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Prognostic significance of leukoaraiosis in intracerebral hemorrhage: A meta-analysis

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ABSTRACT

Background: Patients with intracerebral hemorrhage (ICH) have high disability and mortality. Leukoaraiosis refers to the diffuse abnormalities of white matter on neuroimaging, which has been suggested to be with poor outcome in patients with ICH. This meta-analysis was performed to summarize the current evidence on the prognostic significance of leukoaraiosis in ICH patients.

Methods: Databases were searched for published studies about leukoaraiosis and prognosis in patients with ICH. Data from eligible studies were extracted. Odds ratios (ORs) and their 95% confidence intervals (CIs) from each study were combined with DerSimonian–Laird method and random effect model for quantitative analysis. Begg's funnel plot was adopted to assess the publication bias.

Results: A total of nine studies with 4948 patients were finally included in this meta-analysis. Six studies reported functional outcome, two studies reported mortality, and another study reported both functional outcome and mortality. The meta-analysis showed that leukoaraiosis was significantly associated with worse functional outcome in patients with ICH (OR = 1.40, 95%CI 1.17–1.68, $P < .001$). In addition, leukoaraiosis was also significantly associated with higher mortality in patients with ICH (OR = 1.59, 95%CI 1.21–2.08, $P = .001$).

Conclusions: Leukoaraiosis is significantly associated with both worse functional outcome and higher mortality in patients with ICH. Leukoaraiosis can be a useful imaging marker for predicting outcome in patients with ICH.

1. Introduction

Patients with intracerebral hemorrhage (ICH) have high disability and mortality [1]. Several demographic and clinical factors have been shown as prognostic factors in ICH patients, such as age and Glasgow Coma Scale score. [2,3] Moreover, some findings based on neuroimaging have been suggested to be associated with outcome in patients with ICH, such as hematoma volume, hematoma location, perihematomal edema and intraventricular hemorrhage [4–7]. Leukoaraiosis refers to the diffuse abnormalities of white matter on neuroimaging, which is also called white matter lesions or white matter hyperintensities in some publications [8–10]. Leukoaraiosis has been demonstrated as a prognostic factor in patients with ischemic stroke [11,12]. According to previous studies, obvious leukoaraiosis can be found in 40–50% patients with ICH [13,14]. Previous studies have also suggested that leukoaraiosis is associated with poor outcome in patients with ICH [14–16]. For the better understanding of its prognostic role in ICH patients, this meta-analysis was performed to summarize the current evidence.

2. Materials and methods

2.1. Literature search

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched Pubmed, Embase, Scopus, CNKI, VIP, and Wanfang for published studies about leukoaraiosis and prognosis in patients with ICH on September 23, 2018. The following search strategy was adopted: (intracerebral hemorrhage OR brain hemorrhage OR cerebral hemorrhage OR intracranial hemorrhage) AND (leukoaraiosis OR white matter lesions OR white matter hyperintensities) AND (outcome OR prognosis OR mortality OR death OR survival). Limits for language and publication year were not set in search strategy. Studies in the reference lists of included studies were also screened. After removal of duplications, titles and abstracts of records were screened by two authors

