CONVENTIONAL BRAIN COMPUTED TOMOGRAPHY FOR THE DIAGNOSIS OF NONTRAUMATIC SUBARACHNOID HEMORRHAGE: A SYSTEMATIC REVIEW

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SUMMARY

Purpose: The aim of this study was to determine the diagnostic accuracy of conventional CT versus any other imaging strategies to diagnose non-traumatic subarachnoid hemorrhage. **Methods:** We included cross-sectional, case-control and cohort studies conducted between January 1, 1980 and December 31, 2013. No language restrictions were imposed. Studies should include people of any age and gender group with clinically suspected non-traumatic SAH. Participants must be in the detection phase of the disease entering to the emergency department. There were no preferences in any other demographic characteristic of participants. We intended to compare Conventional CT (index test – including multidetector CT) versus angiography, angiotomography (Computed tomography angiography), digital subtraction angiography (DSA) and Magnetic Resonance (MR). We excluded studies assessing aneurysms with the selected tests. We designed a search strategy for studies published in Medline via PubMed, CENTRAL, LILACS and EMBASE. No language or publication status restrictions. Other electronic sources were used to find additional studies, such as conference abstracts, Google scholar, DARE and PROSPERO. We looked for additional studies in reference lists of selected articles, contact with authors about knowledge of published or unpublished articles. The results of searches were crosschecked in order to eliminate duplicates. Two investigators independently and blindly screened the titles and abstracts to determine the potential usefulness of the articles. Eligibility criteria were applied to the full text articles during the final selection. The risk of bias was assessed independently by at least two researches using the QUADAS2 tool. No meta-analysis was performed due to lack of data. **Results:** 588 articles (3630 patients) were found with the search strategies designed, after exclusions, three studies were included in qualitative analyses (Mitchell et al., 2001; Perry et al., 2011; Van dijk, Hupperts, Van der Jagt, Bijvoet, & Hasan, 2001). The overall sensibility and specificity for the computed tomography for Perry et al., 2011 were 92.9% (CI95% 89-95.5%) and 100% (CI95% 99.9-100%) respectively. Van dijk et al., 2001 found a sensibility of 30% for observer 1 and 46% of observer 2. The specificity was 100% in both cases. Mitchell et al., 2001 found the sensibility for CT of 95%. The sensibility for MR T2 phase was 94% and the specificity was 98.5% compared to CT. There was high risk of bias mainly for flow and timing and patient selection. **Conclusions:** There is a vast clinical and methodological heterogeneity of studies evaluating CT for NTSAH. There is not a gold standard to diagnose this condition. There was high risk of bias related to these studies.

Key words: *Non-traumatic subarachnoid hemorrhage, Multi-detector computed tomography, Cerebral angiography, Emergency department, Stroke*

RESUMEN

Objetivo: Determinar la validez diagnóstica de la Tomografía computarizada convencional (CT) versus cualquier otra estrategia de imagen para diagnosticar hemorragia subaracnoidea no traumática. **Métodos:** Incluimos estudios de corte transversal, casos y controles y cohortes conducidos entre Enero 1 de 1980 y Diciembre 31 de 2013. No hubo restricción de lenguaje. Los estudios incluían personas de cualquier edad y género con hemorragia subaracnoidea no traumática. Los participantes debían estar en cualquier fase de detección de la enfermedad al entrar en la sala de emergencias. No hubo preferencias en cualquier otra de las características demográficas de los participantes. Intentamos comparar la TC convencional (test índice – incluyendo TC multidetector) versus angiografía, angiotomografía (angiografía por tomografía), angiografía por sustracción digital (ASD) y resonancia magnética (RM). Se excluyeron estudios que evaluaran

