Catheter ablation of atrial fibrillation in the young: a systematic review and meta-analysis

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Abstract

Aims The differences in the clinical outcomes of rhythm and safety after catheter ablation in young and old atrial fibrillation (AF) patients remain unclear. The purpose of this study was to compare the clinical outcomes of catheter ablation for in young and old AF patients.

Methods and results The Medline and EMBASE databases were searched for published articles up to October 2022. Studies that met our predefined inclusion criteria were included. The primary endpoints were freedom from AF/atrial tachycardia (AT) recurrence, safety outcomes including the stroke/transient ischaemic attack (TIA), cardiac tamponade and pericardial effusion. After literature search and detailed assessment, 6 studies (9982 patients) were identified. Our analyses showed that the rate of freedom from AF/AT recurrence was higher in young than old AF patients after ablation [odds ratio (OR): 0.58, 95% confidence interval (CI) 0.36–0.92; P = 0.02]. Compared to older patients, there were similar rate of adverse outcomes including pericardial effusion /tamponade (OR=0.61, 95%CI 0.29-1.27,P=0.18), hematoma(OR=1.87, 95%CI 0.62,5.63, P=0.27) and stroke/TIA rate(OR=0.25, 95%CI 0.05,1.41, P=0.12) . Conclusions In younger atrial fibrillation patients, there is a lower major complication rate and a comparable efficacy rate, with a greater chance of being AF free without antiarrhythmic drugs. These findings suggest that it may be appropriate to consider ablative therapy as first-line therapy in this age group.
tachycardia (AT) recurrence, safety outcomes including the stroke/transient ischaemic attack (TIA), cardiac tamponade and pericardial effusion. After literature search and detailed assessment, 6 studies (9982 patients) were identified. Our analyses showed that the rate of freedom from AF/AT recurrence was higher in young than old AF patients after ablation [odds ratio (OR): 0.58, 95% confidence interval (CI) 0.36–0.92; P = 0.02]. Compared to older patients, there were similar rate of adverse outcomes including pericardial effusion/tamponade (OR=0.61, 95%CI 0.29-1.27, P=0.18), hematoma(OR=1.87, 95%CI 0.62, 5.63, P=0.27) and stroke/TIA rate(OR=0.25, 95%CI 0.05, 1.41, P=0.12).

Conclusions

In younger atrial fibrillation patients, there is a lower major complication rate and a comparable efficacy rate, with a greater chance of being AF free without antiarrhythmic drugs. These findings suggest that it may be appropriate to consider ablative therapy as first-line therapy in this age group.

Key words: atrial fibrillation; catheter ablation; complications; young patients

AF is associated with increased mortality and morbidity, with stroke and thromboembolic events being major complications[1]. Antiarrhythmic drug therapy is ineffective and toxic[2]. Catheter ablation is now considered as a first line treatment in patients with AF and is routinely performed in patients with drug refractory AF[3].

The prevalence and incidence of atrial fibrillation (AF) rise with age, while the number of people aged 65 years and older has exceeded 20%[4]. AF can also be seen in young people with or without structural heart disease[5]. In addition, the pathogenesis of AF may differ between young and old AF patients[6]. Optimizing the effectiveness and safety of catheter ablation requires patient stratification and individualized therapy[7]. However, there is a scarcity of data from a large cohort study of younger AF patients on the effectiveness and safety of catheter ablation. As a result, we conducted a systematic review and meta-analysis to compare the clinical outcomes of AF catheter ablation in younger AF patients.

Data sources and searches

We conducted a comprehensive online search of the literature through the Medline and EMBASE databases (to December 2022) to identify all published clinical studies that compared outcomes of catheter ablation of AF in young and old patients. To avoid missing relevant data, the bibliographies of the reviewed manuscripts were manually retrieved. The retrieval strategy used relevant keywords and medical subject heading terms including the following: "pulmonary vein isolation"; "atrial fibrillation"; "Radiofrequency catheter ablation", “Cryoballoon catheter ablation”, “Young adult” both separately and in combination. The study and data collection were performed based on protocols approved by the ethics committee of The second affiliated hospital of nanchang university.