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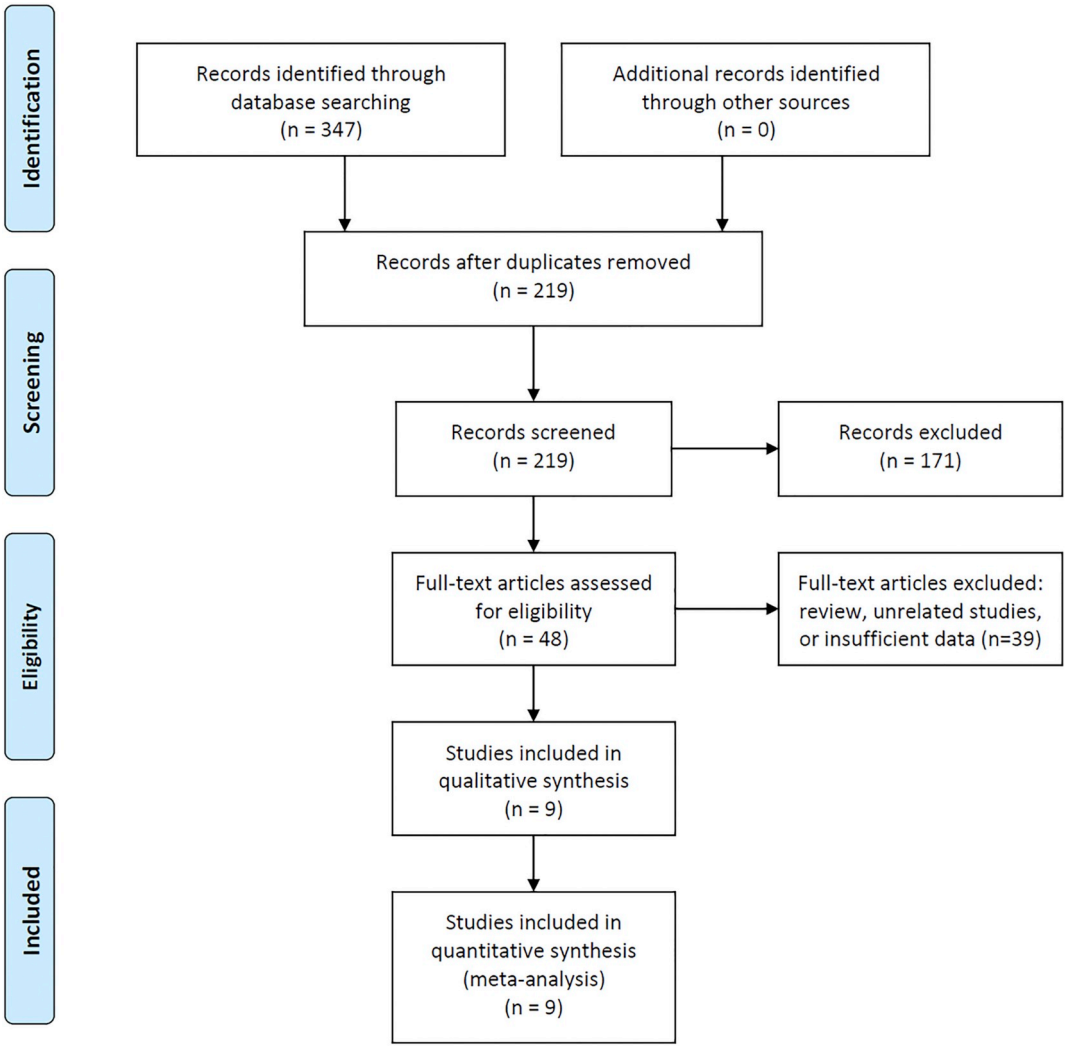

Fig. 1. Flow chart of study selection. A total of nine studies with 4948 patients were finally included in this meta-analysis.

independently and inclusion of the potential studies depended on the screening of the full papers by two authors. Any inconsistency was solved by discussion between two authors.

2.2. Selection criteria

We only included the studies which met the following inclusion criteria: 1) Original publications about leukoaraiosis and prognosis in patients with ICH; 2) Leukoaraiosis was detected by computed tomography (CT) or magnetic resonance imaging (MRI); 3) Sufficient data for quantitative analysis. The studies were excluded if: 1) Case report or review; 2) About secondary intracerebral hemorrhage, subarachnoid hemorrhage or ischemic stroke; 3) Insufficient data for quantitative analysis. If overlapped data were found in different studies, only the study with most patients were included. (Fig. 1).

2.3. Data collection

Two authors extracted data from included studies independently using a standardized form for data collection. The following information in each study was collected: publication year, design of study, country of study, number of included patients, mean age of included patients, percentage of male patients, hematoma location, mean hematoma volume, percentage of intraventricular hemorrhage, neuroimaging for detecting leukoaraiosis, assessment method for leukoaraiosis, definition of outcome and time points for follow-up. Adjusted or unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were extracted for quantitative analysis. Adjusted ORs and their 95% CIs in multivariate analysis were preferred if possible. Quality of included studies was evaluated by the authors using Newcastle-Ottawa scale [17].

2.4. Data analysis

ORs and 95%CIs from each study were obtained and combined following Tierney et al.'s method [18]. Cochran's Q test and Higgins I^2 were used to evaluate the heterogeneity among included studies and $I^2 > 50\%$ was defined as substantial heterogeneity [19]. DerSimonian–Laird method and random effect model were adopted to pool ORs and 95%CIs [20]. Subgroup analysis was conducted to explore the potential confounding factors. Stability of meta-analysis was assessed in sensitivity analysis. Begg's funnel plot was adopted to assess the publication bias [21]. If $P < .05$, statistical significance was considered. Data analysis was completed with STATA 12.0 (STATA, College Station,

Table 1
Characteristics of included studies.

