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The value of sPESI for risk stratification in patients with pulmonary embolism

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Abstract

Introduction Various risk stratification methods exist for patients with pulmonary embolism (PE). We used the simplified Pulmonary Embolism Severity Index (sPESI) as a risk-stratification method to understand the Veterans Health Administration (VHA) PE population.

Materials and methods Adult patients with ≥ 1 inpatient PE diagnosis (index date = discharge date) from October 2011–June 2015 as well as continuous enrollment for ≥ 12 months pre- and 3 months post-index date were included. We defined a sPESI score of 0 as low-risk (LRPE) and all others as high-risk (HRPE). Hospital-acquired complications (HACs) during the index hospitalization, 90-day follow-up PE-related outcomes, and health care utilization and costs were compared between HRPE and LRPE patients.

Results Of 6746 PE patients, 95.4% were men, 67.7% were white, and 22.0% were African American; LRPE occurred in 28.4% and HRPE in 71.6%. Relative to HRPE patients, LRPE patients had lower Charlson Comorbidity Index scores (1.0 vs. 3.4, $p < 0.0001$) and other baseline comorbidities, fewer HACs (11.4% vs. 20.0%, $p < 0.0001$), less bacterial pneumonia (10.6% vs. 22.3%, $p < 0.0001$), and shorter average inpatient lengths of stay (8.8 vs. 11.2 days, $p < 0.0001$) during the index hospitalization. During follow-up, LRPE patients had fewer PE-related outcomes of recurrent venous thromboembolism (4.4% vs. 6.0%, $p = 0.0077$), major bleeding (1.2% vs. 1.9%, $p = 0.0382$), and death (3.7% vs. 16.2%, $p < 0.0001$). LRPE patients had fewer inpatient but higher outpatient visits per patient, and lower total health care costs ($12,021 vs. $16,911, $p < 0.0001$) than HRPE patients.

Conclusions Using the sPESI score identifies a PE cohort with a lower clinical and economic burden.

Keywords Pulmonary embolism · Trauma Severity Index · Cost of illness · Veterans Health Administration

Abbreviations

CCI	Charlson Comorbidity Index
CTA	Computed tomography angiography
DVT	Deep vein thrombosis
ECHO	Echocardiogram
ESC	European Society of Cardiology
HAC	Hospital-acquired complication
HRPE	High-risk pulmonary embolism
HRU	Health care resource utilization
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IMPACT	In-hospital mortality for pulmonary embolism using claims data
LMWH	Low-molecular-weight heparin
LOS	Length of stay
LRPE	Low-risk pulmonary embolism
LV	Left ventricular
NOAC	Novel oral anticoagulant
PE	Pulmonary embolism
SAS	Statistical analysis software
SD	Standard deviation
sPESI	Simplified Pulmonary Embolism Severity Index
STD	Standardized difference
UFH	Unfractionated heparin
VHA	Veterans Health Administration

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VQ Lung ventilation/perfusion
VTE Venous thromboembolism

Highlights

- sPESI score identifies a PE cohort with lower clinical and economic burden.
- LRPE patients were less likely to have HACs and other PE-related outcomes than HRPE patients.
- LRPE patients also had shorter inpatient length of stay and lower health care costs.
- Prognostic risk stratification is fundamental in choosing appropriate PE treatment.

Introduction

Pulmonary embolism (PE) is a major health concern causing hospitalization in the United States, with 176,000 admissions annually [1, 2]. In the span of 20 years, the incidence of PE increased by 81%, from 62.1 to 112.3 cases per 100,000 people [3]. PE is a potentially fatal disease with a 90-day mortality rate of up to 37.2% and ~ 100,000 annuals deaths in the United States [4, 5].

The economic burden of PE is substantial, with estimated annual cumulative costs ranging from $8.5 to $19.8 billion in the United States [6]. Additionally, the annual cost per patient has been estimated at $13,300 to $31,000 in PE patients [7]. However, risk stratification remains a challenge in clinical practice. The American college of chest physicians recommends that low-risk PE (LRPE) patients can benefit from abbreviated hospital stays or outpatient therapy which could substantially reduce the clinical and economic disease burden [8, 9]. Several risk-stratification methods have been developed to identify LRPE patients, including the Geneva score, the Pulmonary Embolism Severity Index (PESI) score, the simplified PESI (sPESI) score, etc [10].

