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Mechanisms of memory impairment in animal models of nontraumatic intracranial hemorrhage: A systematic review of the literature

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Abstract

Mechanisms underlying memory and cognitive dysfunction following spontaneous intracranial hemorrhage are diverse. The aim of this systematic review was to provide a contemporary review of the commonly reported mechanisms responsible for memory impairment following nontraumatic intracranial hemorrhage. PubMed, Embase, and Scopus databases were systematically searched for pre-clinical studies, and results were reported according to PRISMA guidelines. Methodological quality assessment was performed according to the SYRCLE's Risk of Bias tool. Ninety studies met the inclusion criteria. Most of animal studies reported on subarachnoid hemorrhage (48%), followed by intraparenchymal hemorrhage (44%), and intraventricular hemorrhage (8%). Most of subarachnoid hemorrhage studies (30%) reported neuronal apoptosis as a mechanism for memory dysfunction, whereas the most commonly described mechanism following intraparenchymal hemorrhage (40%) and intraventricular hemorrhage (23%) was a proinflammatory response. Based on SYRCLE's Risk of Bias assessment, the average methodological risk of bias of all studies was $56.83 \pm 12.77\%$ on a 0–100% scale. There is a great need not only for more preclinical studies with improved

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methodology, but also for studies reporting negative treatment effects and for multicenter animal studies. In vivo studies on non-rodent animal ICH models can also be helpful.

Keywords

Animal studies; Intracranial hemorrhage; Intraparenchymal hemorrhage; Intraventricular hemorrhage; Memory; Subarachnoid hemorrhage

1. Introduction

Hemorrhagic and ischemic stroke are two main types of cerebrovascular accidents. Spontaneous nontraumatic intracranial hemorrhage (ICH) represents only 10–15% of all strokes, but is associated with substantial morbidity and mortality.[1] The annual incidence of ICH is approximately 28 per 100,000, but is believed to be underdiagnosed and hence underestimated. The prognosis following hemorrhagic stroke is poor with an estimated ten-year survival rate of only 24.1%.[2] The most important risk factors for spontaneous ICH are age and arterial hypertension, occurring in 50–70% of patients. Hypertension is associated with deep cerebral and brainstem ICH and to a lesser extent with lobar hemorrhages.[3] Some of the long-term impairments that develop following ICH are cognitive and memory deficits, which are reported in as high as 44% of survivors of ICH.[4] As of now, there are no FDA-approved therapies on the market that improve functional and memory outcomes in survivors of ICH, thus the need for such therapies is unprecedented.[5] Translational research focusing on elucidating the link between ICH and delayed memory dysfunction is critical in order to develop future therapeutic options for these patients.

No recent systematic review investigating mechanisms and associations between experimental nontraumatic ICH and subsequent memory and cognitive dysfunction has been performed. Thus, the aim of this study was to conduct a thorough contemporary review of the available evidence in the literature as well as summarize the proposed mechanisms and to assess the quality of research supporting these findings. The authors were interested in studying the commonly reported mechanisms for memory dysfunction in animal models following nontraumatic ICH, which comprises intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and intraventricular hemorrhage (IVH). Our main outcomes measures in this study included identified mechanisms of memory impairment for each subgroup of spontaneous hemorrhage. Additionally, since elevated intracranial pressures (ICPs) are not infrequently observed in the clinical setting during all three types of nontraumatic ICH, the authors were also interested in investigating whether ICPs are implicated in memory dysfunction following nontraumatic ICH. Knowledge of the pathways involved in the development of memory dysfunction after nontraumatic ICH may aid in finding targeted therapies for patients who survive hemorrhagic stroke in the near future.

2. Materials and methods

2.1. Search strategy

The search strategy in this systematic review was conducted and reported according to the Preferred reporting items for systematic reviews and *meta*-analysis (PRISMA) guidelines.[6] The authors performed comprehensive search of PubMed/MEDLINE, Embase, and Scopus databases on October 18th of 2020. Key words such as "intracranial hemorrhage" OR "intracerebral hemorrhage" OR "intraventricular hemorrhage" OR "subarachnoid hemorrhage" OR "intraparenchymal hemorrhage" OR "brain hemorrhage" AND "Memory" OR "memory decline" OR "cognition" OR "cognitive deficits" OR "cognitive decline" were used for the search strategy (Table 1). The references of eligible studies were also checked for additional articles not identified by the initial electronic search.

2.2. Study eligibility

All the collected records were imported into Covidence where screening of eligible studies by two independent reviewers (C.P. and A.O.U.) was performed.[7] Screening of studies was first done by title and abstract followed by full text review, and any disagreements were resolved by discussion amongst the two independent reviewers. Results were limited to pre-clinical (in vivo) animal studies. In vivo studies had to be original, with full text available in English language, and had to report on nontraumatic experimental ICH as well as outcomes of memory and/or cognitive testing in animals following the induction of ICH. Studies involving nontraumatic IPH, IVH, and SAH were included, whereas studies involving traumatic brain injury (TBI) animal models, epidural hematomas, subdural hematomas, and other traumatic injuries were excluded. Duplicate studies, in vitro studies, case reports, commentaries, conference abstracts, editorials, letters, reviews, systematic reviews, *meta*-analyses, non-English language studies, and those pertaining to human subjects were excluded. Studies that did not report specific memory and cognition-specific behavioral test outcomes in animals were also excluded from this systematic review.

2.3. Risk of bias assessment

For the critical appraisal, two reviewers (C.P. and A.O.U.) performed screening, independent review, data extraction and analysis of all eligible articles. The risk of bias assessment of each study was independently performed according to the SYRCLE's Risk of Bias tool for experimental animal studies.[8] The following SYRCLE's Risk of Bias ten methodological domains were evaluated by each reviewer: 'Was the allocation sequence adequately generated and applied?', 'Were the groups similar at baseline or were they adjusted for confounders in the analysis?', 'Was the allocation to the different groups adequately concealed?', 'Were the animals randomly housed during the experiment?', 'Were the caregivers and/or investigators blinded from knowledge regarding which intervention each animal received during the experiment?'; 'Were animals selected at random for outcome assessment?', 'Was the outcome assessor blinded?'; 'Were incomplete outcome data adequately addressed?'; 'Are reports of the study free of selective outcome reporting?'; 'Was the study apparently free of other problems that could result in high risk of bias?' The domains were scored with 'yes' (low risk of bias); 'no' (high risk of bias); or 'unclear' (the item was not reported and thus unknown risk of bias). Any differences of opinion between

the two reviewers were resolved via discussion and reaching consensus. For risk of bias assessment specifically, if one of the reviewers rated a study lower than the other reviewer, the lower score was used for final analysis if that reviewer was able to present valid evidence for such.

2.4. Data extraction

Information such as year of publication, total number of animals used, species strain, mechanism of memory and cognitive impairment following experimental ICH, and type of ICH was independently collected from each study by two reviewers (C.P. and A. O.U.), and any conflicts were resolved via discussion and reaching consensus. Covidence was used for screening, while a standardized computerized spreadsheet was used to collect the data.

2.5. Additional analyses

For further analysis, a total quality assessment score was developed to assess the quality of evidence in the literature supporting each reported mechanism of memory decline after ICH. The total quality assessment score was calculated as the sum of mean risk of bias for the studies reporting a specific mechanism or association, mean number of studies reporting that mechanism, and mean number of animals used in those studies. Higher the total quality assessment score correlated with higher quality of available evidence in the literature for a specific mechanism.

3. Results

3.1. Study characteristics and types of reported mechanisms

A total of 1,882 records were identified with 614 records in PubMed/MEDLINE, 858 records in Embase, and 410 records in the Scopus database (Fig. 1). After duplicates were removed and the records were initially screened by title and abstract, 196 full text articles were then assessed for eligibility. No additional articles were identified by searching through the references lists. After full text review of the 196 studies, 90 pre-clinical animal studies were able to be included in the final systematic review. Publication year, total animal number, species strain, and mechanism of memory decline after ICH were collected (Table 2).[9–98] Plurality of studies were published in 2019 (Fig. 2). Most common species strain used was Sprague-Dawley rats (61.1%), and plurality of animal studies reported on SAH (48%), followed by IPH (44%), and IVH (8%) (Fig. 3). The experimental animal model technique as well as hematoma volume varied across literature. All eligible studies also had to report on the memory and cognitive testing outcomes following ICH, which involved Morris water maze test in almost all of the studies. Amongst the studies pertaining to IPH animal models, the most commonly reported mechanism for possible memory dysfunction was proinflammatory response (40%) (Fig. 4A). For SAH, the most commonly described mechanism was hippocampal neuronal apoptosis (30%) (Fig. 4B). And for IVH animal models, the most frequent reported mechanisms in the literature were proinflammatory response and oxidative stress (both 23%) (Fig. 4C).