Study	Country	Period	Study design	n	Mean age	Male, %	ICH location	Mean ICH volume, ml	IVH, %	Imaging	Assessment method	Outcome	Definition of poor outcome	Follow-up time	NOS score
Lee (2010)	Korea	2002–2004	PS	1321	60.3	54.9%	SH, IH	10.4	29.9%	CT	Van Swieten Scale	Mortality	Death	30 days	8
Won (2010)	Korea	2003–2007	RS	238	59.9	60.5%	SH	26.0	32,4%	CT	Van Swieten Scale	FO	GOS < 4	90 days	6
Wang (2012)	China	2010–2011	RS	118	67.5	60.2%	SH	26.7	39.0%	CT	Van Swieten Scale	FO	GOS < 4	90 days	5
Caprio (2013)	USA	2006–2011	PS	95	63.9	49.5%	SH	8.8	NA	MRI	Fazekas Scale	FO	mRS > 3	28 days	7
Tveiten (2013)	Norway	2005–2009	RS	134	75.3	55.2%	SH, IH	17.5	37.3%	CT	Van Swieten Scale	Mortality	Death	30 days	6
Sato (2016)	Australia	2008–2012	PS	2069	63.7	62.6%	SH	11.2	28.9%	CT	Van Swieten Scale	FO	mRS > 2	90 days	8
Kidwell (2017)	USA	2010–2013	PS	600	60.8	55.5%	SH, IH	9.1	34.4%	MRI	Fazekas Scale	FO	mRS > 3	90 days	8
Sykora (2017)	Germany	2005–2007	PS	262	67.3	NA	SH, IH	18.1	28.6%	CT	Van Swieten Scale	Mortality, FO	Death, mRS > 2	90 days	6
Lioutas (2018)	USA	2007–2014	RS	111	72.0	56.8%	SH	20.7	42.3%	MRI	Fazekas Scale	FO	mRS > 2	90 days	7

n = number of patients; NOS = Newcastle–Ottawa Scale; PS = Prospective study; SH = supratentorial hematoma; IH = infratentorial hematoma; CT = Computed tomography; RS = Retrospective study; FO = Functional outcome; GOS = Glasgow Outcome Scale; MRI = Magnetic resonance imaging; mRS = modified Rankin Scale.

Texas).

3. Results

A total of nine studies with 4948 patients met the selection criteria and were finally included in this meta-analysis [14–16,22–27]. (Fig. 1) Five studies were prospective studies and another four were retrospective. The sample size of each study ranged from 95 to 2069. Leukoaraiosis was determined by CT and Van Swieten Scale in six studies and by MRI and Fazekas Scale and in another three studies. Six studies reported functional outcome, two studies reported mortality, and another study reported both functional outcome and mortality. In seven studies providing results of functional outcome, modified Rankin Scale (mRS) was used in five studies and Glasgow Outcome Scale (GOS) was used in another two studies. Follow-up time ranged from 28 days to 90 days. (Table 1).