The European Society of Cardiology (ESC) advocates for the risk stratification of PE patients and the consideration of an outpatient management option for LRPE patients. However, physicians in the United States have not widely adopted an outpatient or observation management strategy [11, 12]. Also, the new recommendations of the ESC suggest using the sPESI score as the first step for prognostic assessment of acute hemodynamic stability of PE [13]. Therefore, we compared the PE-related outcomes, health care resource utilization (HRU), and costs in LRPE vs high-risk PE (HRPE) identified using the sPESI score.

Materials and methods

Data source

This was a longitudinal, retrospective cohort study that used data from the Veterans Health Administration (VHA) during October 1, 2010 to September 30, 2015 (study period). The VHA is the largest integrated health care system in the United States, providing care at 1245 health care facilities—including 170 US Department of Veterans Affairs medical centers and 1065 outpatient clinics—and serving > 9 million enrolled veterans across the country [14].

Institutional Review Board approval was not required because this study did not use individually identifiable data from the VHA.

Study population

Patients were included in the study if they had ≥ 1 inpatient diagnosis for PE (ICD-9-CM codes 415.1, 415.11, and 415.19) during the identification period (October 1, 2011–June 30, 2015), with the hospital discharge date designated as the index date. Patients were required to be aged ≥ 18 years, have a prescription claim for an anticoagulant [unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), warfarin, or novel oral anticoagulants (NOACs)] during the index hospitalization, and be continuously enrolled in their health plan with medical and pharmacy benefits for ≥ 12 months prior to the index date (baseline period) until 3 months post-index date or death (follow-up period), whichever occurred first (Appendix in Supplementary material). Patients administered subcutaneous heparin during the hospital stay were not included, since many patients are given subcutaneous heparin as a prophylaxis for PE. Also, patients with a PE claim or any anticoagulant claim prior to the index hospitalization were excluded.

Eligible PE patients were stratified based on the presence of sPESI parameters during the index hospitalization into LRPE and HRPE cohorts. The sPESI is an extensively validated prognostic tool, encompassing 6 items—including age ≥ 80 years, history of cancer/chronic cardiopulmonary diseases, heart rate ≥ 110/min, systolic blood pressure < 100 mmHg, and arterial oxygen saturation < 90%—each burdening 1 point when present [15, 16]. Patients scoring 0 points are considered at low risk and all others are considered at high risk.

Baseline measures

Patient demographics including age, gender, race, and body mass index during the baseline period were assessed. In addition, clinical characteristics including Charlson Comorbidity Index (CCI) score, past medical history, and the administration of various diagnostic tests were recorded. We assessed the association of hospital-acquired complications (HACs) and clinical markers with the risk level of PE patients during the index hospitalization (Appendix in Supplementary material).

Outcome measures

PE-related clinical outcomes [recurrent venous thromboembolism (VTE), major bleeding, and death] and diagnostic tests, including computed tomography angiography (CTA), echocardiogram, lung ventilation/perfusion scan, and venous Doppler ultrasound, during the 90-day post-discharge period, were evaluated. Recurrent VTE was defined as having a hospitalization claim for deep vein thrombosis (DVT) or PE between 8 and 90 days after the index date. Major bleeding was defined using a previously validated algorithm developed by Cunningham et al. [17] (Appendix in Supplementary material). Additionally, PE-related clinical outcomes were reported during the 30-day post-discharge period. Health care resource utilization (HRU) including the percentage of patients with any (i.e., not disease-specific) inpatient hospitalization, and outpatient visit, as well as the mean number of visits per patient and associated health care costs during the 90-day follow-up period were reported.

Statistical analysis

Descriptive statistics were provided for all study variables, including baseline demographics, clinical characteristics, and outcome variables among the LRPE and HRPE cohorts. Statistical tests of significance (Chi square for categorical variables and Wilcoxon-rank sum test for continuous variables) were conducted to assess differences between the cohorts. All analyses were conducted using Statistical Analysis Software (SAS)® (Version 9.3, SAS Institute, Cary, North Carolina, 2012).