Study selection

Studies were considered if they provided specific information on younger vs. Older patients within the main article or subgroup and if they reported primary endpoints of interest in patients undergoing catheter ablation of AF. Catheter ablation is a type of endocardial ablation procedure (including radiofrequency or cryoablation). The following criteria were used to determine which studies would be included: 1. studies required to offer accurate information on at least one of the main endpoints; and (2) endpoints were to be reported as numerical occurrences rather than just hazard ratios, relative risks, or odds rates. We made an effort to get in touch with the associated authors to request further information if pertinent data were not given in the published studies. Retrieval results were examined by three writers to confirm that studies met the predetermined inclusion criteria.

Outcomes and definitions

The primary endpoints were the rates of freedom from recurrent AF/atrial tachycardia (AT), stroke/transient ischaemic attack (TIA), and all-cause mortality. Secondary endpoints were major complications such as
pericardial effusion/tamponade, major bleeding requiring transfusion, permanent pacemaker implantation (PMI), PV stenosis, and acute coronary syndrome were secondary endpoints (ACS). Freedom from AF/AT recurrence was defined as no episode of AF, flutter or tachycardia [≥30 s in duration after a 1- or 3-month blanking period off of antiarrhythmic drugs (AADs)]. Stroke/TIA and all-cause mortality were defined as new stroke/TIA onset and death from any cause occurring during hospitalization or followup. Acute coronary syndrome was defined as a myocardial infarction (MI) or unstable angina. PV stenosis was defined as moderate to severe stenosis of PV or PV stenosis requiring therapeutic intervention.

Data extraction and quality assessment

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Data abstraction was conducted by three authors (Qianwei Huang, Tian Zheng, Qianghui Huang), who independently used a predefined, standardized protocol, and data collection instrument. The following study-, patient-, and procedure-related data were extracted from the main paper. Any discrepancies were resolved by discussion among the authors. The Newcastle Ottawa Quality Assessment Scale (NOS) for observational trials was used to evaluate the quality of the included studies.

The odds ratio (OR) with 95% confidence intervals (CIs) was used to analyze dichotomous data, whereas weighted mean differences were used to analyze continuous variables. The Cochran Q test was used to assess the presence of heterogeneity among studies, and the Higgins $I^2$ test was used to assess the extent of the observed heterogeneity, which suggests 0-25%, 25-50%, and 50-75% as low, moderate, and high heterogeneity, respectively. Given the inherent differences in study design and demographics, we used a random-effects model to estimate the pooled effects of our meta-analyses.

For the primary endpoints, prespecified sensitivity analyses were performed by iteratively removing one study at a time to confirm that no single study had a significant impact on our results. To further test the stability of our meta analysis, we performed multiple subgroup analyses (based on study group, different surgical methods). A random-effects meta-regression analysis was performed to examine the effect of preselected covariates on the overall effect. In both groups, the logarithm of OR for the primary endpoints was regressed against age, percentage of hypertension, diabetes mellitus, stroke, left ventricular ejection fraction (LVEF), and size of left atrial (LA) diameter.

We examined the asymmetry of the funnel plots in detail and further assessed them using the Begg adjusted rank correlation test and the Egger regression asymmetry test to detect any publication bias in the primary endpoints. All statistical analyses were carried out using the RevMan software package (Review Manager, Version 5.3) and STATA software 12.0. P-values were two-tailed, with 0.05 considered statistically significant.

Results

Characteristics of included studies

Our search approach initially turned up 444 potentially pertinent studies. The review of the title and abstract determined that a total of 388 of these were excluded (Figure 1). After a thorough full-text review, 40 of the remaining studies were disregarded due to the following reasons: surgical epicardial ablation (n = 5), duplicate studies (n = 22), reviews (n = 7), lack of outcomes of interest (n = 4), and insufficient dates for analysis (n = 2). 6 papers published between 2010 and 2021 that satisfied our eligibility criteria and reported the intended clinical outcomes of catheter ablation in young patients compared to older patients were found after thorough review.

