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Vena Cava Filters and In-Hospital Case Fatality Among Patients With Pulmonary Embolism: Results From a Large Population-Based Study

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Abstract

In patients with venous thromboembolism (VTE), vena cava filters (VCFs) are currently only recommended when anticoagulant treatment is contraindicated or if VTE has recurred despite adequate anticoagulation. However, evidence on the efficacy of filter in patients with VTE is not compelling. We evaluated potential efficacy of VCF in reducing in-hospital mortality in a large population of patients presenting with a first episode of pulmonary embolism (PE). Patients were collected using regional hospital-discharge databases covering a population of more than 13 million of inhabitants in Northern Italy. For each year of observation, we calculated the proportion of cases with VCF among all PE incident cases. The temporal trend of VCF application during the study period was also derived. The effect of VCF use on in-hospital case-fatality rate was evaluated with a multivariate regression model and with the use of propensity score matching. During the study period (2002-2012), 60 813 patients were hospitalized for a first episode of acute PE. In-hospital case-fatality rate for PE was 13.3%. Vena cava filters were used in 745 (1.22%) patients. The annual use of VCF remained stable from 2002 to 2008, while it progressively decreased afterward. After adjustment for available confounders, case-fatality rate remained significantly lower in patients who received VCF compared to the one registered in patients who did not (odds ratio [OR] 0.46; 95% confidence interval [CI]: 0.34-0.62). Propensity score matching gave similar results (OR: 0.42; 95% CI: 0.30-0.61). Vena cava filters were infrequently used in patients with acute PE. Insertion of VCF appeared to sensibly reduce all-cause in-hospital mortality in this subgroup of patients.

Keywords

venous thromboembolism, pulmonary embolism, mortality, prognosis, vena cava filters

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Introduction

Pulmonary embolism (PE) is a common and increasingly diagnosed disease.[1] Despite advances in diagnosis and management of this disease, PE remains a major cause of morbidity and mortality.[2,3] Conventional treatment of PE consists of reperfusion therapy in high-risk patients and anticoagulant therapy only (parenteral agents followed by vitamin K antagonists or direct oral anticoagulants) in the remaining patients.[3,4] The role of vena cava filters (VCFs) in patients with acute PE remains controversial. Two randomized controlled trials (RCTs) failed to demonstrate a benefit from VCF's insertion in addition to anticoagulant therapy in patients with acute venous thromboembolism (VTE).[5,6]

Thus, VCFs are currently only recommended when anticoagulant treatment is contraindicated or if VTE has recurred despite adequate anticoagulant therapy.[3] However, evidence on

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the efficacy of filter in patients with VTE is not compelling. The use of VCF is extremely heterogeneous worldwide, being particularly high in the United States.[7,8]

Using data recorded in the Lombardy and Piedmont regions hospital discharge databases, covering a population of more than 13 million inhabitants, we aimed to collect information on the use of VCF in patients presenting with a first episode of PE over a time period of 11 years (2002-2012) and to evaluate their potential efficacy in reducing total in-hospital mortality in this population.

Material and Methods

Patient Selection and Eligibility

The study was conducted in adherence to the Declaration of Helsinki. Source of database, patient selection methods, and eligibility criteria were extensively described in a previous publication.[1] Briefly, information on all hospital admissions for PE between January 1, 2000, and December 31, 2012, in Lombardy and Piedmont regions, Italy (total population: 13 million), were obtained from the hospital discharge databases provided by the 2 Regional Centers for Health Statistics. Patients with PE were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9-CM*). Only patients with a primary or secondary discharge diagnosis corresponding to codes 415.11 or 415.19 were included.

To comply with the national law dispositions in terms of privacy, an ad hoc identification number was developed for each patient so as to eliminate any potential identifiers. In order to identify new cases (incident events), only the first hospitalization with a diagnosis of PE during the entire study period was collected. Since information before 2000 was not available, we excluded all events occurred during the first biennium of observation (2000-2001).

The following information was collected: gender, date of birth, date and hour of hospital admission and discharge, department of admission and discharge, vital status at discharge, duration of the hospitalization (in days), primary and 5 other secondary discharge diagnoses at most, and primary in-hospital procedure with 4 other secondary procedure codes at most.

