

# Utility of Speckle-Tracking Echocardiography For Predicting Atrial Fibrillation Following Ischemic Stroke: A Systematic Review And Meta-Analysis

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## Research Article

**Keywords:** atrial fibrillation, cryptogenic stroke, speckle-tracking echocardiography, strain

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**Utility of Speckle-Tracking Echocardiography for Predicting Atrial Fibrillation following**

**Ischemic Stroke: A systematic review and meta-analysis**

**Running Title:** Predicting Atrial Fibrillation by Speckle-Tracking Echocardiography

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## Abstract

**Purpose:** Undiagnosed atrial fibrillation (AF) is one of the main sources of cryptogenic stroke. And strain indices measured by speckle-tracking echocardiography are associated with atrial remodeling supposed to be the substrate of AF. Therefore, there is a strong need for evaluating the utility of speckle-tracking echocardiography to predict the likelihood of AF in patients with cryptogenic stroke.

**Methods:** PubMed, Embase and Cochrane Database were searched for studies. The random-effects model was used to calculate the pooled results, and summary receiver operating characteristic curve (SROC) analysis was performed to show the overall predictive value.

**Results:** There were 1483 patients with cryptogenic stroke from 8 studies. Meta-analysis showed that strain indices including global longitudinal strain (GLS) (mean difference [SMD]: -0.22, 95% confidence interval [95% CI]: -0.40 to -0.04), left atrial reservoir strain ( $\epsilon_R$ ), (SMD: -0.87, 95% CI: -1.26 to -0.48, conduit strain ( $\epsilon_{CD}$ ) (SMD: -0.56, 95% CI: -0.81 to -0.30), contractile strain ( $\epsilon_{CT}$ ) (SMD: -1.00, 95% CI: -1.39 to -0.61), and left atrial reservoir strain rate (SRe) (SMD: -0.54, 95% CI: -0.80 to -0.28) measured at the period of cryptogenic stroke was significantly decreased in patients with AF occurrence compared to without. SROC analysis suggested an acceptable predictive efficiency of  $\epsilon_R$  for AF occurrence (AUC = 0.799).

**Conclusion:** For patients after cryptogenic stroke, GLS,  $\epsilon_R$ ,  $\epsilon_{CD}$ ,  $\epsilon_{CT}$  and SRe were significantly decreased in AF occurrence compared with non-occurrence. But there was no value in left atrial reservoir strain rate (SRs) and contractile strain rate (SRa) for predicting AF.

**Keywords:** atrial fibrillation, cryptogenic stroke, speckle-tracking echocardiography, strain

## Introduction

Ischemic stroke is a fatal condition which lead it to be one of the five leading causes of death worldwide[1]. So, it is critical to find the cause and the embolic source of ischemic stroke. Approximately 20% of thromboembolic events, including stroke, transient ischemic attack and systemic thromboembolism, are attributed to a cardioembolic source[2]. And atrial fibrillation (AF) is an independent risk predictor of ischemic stroke[2]. However, studies have shown that 20-30% of ischemic strokes could not find the source of the incident and were classified as cryptogenic stroke[3]. It has been reported that undiagnosed AF accounts for 20-30% of cryptogenic stroke[4]. Thus, many researchers explored how to predict AF in patients with ischemic stroke.

The use of cardiac implanted electronic devices (CIEDs) has significantly improved the detection of AF but the invasive characteristic restricts its widespread clinical adoption[5-7]. By contrast, echocardiography which could assess left atrium anatomy and function is noninvasive, and speckle-tracking echocardiography as a novel technology accurately evaluates regional and global left atrial strain which is deemed associated with atrial remodeling[8-10]. Atrial remodeling including atrial enlargement, heterogeneity of the conduction tissue and alterations of atrial electrical and contractile properties provides substrate of AF occurrence and promotes its persistence[11, 12].

Parameters of atrial speckle-tracking echocardiography mainly include left ventricular global longitudinal strain (GLS) and left atrial reservoir strain ( $\epsilon_R$ ), conduit strain ( $\epsilon_{CD}$ ), contractile strain ( $\epsilon_{CT}$ )[13]. Besides, left atrial reservoir strain rate (SRs), conduit strain rate (SR<sub>e</sub>) and contractile strain rate (SR<sub>a</sub>) are also used for evaluation of atrial and ventricular function. It has been reported that these parameters could predict and evaluate AF and its complications[14-17]. Multiple researches explored their predictive value for AF following cryptogenic stroke during follow-up. However, the results of

these studies were not consistent. Therefore, the objectives of current review and meta-analysis of the published literature were to determine the exact value of parameters of speckle-tracking echocardiography to predict the likelihood of AF occurrence in patients with cryptogenic stroke.