3.2. Risk of bias assessment of studies

Methodological risk of bias and quality assessment was performed according to the SYRCLE's Risk of Bias tool for each study (Table 3). Each of the ten domains in the SYRCLE's Risk of Bias tool was given either 5 or 10 points if low risk of bias was determined. The cumulative scores were then calculated on a 0–100% scale. Minimal selective outcome reporting and baseline similarity of groups were two domains with lowest risk of bias, whereas lack of random animal housing and failure of concealment of allocation into different groups were two domains with highest risk of bias amongst all the studies (Fig. 5). Mean methodological risk of bias across all studies was $56.83 \pm 12.77\%$ on a 0–100% scale, and we found no studies that addressed all ten of SYRCLE's Risk of Bias guidelines successfully (Fig. 6).

Further analysis was performed to investigate the quality of evidence for each of the commonly reported mechanisms found to be responsible for memory and cognitive dysfunction after experimental ICH. For this, a total quality assessment score was calculated by adding mean number of studies for each mechanism, mean number of animals used in those studies, and mean risk of bias score for those studies. Based on these metrics, we found that oxidative stress, neuronal apoptosis, and cerebral edema were the top three mechanisms with greatest quality of supporting evidence in the current literature (Fig. 7).

3.3. The role of elevated ICP and hydrocephalus

The authors herein hypothesized that increased ICP may be associated with memory dysfunction that occurs after nontraumatic IPH, SAH, and IVH[68]. However, we found that there is actually limited evidence in the current literature pertaining to this.[28,36,59] Only a handful of studies out of 90 studies included in this systematic review reported on the possible underlying role of hydrocephalus and increased ICPs and hydrocephalus in memory decline. For example, Kamal et al demonstrated that IVH in a rat animal model causes significant deficits in spatial memory acquisition and retention during Morris Water Maze compared to sham animals.[36] That study suggested that the mechanism of the memory decline may arise from mechanical injury in the form of a rapid spike in ICPs during their blood hand injections. Similarly, Qi et al found that IVH induced hydrocephalus and memory deficits in rats.[59] They propose that the space-occupying effect of blood in the ventricles causes obstructive hydrocephalus, which results in increased ICPs.[59] And with respect to SAH animals, Hu et al demonstrated that hydrocephalus exacerbates neurological deficits as well as memory dysfunction following SAH in rats induced by endovascular perforation.[28] There were no IPH animal studies in our systematic review that reported on hydrocephalus and ICPs as drivers for memory dysfunction after IPH. Additionally, there were not studies that monitored ICPs during experimental hemorrhage.

3.4. Reported mechanisms of memory dysfunction in IPH animal models

The most reported mechanism of memory dysfunction following IPH in animal models considered in this review was neuroinflammatory cascade (Fig. 4A). We found a significant number of studies describing the implication of inflammatory cascade of events in secondary brain injury after IPH and in the development of subsequent memory and cognitive decline. Proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-

α are important members of the inflammatory cascade, whereas IL-4, IL-10, and tumor necrosis factor-β have anti-inflammatory mechanism and may play a neuroprotective role.[52] For example, Krafft et al describe how IPH cause the release of proinflammatory cytokines via M1 microglial activation[38]. Additionally, Ding et al reported that IPH activates p38 MAPK resulting in PLA2 and conversion of products by COX-2 into proinflammatory prostaglandins[18]. Inhibiting the activation of neuroinflammatory series of events induced by IPH may serve as a target for alleviating post-IPH cognitive and memory dysfunction, and various studies have already demonstrated this finding.

3.5. Reported mechanisms of memory dysfunction in SAH animal models

We found the majority of SAH animal models reported neuronal apoptosis as the underlying mechanism of memory dysfunction (Fig. 4B). We found 16 studies that demonstrated a link between neuronal apoptosis and development of memory and cognitive dysfunction following SAH in animal models. Various molecular mechanisms that may underly neuronal apoptosis have been investigated in the literature. For example, Dong et al reported increased expression of HIF-α, a regulator of hypoxia, and apoptosis in the hippocampus following SAH[19]. Feng et al showed that early brain injury from SAH in rats induces neuronal apoptosis by activating the Ras/Raf/extracellular signal-regulated kinase (Erk) signaling pathway and phosphorylating p53 tumor suppressor protein in hippocampus.[21] Conversely, inhibiting the activity of Erk results in decreased hippocampal neuronal apoptosis and improvement of cognition in these rats. The Ras/Raf/ERK pathway is well known to play a key role in apoptosis in cerebral ischemia, stroke and various neurodegenerative disorders. It is no surprise that the Ras/Raf/Erk/p53 pathway is involved also in neuronal apoptosis, and perhaps targeting this signaling pathway may be serve as a potential target for the treatment of SAH-induced memory and cognitive decline.[21]

3.6. Reported mechanisms of memory dysfunction in IVH animal models

The most common mechanisms underlying memory dysfunction in studies using the IVH model were proinflammatory response and oxidative stress (Fig. 4C). We found three animal studies mentioning the role of oxidative stress in IVH-induced memory and cognitive dysfunction, and three studies reporting on neuroinflammation as an association. IVH induces oxidative stress by promoting lipid peroxidation, reducing the activity of glutathione peroxidase and superoxide dismutase, increasing nitric oxide levels, and activating free radical generation in hippocampus, hence agents that can suppress this can serve as potential therapeutic targets for alleviation of memory dysfunction after ICH. Rajdev et al report that IVH caused both an increase in oxidative stress evidenced by higher lipid peroxidation-MDA levels, and a proinflammatory response via TNF-α, IL-1β, and IL-10.[62] Similarly, Jiang et al showed an increased count of microglial cells, which can be activated by Ab, in the hippocampus of IVH groups.[34]

4. Discussion

Cognitive and memory dysfunction following spontaneous ICH is a well-known consequence. Before therapies can be tested in humans, conducting quality pre-clinical animal research is essential. With respect to outcomes, behavior, learning and memory

decline, diminished cognition, and cell death are some of the most common end points tested in ICH studies. Of the behavioral tests, the neurological deficit score and forelimb placing are the most widely used. Behavioral tests of cognitive and memory dysfunction, most commonly utilizing Morris water maze, are less common in general.[100]

This systematic review focused on most commonly reported mechanisms underlying memory impairment in animal models of nontraumatic ICH in the current literature. We found that majority of IPH animal models report on proinflammatory response as the possible culprit for memory dysfunction. For SAH, the most implicated mechanism for memory decline was hippocampal neuronal apoptosis. Activation of the Ras/Raf/ pathway in the hippocampus as well as increased expression of hippocampal HIF-α are potential mechanisms leading to cell death and further observed cerebral infarction and larger memory and cognitive deficits after ICH. Studies using IVH models suggest proinflammatory response and oxidative stress cause memory dysfunction. Promoting lipid peroxidation, free radical generation in the hippocampus, and overall mitochondrial dysfunction via oxidative stress may account for reduced neuronal activity and signaling and hence observed learning decline post ICH.[30,62] Interestingly, hydrocephalus and mechanical injury were only reported by three animal studies based on our systematic review.[28,36,59]

In this study, the authors also sought out to find animal studies that reported on hydrocephalus and increased ICPs as possible drivers for memory dysfunction after nontraumatic ICH. However, to our surprise, we only found a handful of studies that reported on this mechanism.[28,36,59] We also did not find any studies included in this systematic review that objectively measured ICPs during the induction of experimental intracranial hemorrhage. Studies measuring ICPs during experimental hemorrhage are not common in general.[103–105] Measuring and monitoring ICPs during nontraumatic ICH can be possible as seen with other ICH animal studies, most of them focusing on SAH.[104–105] For example, studies by Conzen et al and Westermaier et al measured ICPs in rats during acute phase of SAH with sensor probes positioned in the subarachnoid space and intraparenchymal space, respectively.[104–105] These studies were not included in this systematic review as they do not focus on memory impairment following ICH, however, they do demonstrate that direct ICP monitoring during ICH is possible. We think that an intraventricular, subarachnoid, or intraparenchymal sensor may be used for this purpose. The main challenge with using ICP monitoring in rodent models is the accuracy and precision of sensor used. The pressure sensor would have to detect small precise pressure changes of at least one millimeter of mercury in order to provide valid information. While there are many factors known to contribute to memory decline following nontraumatic brain injury, prolonged and elevated ICP may be a strong predictor of this negative trend. For example, a clinical study by Badri et al reported a significant difference between elevated ICP patient group and reduced performance on episodic memory and learning tasks compared to the low ICP group at a six-month post-injury assessment.[101] Additionally, Uzzell et al found that patients with elevated ICP had significantly worse memory function, specifically verbal recall, and exhibited general memory impairment overall.[104] We believe that the number of animal studies reporting on this mechanism are underrepresented and future research should focus on elucidating the role of elevated ICPs in memory impairment following

nontraumatic ICH. Specifically, studies that test memory impairment following ICH with simultaneous ICP measurements can be helpful.

