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Clinical presentation and outcome of venous thromboembolism in COPD

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a moderate risk factor for venous thromboembolism (VTE), but neither the clinical presentation nor the outcome of VTE in COPD patients is well known.

The clinical presentation of VTE, namely pulmonary embolism (PE) or deep venous thrombosis (DVT), and the outcome at 3 months (death, recurrent VTE or bleeding) were compared between 2,984 COPD patients and 25,936 non-COPD patients included in the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry. This ongoing international, multicentre registry includes patients with proven symptomatic PE or DVT.

PE was the more frequent VTE presentation in COPD patients (n=1,761, 59%). PE presentation was more significantly associated with COPD patients than non-COPD patients (OR 1.64, 95% CI 1.49–1.80). During the 3-month follow-up, mortality (10.8% *versus* 7.6%), minor bleeding (4.5% *versus* 2.3%) or first VTE recurrences as PE (1.5% *versus* 1.1%) were significantly higher in COPD patients than in non-COPD patients. PE was the most common cause of death.

COPD patients presented more frequently with PE than DVT. It may explain the worse prognosis of COPD patients, with a higher risk of death, bleeding or VTE recurrences as PE compared with non-COPD patients. Further therapeutic options are needed.

KEYWORDS: Chronic obstructive pulmonary disease, deep venous thrombosis, prognosis, pulmonary embolism, venous thromboembolism

Acute pulmonary embolism (PE) and deep venous thrombosis (DVT) are manifestations of the overall disease known as venous thromboembolism (VTE). Epidemiological studies have demonstrated that DVT is the most frequent clinical presentation of VTE in general settings, with nearly two presentations of DVT to every one presentation of PE [1, 2]. However, this clinical presentation may be influenced by certain risk factors. For example, total knee replacement surgery is a well-known predisposing factor for DVT [3]. Chronic obstructive pulmonary disease (COPD) is a moderate predisposing factor for VTE, principally when associated with hospitalisation [3]. *Post hoc* analyses of administrative healthcare databases using diagnostic codes suggest that the increased risk of VTE in COPD patients may be predominantly manifested in the form of PE rather than DVT [4–7]. An increased expression of VTE as PE in COPD patients may be problematic since the mortality of COPD patients with PE is particularly high [8, 9], and COPD has been integrated in prognostic scores such as the Simplified Pulmonary Embolism Severity Index [10]. COPD has also been associated with inappropriate management in the case of suspected PE [11] and the suggestion of PE may be challenging in COPD patients [12] because of the similarities in symptoms. The former consideration may particularly apply during COPD exacerbation [13–15], a situation in which undiagnosed PE was found in an autopsy study in up to 30% of COPD patients who died [16]. Finally, COPD has been associated with an increased risk of unsuspected fatal PE [17]. Confirming the increased rate of PE in COPD patients should prompt clinicians to enhance PE suspicion in COPD patients at risk for VTE.

The RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry is an ongoing international (Spain, France, Italy, Israel, Switzerland and Germany), multi-centre prospective registry of consecutive patients presenting with

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symptomatic acute VTE. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [18–20]. We then conducted this study with two goals: 1) to check whether COPD patients really present more frequently with PE rather than DVT; and 2) to define the clinical characteristics and outcome of COPD patients with VTE, compared with patients with VTE but without COPD. We were especially interested to determine whether COPD influences a patient's risk of dying from PE or bleeding during treatment.

MATERIALS AND METHODS

Registry design

The RIETE registry is an ongoing international, multi-centre prospective cohort of consecutive patients with symptomatic, objectively confirmed acute VTE (DVT, PE or both). Patients are managed according to the clinical practice of each participating hospital centre and followed up for at least 3 months. There are only two exclusion criteria: a planned follow-up of <3 months and participation in a therapeutic clinical trial. For this analysis, only patients aged >18 yrs were considered.

