

Original Article

Association of leukoaraiosis and the risk of recurrent stroke: a meta-analysis

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Abstract: Stroke is a severe disability with high recurrence rate. Inconsistent results about the association between leukoaraiosis (LA) and risk of recurrent stroke exists. The meta-analysis was aimed to comprehensively evaluate the predicted role of LA for risk of stroke recurrence. Several databases were retrieved from their inception to June, 2015, using the strategies of Leukoaraiosis AND (stroke OR "Cerebral infarction") AND (recurrence OR recurrent OR relapse). Eligible studies were identified based on predefined inclusion criteria. Quality of the selected studies was assessed by the Newcastle-Ottawa Scale. Sensitive analysis and publication bias were also performed. Additionally, subgroup analysis stratified by different follow-up times (<5 years and ≥ 5 years) was conducted. All the statistical analyses were completed using Stata 11.0. The Relative Risk (RR) with corresponding 95% confidence interval (CI) was used as a measure of the effect size. Consequently, we included five studies in our meta-analysis, most of which were high-quality. No reverse results were detected via sensitive analysis, indicating the reliability of this meta-analysis. Moreover, no publication bias was observed (Egger's test: $t = -1.71$, $P = 0.185$). LA was significantly associated with the risk of stroke recurrence in two subgroups (<5 year: RR = 1.47, 95% CI, 1.27 to 1.70, $P < 0.001$; ≥ 5 years: RR = 1.26, 95% CI, 1.12 to 1.43, $P < 0.001$). LA could be used as a predictor for the risk of recurrent stroke. However, more studies with large sample size were required to confirm this finding.

Keywords: Leukoaraiosis, stroke recurrence risk, meta-analysis, prospective cohort study

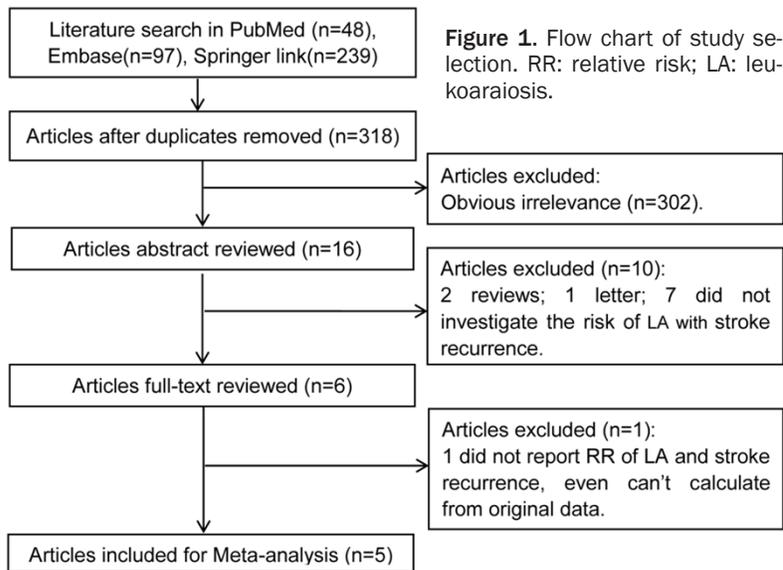
Introduction

Stroke has resulted in tremendous health problems and economic burdens worldwide in addition to cardiovascular disease. Though incidence of stroke has declined in recent years, approximate 795,000 individuals are estimated to experience the disability, and notably 23.3% of them are recurrent [1, 2]. Therefore, it is essential to improve the management of stroke and identify the predicted factors for recurrent stroke risk.