3.1. Leukoaraiosis and functional outcome

The meta-analysis of seven studies about functional outcome showed that leukoaraiosis was significantly associated with worse functional outcome in patients with ICH (OR = 1.40, 95%CI 1.17–1.68, $P < .001$). Substantial heterogeneity was found in these studies ($I^2 = 52.8\%$). (Fig. 2) Subgroup analysis suggested country, study design, mean hematoma volume, imaging category, and method of outcome assessment could influence the results of the meta-analysis. (Table 2) In three studies in USA, leukoaraiosis was not shown to be significantly associated with worse functional outcome (OR = 1.24, 95%CI 0.96–1.60, $P = .093$). However, leukoaraiosis had significant association with worse function outcome in the other four studies in other countries (OR = 1.51, 95%CI 1.23–1.85, $P < .001$). In four prospective studies, leukoaraiosis was significantly associated with worse functional outcome (OR = 1.30, 95%CI 1.12–1.50, $P = .001$), but no significant association was found in another three retrospective studies (OR = 1.77, 95%CI 0.81–3.86, $P = .149$). There were four studies with the mean hematoma volume < 20 ml, and the significant association between leukoaraiosis and worse functional outcome was found (OR = 1.30, 95%CI 1.12–1.50, P = .001). However, no significant association was found in the other three studies with the mean hematoma volume > 20 ml (OR = 1.77, 95%CI 0.81–3.86, P = .149). In four studies using CT for assessment, leukoaraiosis was significantly associated with worse functional outcome (OR = 1.51, 95%CI 1.23–1.85, $P < .001$). However, no significant association was found in studies using MRI (OR = 1.24, 95%CI 0.96–1.60, $P = .093$). Five studies adopted mRS score to assess functional outcome and showed the significant association between leukoaraiosis and functional outcome (OR = 1.27, 95%CI 1.12–1.45, $P < .001$). However, leukoaraiosis was not significantly associated with functional outcome in another two studies using GOS score (OR = 2.44, 95%CI 0.78–7.65, $P = .126$). Sensitivity analysis showed the stability of this meta-analysis. (Fig. 3) Funnel plot did not show obvious publication bias. (Fig. 4).

3.2. Leukoaraiosis and mortality

The meta-analysis of three studies reporting mortality showed that leukoaraiosis was significantly associated with higher mortality in patients with ICH (OR = 1.59, 95%CI 1.21–2.08, $P = .001$). No substantial heterogeneity was found in these studies ($I^2 = 33.8\%$). (Fig. 5) Subgroup analysis suggested study design could influence the results of the meta-analysis. (Table 3) In two prospective studies, no significant association was found between leukoaraiosis and higher mortality (OR = 1.74, 95%CI 1.00–3.02, $P = .051$). However, leukoaraiosis was

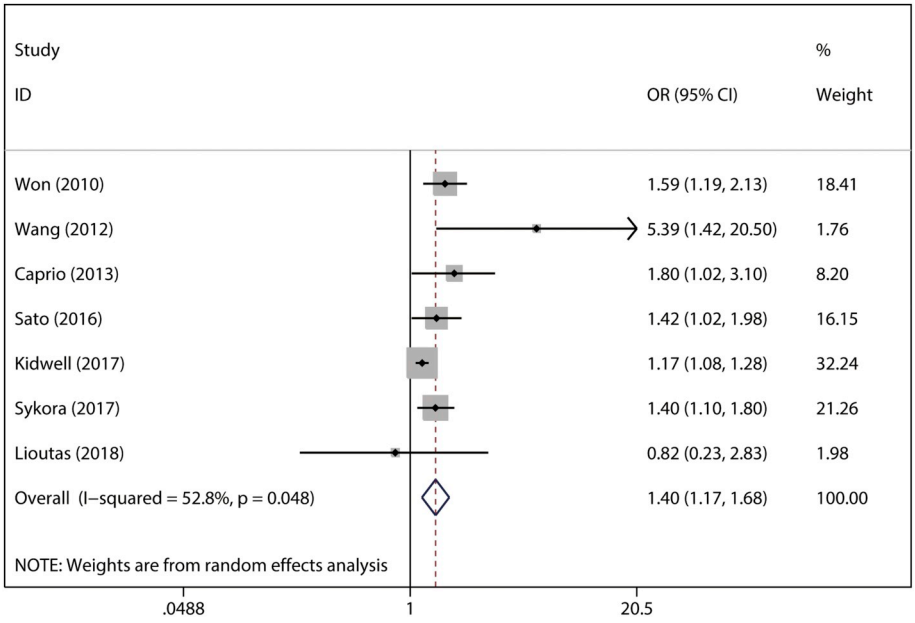

Fig. 2. Forest plot of studies about association between leukoaraiosis and functional outcome. Leukoaraiosis was significantly associated with worse functional outcome in patients with intracerebral hemorrhage (OR = 1.40, 95%CI 1.17–1.68, $P < .001$).

Table 2
Subgroup analysis of studies about leukoaraiosis and functional outcome.

