypertension, obesity, and diabetes. Comparison between the different cohorts revealed a higher frequency of hypertension, obesity, and smoking in the first decade of the 21st-century cohorts (all with $p < 0.05$). However, diabetes and cardiac arrhythmias were more frequent in the LASE registry (Table 1).

Figure 1. Diagnostic workup in hypertensive ICH was performed in the three Latin American registries. ICH: intracerebral hemorrhage; DSA: digital subtraction angiography; TTE: transthoracic echocardiography; US: ultrasonography; MRI: magnetic resonance imaging; CT: computed tomography.



The most common ICH location was deep (68.3%), followed by lobar (21%), and infratentorial (9.6%). Ventricular irruption occurred in 41.9% of cases. In the LASE registry, lobar ICH became more prevalent than in the first decade of the 21st-Century registries; deep ICH was less frequent ($p < 0.05$) (Table 1).

Regarding imaging studies, NCCT was the most frequent study performed in the three registries (98.4%). MRI was performed in 185 (14%) patients, most frequently in the LASE registry ($p < 0.001$). DSA was less often performed (6.1%). Concerning cardiovascular workup, 10.3% had extracranial US, and 6.7% had TTE among the three cohorts, both most frequently performed as a diagnostic workup in the LASE registry ($p < 0.001$). The LASE registry performed more ancillary studies than the previous cohorts, except for NCCT (Figs. 1 and 2).

Concerning the outcome, among the three registries, 45.2% had a poor outcome (Fig. 3 and Table 1). Good outcomes were more common in the LASE registry. In-hospital death was more prevalent in the HCFAA and RENAMEVASC registries (Table 1) (all with $p < 0.001$). Finally, the cohorts from the first decade of this century had a longer hospital stay.

DISCUSSION

The clinical diagnosis of ICH, like any type of stroke, is based on an acute focal neurological deficit, which must be immediately confirmed with brain imaging studies such as CT or MRI, guiding the initial medical or surgical management. Few studies regarding ICH report the frequencies of performed ancillary studies in the diagnostic workup[22]. Most of the reported literature focuses on the radiological signs, diagnostic yield, biomarkers, and improvement in prognosis that each ancillary study offers compared to NCCT, the standard approach.

Due to its availability, cost, faster acquisition time, and high sensitivity, NCCT is the reference study for the initial workup in ICH in the emergency

Figure 2. Distribution of ancillary studies used in hypertensive ICH among three cerebrovascular registries. ICH: intracerebral hemorrhage; CT: computed tomography; MRI: magnetic resonance imaging; DSA: digital subtraction angiography; TTE: transthoracic echocardiography; US: ultrasonography; HCFAA: Hospital Civil Fray Antonio Alcalde; RENAMEVASC: Registro Nacional Mexicano de Enfermedad Vascular Cerebral; LASE: Latin-American Stroke Registry.