## **Methods**

### **Search strategy**

We searched the online databases of PubMed, Embase, and Cochrane Database to identify relevant researches from inception to September 18th 2021. The search terms used were as follows: (“speckle tracking” OR “velocity vector imaging” OR “edge tracking” OR “strain” OR “function” OR “deformation” OR “stiffness”) AND (“left atrial” OR “atrial” OR “atrium”) AND (“atrial fibrillation” OR “AF”) AND (“cryptogenic stroke” OR “ischemic stroke” OR “thrombotic stroke” OR “brain infarction” OR “cerebral infarction” OR “stroke”). We also manually searched the reference lists of relevant studies. Two investigators (Qinggele Gao and Peng Liu) independently screened the potentially relevant studies and extracted the data from these studies using a standardized extraction form. Discrepancies between investigators were judged by the third experienced investigator (Tingting Lv).

### **Selection criteria**

The inclusion criteria for this study were as follow: (a) the study design was cohort analysis; (b) studies that reported left ventricular GLS, and left atrial  $\epsilon R$ ,  $\epsilon CD$ ,  $\epsilon CT$ , SRs, SRe or SRa measured by speckle-tracking echocardiography. (d) studies concerned with the association with strain parameters of speckle-tracking echocardiography and occurrence of AF following cryptogenic stroke. The exclusion criteria including: (a) the identified studies were case reports, letters, comments, reviews or meta-analyses; (b) studies were animal studies. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the included studies.

### **Data extraction**

Two investigators (Qinggele Gao and Peng Liu) independently extracted data from identified studies using a standardized extraction form and disagreements were judged by the third investigator. The data extracted include: (a) authors; (b) year of publication; (c) type of study; (d) follow-up duration; (e) gender; (f) age; (g) sample size; (h) mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score; (i) left ventricular ejection fractions; (j) E/e’; (k) left atrial volume index; (l) indices of strain and strain rate.

### **Statistical analysis**

To perform the meta-analysis, we used STATA MP 14.0 software. For the demographic information, continuous variables were expressed as the mean  $\pm$  standard deviation (SD), and categorical variables were expressed as numbers and percentages. Strain parameters of speckle-tracking echocardiography were described as the mean  $\pm$  SD. The effect measure of the differences of left atrial GLS,  $\epsilon$ R,  $\epsilon$ CD,  $\epsilon$ CT, SRs, SRe or SRa between patients with and without AF occurrence was given as standard mean difference (SMD) with 95% confidence intervals (95% CI). Statistical heterogeneity across studies was assessed by  $I^2$  statistic, which was determined from standard chi-square test. A random-effects model was used in the analysis. Sensitivity analysis using leave-one-out method was applied to identify the source of the heterogeneity. Statistical significance was defined as a 2-tailed  $p$  value of 0.05.

## Results

### Study characteristics

The flow diagram of the search strategy of studies was shown in **Figure 1**. A total of 718 potentially relevant citations were retrieved from PubMed, Embase and the Cochrane Library, of which eight studies containing 1483 patients met the inclusion criteria and were therefore included[1, 18-24]. Among these studies, five, seven, four, six studies investigated the differences in GLS,  $\epsilon$ R,  $\epsilon$ CD,  $\epsilon$ CT, respectively, between patients with and without occurrence of AF following cryptogenic stroke; And three studies investigated the differences in SRs, SRe or SRa, between patients with and without occurrence of AF following cryptogenic stroke. The baseline characteristics of included studies and of the study populations are shown in **Table 1**. The proportion of female participants ranged from 36% to 50.8%, and mean age from 50 to 80 years.

### Difference in GLS between patients with and without occurrence of AF

Five studies[19, 20, 22-24] assessed the difference in GLS between patients with and without occurrence of AF following cryptogenic stroke. One study[24] revealed statistically decreased GLS in patients with AF occurrence compared to patients without. But the other four studies[19, 20, 22, 23] indicated there was no difference in GLS. As meta-analysis, the pooled analysis showed a significant decrease in GLS measured at the period of cryptogenic stroke in patients with AF occurrence compared to patients without AF occurrence. And the pooled SMD was -0.22 (95% CI: -0.40 to -0.04;  $p = 0.016$ ) ( $I^2 = 0.0\%$ ,  $p = 0.684$ ) (**Figure 2**).

### Difference in $\epsilon$ R between patients with and without occurrence of AF

Seven studies[1, 18-23] assessed the difference in  $\epsilon$ R between patients with and without occurrence

of AF following cryptogenic stroke. Five studies[1, 19, 21-23] revealed that  $\epsilon R$  was significantly decreased in patients with AF occurrence compared to patients without. In contrast, the other two studies[18, 20] reported there was no difference in  $\epsilon R$ . As meta-analysis, the pooled analysis showed a significant decrease of  $\epsilon R$  in patients with AF occurrence compared to patients without AF occurrence. The SMD was -0.87 (95% CI: -1.26 to -0.48,  $p < 0.001$ ) with high heterogeneity ( $I^2 = 84.0\%$ ,  $p < 0.001$ ) (**Figure 3A**).