At each participating centre, a registry coordinator controlled the quality of data collection (*e.g.* internal validity and coherence) and recorded the data from each patient on a computer-based case report form. Coordinators ensured that all consecutive patients with confirmed VTE were included in the registry. In addition, the database used for each analysis was controlled. The information was then transferred online, *via* a secure website, to the study coordinating centre responsible for data management. Data quality was also monitored by members of contract research organisations, who compared the data on medical records with the data transferred online during periodic visits to the participating hospitals. All patients gave written consent to their participation in the registry, in accordance with the requirements of the ethics committee of each country. Death (and cause of death), bleeding and VTE recurrence during the follow-up were adjudicated by the RIETE registry coordinators.

Study outcomes

Baseline characteristics, thrombosis risk factors (including the presence of COPD) and clinical presentation of VTE (PE with or without DVT and DVT without any symptomatic PE) were recorded at baseline. In patients with acute respiratory symptoms suggesting PE, symptomatic PE was confirmed if it was objectively documented (by positive helical computed tomography scan, high-probability ventilation/perfusion lung scan, positive pulmonary angiography, visualisation of a thrombus in the right ventricle or in the right atrium on echocardiography, or intermediate-probability ventilation/perfusion lung scan associated with a diagnosis of DVT). DVT was diagnosed in the case of acute symptoms of DVT confirmed by compression ultrasound or contrast venography of the lower limbs. The following information was also collected: demographic data, symptoms on presentation, types and results of diagnostic methods, and risk factors for VTE. Immobilised patients were defined as non-surgical patients who had been immobilised for ⩾4 days during the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation within the 2 months prior to VTE. Patients were categorised as obese if their body mass index (BMI) was ⩾30 $kg \cdot m^{-2}$. The presence of COPD was assessed by the treating physician.

Information on treatment and outcome (*i.e.* occurrence of death, major bleeding, minor bleeding or another objectively confirmed VTE event) was recorded at day 7 and during the 3-month follow-up period. If the patient died, death was considered to be due to PE if this diagnosis had been documented at autopsy, or if the patient died shortly after objectively confirmed symptomatic PE, and in the absence of any alternative diagnosis. Bleeding complications were classified as ''major'' if they were overt and required a transfusion of two or more units of blood, or were retroperitoneal, spinal, intracranial or fatal. Other types of bleeding were classified as ''minor''. Each recurrent VTE event was objectively confirmed using the same criteria as the index VTE event. Every event was adjudicated by the RIETE registry coordinators.

Data analysis

Qualitative data were reported as n (%). Quantitative data were reported as median (interquartile range). A logistic regression model was used to examine the individual relationship between each variable and the presence of COPD. The selection of variables was based on the literature and on expert opinion. Any variable achieving a p-value <0.15 on univariate analysis was included in a multivariate logistic regression analysis. Odds ratios and the corresponding 95% confidence intervals were calculated. Some COPD patients may experience a high rate of exacerbation leading to non-surgical immobilisation [21], a type of immobilisation not applicable to non-COPD patients, by definition. Therefore, we considered two immobilisation variables: 1) all-cause immobilisation, and 2) immobilisation excluding immobilisation for COPD exacerbation. The cumulative rates of death, VTE and bleeding were estimated by the Kaplan–Meier method and compared between COPD and non-COPD patients by the log-rank test. A p-value ⩽0.05 was considered to be statistically significant. Data were processed and analysed using SAS for Windows™ software (version 9.13; SAS Institute Inc., Cary, NC, USA).

RESULTS

Between March 2001 and October 2009, a total of 28,920 consecutive adult patients with objectively confirmed acute VTE were included in the RIETE registry. Of these, 2,984 (10.3%) were diagnosed as having COPD.

Clinical characteristics and VTE presentation in COPD and non-COPD patients

In the univariate analyses (table 1) COPD was significantly associated with male sex, with a male:female ratio of 2:1 in the COPD group. COPD patients were also significantly older, half of them being ⩾75 yrs of age. Obesity was associated to a slightly greater extent with COPD. Regarding thrombosis risk factors, no difference in VTE history was found between COPD and non-COPD patients. COPD exacerbation was the main reason for immobilisation, accounting for approximately one-third of the immobilisation causes in COPD patients, followed by acute infection. Taken together, exacerbation and infection prompted 50% of non-surgical immobilisations among COPD patients.