The baseline characteristics of the included studies are shown in Table 1. 1001 (10.0%) of the 9982 patients who had catheter ablation for AF were younger patients. In four studies, the age of the young group was defined as less than 45 years old, and in the other two studies, the average age of the young group was 30 years old. Old group had a higher history of stroke, DM, heart failure in the past, as well as to have larger LA diameters, and higher CHA2DS2-VASc score.
The quantitative synthesis of independence from AF/AT recurrence in younger group vs old group included 6 research. These investigations showed heterogeneity ($P=0.02; I^2 = 80\%$) pooled research found that at the year follow-up, younger patients had a significantly lower rate of AF/AT recurrence than old patients ($OR=0.58, 95\% CI 0.36,0.92$, Figure 2).

Stroke/transient ischaemic attack

Three studies were included in the analysis of stroke/TIA. There were 29 (0.34\%) events among 8429 participants. Pooled analysis showed that in the young patient was associated with a similar risk of stroke/TIA compared with old patients ($OR: 0.25, 95\% CI: 0.05–1.41; P =0.12; Figure 3$).

Pericardial effusion/tamponade

Four studies were included in the analysis of Pericardial effusion/tamponade. There were 83 (0.90\%) events among 8305 participants. Pooled analysis showed that there was no significant difference between the young patient and old patients ($OR: 0.61, 95\% CI: 0.29–1.27; P =0.18; Figure 4$).

Hematoma

Four studies were included in the analysis of hematoma, including hematoma requiring transfusion, large groin hematoma. There were 18 events among 8305 participants. Pooled analysis showed that there was no significant difference between in the younger patient and old patients ($OR: 1.87, 95\% CI: 0.62–5.63; P =0.27; Figure 5$).

Sensitivity, subgroup, and metaregression analysis

Sensitivity analysis (using the single-study-removed method) showed good stability in the clinical endpoints of freedom from AF/AT recurrence. For the primary endpoints, meta-regression indicated that no significant correlation between the preselected covariates and the overall treatment effect of catheter ablation was observed. Funnel plot indicated that there is no significant bias between all articles included in our metaanalysis, as shown in supplement Figure 1.

Discussion

We compared the procedural characteristics and short-term clinical outcomes of RF ablation of AF in young adults and older adults in this study. Our series demonstrated Patients with young AF have a better chance of being AF-free without the use of antiarrhythmic medications than older patients. AF is strongly age-dependent, affecting 4\% of people over the age of 60 and 8\% of people over the age of 80. The prevalence of AF is 0.1\% in people under the age of 55\textsuperscript{[14,15]}. A large number of studies focused on catheter ablation and stroke treatment in elderly patients \textsuperscript{[16,17]}. In previous studies, younger patients were under-represented. Julian Chun reported 7243 AF ablation patients in the German Ablation Registry collected from 51 German centers between March 2007 and September 2012 revealed that only 8.2\% of patients were under the age of 45\textsuperscript{[9]}. Ghannam demonstrated From January 2000 to January 2019, radiofrequency energy was administered to 82 of 6336 consecutive patients with AF. Because of limited data on procedural characteristics and clinical outcome of catheter ablation in young adults, we are paying closer attention to these patients.

Catheter ablation is recommended as first-line therapy in selected patients with AF and for drug-refractory AF in adults\textsuperscript{[18,19]}. In our study, 77\% of the young patients and 67\% of the old patients were free of recurrent atrial arrhythmias. There are numerous reasons why younger patients may fare better than older patients. Firstly, the dilation of the atrial structure in AF patients, a feature of atrial remodeling, has been identified as a significant predictor of AF recurrence following catheter ablation. Our data revealed that younger patients had smaller atria, which could be a protective factor. And only the older population (21.7\%) had LA scars or Low-voltage areas on voltage maps, indicating LA strucutral alterations and fibrosis, compared to the very young population, which all had normal voltage maps\textsuperscript{[20]}. Secondly, in older patients, other
poor ablation risk factors such as hypertension, obesity, and obstructive sleep apnea syndrome were higher. However, shorter preablation presence of these risk factors and easier lifestyle modifications after PVI in young patients may explain the differences with old patients\[21,22\].