#### **Difference in $\epsilon CD$ between patients with and without occurrence of AF**

Four studies[19-22] assessed the difference in  $\epsilon CD$  between patients with and without occurrence of AF following cryptogenic stroke. Two studies[21, 22] showed a statistically significant decrease of  $\epsilon CD$  in patients with AF occurrence. But the other two studies[19, 20] reported there was no difference. As meta-analysis, the pooled analysis showed  $\epsilon CD$  was significantly decreased in patients with AF occurrence compared to patients without. And the SMD was -0.56 (95% CI: -0.81 to -0.30,  $p < 0.001$ ) with low-moderate heterogeneity ( $I^2 = 42.3\%$ ,  $p = 0.158$ ) (**Figure 3B**).

#### **Difference in $\epsilon CT$ between patients with and without occurrence of AF**

Six studies[1, 19-23] assessed the difference in  $\epsilon CT$  between patients with and without occurrence of AF following cryptogenic stroke. Four studies[1, 19, 21, 23] revealed  $\epsilon CT$  was decreased in patients with AF occurrence compared to patients without. But the other two studies[20, 22] reported there was no difference in  $\epsilon CT$ . The pooled analysis showed a significantly decrease of  $\epsilon CT$  in patients with AF occurrence compared to patients without. SMD was -1.00 (95% CI: -1.39 to -0.61,  $p < 0.001$ ) with high heterogeneity ( $I^2 = 80.6\%$ ,  $p < 0.001$ ). Upon sensitivity analysis by removing one study at a time, Rasmussen et al.[22] study was found to be the cause of heterogeneity and removal of this study reduced heterogeneity to  $I^2 66.4\%$ ,  $p = 0.018$ , but this did not change the SMD significantly. (**Figure 3C**)

#### **Difference in SRs between patients with and without occurrence of AF**

Three studies[18, 20, 24] assessed the difference in SRs. Among these studies, one study[18] reported a statistically significant decrease of SRs in patients with AF occurrence compared to patients without AF occurrence. But the other two studies[20, 24] reported there was no difference in SRs. As meta-analysis, the pooled analysis showed no significantly different SRs in patients with AF occurrence compared to patients without AF occurrence with SMD of -0.46 (95% CI: -1.04 to 0.11,  $p = 0.114$ ) and high heterogeneity ( $I^2 = 80.4\%$ ,  $p = 0.006$ ). Removal of Deferm et al.[18] study reduced heterogeneity to  $I^2 21.2\%$ ,  $p = 0.260$ , but this did not change the SMD significantly (**Figure 4A**).

### **Difference in SRe between patients with and without occurrence of AF**

Three studies[18, 20, 24] assessed the difference in SRe. The three studies indicated statistically decreased SRe in patients with AF occurrence compared to patients without AF occurrence. As meta-analysis, the pooled analysis also showed significantly decreased SRe in patients with AF occurrence compared to patients without AF occurrence. And the SMD was -0.54 (95% CI: -0.80 to -0.28,  $p < 0.001$ ) and low heterogeneity ( $I^2 = 12.2\%$ ,  $p = 0.320$ ) (**Figure 4B**).

### **Difference in SRa between patients with and without occurrence of AF**

Three studies[18, 20, 24] assessed the difference in SRa between patients with and without occurrence of AF following cryptogenic stroke. One study[18] reported statistically decreased SRa in patients with AF occurrence. But the other two studies[20, 24] revealed there was no difference in SRa. As meta-analysis, the pooled analysis showed no significantly different SRa in patients with and without AF occurrence with SMD of -0.35 (95% CI: -0.92 to 0.21,  $p = 0.220$ ) and high heterogeneity ( $I^2 = 79.9\%$ ,  $p = 0.007$ ). Removal of Deferm et al.[18] study reduced heterogeneity to  $I^2 0.0\%$ ,  $p = 0.547$ , but this did not change the SMD significantly. (**Figure 4C**)

### **Predictive effect of $\epsilon R$ on occurrence of AF after cryptogenic stroke**

Three studies[18, 22, 23] analyzed the predictive effect quantitatively. The summary receiver operating characteristic curve (SROC) of decreased  $\epsilon R$  for AF occurrence was shown in **Figure 5**. The area under the curves (AUC) was 0.799. The pooled sensitivity and specificity were 0.76 (95% CI 0.66–0.84) and 0.72 (95% CI 0.67–0.76), respectively. And the pooled positive likelihood ratio and negative likelihood ratio were 2.66 (95% CI 2.14–3.30) and 0.35 (95% CI 0.24–0.50), respectively. The pooled diagnostic odds ratio (DOR) was 7.72 (95% CI 4.66–12.80).