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aneurismas con los exámenes seleccionados. Se diseñó una estrategia de búsqueda para estudios publicados en Medline via Pubmed, CENTRAL, LILACS y EMBASE. Otros recursos electrónicos se usaron para encontrar estudios adicionales, tales como resúmenes de conferencias, Google académico, DARE y PROSPERO. Buscamos en las listas de referencias de los artículos seleccionados, se intentó contacto con los autores y reconocidos expertos en el tema. Dos investigadores de manera ciega evaluaron los títulos y resúmenes para determinar los posibles artículos a seleccionar, posteriormente se aplicaron los criterios de elegibilidad al artículo completo durante la selección final. Se evaluó el riesgo de sesgo con la herramienta QUADAS2 al menos por dos investigadores de manera independiente. No se realizó Meta-análisis. **Resultados:** Se encontraron 588 artículos (3630 pacientes) con las estrategias de búsquedas seleccionadas. Sólo ingresaron al estudio 3 artículos para el análisis cualitativo (Mitchell et al., 2001; Perry et al., 2011; Van dijk, Hupperts, Van der Jagt, Bijvoet, & Hasan, 2001). La sensibilidad y especificidad global para la tomografía computada para Perry et al., 2011 92.9% (IC95% 89-95.5%) y 100% (IC95% 99.9-100%) respectivamente. Van dijk et al., 2001 encontró una sensibilidad de 30% para el observador 1 y 46% para el observador 2. La especificidad fue de 100% en ambos casos. Mitchell et al., 2001 encontró una sensibilidad de 95% para TC y para resonancia magnética T2 de 94%, junto a una especificidad de 98.5% comparada con TC. Hubo algo riesgo de sesgo principalmente por la selección de los pacientes y el flujo de pacientes en el tiempo. **Conclusiones:** Hay una amplia heterogeneidad clínica y metodológica en los estudios que evalúan TC para HSANT. No existe un estándar de oro para diagnosticar esta condición. Hay un alto riesgo de sesgo relacionado con estos estudios.

Palabras clave: *Hemorragia subaracnoidea, Tomografía computarizada, Angiografía cerebral, Accidente cerebrovascular (DECS)*

INTRODUCTION

Nontraumatic subarachnoid hemorrhage (NTSAH) is a neurological disease of greater social and economic impact, existing today. The NTSAH represents about 5% of all strokes and it has greater morbidity and mortality compared to other kind of cerebrovascular condition[1]. This catastrophic event is mostly caused by a ruptured aneurysm and becomes a life-threatening disease[1].

Diagnosis of NTSAH usually begins with imaging studies in patients with symptoms suggestive of a neurological acute disease. The Computed Tomography (CT) during the first 12 hours of onset has a sensitivity of 98% and gradually decreases as time passes[2,3]. Conventional (CT) has been widely used by the neuroradiologists and general physicians for the initial evaluation of patients with stroke-related symptoms. The CT is quick, easy, tolerable and apparently is reliable for the detection of intracranial hemorrhage[4], however, its diagnostic accuracy varies according to the time of symptom onset[3] some authors do not recommend CT as part of the initial flowchart[2].

Table 1
Search strategy

Search strategy for MEDLINE via pubmed	Search strategy for CENTRAL	Search strategy for EMBASE	Search for LILACS
("Subarachnoid Hemorrhage/diagnosis"[Mesh]) AND ("Cerebral Angiography"[mesh] OR "Scanners, X-Ray Computed"[Mesh] OR "Multidetector Computed Tomography"[Mesh] OR "Imaging, Three-Dimensional/methods"[Mesh] OR "Magnetic Resonance Imaging" [Mesh]) AND ("Sensitivity and Specificity"[Mesh]) = 230	("Subarachnoid Hemorrhage/diagnosis"[Mesh]) AND ("Cerebral Angiography"[mesh] OR "Scanners, X-Ray Computed"[Mesh] OR "Multidetector Computed Tomography"[Mesh] OR "Imaging, Three-Dimensional/methods"[Mesh] OR "Magnetic Resonance Imaging" [Mesh]) AND ("Sensitivity and Specificity"[Mesh]) = 3	("Subarachnoid hemorrhage"/exp) AND ("brain angiography"/exp OR "brain computer tomography"/exp OR "multidetector computed tomography"/exp OR "Magnetic Resonance Imaging") AND ("sensitivity and specificity"/exp OR "diagnostic accuracy"/exp) = 345	mh:("Subarachnoid Hemorrhage") AND tw:((mh:("Cerebral Angiography"))) AND mj:("Hemorragia Subaracnóidea") AND clinical_aspect:("diagnosis") OR mh:("scanner X-Ray") OR (mh:("Multidetector Computed Tomography")) OR ("X-ray Computed Tomography" OR "Image Processing, Computer-Assisted" OR "Magnetic Resonance Imaging") AND clinical_aspect: ("diagnosis")mh:("Sensitivity and Specificity") =10 search

