Original Article

Quantitative assessment of the relative effects of patient and pulmonary embolism-related factors on longer-term mortality after pulmonary embolism

I Le Jeune & R Hubbard

Abstract

This observational study used a large audit dataset to examine the relative effects of patient-related factors and those related to the pulmonary embolism (PE) on longer-term mortality after PE. We identified that longer-term mortality is higher in provoked compared to unprovoked PE and that, in this group, obesity is relatively protective. Simplified PE severity index (sPESI), known to link to short term mortality, remains predictive in the longer-term and there is no relationship of mortality to right heart strain or extent of clot. Interestingly mortality is higher in those with negative CTPA scans than those with PE. These clinically important results should encourage careful, holistic clinical assessment of patients in these groups prior to discharge to look for treatable comorbidities.

Keywords

Pulmonary embolism, obesity, body mass index, epidemiology, mortality

Introduction

While prediction of short-term mortality after pulmonary embolism (PE) using well-validated assessment tools is undertaken commonly,[1,2] longer term survival after PE is less well understood. Prognosis is likely to depend on a complex interaction between demographics, comorbidities, physiological disturbance and factors related to the pulmonary embolism including the extent of clot, clinician-defined cause of the PE and the presence of right heart strain at diagnosis. As a step towards developing our understanding of this, we used a large local audit database of consecutive pulmonary embolism patients to construct survival curves and assess the association between some of these factors and longer-term mortality.

Methods

All people with a PE diagnosed in 2020 and 2021 in Nottingham were identified using a clinical audit database from the PE clinic at Nottingham University Hospitals (NUH). This dataset includes all patients referred to this clinic at the time of their PE diagnosis whether they attended or not. Age at diagnosis, sex, postcode, body mass index (BMI), clinician-defined cause of PE, simplified pulmonary embolism severity index (sPESI), presence of right ventricular strain at presentation , size and distribution of the pulmonary emboli and time from diagnosis with PE to death or end of the study period (17/5/22) were taken from the audit dataset. Excel randomisation was used to select a group of patients from those who had CTPA and VQ scans which proved to be negative over the same time period as a comparison group.

Postcode was used as a proxy for index of multiple deprivation score (IMDS). Body mass index was used to group patients both according to the World Health Organisation (WHO) classification (healthy weight (BMI 19-24.9kg/m^2), overweight (BMI 25-29.9 kg/m^2), obesity class 1 (BMI 30-34.9 kg/m^2), obesity class 2 (BMI 35-39.9 kg/m^2), obesity class 3 (BMI >40 kg/m^2), and underweight (BMI <19 kg/m^2)) and into an obese (BMI >30 kg/m^2) category for the purpose of analysis.[1] Information on the largest reported clot size (saddle, main, lobar, segmental or subsegmental) and distribution (single lobe, multilobar or bilateral) taken from consultant-approved imaging reports was combined to give subgroups indicative of the extent of the pulmonary emboli. Group 1 included single sub-segmental and segmental emboli, group 2 multilobar subsegmental, multilobar segmental and single lobar, group 3 bilateral subsegmental, bilateral segmental and multilobar lobar, group 4 multilobar main and bilateral lobar and group 5 bilateral main and saddle emboli. Evidence of right ventricular strain from imaging reports and biomarker (troponin or

Ivan Le Jeune
Nottingham University Hospitals NHS Trust. Respiratory Medicine, D Floor South Block, Queen's Medical Centre, Nottingham, NG7 2UH

Richard Hubbard
Division of Epidemiology and Public Health, School of Medicine, University of Nottingham. Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB

Correspondence
Ivan Le Jeune
Nottingham University Hospitals NHS Trust. Respiratory Medicine, D Floor South Block, Queen's Medical Centre, Nottingham, NG7 2UH
Email: ivan.lejeune@nuh.nhs.uk

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Table 1.