## **Discussion**

This is the first meta-analysis exploring the value of parameters measured by speckle-tracking echocardiography to predict the likelihood of AF occurrence in patients with cryptogenic stroke. Echocardiography is a noninvasive and relatively low-cost method to estimate atrial and ventricular function as well as anatomy. And speckle-tracking echocardiography has been used as a quantitative assessment tool, by which regional and global left atrial function, atrial strain could be evaluated accurately[25].

AF could induce structural and functional remodeling in atrium, and atrial remodeling also could provide substrate of AF occurrence and persistence, the phenomenon which is called “AF beget AF”[26,



27]. Thus, it is meaningful to find an indicator of atrial remodeling to predict AF or diagnose subclinical AF. Atrial strain alteration is expression of atrial remodeling and could be measured quantitatively by speckle-tracking echocardiography[10, 28].

Atrial strain expressing the degree of deformation of matter in response to applied stress could influence reservoir, conduit, and booster pump function. Reservoir function is associated with left ventricular ejection, left ventricular isovolumic contraction and relaxation. Reservoir function is also a marker of left ventricular size and compliance as well as left atrium. Conduit function represents left ventricular relaxation and atrial compliance. Conduit function corresponds to early transmitral flow which is the E wave in M-mode echocardiographic. Contractile function is associated with left atrial preload and afterload which is also the left ventricular end-diastolic pressure. Contractile function could be modulated by venous return and atrial compliance[14]. Indices of Left atrial reservoir, conduit function and contractile function measured by speckle-tracking echocardiography were  $\epsilon_R$ ,  $\epsilon_{CD}$  and  $\epsilon_{CT}$ , respectively. In the current study, the pooled analysis demonstrated that  $\epsilon_R$ ,  $\epsilon_{CD}$  and  $\epsilon_{CT}$  were significantly decreased in patients with AF occurrence compared to patients without. So, for the patients with cryptogenic stroke, decreased  $\epsilon_R$ ,  $\epsilon_{CD}$  or  $\epsilon_{CT}$  could represent severe atrial remodeling and reduced atrial compliance, which were at high risk of occurrence of AF or complicated with subclinical AF. Meanwhile, in our pooled analysis, left ventricular GLS which was changed in HFpEF, stage B heart failure and mitral regurgitation significantly decreased in patients with AF occurrence[29]. We supposed that patients with decreased GLS were more likely to occur AF due to the patients complicated with heart diseases that could induce AF[16, 30].

SRs, SRe and SRa as the rate of  $\epsilon_R$ ,  $\epsilon_{CD}$  and  $\epsilon_{CT}$ , respectively, are also the critical indices of speckle-tracking echocardiography to estimate atrial compliance[10]. In our analysis, the results showed that pooled analyses of SRs and SRa were at high heterogeneity caused by Deferm et al. study. We concluded that the heterogeneity of this study was due to shorter interval between occurrence of cryptogenic stroke and echocardiography compared with other studies, besides, the rhythm monitoring method was 30-day mobile cardiac outpatient telemetry for AF detection. However, removal of this study did not change the result that there were no significantly differences of SRs and SRa between patients with AF occurrence and without. So, it is meaningless for SRs and SRa to predict AF in patients with cryptogenic stroke. SRe, as a parameter of left ventricular relaxation and atrial compliance, were proved significantly decreased in patients with AF occurrence. Thus, SRe is more effective to predict AF than

$\epsilon R$  and  $\epsilon CT$ . Further studies are required to seek the cut-off value of strain and strain rate indices after cryptogenic stroke to evaluate risk of AF occurrence.

### **Limitations**

This study has several limitations. Firstly, the current meta-analysis included relatively small number of studies, which was also due to that there were limited studies involved in association between indices of speckle-tracking echocardiography and occurrence of AF after cryptogenic stroke. Secondly, parameters of strain measured by speckle-tracking echocardiography have some methodologic variations including option of chamber views, timing of initial onset on ECG and measuring roof of the left atrium or not, which was a critical factor of high degree of heterogeneity in our effect estimate. Thirdly, in the identified studies and this meta-analysis, it was hard to figure out if the etiology of stroke was AF or not. We concluded that some patients with cryptogenic stroke were due to subclinical AF, but there was limited way to prove it. Finally, only  $\epsilon R$  was analyzed with predictive effect quantitatively due to limitation of number of relevant studies.