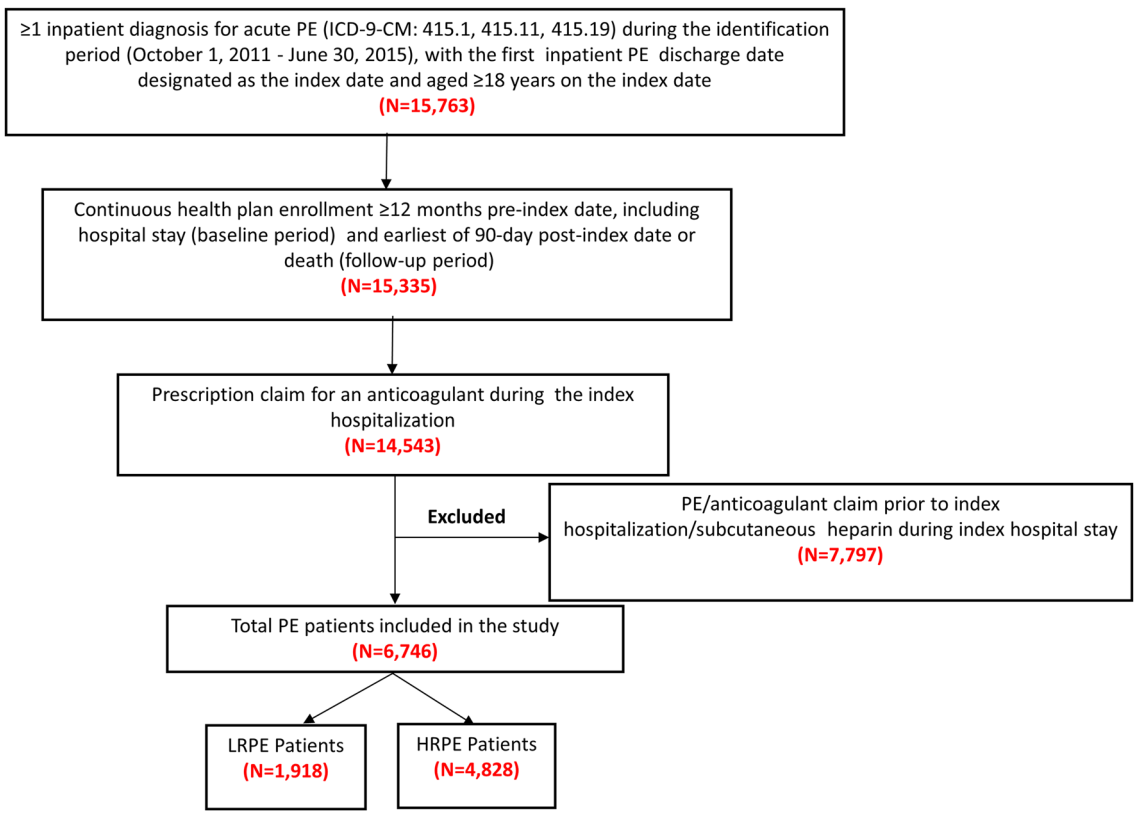

Fig. 1 Study population and cohorts. *HRPE* high-risk pulmonary embolism, *ICD-9-CM* International Classification of Diseases, 9th Revision, Clinical Modification, *LRPE* low-risk pulmonary embolism, *PE* pulmonary embolism

Results

The study included 6746 PE patients, of which 1918 (28.4%) were stratified as LRPE and 4828 (71.6%) as HRPE (Fig. 1).

Baseline characteristics

The demographic and clinical characteristics during the baseline period were summarized in Table 1.

During the index hospitalization, LRPE patients had a shorter average inpatient length of stay (LOS) (8.8 vs. 11.2, $p < 0.0001$) and fewer HACs (11.4% vs. 20.0%, $p < 0.0001$) and were also less likely to have clinical marker testing (Table 1).

90-day follow-up outcomes

During the 90-day follow-up period, LRPE patients had fewer PE-related outcomes, including recurrent VTE (4.4% vs. 6.0%, $p = 0.0077$), major bleeding (1.2% vs. 1.9%, $p = 0.0382$), or death (3.7% vs. 16.2%, $p < 0.0001$). Additionally, the clinical outcomes during the 30-day follow-up period were reported (Table 2).