Leukoaraiosis (LA) is commonly deemed as an abnormal subcortical brain white matter on the Computed Tomography (CT) imaging [3]. LA is age-related and more frequently occurred in the elder patients than young [4, 5]. The degree of LA was tightly correlated with events of stroke. Previously, LA was proposed as an intermediate surrogate of stroke instead of a stroke risk factor, because LA shared several common

pathophysiological mechanisms with stroke [6]. Recently, increasing evidence has confirmed the role of LA as a predictor for the symptomatic intracerebral hemorrhage (sICH) after thrombolytic management for acute stroke patients, clinical outcome after ischemic stroke and the development of stroke recurrence [7-9]. However, the association between LA and the risk of stroke recurrence is controversial due to the heterogeneous characteristics of stroke, distinct methodology and different populations [10]. From the short-term perspective, a study indicates that LA could not predict the recurrent stroke risk within one year [11]. By contrast, a more recent study corroborates the predicted role of LA for the risk of 90-day's recurrent stroke [12]. The long-term recurrence is also concerned in other studies. For instance, Henon and colleagues reveal that LA could be used as a potent predictor of recurrent stroke risk within 3-years after stroke [13], while the follow-up time of patients in Ntaios's study is 10 years

Association of LA and recurrent stroke risk



[14]. However, due to that only a handful of studies involved the long-term period after stroke, there is not a consistent conclusion about the role of LA in the prediction of recurrent stroke risk. Several meta-analyses have comprehensively estimated the association between dementia and risk of recurrent stroke [15], or evaluated the lipid management for the prevention of stroke [16], but rarely assessed the predicted role of LA, which is more related to the stroke recurrence risk than dementia [13]. Therefore, we conducted this meta-analysis, and performed subgroup analysis stratified by the follow-up time (<5-years and \geq 5-years) to further explicate the association between LA and the risk of recurrent stroke.

Materials and methods

Search strategy

Studies were retrieved in the electronic databases such as PubMed, Embase and Springer link, with the strategy of Leukoaraiosis AND (stroke OR "Cerebral infarction") AND (recurrence OR recurrent OR relapse) up to June 27th, 2015. Manual bibliographic search was also applied for the studies published in paper version. Moreover, articles in reference list of the selected studies were also examined for additional eligible studies.

Selection criteria

The inclusion criteria for studies in the meta-analysis were: (1) they were prospective or ret-

rospective cohort studies; (2) the study compared the risk of recurrent stroke in patients with LA with those without LA (control group); (3) the Relative Risk (RR) with the corresponding 95% confidence interval (CI) in the comparison was available, or could be calculated basing on relevant data.

By contrast, the studies were excluded if they: (1) took healthy population as the objects; (2) was a reviewer, a letter or a comment; (3) contained insufficient data for statistical analysis.

Data extraction

After study selection by two independent individuals, the required data were abstracted according to a predefined standardized form, including the following information: first author name; publication time; region for the research; study type; age, follow-up time and recurrence rate of the patients. Discussion with a third investigator was required when disagreements existed.

Quality assessment of the included studies

The Newcastle-Ottawa Scale [17], which developed a strict marking criterion, was applied to evaluate the included studies' quality. Based on the 9-score system, a study attaining the score with more than 7, 4-6 or less than 4 was defined as high-, medium- or low-quality, respectively.

Statistical analysis

The Stata 11.0 software (STATA, College Station, TX, USA) was used to carry out the following statistical analyses. RR with the corresponding 95% CI was used as a measure of effect size to calculate the pooled results. Cochran-based Q statistical test and I^2 test were used to determine the heterogeneity across the studies [18]. If $P < 0.05$ and (or) $I^2 > 50\%$, substantial heterogeneity was indicated, and a random effects model was applied; otherwise, a fixed effects model was employed when there lacked obvious heterogeneity ($P \geq 0.05$, $I^2 \leq 50\%$).

Association of LA and recurrent stroke risk

Table 1. Characteristics of included studies

Study	Country	Duration of time	Design	Sample size, LA/NLA	age, LA/NLA	LA Measure	Recurrent	Follow-up time	events, LA/NLA
Kumral, 2015	Turkey	1998-2014	PCS	9522, 4810/4712	69±11 (30-97), 62±12 (38-95)	MRI	Medical records and neuroimaging results	1 year 5 years	218/127 516/404
Kim, 2014	Korea	2003-2011	RCS	1056/1322	70 (58-80)	MRI	Brain imaging	90 days	56/50
Podgorska, 2002	Poland	na	PCS	370, 65/305	72±12.7, 67±13.6	CT	Hospital diagnosis	1 year	6/24
Ntaios, 2015 (AF)	Greece	1992-2012	PCS	670, 116/554	80.0 (74.8-83.8), 75.0 (69.0-81.0)	CT or MRI	Hospital diagnosis	30 months*	22/106
Ntaios, 2015 (non-AF)	Greece	1992-2012	PCS	1222, 204/1018	72.0 (66.0-80.0), 68.0 (58.0-74.0)				49/174
Putaalaa, 2011	Finland	1994-2007	PCS	655, 50/605	40.0±8.0	MRI	Hospital diagnosis	8.3 years	9/63