Patients with VCF were identified collecting all incident cases in which one of those 5 procedure codes was 387 (according to *ICD-9*).

In-hospital case-fatality rate was calculated as the proportion of fatal cases (patients who died during hospitalization) over the total of incident cases.

Using available primary or secondary discharge diagnoses, the overall comorbid status of each patient was assessed with the Charlson Comorbidity Index (CCI), a cumulative score based on 17 medical conditions with varying weights assigned to different conditions. Patients were subsequently divided into 5 comorbidity categories according to their CCIs (the lowest risk category being "0" and the others being "1," "2," "3," and "4 or more").[9]

We also identified patients at particularly high risk for in-hospital mortality as having at least 1 of the following conditions: (1) cardiogenic shock (at least 1 of the diagnostic codes, being 78550 or 78551); (2) mechanic ventilation (one diagnostic code = V4611); and (3) use of parenteral thrombolytic agents (one procedure code = 9910).

Statistical Analysis

We calculated the proportion of cases with VCF among the total of PE incident cases for each year of observation (2002-2012) and we investigated the possible temporal trend in their application using logistic regression.

General characteristics and comorbidities of VCF and non-VCF cases were compared using Student t test or χ^2 test when appropriate.

First, by applying a univariate logistic regression model, we compared in-hospital fatality between patients with VCF and non-VCF. Then, to estimate the odds ratio (OR) of mortality associated with VCF use, we designed a multivariate logistic model including factors that at univariate analysis resulted to be associated with in-hospital mortality (namely, age, gender, and CCI).

To further control a possible selection bias caused by the nonrandomized assignment of patients to the intervention group (VCF), we performed propensity score matching (PSM).[10-12]

Propensity score defines the probability of each individual patient to be treated based on a given set of covariates. The use of PSM balances the distribution of covariates between treatment and control groups, minimizing the influence of potential biases. Variables related to the decision to treat patients with VCF were included in a logistic regression model. Two different PSMs were performed: the first with a matching ratio 1:1 and the second with a multiple matching 1:10 (nearest neighbor methods, with replacement).

In addition, we repeated all the analyses after excluding all fatal cases with a hospital stay of less or equal to 2 days and patients without sufficient information on the exact duration of hospitalization. This analysis was performed to account for possible immortal time bias. Immortal time bias may occur when the determination of a treatment status involves a delay or wait period in which individuals, who end up in the treated or exposed group, have to be alive and event free until the treatment definition is fulfilled.[13] In this study, all patients who received a filter were obviously alive at the time of the procedure, whereas other patients may have not received a filter because they died before the filter could be placed, thus potentially affecting the validity of our results.[14]

Finally, all the abovementioned principal and sensitivity analyses were repeated for the subgroup of patients defined to be at high risk of mortality (see previous paragraph). Statistical significance was set at 2-tailed $P < .05$. We used psmatch2 for the propensity score analyses and Stata version 11.2 (StataCorp, College Station, Texas) for all data analyses.

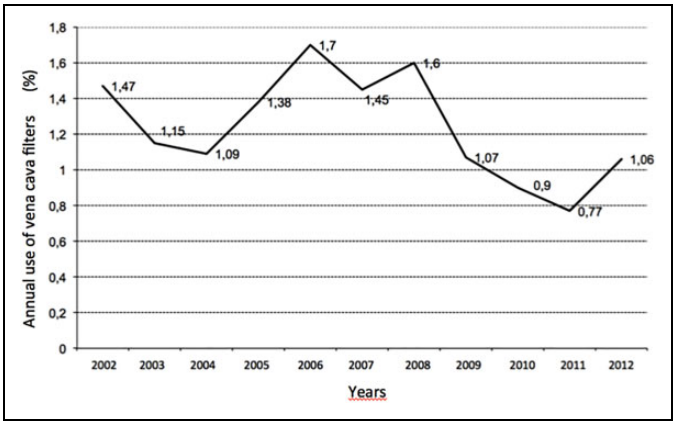

Figure 1. Temporal trend of in the 11 years of observation of the study.

