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Temporal trends in outpatient management of incident pulmonary embolism and associated mortality

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ABSTRACT

Introduction: In clinical trial settings, outpatient management of pulmonary embolism (PE) is feasible and safe, but less is known on its use in routine care. We determined trends in outpatient management of PE and associated mortality in a large non-select patient population.

Methods: All residents of Quebec, Canada with a first-ever work-up for suspected PE in the emergency department (ED) over 10 years were included. Patients could transition to outpatient management and from unconfirmed to confirmed PE in a time-varying fashion. Comparing the years 2005–9 with 2000–4, we assessed the odds ratio (OR) for outpatient management, and relative risk (RR) for all-cause mortality, readmissions for PE, and major bleeding in 30 days. We adjusted the RR for a mortality risk score.

Results: Of 15,217 patients included, 7583 were outpatients (7.5% confirmed PE) and 7634 were inpatients (60.6% confirmed PE). In all, 10.9% of patients with confirmed PE were outpatients, but outpatient management of confirmed PE was more likely in the latter study period (OR 1.73, 95%CI 1.44–2.09). Among outpatients with confirmed PE, mortality (RR 0.84, 95%CI 0.15–4.61) and readmission (RR 1.25, 95%CI 0.45–3.48) rates were stable, and only 3 major bleeding events were noted. Inpatients with confirmed PE had stable mortality rates (RR 0.95, 95%CI 0.72–1.24).

Conclusion: Outpatient PE management increased over 10 years while remaining fairly uncommon. Nevertheless, stable mortality and readmission rates indicate this practice is safe in routine care, and add to the growing evidence in support of outpatient PE management.

1. Introduction

The annual rate of hospital admissions for pulmonary embolism (PE) in the United States has nearly tripled from 1993 to 2012 [1], a dramatic rise in part explained by the increased use of computed tomography (CT) in the emergency department (ED) [2]. Coupled with the growing cost of inpatient PE management [3], outpatient management of low-risk PE is increasingly considered feasible and safe. As early as 2005, the widely-cited Pulmonary Embolism Severity Index (PESI) score was suggested [4] and subsequently used to select low-risk PE patients in a randomized trial assessing the safety of outpatient management [5]. A later trial compared outpatient PE management based strictly on a clinical decision rule [6] with additional N-terminal pro-brain natriuretic peptide testing [7]. However, safety evidence from both trials is limited by a very low number of deaths in outpatient arms. Further, the proportion of cancer in trial subjects ranged from 1% to 8.5% [5,7], while in population-based PE cohorts this proportion exceeds 20% [8,9]. Thus, the generalizability of trial conclusions to routine practice is unclear.

Further, the utilization of outpatient PE management in the 'real world' setting is largely unknown. Using data from a patient registry of almost 51,000 patients with newly diagnosed venous thromboembolism (VTE), it was recently reported that only 1% of European patients presenting with acute PE from 2001 to 2013 were managed as outpatients although about a quarter were low-risk PE [10].

We hypothesized that this potential underuse of outpatient PE management may not be observed in a large non-select population. Thus, the objectives of this study were to examine population-based

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trends in the outpatient management of acute PE and associated mortality during a 10-year period.

2. Methods

2.1. Data sources

We used medical data from the *Régie de l'assurance maladie du Québec* (RAMQ), the provincial healthcare provider as part of the Q-VTE study [9,11]. As of 2009, RAMQ covered > 90%, (~1 million) of individuals > 65 years of age for drug prescription insurance, and 35% (~1.7 million) of individuals < 65 [12]. We obtained demographic information, diagnoses (coded using International Classification of Diseases, 9th Revision [ICD-9]), and pharmacy-filled prescriptions. These data were linked to an inpatient database, *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ÉCHO), to obtain hospital diagnoses and procedures. Finally, these data were linked with the Institut de la statistique du Québec (ISQ) for vital statistics. The study was approved by the Commission d'accès à l'information du Québec, the data custodian.

2.2. Study population

We identified all patients aged > 18 who had a first-ever PE claim (ICD-9 codes 415.0, 415.1, 673.2) recorded in the ED between January 1, 2000 and September 31, 2009. The date of PE claim defined cohort entry. To ensure sufficient baseline data, we included patients with RAMQ prescription drug coverage for ≥ 6 months before cohort entry. We were interested strictly in initial management of PE and thus excluded patients who had diagnoses of venous thromboembolism (VTE) at any time before cohort entry. To further ensure initial management and allow for confirmation of PE diagnoses, we excluded patients with anticoagulant use in the year before cohort entry.