AF/non-AF, participants were patients with and without atrial fibrillation; na, not available; PCS, prospective cohort study; RCS, retrospective cohort study; *median follow-up time; LA, Leukoaraiosis; NLA, no Leukoaraiosis; MRI, magnetic resonance imaging; CT, Computed Tomography.

Table 2. Methodological quality of cohort studies included in the meta-analysis¹

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor ²	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Kumral	☆	☆	☆	☆	☆	☆	☆	☆	8
Kim	☆	☆	☆	--	☆	☆	--	☆	6
Podgorska	☆	☆	☆	☆	☆	☆	--	☆	7
Ntaios	☆	☆	☆	☆	☆	☆	--	☆	7
Putaalaa	☆	☆	☆	☆	☆	☆	☆	☆	8

¹A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. ²A maximum of 2 stars could be awarded for this item.

Association of LA and recurrent stroke risk

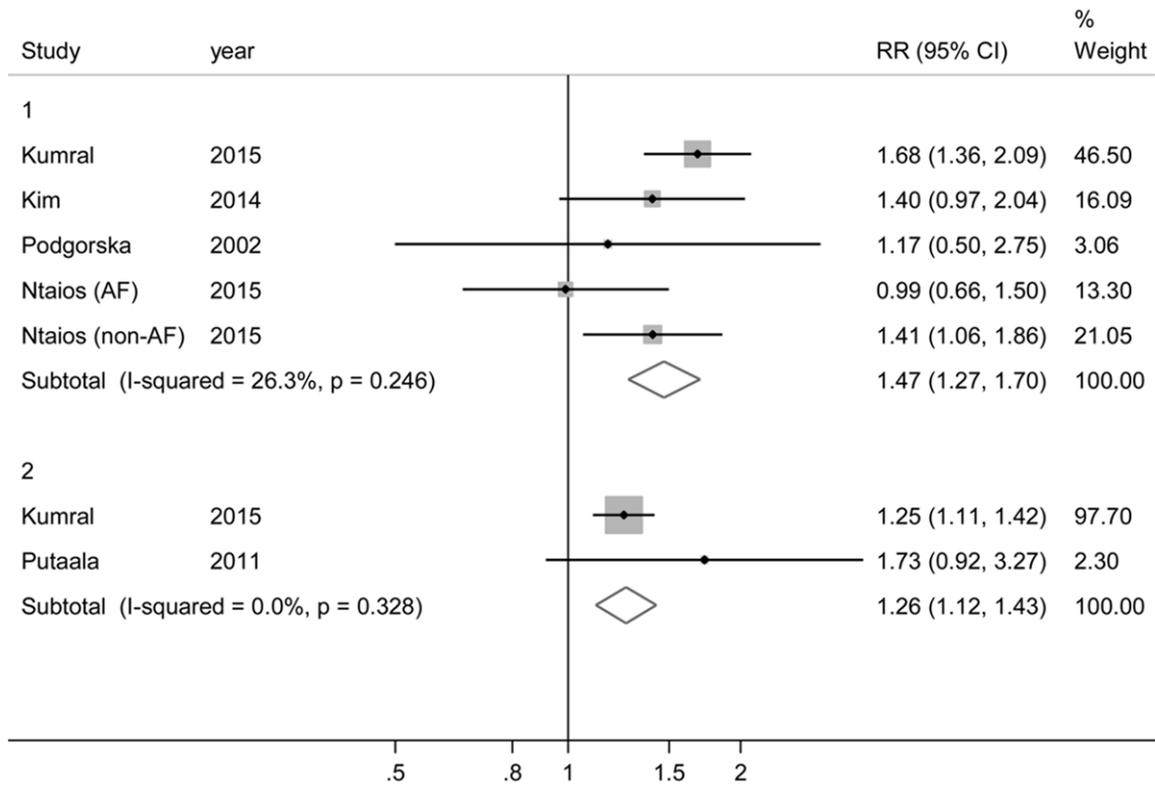