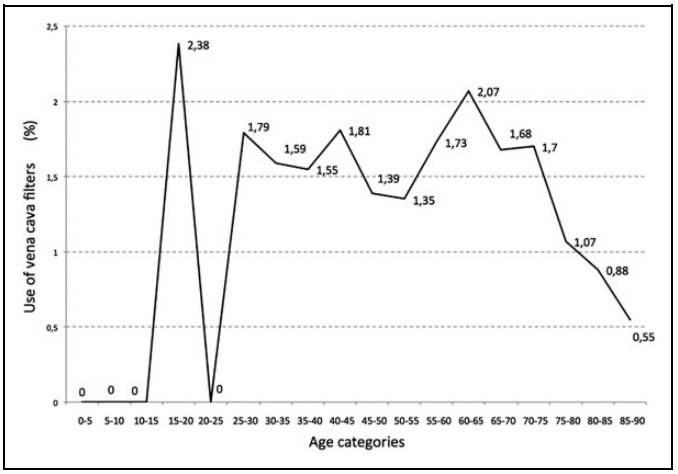

Figure 2. Age-specific use of vena cava filters.

Table 1. Baseline Characteristics and Comorbidities of Patients.[a]

Characteristics	PE Without VCF 60 068 (98.78)	PE With VCF 745 (1.22)	*P* Value[b]
Female, N (%)	35856 (59.7%)	397 (53.3%)	<.001
Mean age (years ± SD)	72.9 ± 14.1	68.9 ± 13.6	<.001
Hospital stay (days)	13 ± 11	20 ± 17	<.001
Acute myocardial infarction, N (%)	1240 (2.1)	18 (2.4)	.50
Chronic heart failure, N (%)	3499 (5.8)	27 (3.6)	.01
Cerebrovascular diseases, N (%)	4136 (6.9)	67 (9.0)	.02
Dementia, N (%)	1177 (1.9)	5 (0.7)	.01
Pulmonary diseases, N (%)	4266 (7.1)	21 (2.8)	<.01
Liver disease, N (%)	325 (0.5)	1 (0.1)	.13
Type 2 diabetes, N (%)	4011 (6.7)	36 (4.8)	.05
Renal disease, N (%)	1860 (3.1)	15 (2.0)	.09
Metastasis, N (%)	3769 (6.3)	63 (8.5)	.01
Patients with cancer, N (%)	6777 (11.3)	140 (18.8)	<.01
Mean CCI ± SD	0.83 ± 1.28	0.97 ± 1.38	.01

Abbreviations: CCI, Charlson Comorbidity Index; PE, pulmonary embolism; SD, standard deviation; VCF, vena cava filter.
[a]Defined as patients with *ICD-9-CM* in at least 1 of 5 comorbidity categories.
[b]Pearson χ^2 test for categorical variables and Student *t* test for continuous variable.

Results

During the 11 years of the study period, a total of 60 813 patients were hospitalized for a first episode of acute PE (according to primary or secondary discharge codes). Of these, 745 (1.22% of the total population) patients received VCF during the index hospital stay.

The annual use of VCFs remained stable from 2002 to 2008, while it progressively decreased afterward (Figure 1).

Baseline characteristics of patients with VCF and non-VCF are summarized in Table 1. Patients with VCF were significantly younger, were more frequently male, and more frequently had concomitant cancer compared to patients with non-VCF.

Mean CCI was significantly higher in patients with non-VCF, given the increased frequency of cancer comorbidities (as well as metastatis) among patients with VCF.

Moreover, we observed a longer hospital duration in patients with VCF and, in terms of age, a decrease in VCF use in patients aged ≥75 years (Figure 2).

A total of 8071 patients died during hospitalization, yielding an in-hospital case-fatality rate of 13.3%. The proportion of fatal cases was significantly lower in patients with VCF (6.2%) compared to those with non-VCF (13.4%; $P < .0001$). Vena cava filter placed in 712 (1.21%) of 58 618 patients defined as having low-risk PE. The in-hospital mortality rate was 40 (5.6%, 95% confidence interval [CI], 4.1%-7.6%) of 712 in patients with VCF and 6724 (11.6%, 95% CI, 11.4%-11.9%) of 57 906 in patients without filter ($P < .001$). Conversely, among the 2195 patients defined as having high-risk PE (patients with cardiogenic shock, use of mechanic ventilation, and use of parenteral thrombolytic agents), a filter was placed in 33 (1.50%) patients. The in-hospital mortality rate was 6 (18.2%, 95% CI: 7.6%-36.1%) of 33 in patients with VCF and 1304 (60.3%, 95% CI: 58.2%-62.4%) of 2162 in patients without filter ($P < .001$).