Additionally, we investigated the quality of the preclinical evidence herein and found it to be limited as some degree of methodological bias was present in all studies. Only a handful of studies address the essential methodological details. Like our results, a review by MacLellan et al found many key issues with pre-clinical ICH literature.[99] First, a significant portion of published studies tend to report only positive treatment effects, emphasizing the presence of publication bias. Second, many studies do not report methodological details such as animal randomization into experimental groups. There are key experimental design issues and great diversity amongst the methodology and outcomes of the studies, making it difficult to validate and compare results.[99] Furthermore, current pre-clinical evidence is also not a true reflection of the prevalence of long-term memory and cognitive dysfunction after nontraumatic ICH in human subjects as studies have demonstrated that learning deficits in animals significantly diminish as early as eight weeks following experimental ICH in animal models.[100] In order to improve the quality and transparency of research, there is a great need not only for more preclinical studies with improved methodology, but also for more studies reporting negative treatment effects and for multicenter animal studies. In vivo studies on non-rodent animal ICH models can also be helpful as in this systematic review we have not found any studies focusing on memory impairment after nontraumatic ICH in non-rodent animals. In particular, preclinical research on primate animals would provide more helpful information that can be translated to human survivors of nontraumatic ICH.

5. Conclusions

In conclusion, to our knowledge this is the first systematic review conducted on animal studies that report on mechanisms of memory impairment after nontraumatic ICH. A total of 90 studies reporting on experimental nontraumatic ICH and subsequent memory and cognitive dysfunction confirmed with animal behavioral testing were included in this systematic review. Neuronal apoptosis was the most commonly implicated mechanism for memory dysfunction in SAH animal models, whereas neuroinflammatory cascade was most frequently reported mechanism in IPH and IVH animal models. We found that a frequent clinical cause of memory impairment in the setting of ICH, hydrocephalus and elevated ICPs, were underrepresented in animal studies. According to the SYRCLE's Risk of Bias tool, we found no study that was able to address all the guidelines successfully and overall bias across the studies was significant. As neuronal apoptosis, inflammatory cascade, oxidative stress, cerebral edema, iron overload, and reduced neuroplasticity are all important substrates of secondary brain injury resulting in cognitive and memory impairment, finding therapies that can target these pathways, would be the most optimal therapeutic strategy. Furthermore, improving the quality of pre-clinical research is essential as it will pave the path for controlled clinical studies that target memory and cognitive dysfunction in patients with ICH in the future.

Funding

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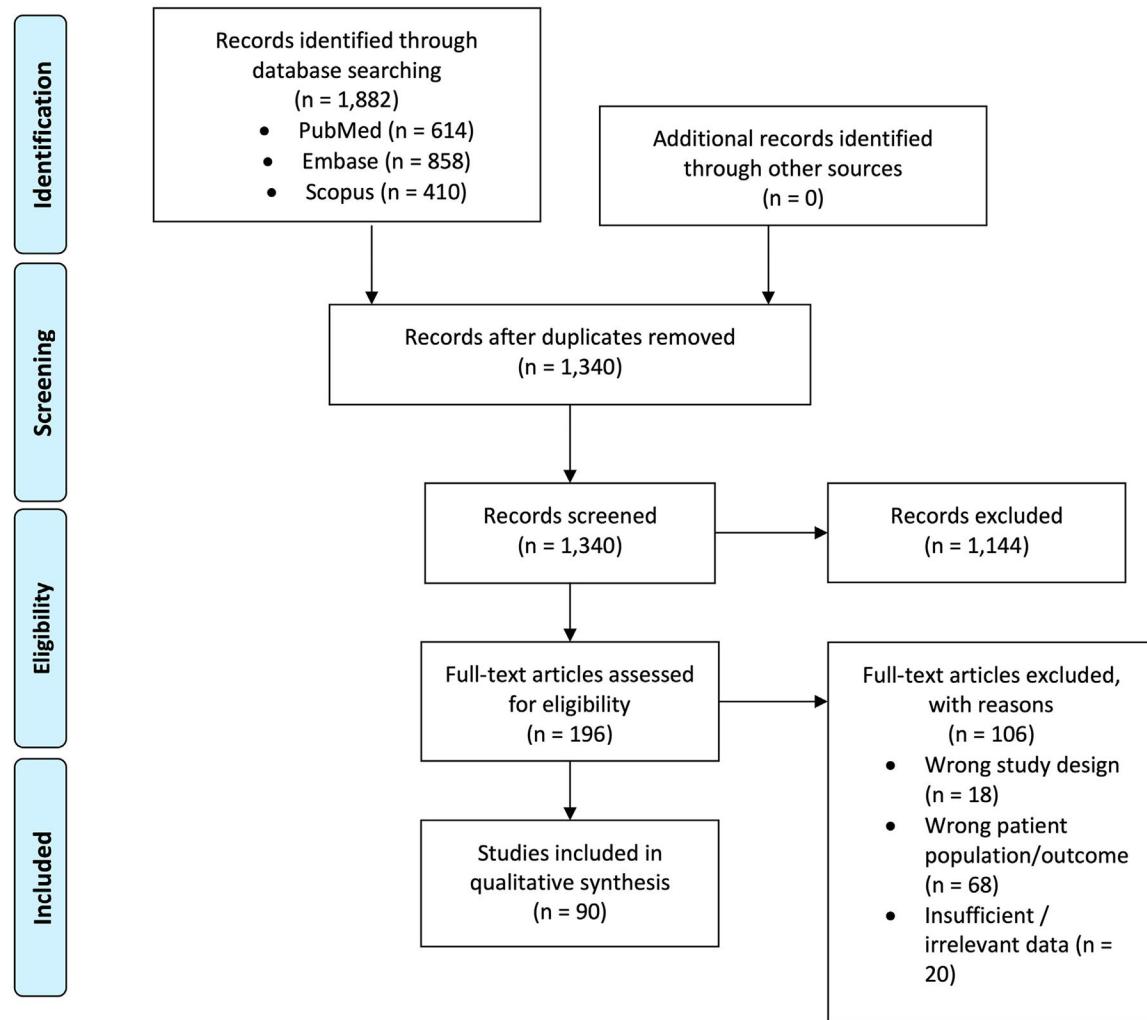
Fig. 1.
PRISMA flow diagram of the search strategy used.
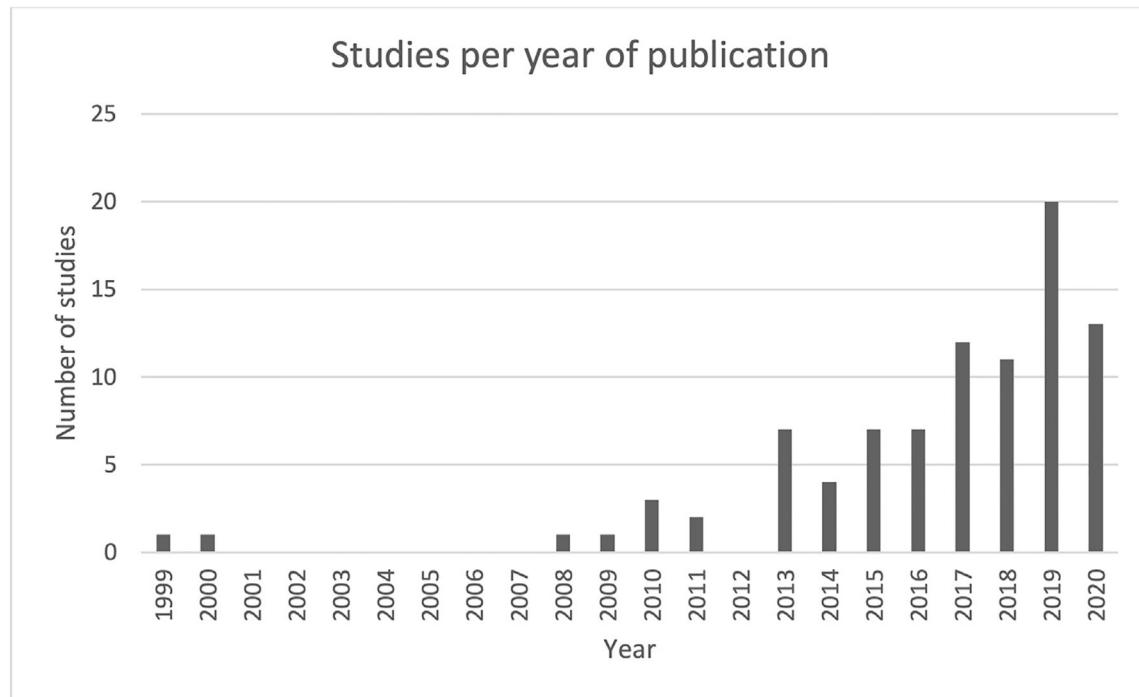
Fig. 2.
Distribution of published studies per year.