Concerning complications, the overall complication rate was low. Clinically significant serious adversey (including death, stroke, TIA) occurred in 120 patients during 6334 procedures. There are several factors that contribute to our study’s lower complication rate. To begin, Spragg\[23\] et al identified age >70 years as a predictor of major complications. The mean age in our cohort of patients was less than 60 years old, which may have contributed to the lower complication rates. The next, another possible explanation is that 80% of the patients in the population were male atrial fibrillation. There were gender differences in AF patients\[24,25\]. Cheng\[26\] conducted a meta-analysis of 151370 patients, 34% of whom were women, and discovered that women who underwent catheter ablation of AF may have a higher risk of stroke/TIA and major complications than men, and that genetic, vascular biology, hormonal, or thromboembolic factors that differ between men and women may lead to a higher risk of complications\[27,28\]. Furthermore, the included population has a relatively high proportion of patients with paroxysmal atrial fibrillation. Patients with persistent atrial fibrillation require longer surgery time and more complex surgical procedures (such as linear ablation, Marshall ligament) could be be accompanied by higher complication rates\[29,30\]. Advances in ablation technology, such as irrigation and contact force sensing, as well as better management of AF risk factors may have contributed to this improvement\[31\], which is also the cause of fewer surgical complications.

Recently, The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) trial looked at the effectiveness of an early rhythm-control strategy in patients who had recently been diagnosed with AF (enrolled median 36 days after AF diagnosis). Early rhythm control reduced the composite primary outcome of cardiovascular death, stroke, and hospitalization for worsening heart failure and acute coronary syndrome by 21% (from 5.0%/year to 3.9%/year) in this trial\[32\]. While AAD therapy has been definitively proven to be superior to placebo in the prevention of arrhythmia recurrence, but the young AF patient must accept a "lifetime" daily intake of AAD as part of a medical rhythm control plan, as well as the possibility of accumulative side effects, leading to high rates of withdrawn (OR 1.63-2.91)\[33\]. It’s interesting to note that young patients had a rate of patients who needed particular AAD treatment and anticoagulant drugs even after catheter ablation that was substantially lower, showing that AF control is more likely to be achieved, this finding is consistent with the CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores’ predictions of a lower prevalence of comorbidities and thromboembolic events\[34\].

AF is a chronic progressive disorder\[35\]. Age and underlying comorbidities are associated with the natural progression rate of PAF to persistent AF, which can reach up to 24.7% over the course of 5 years\[36\]. After catheter ablation of paroxysmal AF, recent long-term follow-up data showed an unexpectedly low progression rate to permanent AF\[37\]. Based on this observation, it may be preferable to do an early AF ablation in the young patient rather than waiting until AF has developed into persistent AF, which may then require a lengthy ablation treatment with a lower chance of success\[38\]. The better outcome was probably caused by younger patients having less electroanatomical remodeling than older patients\[39\]. To better explain the positive response younger patients demonstrated in comparison to the propensity-matched older group, a more extensive assessment of the electroanatomic substrate (such as high-density mapping, evaluation of cardiac fibrosis, and atrial mechanical characteristics) is required.

Study Limitations

The primary limitation of our study is that the data is observational, which makes it susceptible to selection bias. Large registry data, as opposed to controlled randomized trials, may provide additional information to help clarify treatment plan selection and outcome in a "real world" setting. Second, the decision to use RF or CB ablation was left up to the operators, and the CB method was used differently in different centers. These factors may have influenced the findings, but additional subgroup analysis is not possible given the available data. Third, most studies lacked detailed information on factors such as perioperative drug use, structural heart disease, obesity, and excessive activity, as well as AF in the family. Fourth, most of the follow-up reported in these trials was limited to 12 months. Longer-term follow-up is needed to determine
the outcome’s durability in terms of arrhythmia recurrence, healthcare utilization.