### **Conclusion**

Speckle-tracking echocardiography is useful to predict AF in patients with cryptogenic stroke. strain parameters of GLS,  $\epsilon R$ ,  $\epsilon CD$ ,  $\epsilon CT$  were exhibited decreased compared with patients without AF occurrence. And strain parameters were more predictive than indices of strain rate in which only SRe were proved decreased in patients with AF occurrence.

### **Conflict of interest**

The authors have no conflicts to disclose

### **Founding sources**

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### **Data availability statement**

All data generated or analyzed during this study are included in this article.

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**Table 1. The baseline characteristics of studies investigating the differences of speckle-tracking echocardiography indices between patients with and without AF occurrence after cryptogenic stroke**

Author	Year	Type of study	NOS score	Mean follow up	Sample size		Female(%)		Age		Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc score		LVEF (%)		E/e'		LAVI(mL/m <sup>2</sup> )		Strain(%) /strain rate (s <sup>-1</sup> )
					no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	
Skaarup et al	2017	Case-control	6	NR	175	44	39.7	50	51.6 ± 13.5	61.5 ± 12.9	3.3±1.3	3.8±1.3	47±8	46±9	7.3±2.7	8.0±3.0	NR	NR	GLS/ SRs, SRe, SRa
Pathan et al	2017	cohort	8	24months	477	61	43.2	50.8	65 (43–87)	80 (69–91)	4.3±1.47	5.6±1.3	NR	NR	10.3±4.8	13.3±6.3	33.87±11.1	40.92±15.3	ER, ECt, ECd
Olsen et al	2019	cohort	7	36months	43	13	40	54	50 ± 12	65 ± 8	3.0±1.1	3.7±1.2	51±8	51±8	7.3 ± 2.2	8.5 ± 2.3	NR	NR	ER, ECt, ECd/ SRs, SRe, SRa
Rasmussen et al	2019	cohort	6	6months	158	28	36	46	59 ± 14	68 ± 10	3.8 ± 1.57	5.04 ± 1.67	53 ± 7	50 ± 11	8.3 (6.3;10.6)	9.5 (7.2;14)	NR	NR	GLS, ER, ECt, ECd
Sade et al	2020	cohort	7	12months	58	39	36	51	70 ± 9	74 ± 10	4.7 ± 1.6	5.2 ± 1.6	NR	NR	NR	NR	NR	NR	GLS, ER, ECt,
Defermet al	2020	Cohort	6	25months	163	28	45	57	64 ±14	70±11	NR	NR	68 (63-73)	66 (63-70)	9.38 (7.13-12)	12.4 (9.87-15)	31.2 (24.5-39.7)	43.6 (30.9-49.7)	ER/ SRs, SRe, SRa
Kusunose et al	2021	Cohort	6	0.6months	75	46	36	50	73 ±14	80 ±8	NR	NR	58 ±10	58 ±7	10.2 ±4.1	10.4 ±2.6	38 ±17	46 ±20	GLS, ER, ECt, ECd
Ble et al	2021	cohort	6	12months	38	37	39.5	48.6	73.4±9.7	77.6±8.3	4.79±1.4	5.22±1.20	63.2±3.8	63.2±2.8	NR	NR	NR	NR	ER, ECt