90-day follow-up HRU and costs

As compared to HRPE patients, LRPE patients had a fewer number of hospital re-admissions (0.2 vs. 0.3, $p < 0.0001$) with a shorter average re-hospitalization LOS (1.9 vs. 2.5 days, $p < 0.0001$). However, LRPE patients had higher outpatient visits per patient (19.7 vs. 18.4, $p = 0.0002$) (Fig. 2). Also, LRPE patients were more likely to have a venous Doppler ultrasound (8.5% vs. 4.9%, $p < 0.0001$) during the 90-day follow-up than HRPE patients (data not shown). LRPE patients incurred lower inpatient ($4503 vs. $7332, $p < 0.0001$), pharmacy ($1294 vs. $2502, $p = 0.0013$), and total costs ($12,021 vs. $16,911, $p < 0.0001$) than HRPE patients (Fig. 2).

Discussion

The results of our study showed that in a real-world clinical setting, sPESI identifies a subset of PE patients at a lower risk for adverse clinical outcomes, including mortality. These patients might benefit from early discharge or outpatient therapy, thus reducing their economic burden, especially considering the extended length of stay of LRPE in this VA cohort (mean 8.8 days).

Although a few studies have evaluated the value of sPESI in identifying those PE patients at an early risk of adverse clinical events, our study is unique in evaluating the 90-day clinical events [16, 18]. The results of previous studies showed that about 26.1–30.7% of PE patients were stratified as low-risk using the sPESI score [18–20]. Although right ventricular dysfunction (RVD) was considered as a significant predictor of early prognosis in LRPE patients, we observed that very few patients (~ 5) had evidence of RVD during the index hospital stay [21]. The results of our study were consistent with these studies, as 28.4% of the PE patients were classified as low-risk. Additionally, the results of our study showed that LRPE patients had ~ 2 days shorter LOS than the HRPE patients. However, in a study conducted by Shafiq et al. using the PESI criteria, no significant differences were observed in the hospital LOS between the LRPE and HRPE patients [22]. The study also observed that only 9% of the LRPE patients were discharged early (≤ 3 days), albeit the American College of Chest Physicians guidelines recommending early discharge of LRPE patients [22]. Our study also showed that LRPE patients were less likely to have HACs, which could possibly be related to the shorter hospital LOS among these patients. However, as pointed out in earlier studies, we could not conclude if HACs cause a longer LOS or if a longer LOS is caused by the HACs [23, 24]. Therefore, further research is warranted to evaluate the hospital LOS among PE patients stratified using the sPESI criteria.

The results of our study showed that the mortality rate in LRPE patients was 4 times lower than the HRPE patients, while several previous studies observed a 10 times lower mortality rate in the sPESI LRPE patients [16, 18, 25, 26]. A possible explanation for the larger difference in the magnitude of the mortality risk is that these previous studies evaluated the early mortality risk (30-day mortality) while our study assessed the 90-day mortality in PE patients. Similarly, the rate of major bleeding was lower in the LRPE patients, which is similar to the findings from Masotti et al. [16], who observed an increase in the bleeding rate with an increase in the sPESI score. Additionally, the combined rate of non-fatal major bleeding and recurrent VTE was about 5% in our study, which is consistent with a study by Ozsu et al. [18].

There is no evidence in the literature to date that evaluates the HRU and the associated costs among PE patients stratified by using any of the risk-stratification tools. The results of our study showed that LRPE patients had fewer hospital re-admissions well as lower health care costs. Surprisingly, LRPE patients had higher outpatient utilization, which could be related to the higher proportion of LRPE patients with venous Doppler ultrasound imaging during the follow-up period. This may be due to the possibility that clinicians performed more tests to confirm that LRPE patients were at low-risk for the complications and could be safely managed as outpatients or due to a higher death rate in HRPE patients, thus less opportunity for visits and extra testing. However,