Figure 2. Relative Risk (RR) for the patients with leukoaraiosis (LA) vs patients without LA in the association with the risk of recurrent stroke. 1: Subgroup 1: follow-up time <5-years; 2: Subgroup 2: follow-up time ≥5-years. Squares denote the study-specific mean difference (MD) estimates, and size of square represents the study-specific weight. Horizontal lines indicate 95% confidence interval (CI). The diamond denotes the summary MDs with corresponding 95% CI.

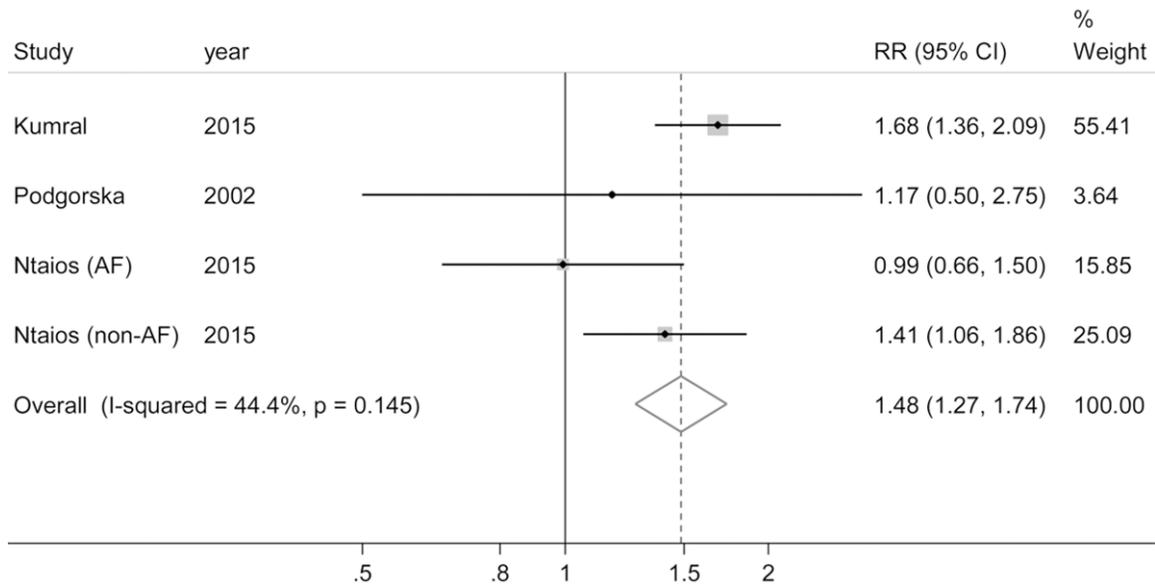


Figure 3. Sensitive analysis after the elimination of the retrospective cohort study. Squares denote the study-specific mean difference (MD) estimates, and the size of square represents the study-specific weight. Horizontal lines indicate 95% confidence interval (CI). The diamond denotes the summary MDs with corresponding 95% CI. RR: relative risk.