2.3. Outpatient and inpatient management

Outpatient management was determined in a time-dependent fashion up to 7 days from cohort entry (Fig. 1, Supplementary Material). During this period, transition from inpatient (which was the default) to outpatient management could occur on days 2 through 7 of follow-up in two scenarios: 1) if the patient had a new drug prescription or new claim made outside the ED and no ED activity (claims or procedures) or hospital admission were recorded on that day; and 2) if one calendar day elapsed after the last ED activity and no hospital admission was recorded. Once a patient transitioned to outpatient management, this category was carried forward to the following days of follow-up. Conversely, if a patient was admitted to the hospital immediately after the ED encounter, they could not transition to outpatient status even if they were discharged through day 7 of follow-up. Patients who did not meet criteria 1 or 2 were inpatients for the entire follow-up.

2.4. Confirmed and unconfirmed pulmonary embolism

In Quebec, claims for PE are used in the ED as rule-out codes rather than confirmed diagnoses. Thus, patients entered the cohort by default with unconfirmed (or suspected) PE and were allowed to transition to confirmed PE following a two-step algorithm. During inpatient management, we identified admission (given the admission date) or primary discharge diagnoses (given discharge date) of PE through day 7 of follow-up. This code was confirmatory for the PE diagnosis if an imaging test (pulmonary scintigraphy, pulmonary angiography, or CT of the chest) was recorded on previous days of follow-up. During outpatient management, we identified new filled prescriptions for anticoagulants (vitamin K antagonists, heparin, or low-molecular-weight heparin) through day 7 of follow-up. These prescriptions were confirmatory if an imaging test had been performed during the initial ED encounter. Thus, exposure during each day from day 2 to day 7 was reclassified as one of four possible combinations of inpatient/outpatient management and unconfirmed/confirmed PE, and was carried forward from day 7 to the remaining days of follow-up (Fig. 1 in Supplementary Material).

2.5. Study outcomes

The primary outcome was all-cause mortality through day 30 of follow-up, as determined by vital statistics from ISQ. Two secondary outcomes were also determined during the 30-day follow-up. First, we defined major bleeding as a hospital stay with a diagnostic code for bleeding into a critical organ, gastrointestinal bleeding, or general bleeding (Table 1, Supplementary Material). These codes correspond to the International Society on Thrombosis and Heamostasis definition for major bleeding [13] and have been previously shown to be concordant with anatomic sites of bleeding [14]. Second, we defined readmissions for PE among outpatients as hospital readmissions with a diagnostic code for PE in the admission or primary position and occurring after the determination of outpatient management.

2.6. Baseline covariates

We identified the following transient, VTE-provoking factors ≤ 91 days before cohort entry: pregnancy, hormonal therapy (oral contraceptive pills, intrauterine device, or hormonal replacement therapy), surgery, trauma, or fracture. Cancer and metastases were defined as diagnoses in the year before cohort entry, whereas chemotherapy and radiotherapy were recorded ≤ 3 months before cohort entry. Concomitant deep vein thrombosis was defined using claims made in the ED at cohort entry. Charlson comorbidity index and atrial fibrillation were determined by diagnoses made any time before cohort entry. Previous major bleeding was identified in the year before cohort entry. Finally, we determined a modified HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history/disposition, labile international normalized ratio [INR], elderly, drugs/alcohol consumption) based on diagnoses at any time before cohort entry and excepting INR [15].

2.7. Statistical analyses

Descriptive statistics were used to summarize the characteristics of outpatients and inpatients stratified by cohort entry in 2000–2004 and 2005–2009. We used logistic regression to assess the odds ratio (OR) with 95% confidence intervals (CI) of a PE patient in 2005–2009 to be an outpatient, with 2000–2004 as reference. For this analysis, if a patient transitioned to outpatient management through day 7 of follow-up, they were considered outpatients. Follow-up for all-cause mortality and major bleeding began at cohort entry, and incidence rates were the number of events divided by the entire person-time spent at the relevant exposure category, with 95% CI based on Poisson distribution. For readmissions for PE, follow-up started on the day of transition to outpatient management, and incidence rates were events divided by observation time as unconfirmed-outpatient or confirmed-outpatient. We used Poisson regression to estimate the relative risk (RR) and corresponding 95% CI, comparing rates in 2005–2009 with those in 2000–2004 as reference. We adjusted the RR to the deciles of a disease risk score (DRS) for mortality at 30 days. The DRS was derived from logistic regression on the 2000–2004 dataset of all suspected PE [16]. The DRS may be more suitable for adjustment than propensity score with a changing exposure pattern and ample historic data, both of which apply to our dataset [16]. Analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).