Table 1 Demographic and clinical characteristics of LRPE versus HRPE patients

	LRPE cohort		HRPE cohort			
	N = (1918)		N = (4828)			
	N/mean	%/SD	N/mean	% SD	p-value	STD
Mean, SD	59.9	11.2	70.7	16.1	< 0.0001*	78
Median (IQR)	62.0 (13.0)		68.0 (16.0)			
Age						
18–45	217	11.3%	156	3.2%	< 0.0001	31.5
46–64	954	49.7%	1487	30.8%	< 0.0001	39.4
65+	747	39.0%	3185	66.0%	< 0.0001	56.2
Gender						
Male	1792	93.4%	4642	96.1%	< 0.0001	12.2
Female	126	6.6%	186	3.9%	< 0.0001	12.2
Race						
White	1223	63.8%	3342	69.2%	< 0.0001	11.6
Black	506	26.4%	980	20.3%	< 0.0001	14.4
Unknown	134	7.0%	429	8.9%	0.011	7
Other	55	2.9%	77	1.6%	0.0007	8.6
Body Mass Index (BMI) (in kg/m^2)						
Mean, SD	31.5	9.1	30.1	51.4	< 0.0001	3.6
Median (IQR)	30.5 (8.2)		28.4 (8.9)			
Baseline comorbid conditions						
Charlson Comorbidity Index Score	1	1.4	3.4	3	< 0.0001	104.6
Myocardial infarction	100	5.2%	427	8.8%	< 0.0001	14.2
Congestive heart failure	0	0.0%	1042	21.6%	< 0.0001	74.2
Peripheral vascular disease	114	5.9%	547	11.3%	< 0.0001	19.3
Dementia	16	0.8%	67	1.4%	0.0628	5.3
Cerebrovascular disease	173	9.0%	573	11.9%	0.0008	9.3
Chronic pulmonary disease	130	6.8%	2121	43.9%	< 0.0001	94.4
Rheumatologic disease or connective tissue disease	28	1.5%	91	1.9%	0.2317	3.3
Peptic ulcer disease	33	1.7%	98	2.0%	0.4063	2.3
Mild liver disease	24	1.3%	113	2.3%	0.0042	8.2
Moderate or severe renal disease	348	18.1%	1484	30.7%	< 0.0001	19.3
Diabetes	515	26.9%	1524	31.6%	0.0001	10.4
Any tumor (including leukemia and lymphoma)	22	1.2%	3476	72.0%	< 0.0001	103.1
Moderate or severe liver disease	30	1.6%	138	2.9%	0.0781	5
Metastatic solid tumor	0	0.0%	3624	75.1%	< 0.0001	53.5
Diabetes + complications	242	12.6%	876	18.1%	0.0002	10.4
AIDS	132	6.9%	306	6.3%	0.7454	0.9
Cardiac dysrhythmia	271	14.1%	1343	27.8%	< 0.0001	34.1
LV dysfunction	39	2.0%	120	2.5%	0.2695	3
Hospitalized DVT	624	32.5%	1280	26.5%	< 0.0001	13.2
Baseline diagnostic tests						
CTA	949	49.5%	2166	44.9%	0.0006	9.3
ECHO	37	1.9%	186	3.9%	< 0.0001	11.5
VQ scan	41	2.1%	143	3.0%	0.0608	5.2
Venous Doppler ultrasound	382	19.9%	636	13.2%	< 0.0001	18.2
Hospital-acquired complications (any) during index hospitalization	218	11.4%	964	20.0%	< 0.0001	23.8
Catheter-associated urinary tract infection	4	0.2%	12	0.3%	0.7606	0.8
Methicillin-resistant *Staphylococcus aureus*	22	1.2%	54	1.1%	0.9202	0.3
Clostridium difficile infection	14	0.7%	65	1.4%	0.0338	6.1

Table 1 (continued)

	LRPE cohort		HRPE cohort			
	N = (1918)		N = (4828)			
	N/mean	%/SD	N/mean	% SD	p-value	STD
Hospital-acquired (bacterial) pneumonia	128	6.7%	711	14.7%	< 0.0001	26.3
Foreign object retained after surgery	1	0.1%	1	0.0%	0.4989	1.7
Pressure ulcer stages III and IV	7	0.4%	25	0.5%	0.4098	2.3
Trauma/injury	57	3.0%	155	3.2%	0.6124	1.4
Poor glycemic control	7	0.4%	28	0.6%	0.2676	3.1
Iatrogenic pneumothorax with venous catheterization	1	0.1%	19	0.4%	0.02	7.2
Vascular catheter-associated infection	5	0.3%	10	0.2%	0.6735	1.1
Surgical site infection	3	0.2%	4	0.1%	0.3973	2.1
Bacterial pneumonia	203	10.6%	1078	22.3%	< 0.0001	32.1
Major bleeding	17	0.9%	28	0.6%	0.1632	3.6
Inpatient length of stay (days) (mean, SD)	8.8	22.4	11.2	34.5	< 0.0001	8.2
Inpatient length of stay (days) (median [IQR])	4.0 (6.0)		5.0 (7.0)			
Clinical marker during the index hospitalization						
Patients with troponin I	676	35.3%	2202	45.6%	< 0.0001	21.2
Patients with troponin T	33	1.7%	183	3.8%	< 0.0001	12.7
Patients with natriuretic peptide testing	676	35.3%	2356	48.8%	< 0.0001	27.7
sPESI score distribution						
sPESI score = 0	1918	100.0%	0	0.0%	< 0.0001	0.0
sPESI score = 1	0	0.0%	2275	47.1%	< 0.0001	133.5
sPESI score = 2	0	0.0%	1674	34.7%	< 0.0001	103.0
sPESI score = 3	0	0.0%	657	13.6%	< 0.0001	56.1
sPESI score ≥ 4	0	0.0%	222	4.6%	< 0.0001	31.0