Association of LA and recurrent stroke risk

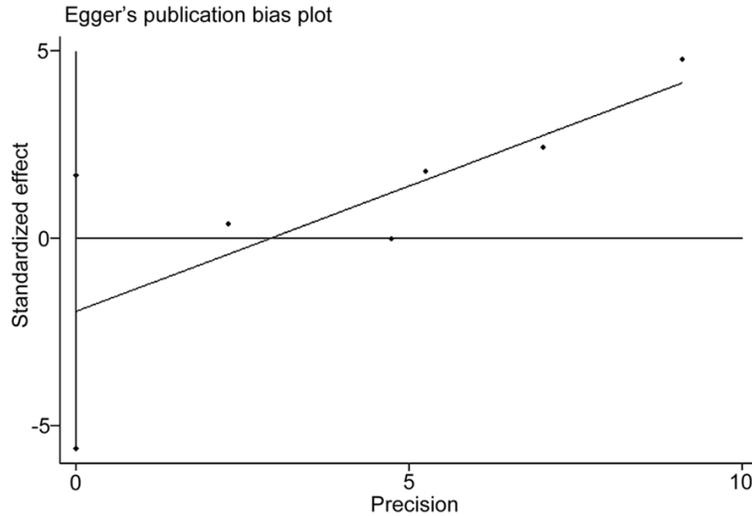


Figure 4. Publication bias of five included studies in the meta-analysis.

Sensitive analysis and publication bias

The Stata 11.0 software was also used for analyses in this section. Two strategies were adopted when we performed the sensitive analysis: (1) successively eliminated an individual study to examine whether the newly pooled result after removal of the study would be reverse from the original result, whereby to evaluate the reliability of the meta-analysis; (2) after eliminating the retrospective cohort study, all the prospective studies were pooled to assess whether significant differences were presented, compared with that before the elimination. Potential publication bias was examined via the Egger's test [19], and a significant bias was considered if $P < 0.05$.

Results

Study selection

Based on the aforementioned criteria, a group of 384 studies was selected after the preliminary screening (97 in Embase, 48 in PubMed and 239 in Springer link). By further screening, 66 duplicate publications were removed and 302 irrelevant studies were eliminated via title browsing. Then by abstract reading, 10 of the 16 studies were also removed (including 2 reviewers, 7 studies not involving the association of LA and stroke, and 1 letter). For the remaining 6 studies, after full-text reading, a study that did not mention the association between LA and the risk of recurrent stroke was further excluded. No additional studies were enrolled by the manual search. Consequ-

ently, five eligible studies [10-12, 14, 20] were included in our meta-analysis. The selection process is presented in **Figure 1**.

Characteristics of the included studies

As shown in **Table 1**, the five studies were published from 2002 to 2015. The average age of patients in each study, except in Putaala's [20], was above 60. Additionally, majority of the studies were prospective cohort studies except one retrospective study [12]. In Kumral's study [10], the recurrences after 1- and 5-years

follow-up time were reported. The factor of atrial fibrillation (AF) was concerned in the study of Ntaios [14]. LA was measured via magnetic resonance imaging (MRI) or CT. Based on descriptions in the five studies, the stroke recurrence was confirmed via diagnosis in the hospital. If the patient was dead during the follow-up periods, a documented death certification or diagnosis result was provided by relatives of the patients.

As indicated in **Table 2**, all the studies achieved a high-quality assessment, except the one of Kim [12], showing a medium-quality.

Association between LA and the recurrent stroke risk

The five years were set as the break-point to perform the subgroup analysis stratified by follow-up time after stroke. Studies with the follow-up time < 5 -years were distributed in Subgroup 1, while those ≥ 5 -years was in Subgroup 2. The fixed effects model was applied for both two subgroups due to the lack of the pronounced heterogeneity ($I^2 < 50\%$, $P > 0.05$). The pooled result indicated that patients with LA had a significant higher recurrent stroke risk than those without LA in both two subgroups (subgroup 1: RR = 1.47, 95% CI, 1.27 to 1.70, $P < 0.001$; subgroup 2: RR = 1.26, 95% CI, 1.12 to 1.43, $P < 0.001$) (**Figure 2**).

Sensitive analysis and publication bias

In subgroup 1, after the successive elimination of a single study, the RR varied from 1.29 (95%

CI: 1.06, 1.56) to 1.54 (95% CI: 1.32, 1.81), and no reverse results were detected. Additionally, removal of the only retrospective cohort study generated a newly pooled RR of 1.48 (95% CI: 1.27 to 1.74, $P < 0.001$) under a fixed effects model ($I^2 = 44.4\%$, $P = 0.145$), which was consistent with the result before the removal (**Figure 3**). Taken together, all the sensitive analysis suggested a reliable result of our meta-analysis.

Based on Egger's test ($t = -1.71$, $P = 0.185$), no obvious publication bias was observed (**Figure 4**).