Conclusion

According to data from our meta-analysis, young adults who undergo catheter ablation of AF have greater 1-year success rates. In comparison to the older group, the young patients tended to have comparable rates of complications (stroke/TIA, hematoma, cardiac tamponade, and pericardial effusion).

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest influenced by the article’s content.

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References


Table 1 Baseline characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Region</th>
<th>Single/multi-centre</th>
<th>Size (n)</th>
<th>Follow-up</th>
<th>Young group</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leong-Sit</td>
<td>2010</td>
<td>Retrospective</td>
<td>London, observational</td>
<td>71.0%</td>
<td>1548</td>
<td>Mean 32 months</td>
<td>&lt;45 year</td>
<td>6</td>
</tr>
<tr>
<td>Julian Chun</td>
<td>2013</td>
<td>Prospective</td>
<td>German</td>
<td>68.9%</td>
<td>7243</td>
<td>12 months</td>
<td>[?] 45 years</td>
<td>7</td>
</tr>
<tr>
<td>Lamyaa Leon</td>
<td>2019</td>
<td>Prospective</td>
<td>Egypt</td>
<td>100.0%</td>
<td>76</td>
<td>12 months</td>
<td>31.6 ± 4.2</td>
<td>5</td>
</tr>
<tr>
<td>Bergau Maxine</td>
<td>2020</td>
<td>Retrospective</td>
<td>Germany</td>
<td>78%</td>
<td>207</td>
<td>Mean 32 months</td>
<td>&lt;45 years</td>
<td>6</td>
</tr>
<tr>
<td>Tijskens Michael</td>
<td>2021</td>
<td>Retrospective</td>
<td>Italy</td>
<td>65%</td>
<td>751</td>
<td>12 months</td>
<td>&lt;45 years</td>
<td>6</td>
</tr>
<tr>
<td>Ghannam</td>
<td>2021</td>
<td>Retrospective</td>
<td>USA</td>
<td>74%</td>
<td>157</td>
<td>5.1 ± 4.6 years</td>
<td>&lt;30 years</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Baseline characteristics of the included studies
<table>
<thead>
<tr>
<th>Study</th>
<th>Men(%)</th>
<th>Men(%)</th>
<th>LA size</th>
<th>LVEF%</th>
<th>LVEF%</th>
<th>CHADS2 score</th>
<th>CHADS2 score</th>
<th>CHA2DS2-VASc score</th>
<th>CHA2DS2-VASc score</th>
<th>Hypertension, n (%)</th>
<th>Hypertension, n (%)</th>
<th>Diabetes, n (%)</th>
<th>Diabetes, n (%)</th>
<th>Heart failure, n (%)</th>
<th>Heart failure, n (%)</th>
<th>LVEF%</th>
<th>LVEF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leong-Sit</td>
<td>179/232 (77%)</td>
<td>372/438 (85%)</td>
<td>4.2±0.7</td>
<td>4.4±0.7</td>
<td>58±10</td>
<td>58±9</td>
<td>0 (0, 1)</td>
<td>1 (0, 1)</td>
<td>NG</td>
<td>NG</td>
<td>50</td>
<td>189</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Julian Chun</td>
<td>83.6%</td>
<td>66.0%</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>0.3</td>
<td>0.9</td>
<td>NG</td>
<td>NG</td>
<td>24.9%</td>
<td>61.6%</td>
<td>2.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamyaa Allam</td>
<td>23/30</td>
<td>34/46</td>
<td>39.6</td>
<td>52.8</td>
<td>65.6</td>
<td>64.2</td>
<td>NG</td>
<td>NG</td>
<td>0.93</td>
<td>2.11</td>
<td>15</td>
<td>28</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allam (76.6%)</td>
<td>3.1</td>
<td>± 4.9</td>
<td>± 3.2</td>
<td>± 4.5</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>± 0.7</td>
<td>± 1.32</td>
<td>(50%)</td>
<td>(60.9%)</td>
<td>(16.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leonard Bergau</td>
<td>14/93</td>
<td>31/114</td>
<td>36.0</td>
<td>50.9</td>
<td>38</td>
<td>54</td>
<td>NG</td>
<td>NG</td>
<td>0.3</td>
<td>0.98</td>
<td>12</td>
<td>NG</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxime Tijskens</td>
<td>162/197</td>
<td>40.9</td>
<td>60.3±6.5</td>
<td>53.7</td>
<td>54</td>
<td>NG</td>
<td>NG</td>
<td>0.7</td>
<td>± 0.9</td>
<td>(13%)</td>
<td>(1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael Ghannam</td>
<td>69(84%)</td>
<td>39±7</td>
<td>0.55±0.1</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>0.54</td>
<td>1.9</td>
<td>± 0.8</td>
<td>1.4</td>
<td></td>
<td></td>
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</tbody>
</table>