Variables	n	I^2	OR	95% CI	P
Country					
USA	3	21.7%	1.24	0.96–1.60	0.093
Others	4	26.4%	1.51	1.23–1.85	< 0.001
Study design					
Prospective	4	35.7%	1.30	1.12–1.50	0.001
Retrospective	3	53.0%	1.77	0.81–3.86	0.149
Sample size					
≤300	5	23.9%	1.55	1.23–1.96	< 0.001
> 300	2	16.2%	1.20	1.06–1.37	0.005
ICH location					
SH&IH	2	43.2%	1.23	1.05–1.44	0.008
SH	5	18.3%	1.58	1.24–2.02	< 0.001
Mean ICH volume					
≤20 ml	4	35.7%	1.30	1.12–1.50	0.001
> 20 ml	3	53.0%	1.77	0.81–3.86	0.149
Imaging					
MRI	3	21.7%	1.24	0.96–1.60	0.093
CT	4	26.4%	1.51	1.23–1.85	< 0.001
Outcome assessment					
mRS	5	20.7%	1.27	1.12–1.45	< 0.001
GOS	2	67.3%	2.44	0.78–7.65	0.126
Follow-up time					
28 days	1	–	1.80	1.03–3.10	0.038
90 days	6	54.5%	1.37	1.14–1.65	0.001

n = number of studies; OR = odds ratio; CI = confidence interval; ICH = intracerebral hemorrhage; SH = supratentorial hematoma; IH = infratentorial hematoma; MRI = magnetic resonance imaging; CT = computed tomography; mRS = modified Rankin Scale; GOS = Glasgow Outcome Scale.

significantly associated with higher mortality in the other retrospective study (OR = 1.60, 95%CI 1.06–2.50, $P = .032$). Sensitivity analysis showed the result of this meta-analysis became insignificant when omitting the study by Tveiten et al. (Fig. 6) Funnel plot did not show obvious publication bias. (Fig. 7).

4. Discussion

This meta-analysis summarized the current evidence on the association between leukoaraiosis and outcome in patients with ICH. Based on nine studies with 4948 patients, this study showed that leukoaraiosis was significantly associated with both worse functional outcome (OR = 1.40, 95%CI 1.17–1.68, $P < .001$) and higher mortality (OR = 1.59, 95%CI 1.21–2.08, $P = .001$) in patients with ICH.

4.1. The role of leukoaraiosis in stroke

Leukoaraiosis is a common finding on neuroimaging, representing abnormal changes of brain white matter [28]. Van Swieten et al. reported a simple scale to assess leukoaraiosis on neuroimaging [29]. Another rating scale defined by Fazekas et al. was also widely adopted [30]. Several studies have shown the important role of leukoaraiosis in prognosis in ischemic stroke. The study by Henninger et al. showed that leukoaraiosis was related to larger infraction volume after occlusion of middle cerebral artery [31]. A retrospective study with 185 patients suggested that leukoaraiosis could be a predictor of worse functional outcome in ischemic stroke [32]. The study by Kim et al. found leukoaraiosis was associated with high risk of early recurrence of ischemic stroke [33]. Senda. et al. conducted a study including 520 patients and found leukoaraiosis was associated with rehabilitation of patients with ischemic stroke [12]. A meta-analysis showed that leukoaraiosis could increase the risk of ICH after intravenous thrombolysis in patients with ischemic stroke [34].

4.2. The association between leukoaraiosis and outcome in ICH

Since the association between leukoaraiosis and outcome in ischemic stroke has been reported in a number of previous studies, its

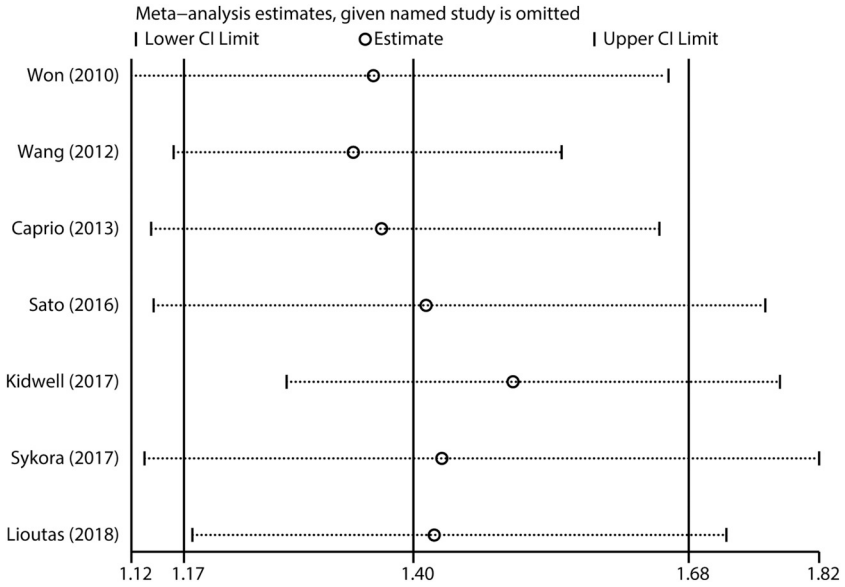

Fig. 3. Sensitivity analysis of studies about association between leukoaraiosis and functional outcome. The stability of this meta-analysis was proved.