TABLE 1 Patient characteristics at baseline, thrombosis risk factors and index venous thromboembolism (VTE) event for 2,984 chronic obstructive pulmonary disease (COPD) *versus* 25,936 non-COPD patients with VTE

	COPD	Non-COPD	Univariate analysis#	Multivariate analysis#
Characteristics				
Males	2005 (67.2)	12216 (47.1)	2.30 (2.12–2.49)	2.72 (2.46–3.01)
BMI ⩾30 kg·m^{-2}	596/2022 (29.5)	4697/17385 (27.0)	1.13 (1.02–1.25)	1.31 (1.18–1.45)
Age yrs	75 (68–80)	70 (55–78)		
Age ⩾75 yrs	1503 (50.4)	9519 (36.7)	1.75 (1.62–1.89)	2.08 (1.89–2.29)
Thrombosis risk factors				
Personal history of VTE	488 (16.4)	4033 (15.5)	1.06 (0.96–1.18)	NS
Cancer	600 (20.1)	5534 (21.3)	0.93 (0.84–1.02)	0.88 (0.79–0.99)
Surgery in the last 2 months	239 (8.0)	3321 (12.8)	0.59 (0.52–0.68)	0.67 (0.57–0.80)
Immobilisation¶	968 (32.4)	6303 (24.3)		
COPD exacerbation	308 (32)	NA		
Trauma without surgery	88 (9)	1290 (21)		
Acute infection	208 (21)	843 (13)		
Mental disorders	57 (6)	958 (15)		
Neoplasia	39 (4)	425 (7)		
Neurological disorders	66 (7)	815 (13)		
Cardiac disorders	39 (4)	313 (5)		
Others	163 (17)	1659 (26)		
Thromboprophylaxis	306 (32)	1492 (23.7)		
Immobilisation+	660 (22.1)	6303 (24.3)	0.88 (0.81–0.97)	0.89 (0.80–1.00)
Index VTE event				
Symptomatic PE	1761 (59.0)	12314 (47.4)	1.59 (1.47–1.72)	1.64 (1.49–1.80)

Data are presented as n (%), n/N (%) or odds ratio (95% confidence interval). Data for age is presented as median (interquartile range). BMI: body mass index; PE; pulmonary embolism; NA: not available; NS: nonsignificant. #: COPD *versus* non-COPD; ¶: prolonged immobilisation (⩾ 4 days) for any non-surgical reason; +: excluding that for COPD exacerbation.

Regarding VTE presentation, PE (with or without DVT) was the most frequent initial clinical presentation of VTE in COPD patients (1,761 out of 2,984; 59%). In the univariate analysis, COPD patients presented with PE more frequently than non-COPD patients.

In the multivariate analysis (table 1), male sex, age >75 yrs and obesity remained positively associated with COPD, whereas surgery, cancer and immobilisation for non-surgical reasons (excluding COPD exacerbations) were more weakly associated with COPD. COPD remained associated with a higher risk of PE presentation than in non-COPD patients (OR 1.64, 95% CI 1.49–1.80).

Therapeutic strategies

Regarding initial VTE treatment, COPD patients received thrombolytics (1%) or inferior vena cava filter (1.6%) less often than non-COPD patients (1.5% and 2.3%, respectively). During the 3-month follow-up, COPD patients were more frequently treated with vitamin K antagonists (76%) than non-COPD patients (73%), and inversely less treated with low-molecular weight heparin (24% *versus* 28%) (table 2).

Early and 3-month clinical outcomes

At day 7 (table 3), the overall mortality was significantly higher in COPD patients (2.6%) than in non-COPD patients (1.7%; log-rank p=0.001). PE was the cause of death in the vast majority of COPD patients (52 out of 78 deaths). There were slightly more VTE recurrences in COPD patients (0.6%) than in non-COPD patients (0.4%) but the difference was not statistically significant (log-rank p=0.09). There were more VTE recurrences as PE in COPD patients (0.6%) than in non-COPD patients (0.3%; p=0.02). There was no statistically significant difference between the groups with regard to the cumulative incidence of major bleeding at day 7 (0.8% *versus* 0.8%, log-rank p=0.76), but COPD patients had a higher 7-day