There are a variety of diagnostic tools as digital angiography, the angiography, and the magnetic resonance (MR), among others. Nevertheless, it is difficult to consider a gold standard due to lack of confidence among studies, for example, there is heterogeneity for the condition of interest (diagnosing the NTSAH or diagnosing the etiology of the NTSAH), and frequently they blend these two conditions[2,5], which means a difficulty when establishing a gold standard.

According to the variety of considerations we planned this systematic review to determine the diagnostic accuracy of conventional CT versus any other imaging strategies to diagnose non-traumatic subarachnoid hemorrhage.

METHODS

This study was conducted according to the recommendations of the Cochrane Collaboration[6] and is reported following the PRISMA Statement. The protocol was registered in the International prospective register of systematic reviews (PROSPERO): CRD42013005380.

ELIGIBILITY CRITERIA

Studies: We included cross-sectional, case-control and cohort studies conducted between January 1, 1980 and November 2013. No language restrictions were imposed. Studies must report at least sensitivity and specificity or data to calculate them.
Participants: People of any age and gender group with clinically suspected non-traumatic SAH. Participants must be in the detection phase of the disease, entering to the emergency department or hospitalized for different reasons. There were no preferences in any other demographic characteristic of participants.
Comparisons: We intended to perform the following comparisons: Conventional CT (index test – including multidetector CT) versus: Angiography, Angiotomography (Computed tomography angiography), Digital subtraction angiography (DSA), and Magnetic Resonance (MR).
Outcome: To diagnose Non-traumatic subarachnoid hemorrhage in acute phase.
Exclusion: Studies to evaluate or diagnose aneurysms with the selected tests.

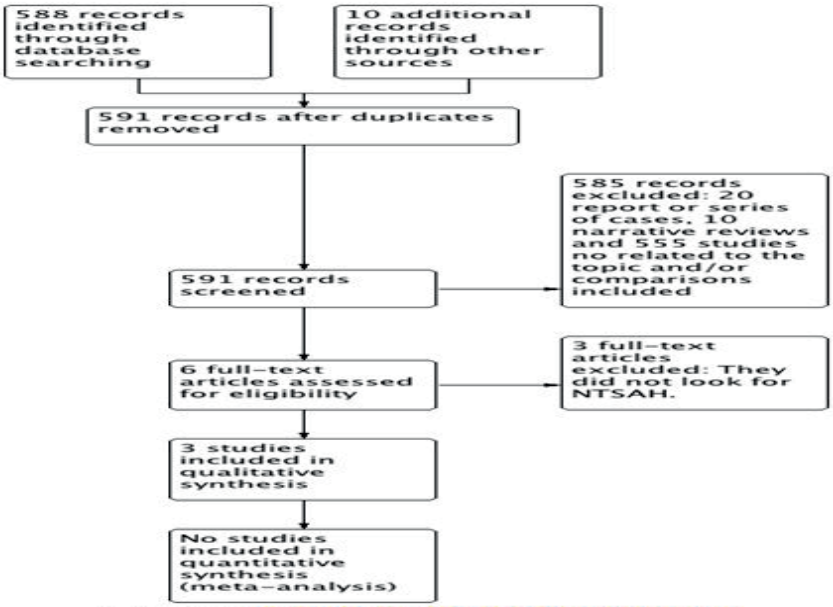

Figure 1 Flowchart of study selection

INFORMATION SOURCES AND SEARCH STRATEGY

We designed a search strategy for studies published in Medline via PubMed, CENTRAL, LILACS and EMBASE. The search strategy was specific for each database and included a combination of the medical subject headings and free text terms for the condition of interest No language or publication status restrictions. We included articles between January 1, 1980 and November 2013. The full search strategies are listed in 13. Other electronic sources were used to find additional studies, such as conference abstracts, Google scholar, DARE and PROSPERO. We looked for additional studies in reference lists of selected articles, contact with authors about knowledge of published or unpublished articles. The results of searches were crosschecked in order to eliminate duplicates.