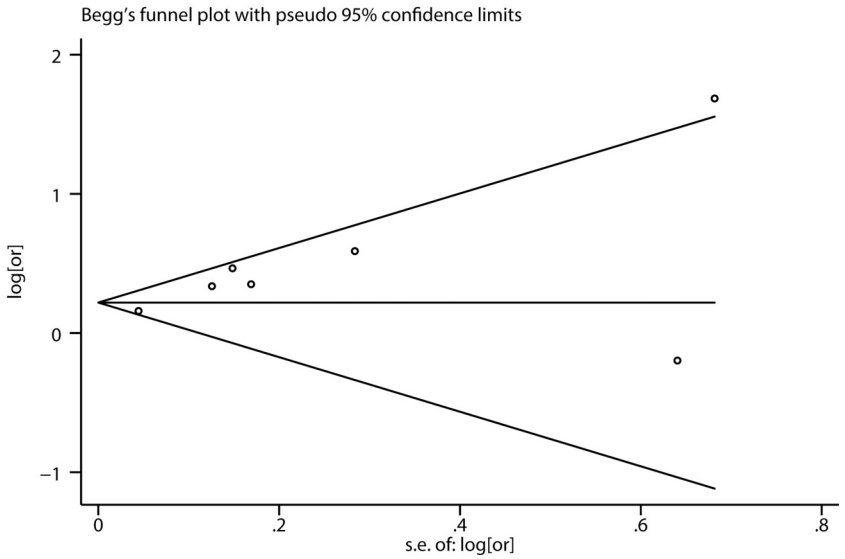

Fig. 4. Funnel plot of studies about association between leukoaraiosis and functional outcome. No obvious publication bias was found.

correlation with outcome in ICH has also caught the attention. Theoretically, leukoaraiosis is related to cerebral microangiopathy, which is a potential mechanism of ICH occurrence [22]. Moreover, leukoaraiosis also represents brain vulnerability [14]. Lee et al. first investigated the association between leukoaraiosis and mortality in a large cohort including 1321 patients with ICH and found leukoaraiosis was a predictor for mortality in these patients [14]. Won et al. explored the association between leukoaraiosis and functional outcome in 238 ICH patients and suggested leukoaraiosis could be independently related to poor functional outcome [22]. The study by Wang et al. confirmed the prognostic significance of leukoaraiosis in 118 Chinese patients with ICH [23]. Caprio et al. adopted MRI to assess leukoaraiosis in 95 ICH patients and found it was independently associated with unfavorable functional outcome [24]. The study by Tveiten et al. was the first European study on leukoaraiosis in ICH patients and suggested leukoaraiosis was significantly associated with mortality in 134 patients [25]. Using a cohort including 2069 patients, Sato et al. showed presence of severe leukoaraiosis was more frequent in ICH patients with worse outcome [15]. The study by Sykora et al. included 262 ICH patients and showed leukoaraiosis was independently associated with worse outcome [16]. However, in the study by Lioutas et al., no significant association was found between MRI-identified leukoaraiosis and functional outcome in 111 ICH patients [27]. Considering most of the previous studies have suggested its correlation with outcome, leukoaraiosis may be a prognostic factor in ICH patients. In addition, the variance among previous studies may be related to different sample size, study design, hematoma volume, and methodology of leukoaraiosis assessment. To summarize the