TABLE 2 Therapeutic strategies

	COPD	Non-COPD	p-value
Patients n	2984	25936	
Initial therapy			
LMWH	2773 (93)	24197 (93)	0.45
Unfractionated heparin	254 (8.5)	2168 (8.4)	0.77
Thrombolytics	30 (1.0)	375 (1.5)	0.053
Inferior vena cava filter	48 (1.6)	607 (2.3)	0.011
Long-term therapy			
LMWH	722 (24)	7152 (28)	<0.001
Vitamin K antagonists	2273 (76)	19047 (73)	0.001

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; LMWH: low-molecular weight heparin.

TABLE 3 Outcome at day 7

	COPD	No n-COPD	p-value
Patients n	2984	25936	
Outcome			
Recurrent VTE#	18 (0.6)	103 (0.4)	0.09
As DVT#	1 (0.03)	24 (0.1)	0.30
As PE#	17 (0.6)	79 (0.3)	0.02
Bleeding			
Major	25 (0.8)	205 (0.8)	0.76
Minor	46 (1.6)	159 (0.6)	<0.0001
Overall death	78 (2.6)	438 (1.7)	0.001
Causes of death			
PE¶	52 (1.7)	245 (1.0)	
Bleeding	4 (0.1)	29 (0.1)	
Disseminated cancer	1 (0.03)	45 (0.2)	
Sudden/unexpected	0	3 (0.01)	
Respiratory insufficiency	7 (0.2)	18 (0.1)	
Heart failure	2 (0.1)	12 (0.05)	
Infection	6 (0.2)	30 (0.1)	
Myocardial infarction	0	2 (0.01)	
Ischaemic stroke	0	3 (0.01)	
Other	6 (0.2)	51 (0.2)	

Data ate presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism. #: only the first recurrent event is presented; ¶: including initial fatal PE and fatal PE during the follow-up.

TABLE 4 Outcome at day 90

	COPD	No n-COPD	p-value
Patients n	2984	25936	
Outcome			
Recurrent VTE#	63 (2.2)	547 (2.2)	0.89
As DVT#	20 (0.7)	280 (1.1)	0.05
As PE#	43 (1.5)	267 (1.1)	0.04
Bleeding			
Major	76 (2.7)	564 (2.2)	0.16
Minor	127(4.5)	567 (2.3)	<0.001
Overall death	322 (10.8)	1970 (7.6)	<0.001
Causes of death			
PE¶	69 (2.3)	373 (1.4)	
Bleeding	19 (0.6)	153 (0.6)	
Disseminated cancer	48 (1.6)	574 (2.2)	
Sudden/unexpected	6 (0.2)	25 (0.1)	
Respiratory insufficiency	47 (1.6)	96 (0.4)	
Heart failure	11 (0.4)	61 (0.2)	
Infection	36 (1.2)	182 (0.7)	
Myocardial infarction	2 (0.1)	9 (0.03)	
Ischaemic stroke	2 (0.1)	19 (0.07)	
Other	80 (2.7)	478 (1.8)	

Data ate presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism. #: only the first recurrent event is presented; ¶: including initial fatal PE and fatal PE during the follow-up.

cumulative incidence of minor bleeding (1.6% *versus* 0.6%, log-rank p<0.0001).

At 3 months (table 4), the cumulative incidence of mortality was significantly higher in VTE patients with COPD (10.8%) than in VTE patients without COPD (7.6%; log-rank p<0.0001) (fig. 1). The main cause of death was PE (2.3%), followed by respiratory insufficiency, disseminated cancer (both 1.6%) and infection (1.2%). Global rate of VTE recurrence was similar between COPD and non-COPD patients (table 4). However, the incidence of VTE recurrences as PE during the 3-month follow-up was significantly higher in COPD patients than in non-COPD patients (1.5% *versus* 1.1%; log-rank p=0.04), whereas the incidence of VTE recurrences as DVT was significantly lower (0.7% *versus* 1.1%; log-rank p=0.05). There was no statistically significant difference between the groups with regard to the cumulative incidence of major bleeding at 3 months (2.7% *versus* 2.2%; log-rank p=0.16), but COPD patients had a higher 3-month cumulative incidence of minor bleeding (4.5% *versus* 2.3%; log-rank p<0.0001).