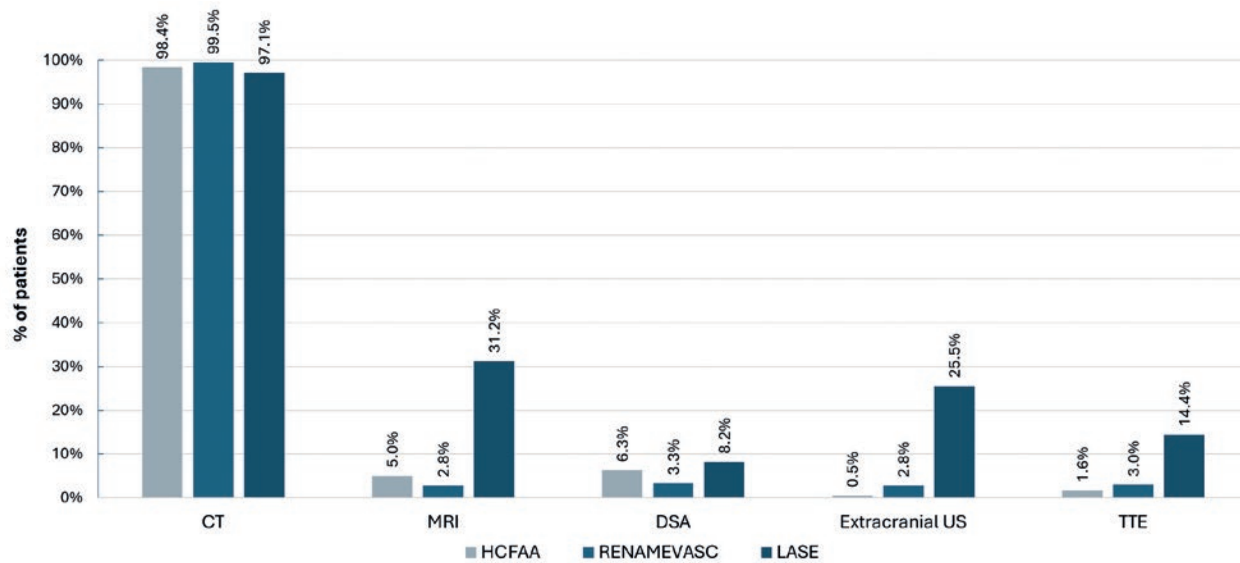
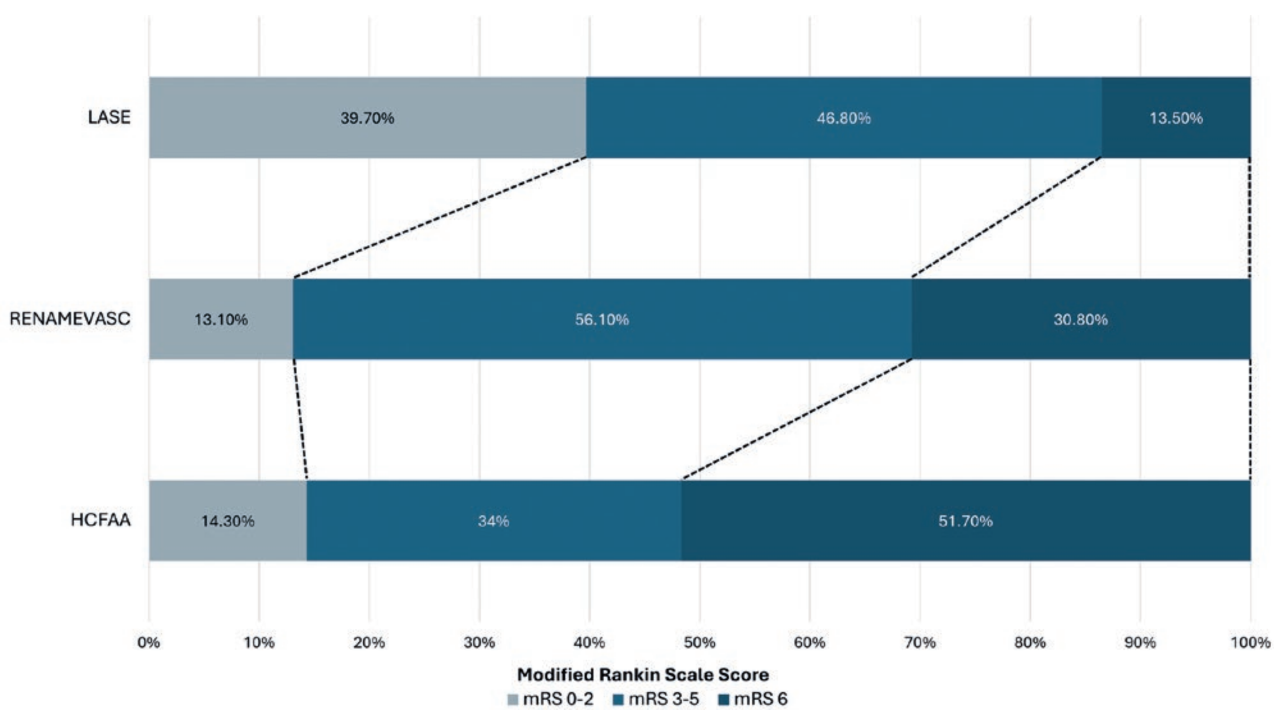