**Figure legends:**

**Figure 1.** The flow diagram of the study.

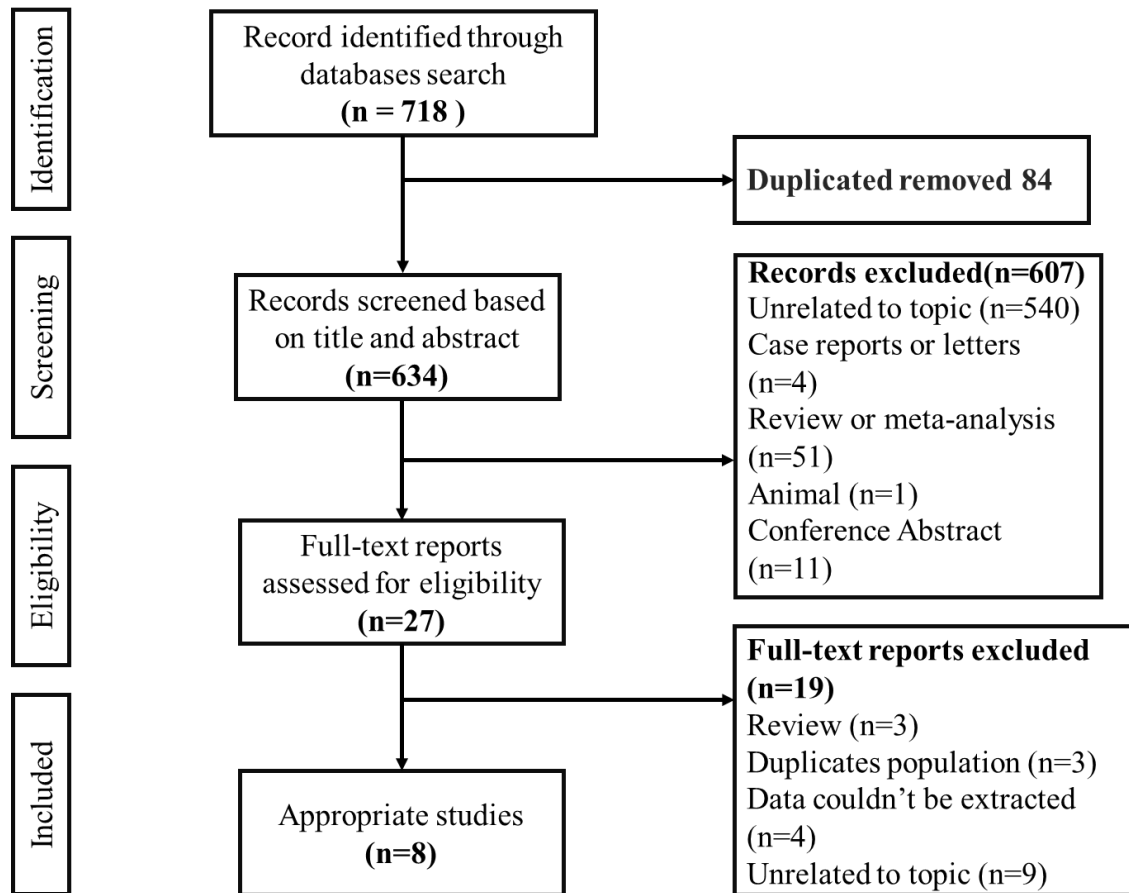
**Figure 2.** Forest plot pooled analysis of standard mean difference of GLS between patients with AF occurrence and without after cryptogenic stroke. Abbreviation: GLS, global longitudinal strain. AF, atrial fibrillation.

**Figure 3.** Forest plot pooled analysis of standard mean difference of  $\epsilon$ R between patients with AF occurrence and without after cryptogenic stroke (a). Forest plot pooled analysis of standard mean difference of  $\epsilon$ CD between patients with AF occurrence and without after cryptogenic stroke (b); Forest plot pooled analysis of standard mean difference of  $\epsilon$ CT between patients with AF occurrence and without after cryptogenic stroke (c). Abbreviation:  $\epsilon$ R, left atrial reservoir strain.  $\epsilon$ CD, conduit strain.  $\epsilon$ CT, contractile strain. AF, atrial fibrillation.

**Figure 4.** Forest plot pooled analysis of standard mean difference of SRs between patients with AF occurrence and without after cryptogenic stroke (a). Forest plot pooled analysis of standard mean difference of SRe between patients with AF occurrence and without after cryptogenic stroke (b); Forest plot pooled analysis of standard mean difference of SRa between patients with AF occurrence and without after cryptogenic stroke (c). Abbreviation: SRs, left atrial reservoir strain rate. SRe, conduit strain rate. SRa, contractile strain rate.

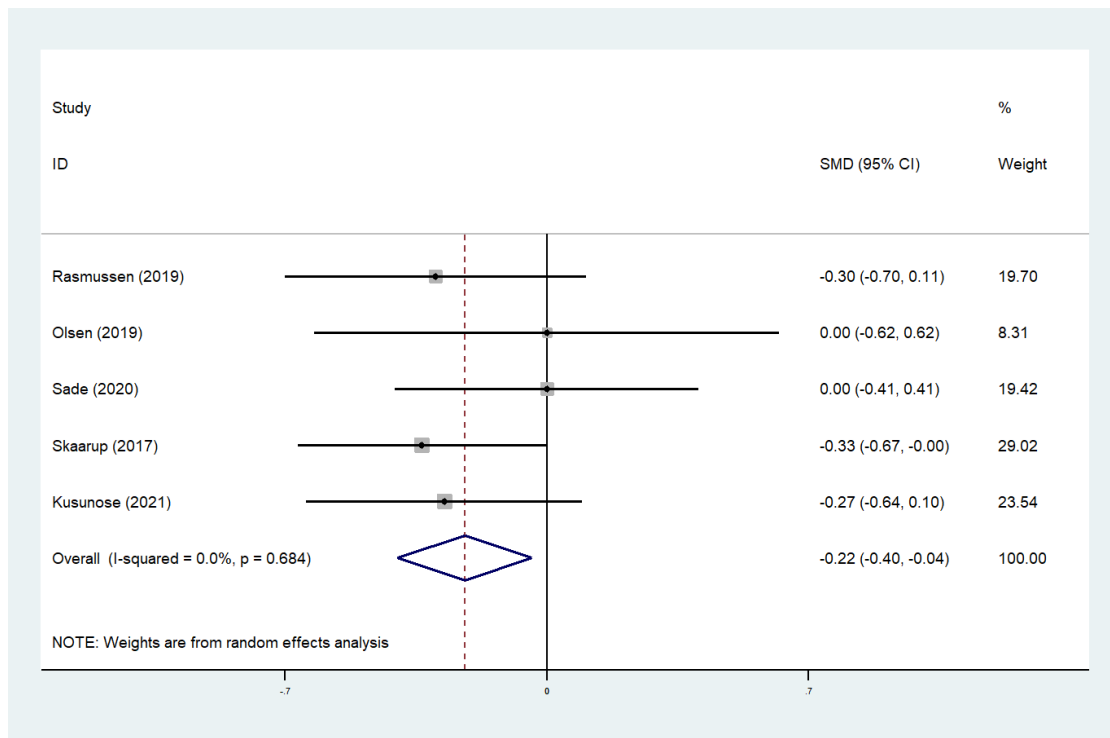
**Figure 5.** The SROC of decreased  $\epsilon$ R for AF occurrence. SROC, summary receiver operating characteristic curve. AF, atrial fibrillation.