DISCUSSION

These data, obtained from a multi-centre clinical registry of consecutive patients with confirmed symptomatic VTE, provide important information about the clinical characteristics of COPD patients presenting with acute symptomatic VTE. We confirm that COPD patients with acute symptomatic VTE present more frequently with PE than with DVT (59% *versus* 41%), with a 60% increase in the risk of presenting with PE rather than DVT compared to non-COPD patients with VTE. COPD patients also have a worse 3-month prognosis than non-COPD patients, with higher rates of death, VTE recurrences as PE and minor bleeding.

Main results

The predominance of males and older patients in the COPD group is easily understood as the prevalence of COPD increases with age and the expected male:female ratio in COPD patients >65 yrs of age is 2:1 [22]. Obesity was found to be slightly more prevalent in COPD patients than in non-COPD patients with VTE, with a median BMI of 27 $kg \cdot m^{-2}$ and a BMI >30 $kg \cdot m^{-2}$ in 30% of COPD patients with VTE. Obesity is a well-known risk factor for VTE [23]. Of note, the prevalence of obesity in our COPD patients with VTE was two-fold higher than that observed in a large primary care population of European patients with COPD [24]. The lower rate of surgery in COPD patients is easily explained by the fragility of these patients, for whom conservative options may generally be preferred.

We confirmed the results of *post hoc* analyses of administrative healthcare data [4–7], finding an increased presentation of VTE as PE in COPD patients. It is possible that PE was more frequently searched for (and found) in COPD patients. By definition, COPD patients present with respiratory symptoms, which can enhance the suspicion of PE. However, the chronicity and variability of symptoms, as well as the frequent exacerbations, may conversely decrease the suspicion of PE in some COPD patients. Thus, FERNANDEZ *et al.* [25] found that COPD patients diagnosed with PE were more likely to

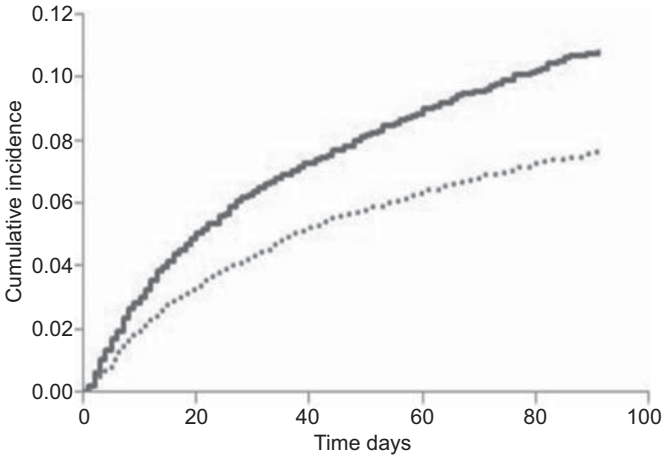

FIGURE 1. Kaplan–Meier curve of 3-month overall mortality in chronic obstructive pulmonary disease (COPD: ——) and non-COPD (·····) patients.

experience a longer delay before diagnosis than non-COPD patients. PINEDA *et al.* [17] found that COPD was associated with a higher risk of unsuspected fatal PE. Therefore, we cannot rule out a possible under diagnosis of PE in COPD patients, but this would rather strengthen our results.

Concerning outcome during the 3-month follow-up, the higher mortality in the COPD group is in accordance with previous studies, in which COPD was associated with a poorer prognosis [26]. This difference is already present at day 7, mainly because of PE-related death. Interestingly, more aggressive treatment, such as thrombolytics or inferior vena cava filters, have been less frequently used in COPD patients with VTE.

We did not find any statistically significant difference in the risk of major bleeding between COPD and non-COPD patients, although such a difference has been evoked in smaller studies [27]. The higher rate of minor bleeding may be explained by the co-prescription of drugs such as steroids or anti-platelets, which may increase the bleeding risk in COPD patients. Moreover, COPD patients were older than non-COPD patients, and this may also account for the differences.