In the whole population, case fatality remained significantly lower in patients who received VCF in comparison to those who did not (OR: 0.46; 95% CI: 0.34-0.62) after adjustment for possible confounders (age, male sex, CCI, cancer) in the multivariate analysis (Table 2).

A large reduction of case-fatality rate with placement of VCF was obtained when the multivariate analysis was restricted to high-risk PE (OR: 0.18; 95% CI: 0.07-0.44).

As a further sensitivity analysis, the 745 patients with VCF were matched with 745 patients with non-VCF with similar characteristics (using a logistic regression model in which variables potentially related to treatment decision were included). Regression models after propensity score-matched pairs showed a significantly decreased risk of in-hospital case-fatality rate for filter insertion compared to no insertion (OR: 0.42; 95% CI: 0.30-0.61).

Table 2. Independent Predictors of In-Hospital Mortality: Multivariate Logistic Model.

	Odds Ratio	95% CI
Age (for 1-year increase)	1.038	1.036-1.040
Male gender	1.21	1.15-1.27
CCI = 1[a]	1.38	1.30-1.47
CCI = 2[a]	1.86	1.73-1.99
CCI = 3[a]	2.30	2.09-2.52
CCI ≥ 4[a]	3.09	2.81-3.39
Vena cava filter	0.46	0.34-0.62

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval.
[a]Reference: CCI = 0.

Finally, to minimize the potential influence of immortal time bias, we excluded from the analysis patients who died within the first 48 hours after hospitalization and patients without sufficient information on the exact duration of hospitalization. The multivariate analysis performed on the patients who survived the first 48 hours of hospital admission confirmed the efficacy of VCF insertion in reducing PE case fatality (OR: 0.51; 95% CI: 0.34-0.78).

Discussion

The results of our study, based on hospital discharge records, show an infrequent and progressively decreasing use of VCF in a large population of patients presenting with a first episode of PE in Northwestern Italy. The rate of insertion was similarly low in the subgroup of patients with a more severe presentation (patients with cardiogenic shock, use of mechanic ventilation, and use of parenteral thrombolytic agents). However, overall mortality rates were significantly reduced by VCF even after adjusting for a number of available potential confounding variables.

Previous observational studies have reported higher rates of VCF insertion in the United States.[8,15,16] Conversely, information on the use of VCF outside the United States is lacking. The use of VCF in patients presenting with acute PE who can receive anticoagulant treatment is not supported by RCTs, where the use of a retrievable inferior VCF plus anticoagulation compared to anticoagulation alone did not reduce the risk of symptomatic recurrent PE even in patients at high risk.[5] Thus, current guidelines suggest the use of these devices only in patients with acute PE and absolute contraindications to anticoagulation or in case of recurrence of PE despite therapeutic levels of anticoagulation.[3] Unfortunately, even in this setting, evidence on the efficacy and safety of VCF is still lacking.

Using Lombardy and Piedmont regions hospital discharge databases, we were able to assess the efficacy of VCF insertion in reducing all cause in-hospital mortality by collecting information on a considerable number of patients with acute PE and then comparing 745 VCF and non-VCF pairs, matched using the propensity score technique. In our study, the insertion of VCF was associated with a reduction in in-hospital total mortality. These findings were confirmed by the results of the subgroup analysis in which only patients with high-risk PE were included and also by the analysis performed, after the exclusion of all fatal cases with a hospital stay of 2 days or less, to reduce the risk of immortal time bias.