**Figure 1.**

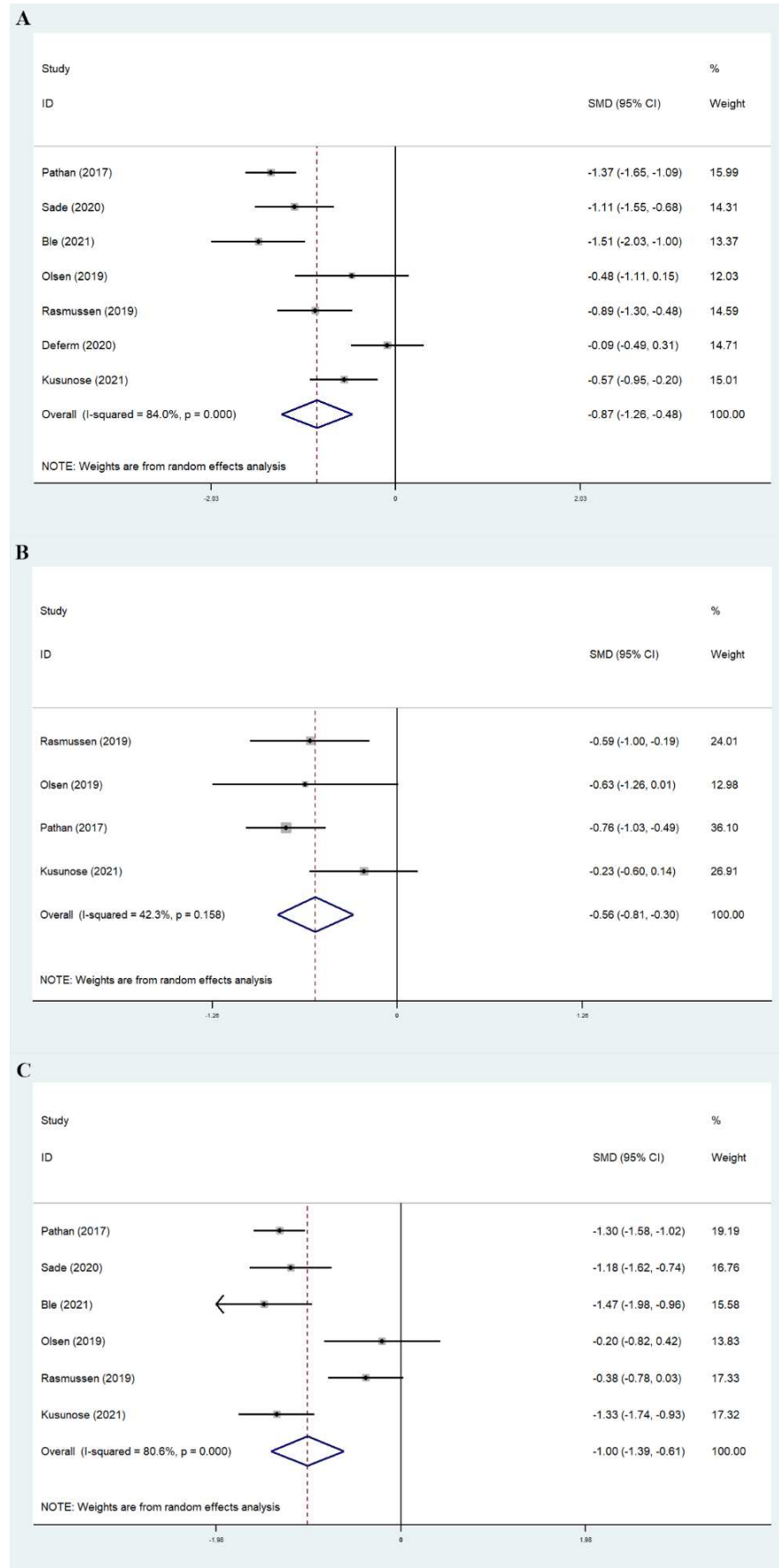




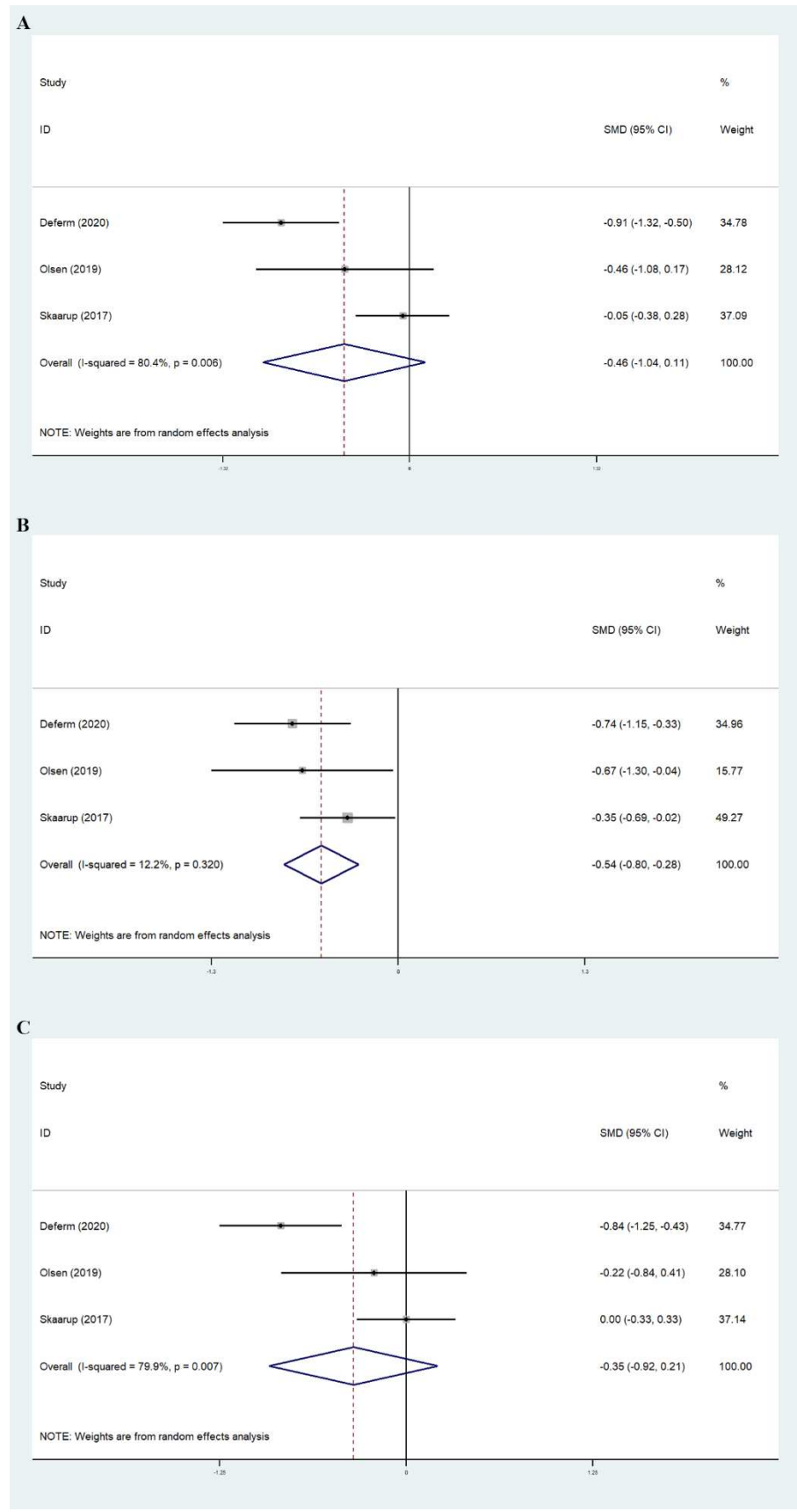
**Figure 2.**



**Figure 3.**



**Figure 4.**



**Figure 5.**