Main limitations

Our study has several limitations. Some are due to the RIETE registry design. By definition, all patients included presented symptomatic and objectively confirmed VTE. However, they were diagnosed according to the clinical practice of each participating centre. Therefore, we cannot exclude the possibility that some patients classified as having DVT in fact had asymptomatic and/or undiagnosed PE. This clinical classification is nevertheless frequently employed, even in randomised controlled therapeutic trials. Therefore, our results cannot be extended to COPD patients with undiagnosed PE. PE may also have been underestimated in COPD patients presenting with signs of DVT and acute respiratory symptoms, as respiratory symptoms are spontaneously attributed to COPD without any screening for PE. Undiagnosed recurrent PE may explain, in part, the high rate of mortality due to PE.

In addition, results of lung function tests were not available for all our COPD patients. Diagnosis of COPD was based solely on the clinical information available to the investigator. Patients may, therefore, have been misclassified as COPD or non-COPD. This lack of lung function tests is unfortunately shared by many studies on this topic [28–31]. For example, data on lung function were available for only 28% of the patients included in a recent study of acute exacerbation of COPD [29]. However, the prevalence of COPD in the RIETE registry is similar to that in general settings [32], as mentioned previously. Moreover, COPD is usually underdiagnosed so if there was any misclassification, this would be under diagnosis (*i.e.* classification of undiagnosed COPD patients as non-COPD patients) than over diagnosis [32]. Furthermore, we could not subdivide COPD patients according to different stages of severity.

Clinical impact, unanswered questions and future research

The clinical characteristics of COPD patients with VTE shown by our study may partly explain the difference between studies searching for PE during COPD exacerbation. The patients included in the study of RUTSCHMANN *et al.* [33] were more similar to ours, in terms of age and sex ratio, than those included in the studies of TILLIE-LEBLOND *et al.* [34] and GUNEN *et al.* [35]. Similarly, the rates of past VTE (25%) or active cancer (43%) were much higher in the study of TILLIE-LEBLOND *et al.* [34] than in our VTE series. Selection bias may explain these differences, resulting in contradictory results.

Our results may also be viewed in a physiological perspective. Recent studies established that COPD may induce an additional specific pro-thrombotic biological situation, particularly during acute exacerbation of COPD [36, 37]. It is worth noting that only one-third of immobilised COPD patients with VTE received thrombosis prophylaxis during immobilisation. Therefore, efforts to improve thromboprophylaxis use are needed. Elsewhere, links between obesity, adipokines and the abnormal inflammatory response seen in COPD are currently debated [38] and the potential effect of these interactions on pro-thrombotic states in COPD patients deserves further research. Moreover, the pulmonary arteries of COPD patients are characterised by endothelial cell dysfunction [39] and the hypothetical COPD-related pro-thrombotic status may predominate with regard to the pulmonary vascular bed, leading to *in situ* thrombosis [40].

Finally, more aggressive VTE treatments, such as thrombolytics or placement of a vena cava filter, have been proposed for COPD patients, particularly those presenting with DVT [30], but we found them to be less frequently used in our COPD patients. Inferior vena cava filters might protect the reduced pulmonary vascular bed of COPD patients from PE, which constitutes the main presentation of VTE in COPD patients according to our results, without any increase in the bleeding risk. However, if we consider that PE may sometimes be an *in situ* thrombosis rather than an embolic complication of a DVT, placement of a vena cava filter might not be appropriate in the former case.

Conclusion

Our study is the largest clinical study to date focusing on clinical presentation and outcome of VTE in COPD patients. We confirmed that PE is more frequently diagnosed in COPD patients, and that such patients have a poorer prognosis than non-COPD patients, with higher rates of mortality and minor bleeding. Treatment with higher efficiency on recurrence risk but with no increase in bleeding risk deserves further evaluation.

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STATEMENT OF INTEREST

A statement of interest for the study itself can be found at www.erj.ersjournals.com/site/misc/statement.xhtml

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