Figure 3. Hypertensive ICH prognosis at discharge in three cerebrovascular registries. ICH: intracerebral hemorrhage; HCFAA: Hospital Civil Fray Antonio Alcalde; RENAMEVASC: Registro Nacional Mexicano de Enfermedad Vascular Cerebral; LASE: Latin-American Stroke Registry; mRS: modified Rankin Scale.



department. ICH can be detected as a spontaneous hyperdense lesion within the brain parenchyma. A CT can also measure volume, hematoma expansion (HE), mass effect, and brain edema[8,24,25]. While NCCT provides high sensitivity and specificity for detecting acute ICH, it is important to highlight that the hemorrhage typically becomes isodense within a week, making it difficult to detect with this imaging modality. Thus, other modalities might be preferable at this stage[26].

After NCCT, CTA is usually the study of choice due to its rapid acquisition (can be obtained after NCCT), high quality of resolution, and accuracy in identifying secondary causes. CTA is recommended for vascular abnormalities that require rapid intervention[27]. It is also beneficial to identify the spot sign, a robust radiological finding in HE, which is associated with longer hospital stays, increased mortality rates, and worse functional outcomes[8]. Other radiological signs with a predictive value for HE, such as hyperdense dot of contrast, island sign, satellite sign, blend sign, black hole sign, hypodensities, swirl signs, fluid-blood levels, and irregular shapes, can only be identified using CTA or MRI[1,8,10,28-30].

Ancillary studies, apart from CTA, that may help to identify the etiology of ICH include MRI, MRA, CT/MRI venography, and DSA. Before the development of CTA, DSA was the gold standard for detecting macrovascular causes. Although the optimal timing for ordering a digital subtraction angiography (DSA) is not well established, it is recommended to perform it promptly if the CTA is negative, in order to identify occult vascular abnormalities[27]. DSA provides time resolution imaging, identifying the direction and rate of flow in brain circulation[8]. However, it does not add much information in patients with hypertensive ICH, with the exception of cases where the hypertension history is unclear, the location of ICH is lobar, it occurs in young patients (< 45 years), and in the absence of small vessel disease (SVD) on NCCT.

MRI is beneficial in identifying the area of hyperacute (within 2 h) hemorrhage; it offers superior diagnostic and monitoring capabilities for cerebrovascular disease compared to CT, even though it is more costly and less widely available[31,32]. MRI is recommended for the detection of CAA, vascular malformations (dural arteriovenous fistulas), and possible non-macrovascular causes (underlying neoplastic process). It is also highly recommended to stratify the risk of recurrence, identify secondary prevention strategies, and increase the probability of survival[27,33]. The Hong Kong criteria was created to identify patients eligible for ancillary studies (angiography) due to their high probability of a structural lesion. A retrospective cohort study used these criteria to develop a clinical decision tool that may identify patients with ICH who require MRI based on age, hypertension, and hemorrhage location[34].

Several studies have investigated the diagnostic accuracy of MRI in detecting ICH. A prospective, multicenter, observational study of 62 patients presenting within 6 h of ICH onset reported specificity, predictive values, and accuracy for ICH detection by experts of 100%[35]. Another study compared the accuracy of CT and MRI in 200 patients; the results were equivalent (96%) for acute ICH. However, MRI could detect 71 patients with any hemorrhage compared to 29 patients detected with CT[7]. According to the AHA/ASA 2022 guidelines, for patients without evidence of macrovascular etiology, MRI is recommended to identify disease markers such as CAA, arteriolosclerosis, and malignant brain tumors, among others[24,36].