TYPE OF EXPERIMENTAL HEMORRHAGE

- Subarachnoid hemorrhage (SAH) 48%
- Intraparenchymal hemorrhage (IPH) 44%
- Intraventricular hemorrhage (IVH) 8%
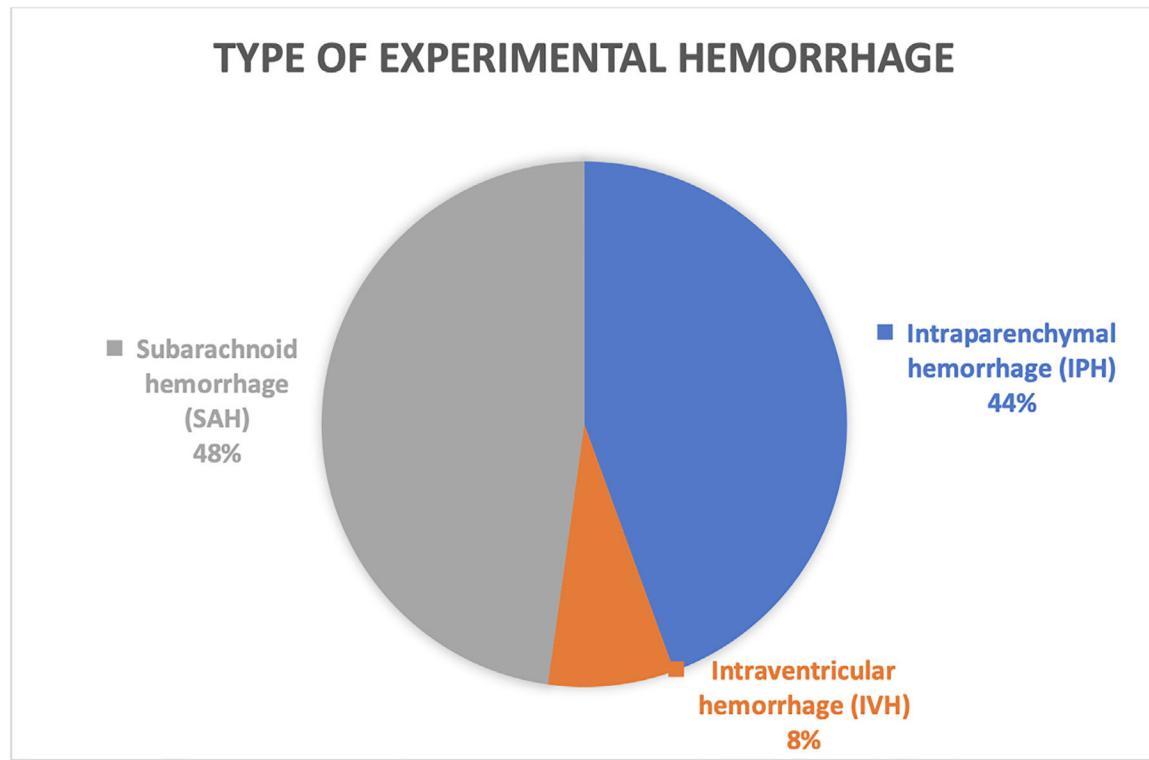
Fig. 3.
Distribution of studies based on type of experimental hemorrhage.
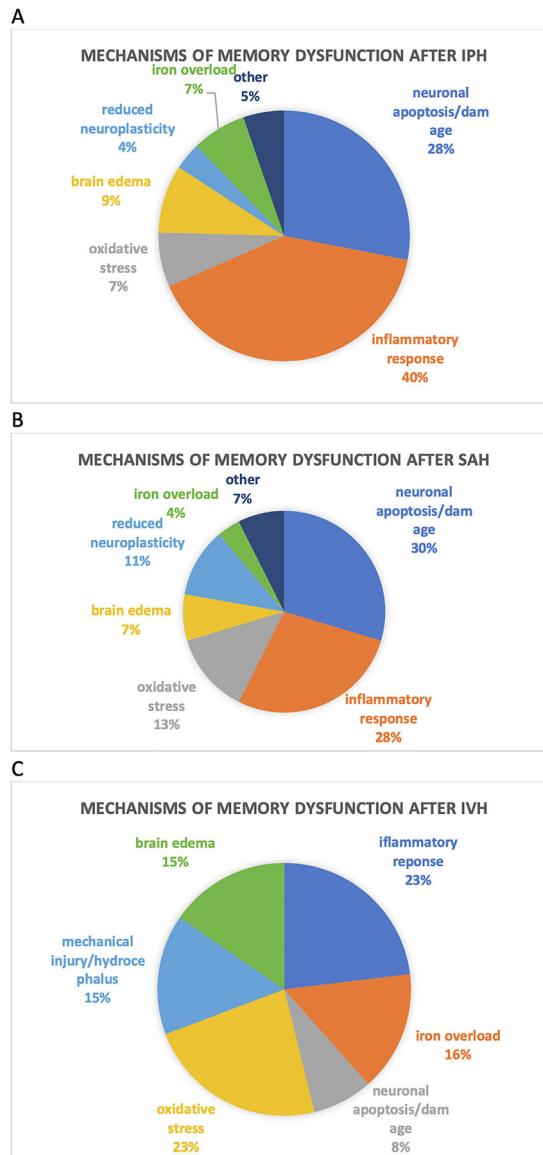
Fig. 4.
Most frequently reported mechanisms for memory decline following (A) IPH, (B) SAH, and (C) IVH. Other: includes studies mentioning mechanical injury, hydrocephalus, hormonal influences, NMDAR activation, and/or white matter injury.
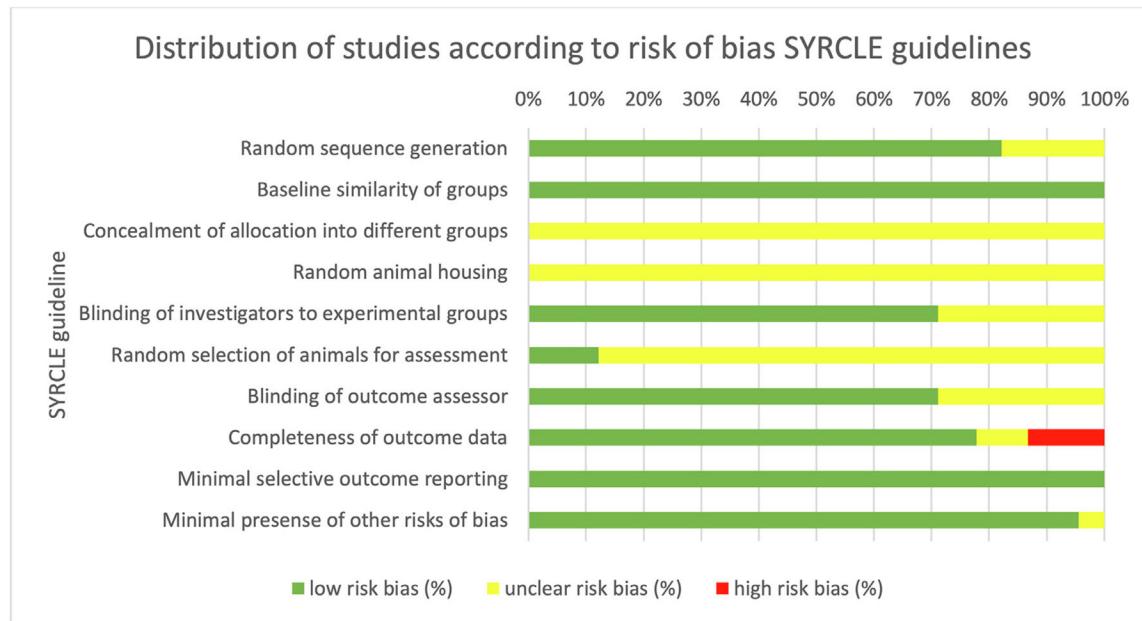
Fig. 5.

