Extensive screening for occult malignancy in unprovoked venous thromboembolism: A meta-analysis

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A B S T R A C T

Background: The present meta-analysis aimed to evaluate the efficacy and sensitivity of an extensive screening strategy for occult malignant diseases in patients with unprovoked venous thromboembolism (VTE).

Methods: We conducted a systematic search of PubMed, Cochrane, EMBASE, and relevant article references. Meta-analysis was used to pool weighted relative risks (RR) for the rate of missed diagnosis, all-cause mortality, and cancer-related mortality. Heterogeneity test was performed using the inconsistency index. Furthermore, pooled analysis of the sensitivity and the proportion of false-positive findings of PET/CT were conducted.

Results: A total of 5 controlled studies were included with 1,115 and 1,159 unprovoked VTE patients receiving limited or extensive screening strategy, respectively. The risk of missed diagnosis (RR, 0.51; 95% CI, 0.20–1.28; P = 0.15) was not significantly different between the limited and extensive screening group. Moreover, there was no statistically significant difference in all-cause mortality (RR, 0.86; 95% CI, 0.58–1.27; P = 0.44) and cancer-related mortality (RR, 0.86; 95% CI, 0.46–1.62; P = 0.65) between the two groups. The pooled sensitivity and proportion of false-positive findings of PET/CT as a screening tool for occult malignancy in patients with unprovoked VTE was 95% (95% CI, 38%–100%) and 33% (95% CI, 20%–47%), respectively.

Conclusions: Extensive screening strategy did not show a clinically significant benefit over limited screening strategy. Considering the high cost and the additional physical and emotional harm, current evidence did not support extensive screening for each patient in the setting.

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1. Introduction

Venous thromboembolism (VTE), which encompasses pulmonary embolism and deep-vein thrombosis, can be the first manifestation of occult malignancy [1]. Unprovoked VTE is a classification of VTE in which patients are not detected with obvious risk factors such as surgery, immobility, trauma, pregnancy, or diagnosed cancer (as opposed to provoked VTE). Up to 10% of patients with unprovoked VTE may receive a diagnosis of cancer in the year following the unprovoked VTE episode [2]. Therefore, screening for occult malignancy in these patients for early detection and intervention has been strongly advocated by clinicians and policymakers [3–6].

Currently, screening strategy is classified as limited or extensive screening. Several studies have confirmed that limited screening strategy, including medical history, physical examination, routine blood tests, chest radiography, and some gender-specific cancer screening tests, is adequate for identifying the majority of occult cancers [7,8]. Computed tomography (CT) and 18F-fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) are also suggested by some researchers because they are more highly sensitive and reduce delays in diagnosis [9,10]. However, considering the cost and unimproved prognosis, the clinical value of extensive screening strategy is controversial [11,12]. Recently, several high-quality randomized controlled trials comparing the outcomes of limited and extensive screening strategies for occult malignancy in unprovoked VTE patients have been published [13–15]. Thus, we reviewed currently available clinical studies and conducted this meta-analysis to evaluate the efficacy and sensitivity of extensive screening strategy.

2. Material and methods

2.1. Data sources and searches

We searched PubMed, Cochrane, and EMBASE for all relevant studies from inception to January 21, 2017. There was no language restriction.
The following keywords were used: “screening” or “detection,” “cancer” or “tumor” or “malignancy,” and “unprovoked venous thromboembolism” or “idiopathic venous thromboembolism.” The bibliographies of included articles and reviews were also searched manually for potentially suitable references.

2.2. Study selection

Two investigators independently reviewed titles and abstracts from the initial literature search for eligibility. Discrepancies were resolved by consensus. The included studies met the following criteria: (1) evaluating the performance of extensive screening strategy (CT or PET/CT) for occult malignant diseases in patients with unprovoked VTE, (2) using appropriate reference standards for the diagnosis of malignancy, (3) reporting the necessary data to calculate the risk ratio (RR) of missed diagnosis and mortality (all-cause mortality or cancer-related mortality) or the true positive, false positive, false negative, and true negative screening results. Studies were excluded if they: (1) were comments, case reports, reviews, or conference abstracts, (2) reported on patients who overlapped with other studies. The corresponding authors of selected articles were contacted for further information, if necessary.