Table 2
Characteristics of included studies

Study	Study design	Selection of individuals	Target condition and reference standard	Definition of subarachnoid hemorrhage (diagnostic criteria)	Description
Perry et al, 2011 (Canada)	Cohort study	They included 3123 patients. The evaluated test was CT. The prevalence of the target condition in the population 7.7%. Thunderclap headache patients: "Older than 15 years were included alert patients presents headache nontraumatic acute or syncope associated with headache. Definitions: "alert": a 15 points Glasgow coma scale. "non-traumatic"" as no falls	To measure the sensitivity of modern third generation computed tomography in emergency patients being evaluated for possible subarachnoid haemorrhage, especially when carried out within six hours of headache onset. Final diagnosis: Benign headache 1750 (55.9) Migraine 629 (20.1), Subarachnoid haemorrhage 240 (7.7), Viral illness 90 (2.9), Acute ischaemic stroke/transient ischaemic attack 65 (2.1), Postcoital headache 55 (1.8), Sinusitis 36 (1.1) Syncope 33 (1.1), Neck strain 13 (0.4) Brain tumour with mass effect 9 (0.3), Subdural haematoma 9 (0.3), Intracerebral haemorrhage 8 (0.3) Hypoglycaemia 4 (0.1), Weakness—not determined 4 (0.1), Bacterial meningitis 1 (0.03) , Other benign cause* 186 (5.9) In 4% to 31% of patients with acute subarachnoid hemorrhage (SAH), no underlying cause was identified. Blood is restricted to the perimesencephalic cisterns in about two thirds of these patients. These patients were identified as having perimesencephalic nonaneurysmal subarachnoid hemorrhage (PNSAH), a syndrome based on the interpretation of computed tomography (CT) findings on admission, with an excellent prognosis, far better than other patients with SAH with or without an aneurysm. However, the diagnosis is subject to interrater variability, and differentiation between PNSAH and ruptured supratentorial aneurysm by means of CT has not been investigated. Therefore we investigated the validity of prediction of PNSAH with CT scan.	Positive blood on computed tomography, visual xanthochromia, or red blood cells in the final tube of cerebrospinal fluid with abnormal cerebral angiography.	Of the 3132 patients enrolled 240 had subarachnoid haemorrhage (7.7%). The sensitivity of computed tomography overall for subarachnoid haemorrhage was 92.9% (95% confidence interval 89.0% to 95.5%), the specificity was 100% (99.9% to 100%), the negative predictive value was 99.4% (99.1% to 99.6%), and the positive predictive value was 100% (98.3% to 100%). For the 953 patients scanned within six hours of headache onset, all 121 patients with subarachnoid haemorrhage were identified by computed tomography, yielding a sensitivity of 100% (97.0% to 100.0%), specificity of 100% (99.5% to 100%), negative predictive value of 100% (99.5% to 100%), and positive predictive value of 100% (96.9% to 100%).
Van Dijk et al, 2001 (Netherlands)	Cross sectional	They included 466 patients. The evaluated test was CT/ DSA. The prevalence of the target condition in the population 65%. Study included patients with signs and symptoms of subarachnoid hemorrhage within the first 72 hours of the clinical presentation and diagnosis was confirmed by computed tomography and analysis of cerebrospinal fluid or postmortem examination. Male and female Patients between 19 - 80 years.	In 4% to 31% of patients with acute subarachnoid hemorrhage (SAH), no underlying cause was identified. Blood is restricted to the perimesencephalic cisterns in about two thirds of these patients. These patients were identified as having perimesencephalic nonaneurysmal subarachnoid hemorrhage (PNSAH), a syndrome based on the interpretation of computed tomography (CT) findings on admission, with an excellent prognosis, far better than other patients with SAH with or without an aneurysm. However, the diagnosis is subject to interrater variability, and differentiation between PNSAH and ruptured supratentorial aneurysm by means of CT has not been investigated. Therefore we investigated the validity of prediction of PNSAH with CT scan. .	On the basis of specific CT scan criteria, a perimesencephalic pattern of hemorrhage predicts a negative angiogram. This perimesencephalic nonaneurysmal subarachnoid hemorrhage (PNSAH) is a clinical entity characterized by mild clinical signs, infrequent complications, and an invariably excellent clinical outcome.	We found an interrater agreement for the diagnosis perimesencephalic nonaneurysmal subarachnoid hemorrhage of 93% and a value of 0.65. Sensitivity was 30% for observer 1 and 46% for observer 2. The positive predictive value was 73% for observer 1 and 76% for observer 2. Among those diagnosed as