Using data from the US Nationwide Inpatient Sample database that collected information on more than 2 million of hospitalizations for acute PE form 1999 to 2008, Stein et al compared the in-hospital all-cause case-fatality rate of this disease according to the use of VCF.[15] The study showed a significant reduction in case-fatality rate with VCF placement both in unstable patients, regardless whether or not they received thrombolytic therapy, and in stable patients who received thrombolytic therapy suggesting a potential benefit in these groups of patients. However, the absolute risk reduction in the mortality rate in the latter group may be considered clinically irrelevant (<1%) and findings of this study should be interpreted with caution since the results were not adjusted for potential confounders. In more recent retrospective analyses of the Premier administrative database, use of VCF was associated with a lower mortality in patients with unstable PE and in patients with PE who underwent pulmonary embolectomy or who receive thrombolytic therapy.[16,17] Finally, Muriel et al evaluated the efficacy and safety of VCF insertion in patients with acute DVT or PE judged at high risk of bleeding collected from the RIETE registry.[18] After PSM, 344 patients with VCF had a nonsignificant trend toward a lower risk of all-cause death, a significantly lower rate of PE-related mortality and a higher rate of VTE recurrence compared to 344 patients with non-VCF. However, despite the perceived risk of bleeding, many of the included patients were treated with concomitant anticoagulation, although generally at a lower dose than the standard one. Furthermore, results were not adjusted for the presence of immortal time bias.

Thus, considering the results of our and previous studies, the insertion of VCF appears to be beneficial in patients with PE with more severe presentation as well as in patients with a contraindication to anticoagulation. However, definition of patients with "more severe presentation" and/or at "high risk" is quite variable among the studies, leaving uncertainty in the identification of the patients who may benefit from VCF insertion. Despite some studies suggest a potential benefit of VCF in reducing the overall mortality even in selected categories of patients with stable PE, these findings should be interpreted with caution since information about concomitant antithrombotic therapies in these studies is generally lacking.[19]

Of note, in-hospital mortality in our study seems to be higher compared to other studies who evaluated the role of VCF in this setting. However, usually, patients included in RCTs are selectively chosen and tend to have a lower mortality rate than patients included in epidemiological observational studies. Other previous large cohort studies, including unselected patients, gave results similar to our study.[2]

Contrary to previous studies,[20] we found an age-specific reduction in the use of VCF. This may be due to a perceived difference by local physicians in the efficacy of VCF in older

patients. Alternatively, considering the very low number of patients treated with VCF in each age-group, this difference may be due to chance.

We are fully aware that our study has some limitations, typical of epidemiological studies based on discharge records databases. First, although previous studies demonstrated a good accuracy of discharge codes for the identification of patients with objectively confirmed acute PE and although we only selected patients with first or second diagnostic codes of PE in order to avoid potential false-positive diagnoses, a low sensitivity and specificity of this method in this specific setting cannot be excluded.[21,22] Comorbidities could be identified only using discharged codes (*ICD-9-CM*) and information on concomitant diseases and risk factors is unsatisfactory and probably quite underreported. Thus, in multivariate analysis, we could only adjust our results for a limited number of factors and our findings should be considered with extreme caution.

Second, we have no information about concomitant antithrombotic therapies nor about the clinical reason for VCF implantation; thus, we were not able to adjust our results accordingly. Despite our trying to make patients groups comparable, using PSM according to the measured characteristics, residual confounding factors may still have occurred since only a limited number of variables could be evaluated.

Third, we focused our study on in-hospital mortality rates, the only available in hospital discharge records databases, but we were not able to assess long-term mortality of our patients.

Finally, the presence of immortal time bias could have positively influenced our results.

Patients who survived acute phase of PE are more likely to be treated with a VCF. This may result in unrealistic low mortality rate for patients treated with a VCF. Although we are aware that the best way to prevent immortal time bias would be to perform a time-dependent analysis, this approach could not be used since information on the day of VCF placement is lacking. Therefore, we decided to exclude all fatal cases with a hospital stay less or equal to 2 days, since these seriously ill patients were less likely to be treated with a VCF. This approach yielded similar findings, confirming the results of our primary analysis.

In conclusion, VCFs were infrequently used in patients with acute PE in our large cohort from Northwestern Italy. However, insertion of VCF appeared to reduce all-cause in-hospital mortality in this population.

However, these findings can be considered only hypothesis generating and need to be confirmed in specifically designed prospective studies with a better control of individual clinical variables.

Declaration of Conflicting Interests

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