2.3. Data extraction and quality assessment

Two reviewers independently extracted information on study characteristics, enrolled participants, and outcome measurements according to a standardized form. The integrated results were checked for accuracy by the third investigator and disagreements were resolved by discussion. The “risk of bias” assessment method, recommended by the Cochrane Handbook of Systematic Reviews, was used to assess the quality of four randomized controlled trials (RCT) and one prospective concurrently controlled cohort study. For the four diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies Version 2 (QUADAS-2) was applied to evaluate the patient selection, index test, reference standard, and flow of patients throughout the study, and timing of the index test and reference standard [16].

Primary outcomes of interest were comparing the rate of missed diagnosis, all-cause mortality, and cancer-related mortality between the extensive screening group and the limited screening group. The sensitivity and proportion of false-positive findings of PET/CT as a screening tool for occult malignancy in patients with unprovoked VTE were assessed as secondary outcomes.

2.4. Statistical analysis

All meta-analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [17]. Heterogeneity was explored by the Cochran Q test and quantified by the inconsistency index ($I^2$) value. With regard to the Cochran Q test, $P < 0.05$ indicated that heterogeneity existed beyond what was expected by chance alone. The $I^2$ statistic measures the percentage of the total variation across studies, which ranges from 0% to 100%. We defined $I^2 > 50\%$ as substantial heterogeneity.

Given the small number of included studies, different screening strategy applied and clinical heterogeneity of patient characteristics, the random-effects model was used in this meta-analysis. For each primary outcome of interest, we calculated the pooled RR and the corresponding 95% confidence interval (CI) across studies in a random-effects model. For the assessment of PET/CT for occult malignancy in patients with unprovoked VTE, pooled sensitivity and proportion of false-positive findings was generated in a bivariate model and random-effects model, respectively. Each result was presented in forest plots. When significant heterogeneity was identified, we intended to perform several sensitivity analyses to investigate the possible sources for heterogeneity. Publication bias could be examined by a funnel plot asymmetry test and quantitatively assessed by Begg’s regression tests.

3. Results

3.1. Literature search results

The literature search from the database of PubMed and EMBASE, and additional citation tracking of reviews, yielded a total of 357 potentially relevant references. After reviewing the title and abstract, we excluded 321 studies that were unrelated to the topics, case reports, conference abstracts, and comments. Of the 36 retrieved studies, 27 papers were further excluded for the following reasons: evaluating only limited screening strategy, enrolling patients with provoked VTE, unclear reference standards for cancer diagnosis, and insufficient data. Finally, we identified 5 studies [9,13–15,18] comparing the outcomes of two screening strategies and 4 articles [10,19–21] reporting the efficacy of CT or PET/CT as a screening tool for occult malignancy in patients with unprovoked VTE (Fig. 1). Tables 1 and 2 showed the detailed characteristics of included studies. The assessment of methodological quality was summarized in Figs. 2 and 3.

3.2. Outcomes of extensive vs limited screening strategy

From the four RCTs and one prospective concurrently controlled cohort study, 1115 and 1159 patients with unprovoked VTE received limited or extensive screening strategy, respectively. Except for the SOMIT trail in 2004, the other four studies were conducted in the past 6 years. The limited screening strategy included medical history, physical examination, routine blood tests, chest radiography, and some gender-specific cancer screening tests. Only one extensive screening strategy used PET/CT; the other 4 performed a mandatory CT scan of the chest, abdomen, or pelvis. The median time of follow-up ranged from 1 to 2.5 years. The incidence of occult malignancy in unprovoked VTE ranged from 3.9% to 11.9% in these included studies (Table 1). The quality of methodology of 4 RCTs was high, while the other 1 intervention trial failed to show high quality due to non-randomized design (Fig. 2).