Mitchell et al, 2001	Cross sectional	All patients presenting to the departments of Neurology and Neurosurgery at the Royal Hallamshire Hospital with a history compatible with SAH from March 1998 to April 1999 were considered candidates for the study. Patients well enough to perform MR and CT. Only 41 patients were included after 126 patients candidates. Exclusion criteria: Trauma. 25 female and 16 male patientes between22 to 76 years old were included in the acute and subacute phase.	The evaluated test was MR and the reference test was CT although if there was a negative CT, a lumbar puncture was needed. All MRI was performed on a 1.5T system with 27 mT/m gradients (Eclipse, Picker Medical Systems, Cleveland, Ohio, USA). Five MR sequences were assessed. These were a spin echo T1 sequence, a fast spin echo T2 sequence, a single shot fast spin echo T2 (express) sequence, a fluid attenuation inversion recovery (FLAIR) sequence, and a gradient echo T2* sequence.	CT positive and where CT was negative then a lumbar puncture was performed. The patient was considered to have had an SAH unless both the CT and lumbar puncture were negative. A positive diagnosis of SAH was made if high signal was seen in the subarachnoid space on T1 or FLAIR images (FLAIR images suppress the normally high signal from CSF). An SAH was diagnosed on T2* images if loss of signal with "blooming" was seen in the subarachnoid space	Diferent protocols for scanning. The sensitivities for the MR sequences compared with the CT and LP combination in the acute group were T1 50%, T2 56%, express 50%, FLAIR 81%, and T2* 94% (and CT 95%). The one case missed by the T2* sequence was also missed by all other MR sequences and only seen on CT. In the subacute group the overall sensitivities were T1 33%, T2 47%, express 33%, FLAIR 87%, and T2* 100% (and CT 75%). If the groups were pooled the overall time independent sensitivities were T1 42%, T2 52%, express42%, FLAIR 84%, and T2* 97% (and CT 90%). The false positive rate is therefore less than 1:69 giving a specificity of more than 98.5% (95% CI 96.75–100%). It must be borne in mind that the population studied was selected in that all patients were referred to a specialist neurology centre.

STUDY SELECTION

Two investigators independently and blindly screened the titles and abstracts to determine the potential usefulness of the articles. Eligibility criteria were applied to the full text articles during the final selection. When discrepancies occurred, an agreement was made to take a final decision. If they could not agree, a third reviewer made the final decision.

DATA COLLECTION PROCESS

Relevant data were collected using a standardized data extraction sheet, which contained: study design, methods, participants, index test, standard of reference and final outcomes details. Reviewers confirmed all data entries and checked at least twice for completeness and accuracy. If some information were missing, we contacted authors in order to get data completed.

Risk of bias in individual studies and across them. The risk of bias was assessed independently by at least two researches using the QUADAS2 tool. We solved disagreements by consensus. The "Risk of bias table" (within and across studies) was edited using Review Manager Software Version 5.2® (RevMan) to illustrate the judgments for each study.

Summary measures. No meta-analysis was performed due to lack of data.

Additional analyses. We intended to do the following Subgroup analysis: Time to progression and Fisher scale, but studies lack this information.

Publication bias. This was not performed due to the number of studies found (less than 10 studies) according to Higgins[6].

RESULTS

Study selection. 588 articles were found with the search strategies designed, after exclusions, three studies were included in qualitative analyses[3,7,8]. (Figure 1).