MRA is an effective and non-invasive imaging modality that is recommended to visualize vascular anomalies such as aneurysms, stenosis, and carotid bifurcation[37,38]. It has a 98% sensitivity and a 99% specificity for detecting macrovascular etiologies and is statistically similar to CTA[39].

In an observational cohort study of 289 patients, there were no cases of unidentified intraventricular hemorrhage detection by MRI, whereas CT missed the diagnosis in 3% of subjects[9]. MRI is also helpful in the diagnosis of microbleeds markers in a variety of diseases, including severe hypertension, CAA, moya-moya disease, fat emboli, cerebral autosomal dominant arteriopathy, subcortical infarcts, leukoencephalopathy, infective endocarditis, among others[40]. Several markers detected by MRI have also been postulated for detecting SVD in ICH, such as cerebral microbleeds, cortical superficial siderosis, centrum semiovale perivascular spaces, and white matter hyperintensities[41]. Furthermore, white matter injury detected in MRI with the Fazekas score is more significant in lobar ICH, but it is not associated with unfavorable outcomes[42]. Hyperintensities in DWI increase the risk of recurrence, cognitive decline, and death within the first 3 months post-ICH[43].

T2* MRI sequences should be included in the diagnostic workup to identify the underlying vessel disease and assess the risk of recurrent ICH and the therapeutic approaches. Susceptibility-weighted imaging (SWI) and gradient-recalled echo (GRE) T2* are more sensitive to chronic hemorrhagic lesions; however, these sequences can also detect hyperacute ICH with high accuracy[31,35]. SWI is more sensitive than GRE.

Hypointensities detected by both techniques correspond to the lesion, and a magnetic dipole around the focus is called the "blooming effect," which exaggerates the size[40].

CT and MRI venography are the best imaging modalities and are recommended for diagnosing cerebral venous thrombosis. In a study by Zuurbier et al.,[44] CT venography possessed a sensitivity of 95% and a specificity of 91%. MRI statistical analysis is unknown, and significant information on hypertensive ICH was not provided.

In our study, the NCCT was the most available imaging study for ICH detection. A mean of 98.4% in three LATAM registries performed a head CT scan as the initial imaging modality. However, ancillary studies such as MRI, DSA, TTE, and extracranial US were only part of the diagnostic workup in 14%, 6.1%, 6.7%, and 10.3%, respectively. Data from developed countries such as the United States, Sweden, and Germany usually present higher rates of supplementary studies performed. The reported frequency of MRI for acute stroke in the US ranges from 20 to 70%, although higher rates tend to come from specialized stroke centers[14,15]. The Swedish Stroke Register reports a frequency of MRI similar to our study with 16% of patients[16]. A study from the Massachusets General Hospital reports a frequency of CTA of 65%[17]; however, the Swedish Stroke Register revealed that 32% of ICH patients were examined with a CTA[16]. Transthoracic and transesophageal echocardiography were reported in 63.3% and 21.3% of patients with acute stroke in stroke centers in Germany[18].

Based on these data, it is true that LATAM hospitals are underusing ancillary studies. It is also important to highlight that the registries from the first decade performed significantly fewer studies than the registry from the second decade. This may be due to the increased awareness of secondary causes of ICH, the development of higher-quality equipment as well as greater accessibility in certain hospitals. According to the literature previously presented, ancillary studies would be beneficial not only for a finer diagnostic accuracy of hypertensive arteriopathy, CAA, and macrovascular causes, but also for identifying risk factors and risk of recurrence.