The RR of missed diagnosis in the five included studies ranged from 0.11 to 1.27, and only one trial found that limited screening strategy was more sensitive than extensive screening strategy. The pooled RR of 0.51 (95% CI, 0.20–1.28; $P = 0.15$) with no substantial heterogeneity ($I^2 = 48\%$, $P = 0.10$) verified that the risk of missed diagnosis was not significantly different between the extensive and limited screening group. Moreover, there was no statistically significant difference in cancer-related mortality between the two groups, with a pooled RR of 0.86 (95% CI, 0.46–1.62; $P = 0.65$) and no significant heterogeneity ($I^2 = 15\%$, $P = 0.32$). All-cause mortality in limited and extensive screening groups was not mentioned in one study. In the remaining four studies, we still observed no significant reduction in all-cause mortality in the extensive screening group, with a pooled RR of 0.86 (95% CI, 0.58–1.27; $P = 0.44$) and good homogeneity ($I^2 = 0\%$, $P = 0.90$) (Fig. 4).

3.3. Sensitivity and proportion of false-positive findings of PET/CT

Seven of the included studies provided sufficient data to calculate the absolute numbers of true positive, false negative, false positive, and true negative test results of extensive screening tools. Among them, three studies involved the performance of CT-based screening strategy in a total of 572 patients with unprovoked VTE; the other four articles focused on the assessment of PET/CT in 386 patients. All seven of these studies were published between 2010 and 2016. The study design and quality of methodology are summarized in Table 2 and Fig. 3.

The pooled sensitivity and proportion of false-positive findings of PET/CT for occult cancer in patients with unprovoked VTE was 95% (95% CI, 38%–100%) and 33% (95% CI, 20%–47%), respectively. There...
was no substantial heterogeneity in the pooled analysis of sensitivity ($I^2 = 0\%$, $P = 0.43$), while significant heterogeneity was observed in the analysis of proportion of false-positive findings ($I^2 = 85.4\%$, $P < 0.01$) (Fig. 5).

### 3.4. Sensitivity analyses and publication bias

Sensitivity analyses were performed to evaluate the stability of our results. Each statistical analysis was conducted by excluding one study. The data indicated that no significant change was observed in these sensitivity analyses. Specially, excluding the non-randomized trial also did not affect the primary outcomes (Fig. 6). Moreover, we observed no evidence of publication bias by assessing each funnel plot and Begg’s regression test.

### 4. Discussion

Currently, there are still debates regarding cancer screening strategies in patients with unprovoked VTE. In this meta-analysis, we included five large-scale controlled studies and found that extensive screening strategy did not reduce the risk of missed diagnosis compared with limited screening strategy. Moreover, pooled analysis showed that neither

#### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Extensive Screening Strategy</th>
<th>Limited, n</th>
<th>Extensive, n</th>
<th>Limited MD</th>
<th>CRM</th>
<th>ACM</th>
<th>Extensive MD</th>
<th>CRM</th>
<th>ACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandoni et al.</td>
<td>2016</td>
<td>Italy</td>
<td>RCT</td>
<td>CT of the chest, abdomen, and pelvis</td>
<td>97</td>
<td>98</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Carrier et al.</td>
<td>2015</td>
<td>Canada</td>
<td>RCT</td>
<td>CT of the abdomen and pelvis</td>
<td>431</td>
<td>423</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Piccioli et al.</td>
<td>2004</td>
<td>Italy, Spain, Netherlands</td>
<td>RCT</td>
<td>CT of the abdomen and pelvis</td>
<td>102</td>
<td>99</td>
<td>10</td>
<td>4</td>
<td>U</td>
<td>1</td>
<td>2</td>
<td>U</td>
</tr>
<tr>
<td>van Doormaal et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>CT of the chest and abdomen</td>
<td>288</td>
<td>342</td>
<td>14</td>
<td>8</td>
<td>24</td>
<td>12</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Robin et al.</td>
<td>2015</td>
<td>France</td>
<td>RCT</td>
<td>PET/CT</td>
<td>197</td>
<td>197</td>
<td>9</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, Randomized Controlled Trial; MD, missed diagnosis; CRM, cancer-related mortality; ACM, all-cause mortality. Limited, limited screening strategy; Extensive, extensive screening strategy; U, unclear.
all-cause mortality nor cancer-related mortality was improved by extensive screening strategy. We supposed that these results might be due to several reasons: First, owing to the systematic screening of cancer in developed countries, the incidence of occult cancer of these included studies was generally lower than previous reports [2,22,23], which may underestimate the difference of screening accuracy between the two screening strategies. Second, information about comorbidity of patients, which potentially affected all-cause mortality, was not provided by these studies. In fact, the occurrence of VTE in patients with malignant diseases has negative effects on overall survival, particularly in patients with early-stage cancer [24]. Third, most of the detected occult cancers were at metastatic stage and therefore associated with poor survival. Despite earlier diagnosis, it was still difficult to significantly improve the prognosis of these advanced-stage patients [13,14,18,25].