Characteristics of included studies. 3630 patients were found in the studies of Mitchell et al.[3], Perry et al.[7] y Van Dijk et al.[8]. Both studies included male and female patients over 15 years old and the general characteristics are shown in table 2. The study of Perry et al.[3], included 3123 female and male patients over 15 years-old. They included 15 points Glasgow scale (alert people) who entered emergency room with acute non-traumatic headache or syncope with headache. The index test was CT and the reference test was angiography. Overall sensitivity was 92.5% and specificity was 100%. On the other hand, Sensitivity and specificity limited to the first six hours was 100% for both of them. The study of Van Dijk et al.[8], included 466 patients older than 19 years old. They included patients with suspected SAH within the first 72 hours. The evaluated test was CT/DSA. The prevalence of the target condition in the population was 65%. Sensitivity was 30% for observer 1 and 46% for observer 2 and specificity was 100%. Mitchell et al.[7], included 41 patients with suspected NTSAH. All of them underwent CT and MR (CT underwent first), and then the MR.

Characteristics of excluded studies. We excluded the studies of Agid[9], Cortnum[10] y Lourenco[11], because they included a different index or reference test.

Risk of bias of included studies. We evaluated the quality in conducting and reporting the diagnostic methods of the two included studies according to the recommendations of Higgins[6] y Loke[12]. According to the QUADAS2 assessment, the study of Perry et al.[3], had unclear and high risk of bias about index (no blinding) and reference test (blended lumbar puncture and angiography- this aspect is unclear), flow and timing (many patients were lost during follow-up) and also about the applicability of the index and reference tests. On the other side, the study of Van Dkijk et al.[8], had high risk of bias about patient selection (case-control study) and flow and timing (not all patients received the same standard of reference) but also unclear risk of bias related to the applicability of the patient selection. Mitchell et al.[7], had high risk of bias in flow and timing item (It is not well defined the acute or sub-acute time of the disease) and unclear risk of bias in index and reference standard items (CT was performed before MR; CT was used as reference standard for MR and lumbar puncture was used as standard for CT). The patient selection looks with low risk of bias. In a broad vision, looking at the risk of bias table across studies, we could notice that they had flaws about the quality in all areas (patient selection, index and reference test, flow and timing and their applicability), mainly in patient selection and flow and timing (Table 3 and 4).

Results of individual studies. The overall sensibility and specificity for the computed tomography for Perry et al.[3] were 92.9% (CI95% 89-95.5%) and 100% (CI95% 99.9-100%), respectively. The negative predictive value was 99.4% (99.1% to 99.6%) and the positive predictive value was 100% (98.3% to 100%). For patients screened within the first six hours of headache onset, the sensitivity was 100% (CI95% 97.0-100.0), specificity was 100% (CI95% 99.5-100), negative predictive value was 100% (CI95% 99.5-100), and the positive predictive value was 100% (CI95% 96.9-100) (table 2). Van Dijk et al.[8], found a sensibility of 30% for observer 1 and 46% of observer 2. The specificity was 100% in both cases. The positive predictive value was 73% for observer 1 and 76% for observer 2 (table 2). According to the results from Mitchell et al.[7], the sensibility for CT was 95%. The sensibility for MR T2 phase was 94% and the specificity was 98.5% compared to CT although this last study used the CT as the reference standard when assessed MR and lumbar puncture as reference standard when assessed CT (table 2). Due to these results, the risk of bias assessment and clinical heterogeneity, the evidence synthesis (Meta-analysis) was not performed.

DISCUSSION

Summary of results. Only three studies were included in qualitative analysis and no meta-analysis was performed. 3630 patients were included in three studies[3,7,8]. Perry et al.[7], showed a sensitivity and specificity of 92% and 100% respectively, including patients with suspected NTSAH. The reference test was angiography. On the other hand, Van Dijk[8], included patients within 72 hours of suspected NTSAH but the reference test was DSA. The sensitivity and specificity were 30-46% (due to interrater variability) and 100% respectively. Mitchell et al.[3], found 95% sensibility for CT. The MR T2-phase sensibility was 94% and the specificity was 98.5% compared to CT.