LA left atrium, LVEF LV ejection fraction IQR indicates interquartile range (25th and 75th percentiles), LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation;

Table 3.Baseline demographics in the included studies for the different endpoints

<table>
<thead>
<tr>
<th>Study</th>
<th>AF/AFL/AT recurrence</th>
<th>AF/AFL/AT recurrence</th>
<th>Hematoma</th>
<th>Hematoma</th>
<th>Pericardial Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leong-Sit</td>
<td>40/309</td>
<td>70/583</td>
<td>1/309</td>
<td>2/583</td>
<td>0/309</td>
</tr>
<tr>
<td>Julian Chun</td>
<td>150/374</td>
<td>1840/3884</td>
<td>0/537</td>
<td>7/5975</td>
<td>6/537</td>
</tr>
<tr>
<td>Lamyaa Allam</td>
<td>5/30</td>
<td>10/46</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Leonard Bergau</td>
<td>14/93</td>
<td>31/114</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Maxime Tijskens</td>
<td>22/197</td>
<td>89/249</td>
<td>1/197</td>
<td>1/249</td>
<td>0/197</td>
</tr>
<tr>
<td>Michael Ghannam</td>
<td>18/75</td>
<td>27/75</td>
<td>5/75</td>
<td>1/75</td>
<td>1/75</td>
</tr>
</tbody>
</table>

6 studies were included in quantitative synthesis

Records identified through database searching (n = 40)
Records after duplicates removed (n=388)
Records identified through database searching (n = 40)
Additional records identified through other sources (n = 41)
Records excluded based on title and abstract (n=348)
34 Excluded
1. Lack of interest in clinical outcome
2. Reviews
3. Detailed data cannot be acquired
Figure 1. Flow diagram of the study selection process.

![Flow diagram](image)

Figure 2. Forest plot of freedom from AF

![Forest plot](image)

Heterogeneity: Tau^2 = 0.24, Chi^2 = 24.61, df = 5 (P = 0.002), I^2 = 80%
Test for overall effect: Z = 2.33 (P = 0.02)

Figure 3. Forest plot of stroke/TIA after catheter ablation

![Forest plot](image)

Heterogeneity: Chi^2 = 0.37, df = 2 (P = 0.83), I^2 = 0%
Test for overall effect: Z = 1.57 (P = 0.12)

Figure 4. Forest plot of tamponade, pericardial effusion.

![Forest plot](image)

Heterogeneity: Chi^2 = 3.81, df = 3 (P = 0.28), I^2 = 21%
Test for overall effect: Z = 1.33 (P = 0.18)

Figure 5. Forest plot of hematoma after catheter ablation

![Forest plot](image)

Heterogeneity: Chi^2 = 1.67, df = 3 (P = 0.64), I^2 = 0%
Test for overall effect: Z = 1.11 (P = 0.27)