Patients presenting with ICH may benefit from additional interventions aimed at identifying and managing treatable vascular risk factors to guide optimal treatment. Echocardiography and transcranial/extracranial US are supplemental interventions that are not brain-related but should be considered in an etiological workup of ICH. Echocardiography should be part of the diagnostic approach to ischemic and hemorrhagic stroke since the heart is directly related to several central nervous system pathologies, "the brain-heart axis," either as a cause or as an effect. An observational cohort study reported that patients with hypertensive ICH had more left ventricular hypertrophy as well as left atrial enlargement (OR of 2.95 and 3.33, respectively)[45]. A retrospective study of 110 patients with acute ICH evaluated the echocardiography characteristics, reporting contraction band necrosis, catecholamine myotoxicity, and a directed correlation of the amount of basal ganglia hemorrhage with a decrease in left ventricular diastolic function[12].

Just as with DSA and MRI, cardiovascular workup was rarely performed in our study, with an average of 6.7% of echocardiograms being performed in patients with ICH. It is also important to underline that the study focuses on hypertensive ICH and most of the population had a history of hypertension (79.2%). Fortunately, the registry from the second decade of the century performed TTE considerably more (one-seventh of its population had a TTE) compared to the other registries. Echocardiography not only helps with the diagnosis of cardiovascular diseases correlated to the hemorrhage, but it also reflects the cardiovascular dysfunction concomitant to the ICH, and hypertension can act either as a risk or a prognostic factor. Addressing these uncertainties is needed to raise awareness of the cardiovascular etiologies and complications related to ICH.

Transcranial Doppler sonography provides valuable information about cerebral blood flow, hemodynamics, and autoregulation, particularly in acute ICH and HE[13]. On the other hand, extracranial US is an imaging modality frequently used in the etiological workup of ischemic stroke. Extracranial US helps detect biomarkers of carotid atherosclerosis such as carotid intima-media thickness, arterial stiffness, and carotid distensibility, both significantly associated with ischemic stroke, which occasionally could be transformed into ICH, US may also add in cardiovascular risk prediction, another important risk factor for poorer outcomes in ICH[46].

Not all three registries had information on transcranial US; however, all reported the performance of extracranial US, which was also infrequent. An average of 10.3% extracranial US was performed between the three centers. As with the TTE, the latest registry performed exponentially more (one-quarter of this study population); however, this registry also included patients evaluated in the outpatient department, allowing for an opportunity to complete the diagnostic workup.

It is important to recall that this study is merely descriptive epidemiological, to report the frequency with which ancillary studies are being performed in patients with hypertensive ICH in LATAM. Even though studies such as MRI, CT/MRI angiography, DSA, CT/MRI venography, echocardiography, and the US provide a higher diagnostic value in identifying both microvascular and macrovascular causes of ICH, they cannot be performed in all patients. Different criteria and diagnostic decision trees have been created to identify patients who require further evaluation testing[25,26,33,47]. Another point of consideration is that although developing countries present higher risks of ICH, there are significant shortages of imaging equipment in health-care facilities, and less than one CT scan is available per million inhabitants[14].

There are some limitations to our study. The studied registries do not contain standardized data information, and additional variables; for example, time from arrival to the emergency department, acquisition of the initial imaging study, coagulation test results, continuous blood pressure monitoring, and Holter studies were not included in the study. The LASE database contains information from hospitalized patients as well as from those examined at follow-up, which may contribute to a better prognosis, fewer time of hospital stay, and greater use of diagnostic workup studies.

Another limitation of our study is the variation in the inclusion periods across the different subpopulations. While this temporal discrepancy could introduce confounding factors related to changes in clinical practices, diagnostic criteria, or population characteristics over time, it was an unavoidable aspect given the nature of data collection across diverse settings. We took care to account for these variations in the analysis to minimize their impact on the study's outcomes. Despite these challenges, we believe our findings provide valuable insights and contribute meaningfully to the existing body of knowledge, setting a foundation for future research to build upon.

In conclusion, ancillary studies in patients with hypertensive ICH in three Latin American Registries were scarcely used. Mortality was high and short-term functional outcome was poor among in all three registries. More prospective studies addressing the long-term outcomes of patients as well as the diagnostic workup for ICH are needed to address this issue in developing regions.

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