Condition of interest. NTSAH impacts social and economically either the patient and or the government due to its high mortality, morbidity and its impact in daily living activities functions[1,13]. Multiple etiologies could produce this condition moreover this could explain clinical heterogeneity found in the present systematic review. Mortality is around 45% of patients having stroke related symptoms and 10 to 15% have died before they could reach the hospital[13]. Some of the problems that collaborate with this mortality are mistaken diagnostic process, a variety of technological devices and the characteristics of the affected population[14]. Some authors and clinicians believe that identifing SAH by CT or any other diagnostic modality is a finished topic, fully justified in literature and clinical practice. However, according to this systematic review and studies reviewed, this topic and this research question is not completely answered according to a variety of conditions describe in the following words. Perry et al.[3], sugests the clinical utility of CT favoring the diagnosis of SAH, among certain conditions as: CT under six first hours of the symptoms onset, using a multi-slice technological equipment and a very well trained radiologist. On the other side, Van Dijk et al.[8], reported the rate of agreement between two trained neuroradiologist and the accuracy of CT to diagnose SAH. Results were non-satisfactory, however, it depends on subjectivity of the trained observer, also depends on the training and the etiology

of the SAH (for example those SAH secondary to a ruptured aneurysm). Mitchell et al.[7], considers the CT as the gold standard, however, he tries to compare MR vs CT and CT vs lumbar puncture (LP) (since there are some cases where CT is negative and LP is positive) which means a mixture of different tests without any clear established gold standard.

Factors affecting the diagnostic accuracy. The conventional CT is a cheap and broadly used technology used in emergency rooms to diagnose people with neurological symptoms. As we were discussing briefly before, the diagnostic accuracy depends on a variety of factors described in the following: the onset of symptoms, the equipment, the radiological technique, the patient´s hematocrit and the experience of the radiologist or the physician who interprets the images[15,16]. As a variety of studies have shown results to this topic, it is important to remember that diagnostic accuracy of CT for NTHAS diminishes as time flows after the onset of the symptoms[2,3,15]. As physicians know, there are different causes for these neurological symptoms and especially for NTSAH moreover when there is a ruptured aneurysm, its sensibility and specificity are lower. This could controvert the results due to there are some patients with ruptured aneurysms involved in the studies included in the present systematic review[5,17,18]. The gold standard is difficult to choose: Arteriography, as a gold standard, is important to detect a ruptured aneurysm but it could not be relevant for those who have another etiology[5,18]. Other studies suggest choosing lumbar puncture as the gold standard, however literature lacks about this topic[3]. On the other side, other studies suggest magnetic resonance (specially FLAIR sequences) as the gold standard for diagnosis of NTSAH apart of diagnosing the etiology of the condition[19-21]. We showed the results from three included studies, one used conventional angiography, the other utilized digital angiography and the last one used MR and/or CT as gold standards.

Limitations. None of the studies found were summarized in a Meta-analysis due to their clinical heterogeneity. Although inclusion criteria were very well established, they were broad and the three studies had some differences about the populations, for example the time to assess the condition, the reference standard, the etiology of the NTSAH, type of study design (Cohort and cross sectional) which limit the findings[22]. Regarding the risk of bias of these three diagnostic studies, it is important to notice that Perry et al.[3], showed high risk of bias in flow and timing and unclear risk in index test and reference standard, moreover, Van Dijk et al.[8], had high risk of bias in patient selection and flow and timing and Mitchell et al.[7], found high risk of bias in flow and timing. We found high risk of bias across the studies in patient selection and flow and timing, generating applicability concerns. The quality of these studies has not reached the standards. This is another important factor that limits the results of the present systematic review. There is no clear and established gold standard neither for diagnosis of NTSAH or for determining the etiology of this condition. This is why studies have a great heterogeneity about the establishing the condition of interest[3,8,19,21] then this is a big concern for us.

According to this systematic review, we concluded that there is a vast clinical heterogeneity of studies evaluating CT for NTSAH and there is not a gold standard to diagnose this condition. There is high risk of bias related to these studies that limits the generalizability of the results. Finally, there is not enough evidence to support CT as the preferred study for NTSAH then we need more research in this field, perhaps evaluating other kinds of diagnostic studies or in different settings.

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