CTA computed tomography angiography, *DVT* deep vein thrombosis, *ECHO* echocardiogram, *HRPE* high-risk pulmonary embolism, *LRPE* low-risk pulmonary embolism, *LV* left ventricular, *SD* standard deviation, *STD* standardized difference, *VQ* lung ventilation/perfusion

Table 2 PE-related outcomes among LRPE versus HRPE patients

PE-related clinical outcomes during the 90-day follow-up period	LRPE cohort				HRPE cohort					
	N = 1918				N = 4828					
	N/mean	%/SD	Median	IQR	N/mean	%/SD	Median	IQR	p-value	STD
Recurrent VTE	84	4.4%			291	6.0%			0.0077	7.4
Time to first VTE, days	32.6	24.5	24	34	32.3	21.7	25	34	0.5292	1.3
Major bleeding	23	1.2%			93	1.9%			0.0382	5.9
Time to first major bleeding, days	25.8	22.1	23	26	29.2	26	17	41	0.9282	14
Death	71	3.7%			780	16.2%			< 0.0001	42.6
Time to death, days	32.1	23	25	25	32.3	22.1	26	31	0.875	0.7
PE-related clinical outcomes during the 30-day follow-up period										
Recurrent VTE	50	2.6%			160	3.3%			0.1314	7.4
Time to first VTE, days	15.66	6.86	13	13	15.92	5.49	15	7	0.3348	1.3
Major bleeding	15	0.8%			56	1.2%			0.1701	5.9
Time to first major bleeding, days	13.53	8.21	10	17	11.21	8.42	9	13	0.2805	14
Death	48	2.5%			460	9.5%			< 0.0001	42.6
Time to death, days	18.69	8.55	21	13	16.95	8.25	18	14	0.1505	0.7

HRPE high-risk pulmonary embolism, *LRPE* low-risk pulmonary embolism, *SD* standard deviation, *STD* standardized difference, *VTE* venous thromboembolism