	Pulmonary Emboli	Deaths within study	Unadjusted hazard ratio	95% Confidence interval	Adjusted hazard ratio	95% Confidence interval	Adjusted HR p value	Likelihood-ratio test p value
Total	1137	158 (14%)						
Male sex	592 (52%)	91 (15%)	1.24	0.91 – 1.70	1.41	1.03 – 1.94	0.034	
Age group								<0.0001
0 - 39 years	120 (11%)	1 (1%)	Reference					
40 – 49 years	130 (11%)	5 (4%)	4.60	0.54 – 39.4	4.37	0.51 – 37.4	0.178	
50 – 59 years	219 (19%)	17 (8%)	9.53	1.27 – 71.6	9.09	1.21 – 68.4	0.032	
60 – 69 years	217 (19%)	25 (12%)	14.5	1.96 – 107	13.9	1.88 – 103	0.010	
70 – 79 years	253 (22%)	47 (19%)	24.1	3.33 – 175	23.2	3.21 – 169	0.002	
80 years and over	198 (17%)	63 (32%)	46.6	6.47 – 336	47.2	6.54 – 340	<0.001	
Mean age (years)	62.6	74.3						
IMD10					Not included in multivariate analysis			0.64
1	167 (15%)	21 (13%)	Reference					
2	162 (14%)	23 (14%)	1.17	0.65 – 2.11				
3	111 (10%)	16 (14%)	1.19	0.62 – 2.27				
4	88 (8%)	10 (11%)	0.92	0.43 – 1.94				
5	86 (8%)	11 (13%)	1.05	0.51 – 2.18				
6	88 (8%)	7 (8%)	0.67	0.28 – 1.57				
7	97 (9%)	16 (17%)	1.37	0.72 – 2.63				
8	86 (8%)	12 (5%)	1.15	0.56 – 2.33				
9	106 (9%)	14 (14%)	1.04	0.53 – 2.05				
10	144 (13%)	28 (19%)	1.61	0.91 – 2.83				
missing	2	0						

BNP) elevation was used to assess the likelihood of right heart strain according to the European Society of Cardiology guidelines.[2]

Hazard ratios (HR) were calculated by data analysis on STATA 17 using cox regression.

Kaplan Meier survival curves were plotted for unprovoked, covid-provoked, cancer-provoked and those provoked by other causes in addition to an equivalent for those with negative scans.

Results

1137 patients were diagnosed with pulmonary emboli in 2020 and 2021. 513 patients where pulmonary emboli had been suspected but subsequently excluded with negative scans over the same time period were randomly selected as the control group. The survival in those with pulmonary emboli identified on their scan was better than those with a negative scan with an unadjusted hazard ratio (HR) for death in the group with pulmonary emboli of 0.60 (p<0.001) or 0.71 (confidence interval 0.56-0.91, p=0.007) when adjusted for age, sex, BMI and IMDS.

Subsequent analysis excluded those with negative scans and focused on factors that influenced mortality in those who had been diagnosed with pulmonary embolism. Table 1 contains the unadjusted and adjusted hazard ratios for mortality in all patients with PE looking at demographics (sex, age group, IMDS). Male sex had an adjusted HR of 1.41 (p=0.034) and there was a strong association of mortality with increasing age (likelihood ratio <0.0001) whereas IMDS showed no significant association with mortality. Further analysis was therefore adjusted for age and sex.

Adjusted hazard ratios in Table 2 demonstrate a 5 times greater risk of mortality in patients with provoked clots when compared to the unprovoked group (HR 4.98; p<0.001). This effect is contributed

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Table 2.

	Pulmonary Emboli	Deaths within study	Unadjusted hazard ratio	95% Confidence interval	Adjusted hazard ratio	95% Confidence interval	Adjusted HR p value	Likelihood-ratio test p value
Clot type								<0.0001
Unprovoked	553 (49%)	31 (6%)	Reference					
Provoked (All)	584 (51%)	127 (22%)	4.50	3.03 – 6.67	4.98	3.36 – 7.38	<0.001	
Provoked - cancer	150 (13%)	71 (47%)	12.2	7.96 – 18.6	11.7	7.61 – 17.9	<0.001	
Provoked - COVID	166 (15%)	14 (8%)	1.66	0.88 – 3.12	2.22	1.17 – 4.19	0.014	
Provoked - other	268 (24%)	42 (16%)	3.03	1.91 – 4.82	3.17	1.99 – 5.06	<0.001	

to significantly by all sub-groups of provoked clots with the greatest effect in the provoked – cancer group (HR 11.7; p<0.001) and provoked – other group (HR 3.17; p<0.001) and a small effect in the provoked – COVID group (HR 2.22; p=0.014).

The impact of body mass index on mortality after PE is outlined in Table 3. This effect is described in terms of the difference in mean BMI, by WHO classification of BMI, by comparison of obese to healthy weight and by the effect of every additional 1kg/m^2. In all analyses the effect is significant with high BMI being associated with lower mortality. The extent of the effects can be seen in detail in the table but, by way of example, obese patients have an adjusted hazard ratio of 0.35 when compared to patients of a healthy weight and every additional 1kg/m^2 is associated with a 7% drop in mortality in PE patients. When analysed by clot type, the effect of obesity on mortality after PE can be seen to have been due to the effect in the combined provoked group (HR 0.31; p<0.001) rather than the unprovoked group (HR 1.44; p=0.484). Breaking this down to subgroups of provoked pulmonary emboli, only provoked – other remained significant though there were clear trends in both the cancer and COVID subgroups.