Discussion

In the present meta-analysis, we combined five prospective or retrospective cohort studies using meta-analysis and found LA had a pronounced association with the recurrent stroke risk, during the short-term (<5-years) or long-term (≥ 5 -years) follow-up period after stroke.

LA is a common feature of patients with stroke, and accumulating evidence has supported the concept that LA could be served as an independent predictor of stroke outcomes [21]. The presence of LA is linked to the prediction of stroke in patients suffered from first-ever lacunar stroke, while recurrent stroke is the predominant lacunar type [6]. Notably, the presence of severe LA could highly increase the risk of future stroke [22]. In patients with severe LA, it is ascertained that LA has an influence on short-term risk of stroke recurrence via altering the brain's ability to tolerate an ischemic insult [10, 23]. It is pointed out that the close relationship between LA and stroke recurrence risk could not be explained just by sharing the common risk factors because LA has been widely implicated as a predictor of stroke risk after controlling the vascular risk factors [24].

Ischemic stroke is the main type of stroke and only a small portion of patients with this stroke would recover with little deficit [8]. Therefore, subjects in most of the studies in our meta-analysis were patients with ischemic stroke. The recurrence rate was as high as 22% in one of the subtypes of ischemic stroke, cardioembolism, after 2-years follow-up time [25]. Pathology of ischemic stroke is multifactorial; and age, initial stroke severity as well as infarct volume are the primary risk factors [26-28].

Notably, after adjusting these factors, LA is still identified as a predictor for risk of recurrent stroke after ischemic stroke [29]. Though long-term follow-up time is not extensively investigated, studies taking long period after ischemic stroke into consideration all favor the close relationship between LA and recurrent stroke risk. For instance, LA is strongly associated with the risk of recurrent stroke within 3-years and 5-years after stroke [13, 29]. Two studies in our meta-analysis concerning the long-term follow-up period (5-years) after stroke all supported the predicted role of LA for risk of recurrent stroke [10, 20]. Notably, the combined RR (1.26, 95% CI, 1.12 to 1.43, $P < 0.001$) of the two studies also favored this notion, which confirmed that LA could indeed act as a predictor for the risk of recurrent stroke after long period of stroke. Meanwhile, though several previous studies discovered that LA did not predict the recurrent stroke after one month or one year [11, 30], emerging evidence validates that LA is tightly correlated with the prediction of recurrent stroke risk after short term period [31, 32]. In consistent with these findings, one study in our meta-analysis exhibited that extensive LA contributed to the prediction of the 90-day recurrent stroke risk after ischemic stroke [12], suggesting LA might also have the prognostic value as a predictor for the risk of early recurrent stroke.

These findings collectively suggest that LA is highly associated with the risk of recurrent stroke, and could be used as the predictor during a short- or long-term period after stroke. As majority of the included studies achieved a relative high quality and the sensitive analysis did not present any reverse result, our result of this meta-analysis was more accurate and reliable. Additionally, no significant heterogeneity was detected among all the studies. Furthermore, the subgroup analysis stratified by different follow-up time contributed to more precise evaluation. Despite these obvious advantages, several limitations should be discussed. The sample size was relatively small and only 5 studies were included. Moreover, the complication such as AF, one of the thromboembolic events [33] that might influence the stroke recurrence was only mentioned in one study in our meta-analysis. Therefore, we did not ensure whether LA was also closely associated with recurrent stroke risk in stroke patients accompanied with

AF. In addition, neither the subtype of stroke nor the specific extent of LA was concerned, which might affect accuracy of the estimation. Last but not the least, as all the included studies were observational studies, the pooled RR with its corresponding 95% CI were directly calculated from the crude results using a 2×2 table, thus the meta-analysis lacked the adjustment of the confounding factors such as age, obesity and hypertension, which might cause several deviations of the pooled result and should be considered into the further investigation.

In conclusion, our results supported the concept that LA could be used as a predictor for the risk of recurrent stroke. However, more studies with large sample size are required to confirm this finding.

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Disclosure of conflict of interest

None.

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Association of LA and recurrent stroke risk

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