Recently, a similar meta-analysis has been published. As oncologists, Klein et al. focused on the cancer stage and clinical characteristics of patients with occult cancer at diagnosis [26]. However, from the view of vascular surgeons, we were concerned about the screening accuracy, risk and benefits of different screening strategies. Thus, we also evaluated the sensitivity and proportion of false-positive findings of PET/CT for occult cancer in patients with unprovoked VTE. Considering that the diagnosis of malignancy mainly depended on biopsy and histology, the pooled specificity and summary receiver operating characteristic curve were not generated in our study. Limited by the small number of studies, the performance of CT-based screening strategy was not evaluated either. Finally, the pooled sensitivity and proportion of false-positive findings of PET/CT was 95% and 33%, respectively. High sensitivity may be attributed to the feature that PET/CT could systematically scan the whole body and the fact that all locations and types of cancer could be comorbid with VTE [27]. Rondina et al. suggested that PET/CT could be a single, comprehensive imaging examination for the early detection of occult cancer in patients with unprovoked VTE [10]. However, one of the main drawbacks of PET/CT is the possibility of false-positive findings. Robin et al. assessed the frequency and invasiveness of additional testing following extensive and limited screening strategies in MVTEP trial, a higher number of additional invasive procedures were found in PET/CT group [28]. It did allow the detection of most cancers, but false-positive findings might cause unnecessary physical harm and financial loss.

Furthermore, a cost effectiveness analysis of 630 patients with unprovoked VTE concluded that extensive screening strategy with abdominal and chest CT and mammography in women resulted in additional costs (€365.75 per patient) because of the high percentage of false-positive findings leading to extra diagnostic investigations [29]. Coyle et al. also verified that the addition of abdominal and pelvic CT for the screening of occult cancer in patients with unprovoked VTE did not improve the utility values or the number of missed diagnoses, but it was associated with higher costs ($551 CDN) [30]. Radiation exposure of the extensive screening strategy was also concerning; a multiphasic CT scan of the abdomen and pelvis was determined to be equivalent to 442 chest radiographs, which was also contraindicated in patients with

### Table 2
Characteristics of 7 studies involving the performance of extensive screening tools for occult malignancy in patients with unprovoked VTE.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Tools</th>
<th>Patients, n</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sensitivity</th>
<th>FPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandoni et al.</td>
<td>2016</td>
<td>Italy</td>
<td>RCT</td>
<td>CT</td>
<td>98</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>83</td>
<td>83.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Carrier et al.</td>
<td>2015</td>
<td>Canada</td>
<td>RCT</td>
<td>CT</td>
<td>423</td>
<td>14</td>
<td>5</td>
<td>49</td>
<td>355</td>
<td>73.7%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Carrier et al.</td>
<td>2010</td>
<td>Canada</td>
<td>Pilot study</td>
<td>CT</td>
<td>51</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>43</td>
<td>100%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Robin et al.</td>
<td>2015</td>
<td>France</td>
<td>RCT</td>
<td>PET/CT</td>
<td>197</td>
<td>9</td>
<td>1</td>
<td>38</td>
<td>124</td>
<td>90%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Rondina et al.</td>
<td>2012</td>
<td>USA</td>
<td>Observational study</td>
<td>PET/CT</td>
<td>40</td>
<td>1</td>
<td>0</td>
<td>24</td>
<td>15</td>
<td>100%</td>
<td>61.5%</td>
</tr>
<tr>
<td>Alfonso et al.</td>
<td>2013</td>
<td>Spain</td>
<td>Cohort study</td>
<td>PET/CT</td>
<td>99</td>
<td>7</td>
<td>2</td>
<td>24</td>
<td>66</td>
<td>77.8%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Chauchard et al.</td>
<td>2014</td>
<td>France</td>
<td>Observational study</td>
<td>PET/CT</td>
<td>50</td>
<td>12</td>
<td>0</td>
<td>10</td>
<td>28</td>
<td>100%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, Randomized Controlled Trial; TP, true positive; FN, false negative; FP, false positive; TN, true negative; FPP, proportion of false-positive findings.
renal failure [31]. Moreover, a diagnosis of pulmonary embolism was made by CT pulmonary angiography, which was adequate for detecting lung cancer; the additional chest CT screening would cause extra radiation burden. Notably, patients and their families might also experience fear, anxiety, and stress with more testing. To date, the psychological impact of false-positive test results on patients has not been assessed yet, which may be considered for future studies.