Assessment of the impact of PE-related factors such as clot group and right ventricular strain showed no association with mortality. The sPESI score, however, was a strong predictor of mortality in the longer time-frame of the study (likelihood ratio p<0.0001). These results are shown in Table 4.

Figure 1 demonstrates the effect of WHO obesity class on the distribution of sPESI scores: while a consistent proportion of patients with PE in all WHO groups had an sPESI score of 1, the proportion with sPESI≥2 fell with increasing weight and sPESI=0 showed a corresponding rise.

Kaplan-Meier survival curves in Figure 2, constructed out to 1 year, illustrate the mortality differences between the groups by clot type for those patients who had pulmonary emboli and include a similar curve for the control group with negative scans. Survival was best in the unprovoked pulmonary emboli (7.2% mortality at 1 year) and worst in those provoked by cancer (40% mortality at 1 year). Those with negative scans had a 19.4% mortality at 1 year. Though limited data on cause of death were available for only 234 of the 275 patients who died in the audit, cancer was found to be the primary cause of death in 53/71 (74.6%) of the cancer-provoked group and 48/108 (44.4%) of those with negative scans.

Discussion

This study provides a detailed analysis of patient and PE-related factors associated with longer-term mortality after PE.

In terms of patient-related factors, results demonstrate that the risk of longer-term mortality after any PE is associated with male sex and increasing age but that patients with elevated BMI have lower mortality if their PE was provoked.

Other studies have given us a good understanding of the short-term prognostic assessment after pulmonary embolism and well-validated assessment tools such as the pulmonary embolism severity index (PESI)[3] and, derived from it, the simplified pulmonary embolism severity index (sPESI)[4] are commonly used. Their primary benefit is to identify those at low risk of mortality who might, therefore, be treated in an ambulatory setting or discharged from hospital early. These results show that sPESI continues to correlate strongly with the mortality risk in the longer term and confirm that there is no association between longer-term mortality and other aspects of the clot at presentation including extent of clot and impact on right ventricular function.

Longer-term mortality is significantly higher in provoked pulmonary emboli than in the unprovoked group and, while this is driven to a large extent by cancer deaths in the group of patients known to have cancer at the time of diagnosis, there remains a significant effect in patients with PE provoked by both COVID and other factors. Previous studies looking at longer-term mortality are relatively limited. A large registry demonstrated an increased risk of mortality at 3 months in PE patients with cancer, immobility and

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Table 3.

	Pulmonary Emboli	Deaths within study	Unadjusted hazard ratio	95% Confidence interval	Adjusted hazard ratio	95% Confidence interval	Adjusted HR p value	Likelihood-ratio test p value
Body mass index								
Mean BMI (kg/m2)	29.8	26.1						
By WHO classification								<0.0001
<19 kg/m2	33 (3%)	13 (39%)	1.74	0.95 – 3.16	2.13	1.17 – 3.88	0.014	
19 – 24 kg/m2	244 (21%)	62 (25%)	Reference					
25 – 29 kg/m2	350 (31%)	48 (14%)	0.50	0.34 – 0.72	0.50	0.34 – 0.73	<0.001	
30 – 34 kg/m2	224 (20%)	18 (8%)	0.28	0.17 – 0.48	0.33	0.20 – 0.57	<0.001	
35 – 39 kg/m2	120 (11%)	9 (8%)	0.26	0.13 – 0.52	0.35	0.17 – 0.72	0.004	
40 kg/m2 and above	127 (11%)	8 (6%)	0.21	0.10 – 0.44	0.39	0.18 – 0.84	0.016	
Missing	39 (3%)	0						
By BMI as continuous variable								
Risk of death per additional kg/m2			0.91	0.89 – 0.94	0.93	0.90 – 0.95	<0.001	
By obesity (BMI>30 kg/m2) vs healthy weight								0.0031
BMI ≥30 kg/m2	471 (41%)	35 (7%)	0.26	0.17 – 0.39	0.35	0.23 – 0.55	<0.001	
Obesity by clot type								
Unprovoked	297 (63%)	21 (7%)	1.00	0.38 – 2.64	1.44	0.52 – 3.94	0.484	
Provoked (All)	174 (37%)	14 (8%)	0.21	0.12 – 0.38	0.31	0.17 – 0.58	<0.001	
Provoked - cancer	31 (7%)	10 (32%)	0.43	0.21 – 0.88	0.55	0.25 – 1.22	0.143	
Provoked - COVID	78 (17%)	3 (4%)	0.29	0.06 – 1.28	0.42	0.09 – 1.90	0.259	
Provoked - other	65 (14%)	1 (2%)	0.05	0.01 – 0.41	0.11	0.01 – 0.87	0.036	