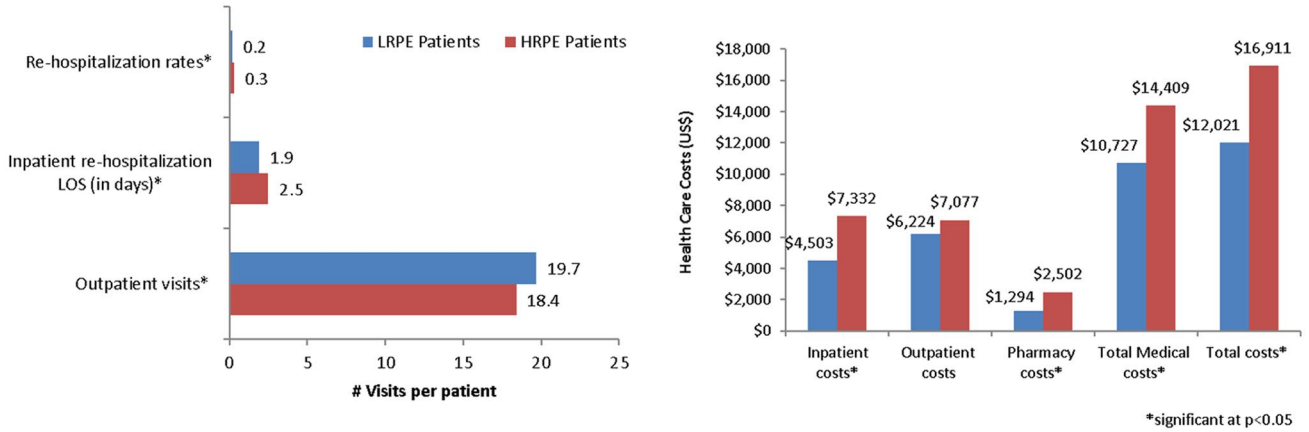

Fig. 2 HRU and health care costs among LRPE versus HRPE patients during the 90-day follow-up period. *HRPE* high-risk pulmonary embolism, *HRU* health care resource utilization, *LOS* length of stay, *LRPE* low-risk pulmonary embolism

previous studies validating the sPESI score suggested that PE patients with a sPESI score of 0 do not require further prognostic imaging procedures or laboratory biomarker testing to define the low risk [8, 16]. Therefore, the burden of diagnostic tests can be reduced in the LRPE patients. Several previous studies suggested that reducing the hospital LOS, which is an important cost driver among PE patients, would substantially reduce the costs [18, 27, 28]. Also, in a previous study using the In-hospital mortality for pulmonary using claims data (IMPACT) criteria for the risk stratification of PE patients, the LRPE patients discharged early ($\leq$3 days) had lower health care costs than those who stayed longer in the hospital [29]. Previous studies have suggested that PE outpatient management has cost savings in the range of $500 to $2500 per patient [7, 9]. Our study showed that LRPE patients incurred $4890 lower health care costs than the HRPE patients. However, further research is warranted to support the findings of our study in using sPESI for the outpatient management of the LRPE patients.

The findings from our study should be viewed in the context of some study limitations. First, the study relied on retrospective claims data. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, and costs, they are collected for payment and not research. To ensure exclusion of any rule-out PE diagnosis, PE patients were required to have an anticoagulant claim during their hospital stay. The presence of a claim for a filled prescription does not indicate the medication was consumed or taken as prescribed. Thus, the true number of medications prescribed may not be accurately recorded. Third, certain clinical and disease-specific parameters are not readily available in claims data, which could influence study outcomes. Additionally, the risk stratification in our study did not consider right ventricular dysfunction or elevated cardiac biomarkers which are considered as two of the important prognostic values in PE, and further analysis using these measures is warranted. Also, our study only quantified the overall clinical burden in the index hospitalization, and further research aiming to understand the early versus late complications after admission would be more beneficial in clarifying that the early discharge would minimize the risk of these HACs. The current study also represented only US data from a specific subpopulation (VHA veterans) who were mostly elderly men. Therefore, the general applicability of our findings to young male patients or females requires further study.

Conclusions

In summary, the results of this study showed that LRPE patients stratified using the sPESI score were unlikely to have complications or adverse clinical outcomes; hence, they had a lower clinical and economic burden than HRPE patients. Therefore, prognostic risk stratification may be considered a fundamental tool in choosing appropriate treatment in PE patients, and may substantially reduce the economic burden in LRPE patients.

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Compliance with ethical standards

Conflict of interest WFP has received grants from Abbott, Alere, Banyan, Cardiorentis, Janssen, Portola, Pfizer, Roche, and ZS Pharma; is a consultant to Alere, Beckman, Boehringer-Ingelheim, Cardiorentis, Instrument Labs, Janssen, Phillips, Portola, Prevencio, Singulex, The Medicine's Company, and ZS Pharma; and also has ownership interests at the Comprehensive Research Associate LLC, Emergencies in Medicine LLC. CIC has received grant funding and consulting fees

from Janssen Scientific Affairs, LLC, Raritan, NJ and Bayer Pharma AG, Berlin, Germany. PW receives speaker fees from Bayer Healthcare and Daiichi Sankyo, writing committee fees from Itreas, and grant support fees from Pfizer/BMS. GJF has received research support from Novartis, Siemens, Pfizer, Portola, and PCORI; has advised Janssen Scientific Affairs, LLC; and receives speaker fees from Janssen. CC and JS and are employees of Janssen Scientific Affairs. LW and OB are employees of STATinMED Research, which is a paid consultant to Janssen Scientific Affairs.

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