The SOME trial suggested that only 4% of patients with unprovoked VTE might have an underlying malignancy [14]. Given this low incidence of cancer and the potentially physical and emotional harm, extensive screening for each patient did not seem reasonable. The next step could be to select patients for screening by identifying patients at high risk of occult cancers who might benefit from extensive screening strategy. A RIETE trial reviewed 5863 patients, 444 of which were diagnosed with occult cancer, and found that gender, age, weight loss, chronic lung disease, raised platelet count, and anemia were associated with higher risk of occult cancer. On the contrary, prior VTE, recent surgery, hormone use, and varicose veins have negative correlation with occult malignancy. Thus, a prognostic score was built assigning 1 point to male gender, raised platelet count, or chronic lung disease; 2 points

![Fig. 4. Primary outcomes: pooled risk ratio and the corresponding 95% CI for the risk of missed diagnosis (A), cancer-related mortality (B), and all-cause mortality (C).](image1)

![Fig. 5. Secondary outcomes: pooled sensitivity and proportion of false-positive findings of PET/CT.](image2)
to age > 70 years or anemia; and 2 negative points to postoperative or prior VTE to identify unprovoked VTE patients at increased risk for occult malignancy [32]. In addition, based on the epidemiological evidence, occult pancreas and breast cancers have been found to be the most common type [27]. Therefore, some high-risk potential cancer sites deserved more attention.

According to the National Institute for Health and Care Excellence (NICE) guidelines, in patients aged over 40 years with a first unprovoked VTE episode, an abdominal and pelvic CT, plus a mammogram for females, should be performed after normal routine tests [33]. However, considering the results of this meta-analysis, physicians should carefully inform these patients of the risks and benefits of extensive screening strategy. In the absence of solid data on cost-effectiveness and mortality reduction, one has to discuss both strategies with the patient [34]. Furthermore, low-molecular-weight heparin was the only suggested anticoagulation therapy for patients with unprovoked VTE and malignant diseases [35,36].

Our meta-analysis has several limitations. First, the screening tools of each screening strategy were not totally identical, and the sensitivity was different among these imaging tools. Thus, for each study, we determined the rate of missed diagnosis, all-cause mortality, and cancer-related mortality for the limited and extensive screening groups, and we calculated a RR and its 95% CI. Ultimately, we pooled RRs across studies by using a random-effects model approach. Second, the primary endpoints were different among these studies, which led to different estimates in the number of patients to be included in the power calculation. Third, despite the large sample size of enrolled studies, mortality was still low, which may be underpowered to detect the difference between extensive and limited screening strategy. In addition, the mean time of follow-up of the included studies was relatively short, long-term mortality was unclear. Finally, the statistical analysis used in the enrolled studies was intention-to-test analysis without considering the loss to follow-up, the number of patients who did not receive the assigned intervention, and the number of patients who withdrew consent.

5. Conclusions

Extensive screening strategy did not show a clinically significant benefit over limited screening strategy in detecting underlying malignancy in patients with unprovoked VTE. Considering the high cost and added physical and emotional harm, current evidence did not support a net clinical benefit to perform an extensive occult cancer screening in the setting, and the decision to conduct additional imaging tests should be made on a case-by-case basis. Future studies are warranted to identify patients at a high risk of occult cancer who could substantially benefit from extensive screening strategy.

Declaration of interests

All authors declare no conflicts of interest.

References


M. Chauchard, K. Benali, T. Papi, K. Sacre, Positive emission tomography combined with computed tomography as a screening tool for occult malignancy in patients