Risk of bias assessment. Results of risk of bias and methodological quality indicators of included studies in the systematic review according to SYRCLE guidelines. % represent the percentage of the studies that fulfilled the requirements for 'Low risk of bias' (green), 'Unclear risk of bias' (yellow), and 'High risk of bias' (red).
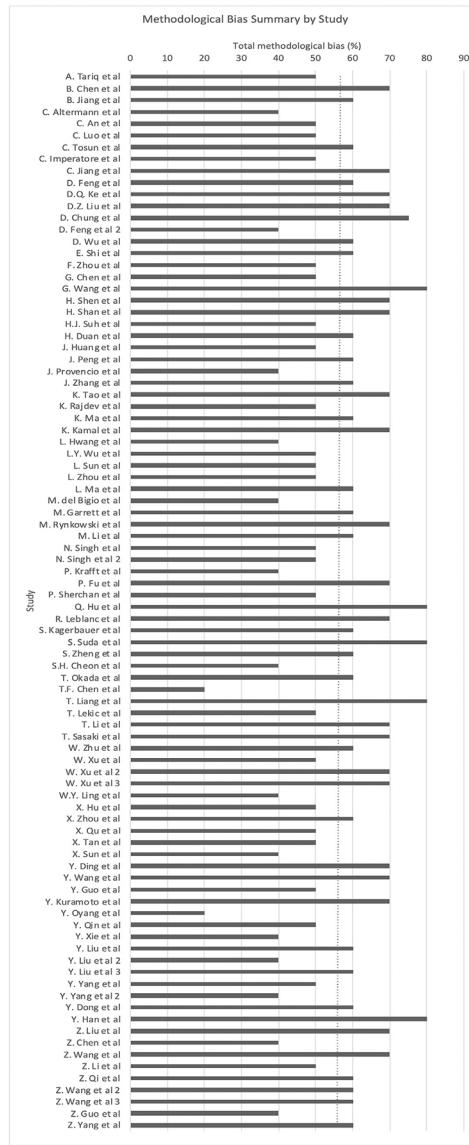
Fig. 6.
Methodological risk of bias by individual study. The reference line indicates mean
methodological bias across all studies, 56.83 ± 12.77%.
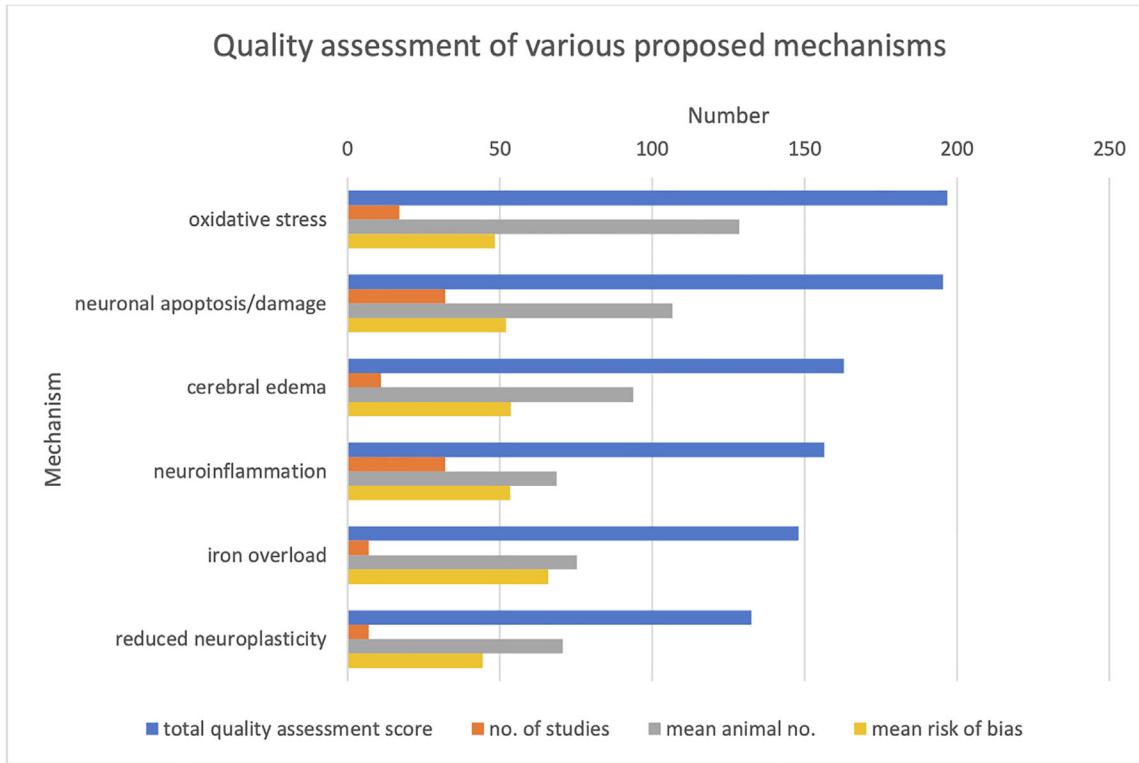
Fig. 7.
Quality assessment of most reported mechanisms. Total quality assessment score was derived from sum of number of studies supporting certain mechanism, mean number of animals used in those studies, and mean risk of bias.

Table 1

Search syntax.

PubMed/MEDLINE search accessed on October 18, 2020 (614 articles)[*]	EMBASE search accessed on October 18, 2020 (858 articles)[*]	Scopus search accessed on October 18, 2020 (410 Articles)[*]
((((((intracranial hemorrhage) OR (intracerebral hemorrhage)) OR (intraventricular hemorrhage)) OR (subarachnoid hemorrhage)) OR (intraparenchymal hemorrhage)) OR (brain hemorrhage)) AND ((((memory) OR (memory decline) OR (cognition)) OR (cognitive deficits)) OR (cognitive decline)) Filters: English, Other Animals	intracranial AND hemorrhage OR (intracerebral AND hemorrhage) OR (intraventricular AND hemorrhage)) OR (subarachnoid AND hemorrhage) OR (intraparenchymal AND hemorrhage) OR (brain AND hemorrhage) AND memory OR (memory AND decline) OR cognition OR (cognitive AND deficits) OR (cognitive AND decline) AND ('animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'in vitro study'/de OR 'in vivo study'/de OR 'nonhuman'/de)	((TITLE-ABS-KEY (intracranial AND hemorrhage) OR TITLE-ABS-KEY (intracerebral AND hemorrhage) OR TITLE-ABS-KEY (intraventricular AND hemorrhage) OR TITLE-ABS-KEY (subarachnoid AND hemorrhage) OR TITLE-ABS-KEY (intraparenchymal AND hemorrhage) OR TITLE-ABS-KEY (brain AND hemorrhage)) AND ((TITLE-ABS-KEY (memory) OR TITLE-ABS-KEY (memory AND decline) OR TITLE-ABS-KEY (cognition) OR TITLE-ABS-KEY (cognitive AND deficits) OR TITLE-ABS-KEY (cognitive AND decline)) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re")) AND (LIMIT-TO (SRCTYPE, "j")) AND (EXCLUDE (EXACTKEYWORD , "Human") OR EXCLUDE (EXACTKEYWORD , "Humans")))

[*]
Limited to full text available in English language and in vivo studies.

Table 2

Studies included in the systematic review.

	Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
1	Tariq et al., 2010	26	Sprague-Dawley rats	50	SAH	SAH is associated with loss of long-term potentiation at the Schaffer collateral—CA1 synapses in the hippocampus.
2	Chen et al., 2019	136	ICR and C57BL/6 mice	70	IPH	ICH leads to neuronal ferroptosis in acute phase in brain areas distant from ICH; Fer-1 inhibitor showed long-term neuroprotective effects and alleviates cognitive deficits.
3	Jiang et al., 2017	186	Sprague Dawley rats	60	IPH	Sur1-Trpm4 channel is up-regulated following ICH. Glibenclamide inhibits this channel, reducing brain edema, protecting blood brain barrier integrity by reducing the activity of metalloproteinases, and subsequently improving cognition after ICH.
4	Altermann et al., 2017	80	Wistar rats	40	IPH	ICH increases oxidative stress and lipid peroxidation in hippocampus, which green tea administration reverses. Green tea prevents memory deficits after ICH. Hence, oxidative stress in hippocampus is associated with memory decline after ICH.
5	An et al., 2017	120	Sprague Dawley rats	50	SAH	SAH induces neuronal damage in the hippocampus, with an upregulation of phosphorylated PI3-K, Akt and mTOR. BQ-123 improved memory by downregulating mTOR. Increased mTOR activity associated with memory loss following SAH.
6	Luo et al., 2018	40	Sprague Dawley rats	50	IPH	Microglial activation and pro-inflammatory markers are associated with memory decline after ICH. Ginkgo biloba extract alleviates the cognitive dysfunction by regulating the expression of inflammatory factors secreted by microglia.
7	Tosun et al., 2015	43	Wistar rats	60	SAH	Sulfonylurea receptor 1-transient receptor potential melastatin 4 (Sur1-Trpm4) channel is upregulated in SAH. Inhibiting this channel activity reduces neuroinflammation and subsequently reduces memory deficits following SAH.
8	Imperatore et al., 2000	70	Albino Sprague Dawley rats	50	SAH	Hydroxyl radical scavenger AVS has neuroprotective effects on cognition and memory following SAH, hence free radicals might contribute to cognitive decline after SAH
9	Jiang et al., 2018	18	Sprague Dawley rats	70	IVH	Amyloid Beta accumulation with enhanced neuroinflammation throughout the hippocampus are observed after IVH, resulting in memory decline. Iron overload may be involved in amyloid beta accumulation.
10	Feng et al., 2014	138	Sprague Dawley rats	60	SAH	Ceftriaxone exerts protective effects on cognition following SAH by upregulating the excitatory amino acid transporter 2 (EAAT2) expression, modulating the PI3K/Akt/NF-jB signaling pathway, and reducing hippocampal apoptosis.
11	Ke et al., 2020	177	Sprague Dawley rats	70	SAH	Inhibition of caspase-8 improved memory following SAH by suppressing inflammation. Hence, inflammation may play a key role in memory decline following SAH.
12	Liu et al. 2017	58	Sprague Dawley rats	70	IVH	Thrombin mediates the hippocampal neuronal cell death and spatial memory deficits produced by IVH, and these can be blocked by inhibition of Src family kinases or by inhibiting Fyn.
13	Chung et al., 2020	unclear	C57BL/6J mice	75	SAH	SAH leads to early and persistent changes in resting state functional connectivity and deficits in spatial learning and working memory tasks.
14	Feng et al., 2016	25	Sprague Dawley rats	40	SAH	During SAH, Ras/Raf/Erk pathway contributes to hippocampal apoptosis through the phosphorylation of p53 and leads to cognitive deficits.
15	Wu et al., 2020	108	Sprague Dawley rats	60	IPH	WNK3/SPAK/NKCC1 signaling pathway is upregulated after ICH, leading to apoptosis, neuroinflammation, and subsequent memory deficits.

Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
16	Shi et al., 2019	30	C57Bl/6J mice	60	IPH	ICH leads to hippocampal neuronal loss, and persistent diffuse brain inflammation (accumulation of microglia, infiltration of peripheral immune cells, and generation of reactive oxygen species), resulting in cognitive decline.
17	Zhou et al., 2011	70	Sprague Dawley rats	50	SAH	Tetramethylphrazim, an alkaloid monomer, improves spatial learning and memory impairment caused by SAH by increasing activity of superoxide dismutase and attenuating oxidative stress.
18	Chen et al., 2013	90	Rats	50	SAH	NR2B, a subunit of N methyl D aspartate receptor (synaptic plasticity protein), alleviates cognitive deficits after SAH. It is down-regulated in the brain after SAH, leading to cognitive decline.
19	Wang G et al., 2018	231	CD-1 mice	80	IPH	Heme and iron are key factors responsible for secondary insults after ICH. Toll-like receptor 7 TLR7 is involved in heme scavenging after ICH by modulating the BTK-CRT-LRP1-Hx pathway, thus promoting heme resolution and alleviating memory deficits after ICH.
20	Shen et al., 2015	228	Sprague-Dawley rats	70	SAH	SAH decreased expressions of neurexin-1β and neuroligin-1 (proteins involved in synaptic structures), resulting in memory decline. Neurexin-1 β and neuroligin-1 might be good targets for improving cognitive function after SAH.
21	Shan et al., 2019	42	CD-1 mice	70	IPH	H2S attenuates ICH-induced brain cognitive deficits by suppressing apoptosis and autophagic cell death following ICH. Hence, neuronal apoptosis might be important in creation of memory deficits after ICH.
22	Suh et al., 2011	50	Sprague Dawley rats	50	IPH	Tamsulosin, an alpha 1 receptor antagonist, facilitates memory recovery by inhibiting hippocampal cell apoptosis and proliferation following ICH, hence, hippocampal CA-1 apoptosis after ICH contributes to memory decline.
23	Duan et al., 2020	48	Sprague Dawley rats	60	SAH	Microglial inflammation contributes to cognitive impairment after SAH. Hydrogen sulfide reduces cognitive impairment of rats after SAH by ameliorating neuroinflammation via the TLR4/NF-kB pathway.
24	Huang and Jiang, 2019	136	C57/BL6 mice	50	IPH	ICH increases brain oxidative stress levels and reactive oxygen species, which contribute to memory deficits. Dexmedetomidine decreases oxidative stress and subsequently alleviates memory deficits.
25	Peng et al., 2019	217	Sprague Dawley rats	60	SAH	Low-density lipoprotein receptor-related protein-1 (LRP1), scavenger receptor for ApoE, attenuates white matter injury and improves cognition after SAH by modulating M2 microglial polarization through Shc1/PI3K/Akt signaling. White matter injury is associated with cognitive dysfunction after SAH.
26	Provencio et al., 2016	unclear	C57BL/6 mice	40	SAH	Loss of late long-term potentiation due to dysfunction of the NMDA receptor and inflammation contribute to memory dysfunction after SAH. Suppression of innate immune cell activation leads to improved memory after SAH.
27	Zhang et al., 2020	204	Sprague Dawley rats	60	SAH	Nix recognizes injured mitochondria after SAH and leads to amelioration of memory deficits after SAH and reduced total number of apoptotic cells. Hence, early brain injury and apoptosis may play a role in memory deficits after SAH.
28	Tao et al., 2020	86	C57BL/6 mice	70	SAH	Dysfunction of glutamate transporter 1 (GLT-1)-mediated glutamate uptake in astrocytes may be involved in delayed cognitive impairment after SAH. Also, expression of histone deacetylase 2 (HDAC2) increased in astrocytes after SAH.
29	Rajdev et al., 2020	54	Wilstar rats	50	IVH	IVH induce complex mitochondrial enzyme dysfunction, neurochemical disruptions, oxidative stress elevation, and increased neuroinflammatory markers that contribute to memory and cognitive loss.

	Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
30	Ma et al., 2018	147	Sprague Dawley rats	60	SAH	Hippocampal neuron apoptosis via the mitochondrial apoptosis pathway is associated with memory deficits following SAH.
31	Kamal et al., 2020	unclear	Sprague Dawley rats	70	IVH	Blood and mechanical injury are the predominant mechanisms of memory decline after IVH. Microglial activation in dentate gyrus is also seen after IVH.
32	Hwang et al., 2013	40	Sprague Dawley rats	40	IPH	Dexmedetomidine ameliorates ICH-induced memory impairment by exerting anti-apoptotic effects in hippocampus, hence hippocampal apoptosis contributes to memory loss after ICH.
33	Wu et al., 2017	120	Sprague Dawley rats	50	SAH	Pannexin-1 channels, inflammatory response and neurobehavioral dysfunction through the TLR2/TLR4/NF-kB-mediated pathway contribute to cognitive deficits after SAH.
34	Sun et al., 2018	36	Sprague Dawley rats	50	SAH	Hippocampal neuronal cell death and upregulation of ROCK2 lead to memory deficits after SAH.
35	Zhou et al., 2018	146	Sprague Dawley rats	50	IPH	Upregulation of Pannexin-1 expression may be involved in apoptosis and degeneration of neurons, leading to subsequent cognitive dysfunction after ICH.
36	Ma et al., 2016	unclear	ICR mice	60	IPH	B7–1 (CD80)/CD28 signaling pathway in T cells contributes to memory deficits after ICH. Thus inflammatory and immune responses contribute to memory deficits.
37	Del Bigio et al., 1999	29	Sprague Dawley rats	40	IPH	Sulfated polysaccharide fucoidan has been found to lead to better memory retention after ICH. Inflammatory responses is associated with subsequent memory deficits after ICH.
38	Garrett et al., 2009	unclear	C57BL/6J mice	60	IPH	Inflammation and brain edema contribute to memory decline after ICH. Simultaneous blockade of the C3a and C5a (part of complement cascade) inflammatory receptors alleviates memory deficits.
39	Rynkowski et al., 2009	unclear	C57BL/6J mice	70	IPH	C3 is involved in complement-mediated cerebral injury after ICH and along with brain edema contributes to memory deficits.
40	Li et al., 2016	115	C57BL/6J mice	60	SAH	Brain edema, hippocampal apoptosis, and increased oxidative stress contribute to cognitive deficits after SAH.
41	Singh et al., 2017b	40	Wistar rats	50	IPH	Oxidative stress via generation of free radicals and inflammation lead to memory decline after ICH. Resveratrol, antioxidant, reduces oxidative stress and TNF alpha activity and alleviates ICH-induced memory decline.
42	Singh et al., 2017a	40	Wistar rats	50	IVH	Inflammatory cytokines and oxidative stress contribute to IVH-induced memory deficits. Naringin a natural antioxidant bioflavonoid, has been found to reverse these effects.
43	Krafft et al., 2017	66	CD-1 mice and Sprague Dawley rats	40	IPH	Neuroinflammation contributes to memory deficits after ICH. α7 nicotinic acetylcholine receptor stimulation reduces neuroinflammation via activation of the JAK2-STAT3 pathway, thus ameliorating memory deficits after ICH.
44	Fu et al., 2020	72	Sprague Dawley rats	70	IPH	Monascin, agonist of PPAR gamma and Nrf2, improves memory by facilitating hematoma clearance, attenuating iron overload and brain atrophy after ICH. Thus iron overload contributes to memory deficits after ICH.
45	Sherchan et al., 2011	118	Sprague Dawley rats	50	SAH	Minocycline, a neuroprotectant agent, improves spatial memory and attenuated neuronal loss in the hippocampus and cortex after SAH. Hippocampal neuronal loss is associated with memory decline after SAH.
46	Hu et al., 2014	38	Sprague Dawley rats	80	SAH	Hydrocephalus after SAH contributes to learning and memory deficits.

	Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
47	Leblanc et al., 2016	unclear	C57BL/6 mice	70	SAH	Deferoxamine, an iron-chelator, decreases inflammation and mitochondrial superoxide anion production after SAH, improving memory deficits. Thus, iron overload and neuroinflammation may play a role in memory decline after SAH.
48	Kagerbauer et al., 2019	89	Sprague Dawley rats	60	SAH	Cognitive performance after SAH is worse in male animals, and also influenced by higher anxiety levels in males.
49	Suda et al., 2015	110	Long Evans rats	80	IPH	Bone marrow-derived mononuclear cells reduce neurotrophil infiltration, number of inducible nitric oxide synthase-positive cells, and the expression of inflammatory-related signaling, reducing memory decline after ICH. Neuroinflammation play a role in memory decline after ICH.
50	Zheng et al., 2019	26	Sprague Dawley rats	60	IPH	Exercise training improves spatial memory in ICH via down-regulating NR1 and NR2B expression in CA3 region of hippocampus. Activation of NMDAR, a glutamate receptor, after ICH caused damage to nerve cells and cognitive impairment.
51	Cheon et al., 2015	60	Sprague Dawley rats	40	IPH	Decreased neuroplasticity and reduced expression of GAP-43 contribute to cognitive decline after ICH.
52	Okada et al., 2019	42	Sprague Dawley rats	60	SAH	Fibroblast growth factor 2 reduces memory deficits after SAH by reducing brain edema and neuronal apoptosis. Thus neuronal apoptosis and brain edema contribute to memory decline.
53	Chen TF et al., 2019	unclear	Wistar rats	20	SAH	Dental pulp stem cells alleviate cognitive deficits after SAH by improving microcirculation, alleviating neuroinflammation, and microglial activation. Thus neuroinflammation partially via IGF-1 plays a role in cognitive decline after SAH.
54	Liang et al., 2020	unclear	Sprague Dawley rats	80	IPH	Galactose lectin-9 (Gal-9) improves memory deficits after ICH by recuing microglial activation and inflammation. Thus, microglial activation, cell death and neuroinflammation contribute to memory deficits after ICH.
55	Lekic et al., 2010	76	Sprague Dawley rats	50	IPH	Melatonin reduces oxidative stress and alleviates memory decline after ICH. Oxidative stress and reactive oxygen species play a role in memory decline after ICH.
56	Li et al., 2017	150	Wistar rat	70	SAH	Hydrogen sulfide alleviates cognitive dysfunction after SAH by activating Akt/ERK-related antiapoptosis pathway. Apoptosis contributes to cognitive dysfunction after SAH.
57	Sasaki et al., 2016	70	Wilstar rats	70	SAH	SAH causes histologic damage in the medial prefrontal cortex, perirhinal cortex, and hippocampal CA1 regions, resulting in long term cognitive deficits.
58	Zhu et al., 2018	433	C57BL/6 mice	60	IPH	ICH causes microglia/macrophage activation, leading to cognitive dysfunction.
59	Xu et al., 2019a	395	Sprague Dawley rats	50	IPH	Sodium benzoate attenuates memory dysfunction after ICH via inhibiting neuronal apoptosis and reducing mitochondria-mediated oxidative stress via DJ-1/Akt/IKK/NFkB pathway. Hence, neuronal apoptosis and oxidative stress contribute to memory dysfunction after ICH.
60	Xu et al., 2019b	312	Sprague Dawley rats	70	SAH	Apelin-13 improves memory after SAH by suppressing microglia activation, preventing ER stress from overactivation, and reducing oxidative stress. Thus, (ER)-stress-associated inflammation and oxidative stress lead to memory deficits after SAH.
61	Xu et al., 2020	194	Sprague Dawley rats	70	SAH	Microglial activation and neutrophil infiltration contribute to memory decline after SAH.
62	Ling et al., 2020	100	C57BL/6 mice	40	IPH	Activation of M1 glutamatergic neurons improves cognition after ICH by attenuating mitochondrial dysfunction. Mitochondrial dysfunction plays a role in cognitive deficits after ICH.
63	Hu et al., 2018	77	Sprague Dawley rats	50	SAH	Brain edema and neuronal apoptosis contribute to long term memory dysfunction after SAH.

Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
64	Zhou et al., 2019	108	C57BL/6 Mice	60	SAH	Platelet-derived growth factor receptor b alleviates memory dysfunction after SAH by improving synaptic recovery. Loss of synapsis contributes to memory decline after SAH.
65	Qu et al., 2019	275	C57BL/6 mice	50	IPH	Mitochondrial dysfunction-mediates oxidative stress contributes to memory dysfunction after ICH.
66	Tan et al., 2019	195	Sprague Dawley rats	50	IPH	Luteolin alleviates brain edema and ameliorates memory dysfunction after ICH via activation of the p62-Keap1-Nrf2 pathway. Neuronal oxidative stress is involved in memory dysfunction after ICH.
67	Sun et al., 2013	112	Sprague Dawley rats	40	SAH	Tamoxifen attenuates TLR4/NF-kappaB-mediated inflammatory response in SAH and reduces cognitive dysfunction. Results support the idea that neuroinflammation contributes to memory impairment after SAH.
68	Ding et al., 2020	unclear	CD-1 mice	70	IPH	Annexin A1 improves memory function after ICH by attenuating neuroinflammation. Neuroinflammatory mechanisms contribute to memory dysfunction after ICH.
69	Wang et al., 2018	90	C57BL/6 mice	70	IPH	Sparsolonin attenuates LPS-induced inflammatory response and brain edema in ICH. Inflammation and brain edema contribute to memory impairment after ICH.
70	Guo et al., 2017	30	Sprague Dawley rats	50	IPH	ICH impairs spatial learning and memory and the mechanism may be related to decreased neuronal plasticity due to decreased cerebral expression of BDNF (brain derived neurotropic factor) and NGB (neuroglobin).
71	Kuramoto et al., 2019	30	C57BL/6 mice	70	IPH	Neuroinflammation leads to memory impairment after ICH and human adipose derived stem cells reduce inflammation and memory deficits.
72	Oyang et al., 2019	60	Sprague Dawley rats	20	IPH	Neuroinflammation contributes to cognitive deficits in ICH and Haemin was found to reduce inflammation and neuronal apoptosis, thus improve cognition.
73	Qin et al., 2019	70	Sprague Dawley rats	50	SAH	Deferoxamine reduces neuronal cell death and ameliorated cognitive function after SAH. Neuronal apoptosis and iron overload may a play a role in memory deficits after SAH.
74	Xie et al., 2015	210	Sprague Dawley rats	40	SAH	Albumin reduces neuronal apoptosis and blood brain barrier disruption and alleviates cognitive deficits after SAH. Neuronal apoptosis and blood brain barrier leakage contribute to cognitive deficits after SAH.
75	Liu et al., 2019	234	Sprague Dawley rats	60	IPH	Neuronal apoptosis contributes to cognitive dysfunction following ICH.
76	Liu et al., 2015	80	Sprague Dawley rats	40	SAH	Dimethylfumarate alleviates cognitive dysfunction after SAH by inhibiting inflammatory response and oxidative stress. Inflammation and oxidative stress lead to cognitive deficits in SAH.
77	Liu et al., 2014	100	Sprague Dawley rats	60	SAH	Autophagy pathway is activated in SAH and plays a beneficial role in alleviating cognitive dysfunction.
78	Yang et al., 2015b	40	C57BL/6 mice	50	IPH	Microglia/macrophages activation induced by ICH is responsible for the spatial memory deficit.
79	Yang et al., 2015a	56	C57BL/6 mice	40	IPH	Cell apoptosis in dentate gyrus of hippocampus in ICH contributes to memory dysfunction.
80	Dong et al., 2013	72	Sprague Dawley rats	60	SAH	SAH leads to hippocampal apoptosis and subsequent memory deficits.
81	Han et al., 2018	16	Wistar rats	80	IPH	Multipotent mesenchymal stromal cells improve cognition after ICH by promoting angiogenesis and neurogenesis. Neuronal apoptosis contributes to cognitive deficits after ICH.
82	Liu et al., 2018	234	Sprague Dawley rats	70	IPH	Lithium chloride improves glutamate-mediated excitotoxicity-induced cognitive deficits after ICH. Glutamate-mediated excitotoxicity and neuronal death contribute to cognitive deficits after ICH.

Study, Year (Reference)	Total Animals (n)	Species	Quality Assessment Score (%)	Type of ICH	Description
83	Chen et al., 2014	48	Sprague Dawley rats	40	IVH	Brain edema and oxidative stress lead to memory impairment after IVH.
84	Wang et al., 2013a	209	Sprague Dawley rats	70	IPH	Neuronal cell death and neuroinflammation contribute to memory deficits after ICH.
85	Li et al., 2018	60	Sprague Dawley rats	50	SAH	SNAP25 blocks inflammation, reduces apoptosis, and promotes neuroplasticity after SAH, alleviating cognitive deficits. Neuronal cell death, inflammatory responses, and reduced neuroplasticity contribute to cognitive dysfunction in SAH.
86	Qi et al., 2017	157	Sprague Dawley rats	60	IVH	Hydrocephalus, blood brain permeability and brain edema contribute to memory deficits after IVH. Curcumin reverses these effects.
87	Wang et al., 2014	120	Sprague Dawley rats'	60	SAH	Brain edema, oxidative stress, and neuronal apoptosis contribute to memory impairment after SAH.
88	Wang et al., 2013b	80	Sprague Dawley rats	60	SAH	Inflammation, oxidative stress and neuronal apoptosis contribute to memory impairment after SAH. Melatonin reverses these effects.
89	Guo et al., 2016	238	Sprague Dawley rats	40	SAH	Lipoxin A4 reduces inflammation and improves memory after SAH. Inflammatory response contributes to memory deficits after SAH.
90	Yang et al., 2019	unclear	ICR mice	60	IPH	Microglial activation, neuronal cell loss and iron overload contribute to cognitive dysfunction after ICH.