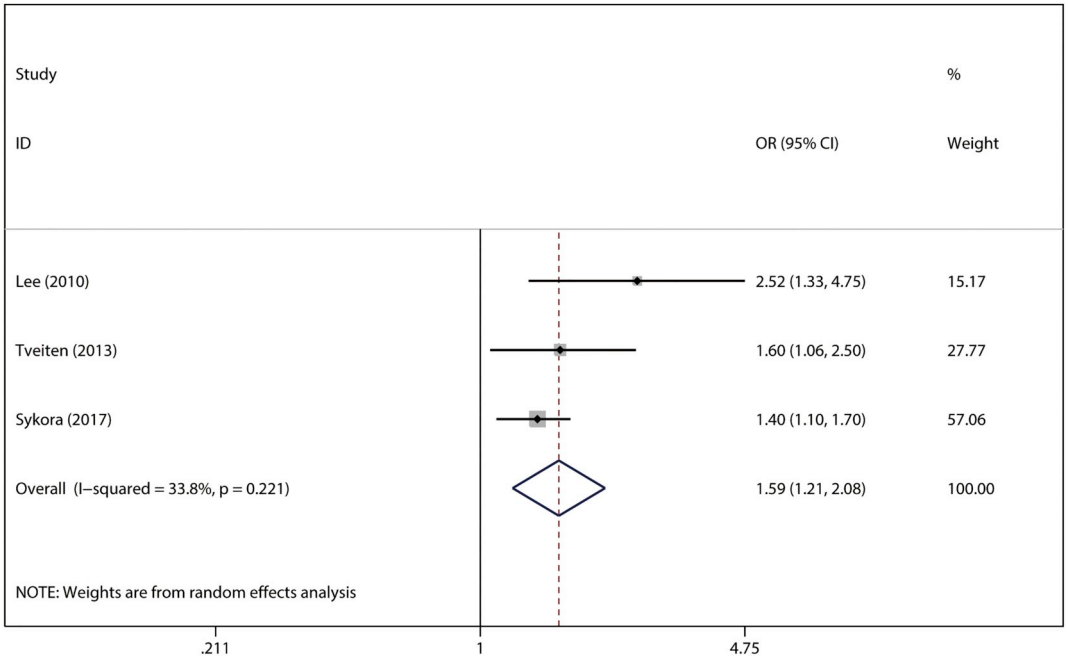

Fig. 5. Forest plot of studies about association between leukoaraiosis and mortality. Leukoaraiosis was significantly associated with higher mortality in patients with intracerebral hemorrhage (OR = 1.59, 95%CI 1.21–2.08, *P* = .001).

Table 3
Subgroup analysis of studies about leukoaraiosis and mortality.

Variables	n	I^2	OR	95% CI	P
Area					
Europe	2	0.0%	1.44	1.18–1.75	< 0.001
Asia	1	–	2.52	1.33–4.75	0.004
Study design					
Prospective	2	65.9%	1.74	1.00–3.02	0.051
Retrospective	1	–	1.60	1.06–2.50	0.032
Sample size					
≤300	2	0.0%	1.44	1.18–1.75	< 0.001
> 300	1	–	2.52	1.33–4.75	0.004
Follow-up time					
30 days	2	25.7%	1.88	1.23–2.89	0.004
90 days	1	–	1.40	1.13–1.74	0.002

n = number of studies; OR = odds ratio; CI = confidence interval; MRI = magnetic resonance imaging; CT = computed tomography; mRS = modified Rankin Scale; GOS = Glasgow Outcome Scale.

current evidence, we evaluated the association between leukoaraiosis and outcome in ICH patients using meta-analysis. The results of our study showed that leukoaraiosis was significantly associated with both worse functional outcome and higher mortality in ICH patients, which suggested that leukoaraiosis could be a useful imaging marker for predicting outcome in ICH patients.

4.3. Possible mechanism

The underlying mechanism of the association between leukoaraiosis and outcome in ICH patients is still unclear. Leukoaraiosis may represent the decreased connectivity and plasticity of brain, which influences the recovery after onset of ICH [35]. In addition, previous studies have shown that leukoaraiosis is related to cognitive impairment and dementia, which may have an impact on functional outcome in ICH patients [36,37]. Moreover, leukoaraiosis has association with other prognostic factors in ICH. Leukoaraiosis is more frequent in older patients and age is an important predictor of outcome in ICH patients [38,39]. In a retrospective study with 79 ICH patients, leukoaraiosis had correlation with larger hematoma volume and hematoma growth [13]. The study by Gioia et al. included 117 patients and found leukoaraiosis was correlated with ischemia after ICH [40]. Further studies are still necessary to determine the underlying mechanism of the prognostic role of leukoaraiosis in ICH patients.

4.4. Limitations

Several limitations should be noticed in this study. First of all, only nine studies met the selection criteria and were included in this meta-analysis, which limited the accuracy of this study. Second, substantial heterogeneity was found in included studies and subgroup analysis showed several potential confounding factors, such as country, study design, imaging category, hematoma volume, and method of outcome assessment, could be the sources of this heterogeneity. Moreover, only three studies reported the results of mortality and sensitivity analysis suggested the result of the meta-analysis was unstable, mainly due to the limited number of studies. Thus, the results of this meta-analysis should be confirmed by more original investigations.

4.5. Conclusions

This meta-analysis has shown that leukoaraiosis is significantly associated with both worse functional outcome and higher mortality in patients with ICH. Leukoaraiosis can be a useful imaging marker for predicting outcome in patients with ICH.

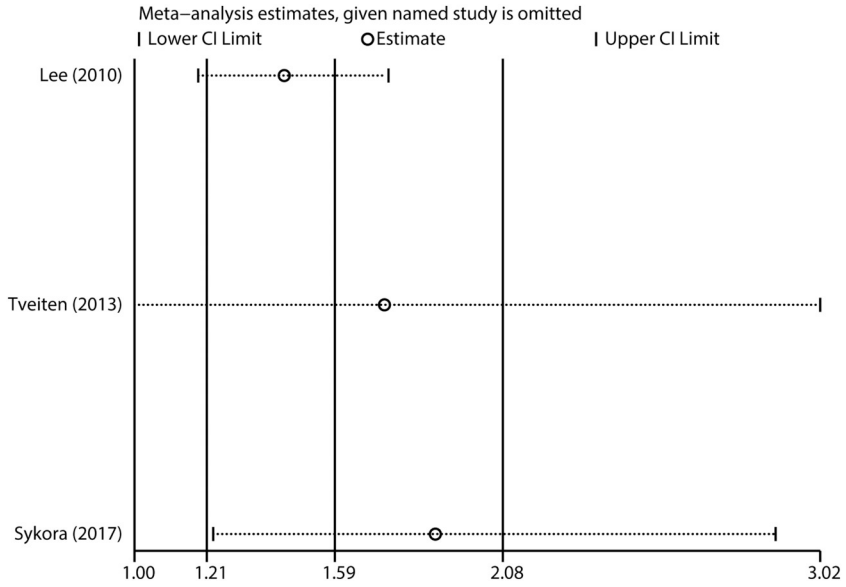

Fig. 6. Sensitivity analysis of studies association between leukoaraiosis and mortality. The result of this meta-analysis became insignificant when omitting the study by Tveiten et al.

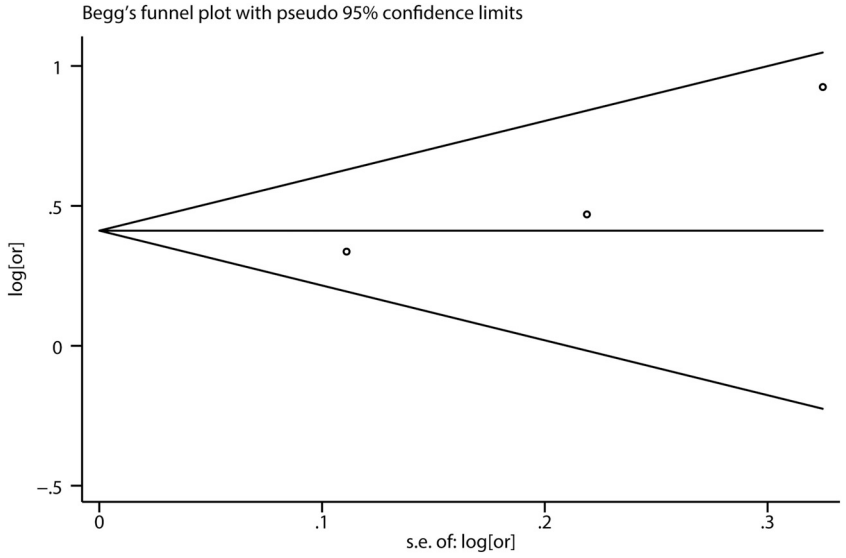

Fig. 7. Funnel plot of studies about association between leukoaraiosis and mortality. No obvious publication bias was found.

Conflicts of interest

None.

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