Abbreviations: ICH, intracranial hemorrhage; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

Table 3

Risk of bias summary at individual study level.

	Study, Year (Reference)	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation to the different groups adequately concealed during?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Total score (%)
1	Tariq et al, 2010	+	+	?	?	+/?	?	+/?	−	+	+	50
2	Chen et al, 2019	+	+	?	?	+/?	+	+/?	+	+	+	70
3	Jiang et al, 2017	+	+	?	?	+/?	?	+/?	+	+	+	60
4	Altermann et al, 2017	?	+	?	?	+/?	?	+/?	−	+	+	40
5	An et al, 2017	+	+	?	?	?	?	?	+	+	+	50
6	Luo et al, 2018	+	+	?	?	?	?	?	+	+	+	50
7	Tosun et al, 2015	+	+	?	?	+/?	?	+/?	+	+	+	60
8	Imperatore et al, 2000	+	+	?	?	?	?	?	+	+	+	50
9	Jiang et al, 2018	+	+	?	?	+	?	+	+	+	+	70
10	Feng et al, 2014	+	+	?	?	+/?	?	+/?	+	+	+	60
11	Ke et al, 2020	+	+	?	?	+	?	+	+	+	+	70
12	Liu et al, 2017	+	+	?	?	+	?	+	+	+	+	70
13	Chung et al, 2020	+	+	?	?	+	+/?	+	+	+	+	75
14	Feng et al, 2016	+	+	?	?	?	?	?	−	+	+	40
15	Wu et al, 2020	+	+	?	?	+/?	?	+/?	+	+	+	60
16	Shi et al, 2019	+	+	?	?	+	?	+	−	+	+	60
17	Zhou et al, 2011	+	+	?	?	?	?	?	+	+	+	50
18	Chen et al, 2013	+	+	?	?	+/?	?	+/?	−	+	+	50

	Study, Year (Reference)	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation to the different groups adequately concealed during?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Total score (%)
19	Wang G et al, 2018	+	+	?	?	+	+	+	+	+	+	80
20	Shen et al, 2015	+	+	?	?	+	?	+	+	+	+	70
21	Shan et al, 2019	+	+	?	?	+	?	+	+	+	+	70
22	Suh et al, 2011	+	+	?	?	?	?	?	+	+	+	50
23	Duan et al, 2020	+	+	?	?	+/?	?	+/?	+	+	+	60
24	Huang and Jiang, 2019	+	+	?	?	+/?	?	+/?	−	+	+	50
25	Peng et al, 2019	+	+	?	?	+/?	?	+/?	+	+	+	60
26	Provencio et al, 2016	?	+	?	?	?	?	?	+	+	+	40
27	Zhang et al, 2020	+	+	?	?	+/?	?	+/?	+	+	+	60
28	Tao et al, 2020	+	+	?	?	+	?	+	+	+	+	70
29	Raj dev et al, 2020	+	+	?	?	?	?	?	+	+	+	50
30	Ma et al, 2018	+	+	?	?	+/?	?	+/?	+	+	+	60
31	Kamal et al, 2020	?	+	?	?	+	+	+	+	+	+	70
32	Hwang et al, 2013	+	+	?	?	?	?	?	?	+	+	40
33	Wu et al, 2017	+	+	?	?	?	?	?	+	+	+	50
34	Sun et al, 2018	+	+	?	?	?	?	?	+	+	+	50
35	Zhou et al, 2018	+	+	?	?	?	?	?	+	+	+	50
36	Ma et al, 2016	+	+	?	?	+/?	?	+/?	+	+	+	60
37	Del Bigio et al, 1999	?	+	?	?	+/?	?	+/?	+	+	?	40

	Study, Year (Reference)	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation to the different groups adequately concealed during?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Total score (%)
38	Garrett et al, 2009	+	+	?	?	+/?	?	+/?	+	+	+	60
39	Rynkowski et al, 2009	+	+	?	?	+	?	+	+	+	+	70
40	Li et al, 2016	+	+	?	?	+/?	?	+/?	+	+	+	60
41	Singh et al, 2017b	+	+	?	?	?	?	?	+	+	+	50
42	Singh et al, 2017a	+	+	?	?	?	?	?	+	+	+	50
43	Krafft et al, 2017	?	+	?	?	+/?	?	+/?	–	+	+	40
44	Fu et al, 2020	+	+	?	?	+	?	+	+	+	+	70
45	Sherchan et al, 2011	+	+	?	?	?	?	?	+	+	+	50
46	Hu et al, 2014	+	+	?	?	+	+	+	+	+	+	80
47	Leblanc et al, 2016	+	+	?	?	+	?	+	+	+	+	70
48	Kagerbauer et al, 2019	?	+	?	?	+/?	+	+/?	+	+	+	60
49	Suda et al, 2015	+	+	?	?	+	+	+	+	+	+	80
50	Zheng et al, 2019	+	+	?	?	+/?	?	+/?	+	+	+	60
51	Cheon et al, 2015	+	+	?	?	?	?	?	?	+	+	40
52	Okada et al, 2019	+	+	?	?	+/?	?	+/?	+	+	+	60
53	Chen TF et al, 2019	?	+	?	?	?	?	?	?	+	?	20

	Study, Year (Reference)	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation to the different groups adequately concealed during?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Total score (%)
54	Liang et al, 2020	+	+	?	?	+	+	+	+	+	+	80
55	Lekic et al, 2010	+	+	?	?	+/?	?	+/?	?	+	+	50
56	Li et al, 2017	+	+	?	?	+/?	+	+/?	+	+	+	70
57	Sasaki et al, 2016	+	+	?	?	+	?	+	+	+	+	70
58	Zhu et al, 2018	?	+	?	?	+	?	+	+	+	+	60
59	Xu et al, 2019a	+	+	?	?	?	?	?	+	+	+	50
60	Xu et al, 2019b	+	+	?	?	+	?	+	+	+	+	70
61	Xu et al, 2020	+	+	?	?	+	?	+	+	+	+	70
62	Ling et al, 2020	+	+	?	?	?	?	?	−	+	+	40
63	Hu et al, 2018	+	+	?	?	+/?	?	+/?	−	+	+	50
64	Zhou et al, 2019	+	+	?	?	+/?	?	+/?	+	+	+	60
65	Qu et al, 2019	+	+	?	?	+/?	?	+/?	?	+	+	50
66	Tan et al, 2019	+	+	?	?	+/?	?	+/?	?	+	+	50
67	Sun et al, 2013	+	+	?	?	?	?	?	?	+	+	40
68	Ding et al, 2020	+	+	?	?	+	?	+	+	+	+	70
69	Wang et al, 2018	+	+	?	?	+	?	+	+	+	+	70
70	Guo et al, 2017	+	+	?	?	?	?	?	+	+	+	50
71	Kuramoto et al, 2019	+	+	?	?	+	?	+	+	+	+	70
72	Oyang et al, 2019	?	+	?	?	?	?	?	−	+	?	20
73	Qin et al, 2019	?	+	?	?	+/?	?	+/?	+	+	+	50

	Study, Year (Reference)	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation to the different groups adequately concealed during?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Total score (%)
74	Xie et al, 2015	+	+	?	?	+/?	?	+/?	−	+	?	40
75	Liu et al, 2019	+	+	?	?	+/?	?	+/?	+	+	+	60
76	Liu et al, 2015	?	+	?	?	?	?	?	+	+	+	40
77	Liu et al, 2014	+	+	?	?	+/?	?	+/?	+	+	+	60
78	Yang et al, 2015b	?	+	?	?	+/?	?	+/?	+	+	+	50
79	Yang et al, 2015a	?	+	?	?	?	?	?	+	+	+	40
80	Dong et al, 2013	+	+	?	?	?	+	?	+	+	+	60
81	Han et al, 2018	+	+	?	?	+	+	+	+	+	+	80
82	Liu et al, 2018	+	+	?	?	+	?	+	+	+	+	70
83	Chen et al, 2014	?	+	?	?	?	?	?	+	+	+	40
84	Wang et al, 2013a	+	+	?	?	+	?	+	+	+	+	70
85	Li et al, 2018	+	+	?	?	+/?	?	+/?	?	+	+	50
86	Qi et al, 2017	+	+	?	?	+/?	?	+/?	+	+	+	60
87	Wang et al, 2014	+	+	?	?	+/?	?	+/?	+	+	+	60
88	Wang et al, 2013b	+	+	?	?	+/?	?	+/?	+	+	+	60
89	Guo et al, 2016	?	+	?	?	+/?	?	+/?	−	+	+	40
90	Yang et al, 2019	?	+	?	?	+	?	+	+	+	+	60

Risk of bias summary assessment of each study. Results are sorted alphabetically by the first initial of first author. Abbreviations: green (+) and orange (+/?) low risk of bias; red (−) high risk of bias; yellow (?) unclear risk of bias. Green (+) were given 10 points if all variables met the criteria for low bias, and orange (+/?) were given 5 points if only some variables were met.