increasing age.[5] The overall mortality for pulmonary emboli in this study was 7.9% at 3 months which would be comparable to the figure of 8.2% extrapolated from our dataset. At 3 months 26.4% of the cancer vs 4.1% of other PE patients had died again in keeping with our results. A Canadian database showed that the mortality in cancer-associated PE patients was 40% at 1 year and 61% at 5 years, compared to 7% and 20% in other provoked and 6% and 15% in unprovoked PE respectively.[6] Our survival curve for patients with cancer –provoked pulmonary emboli demonstrates similar results at 1 year lending weight to the validity of our results. Although the Canadian group did look at provoked and unprovoked PEs separately, they did not demonstrate a significant difference between the groups. In our data there is a clear and significant difference in adjusted hazard ratios for mortality in each of the provoked groups (cancer, COVID and other) when compared to unprovoked pulmonary emboli, though the magnitude of the difference was predictably greatest in the cancer-provoked group. The survival curve for the COVID-provoked group demonstrates that the small excess mortality compared to those with unprovoked clots happens early on with curves being similar after the first 3 months.

Of interest, patients with negative scans had a 19.4% mortality at 1 year, and a higher mortality than patients with pulmonary emboli identified on their scans. This is a novel finding. Clinically there is a temptation to exclude PE and not pursue the clinical

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Table 4.

	Pulmonary Emboli	Deaths within study	Unadjusted hazard ratio	95% Confidence interval	Adjusted hazard ratio	95% Confidence interval	Adjusted HR p value	Likelihood-ratio test p value
sPESI								<.0001
0	455 (40%)	18 (4.0%)	Reference					
1	362 (32%)	43 (11.9%)	3.11	1.79 – 5.40	2.36	1.34 – 4.14	0.003	
2	220 (19%)	68 (30.9%)	9.54	5.67 – 16.0	6.80	3.91 – 11.8	<0.001	
3	69 (6%)	25 (36.2%)	11.3	6.18 – 20.8	6.60	3.42 – 12.7	<0.001	
4	8 (1%)	3 (37.5%)	13.0	3.84 – 44.2	8.12	2.33 – 28.2	0.001	
Missing	23 (2%)	1 (4.3)						
Clot group								
1	254 (22%)	37 (14.7%)	Reference					
2	103 (9%)	23 (22.3%)	1.69	1.00 – 2.84				
3	263 (23%)	33 (12.5%)	0.84	0.52 – 1.34				
4	241 (21%)	35 (14.5%)	1.01	0.64 – 1.61				
5	276 (24%)	30 (10.9%)	0.70	0.43 – 1.13				
Right ventricular strain								
No markers	692 (61%)	92 (13.3%)	Reference					
Imaging or biomarkers	255 (22%)	39 (15.3%)	1.21	0.83 – 1.75				
Imaging and biomarkers	180 (16%)	27 (15%)	1.12	0.73 – 1.72				
Cardiovascular compromise	10 (1%)	0	-	-				

cause for symptoms in these cases. These results should prompt clinicians to think carefully about possible co-morbidities which might explain the symptoms which led to exclusion of PE and look for other investigations and interventions which might improve prognosis. Although not the full explanation, the increased propensity to undertake imaging to exclude PE in the cancer population because of the known risks and impact of cancer on both Wells Score and D dimer is likely to skew these results. Though data is incomplete, it is noteworthy that 44.4% of these patients with negative scans who died and had a known cause of death, died of cancer-related problems.

The protective effect of high BMI on mortality has been called 'the obesity paradox' and has been applied to various disease categories. Previous authors have recognised the apparent protective effect of a higher BMI on mortality after PE.[7] Our results demonstrate that this effect is significant however it is analysed (table 3), but, most simply expressed, an obese person (BMI>30 kg/m^2) with a PE has an adjusted hazard ratio for mortality of 0.35 compared to a patient of healthy weight.

There is an obvious temptation to ascribe this effect to ascertainment bias whereby symptomatic breathlessness in the obese group leads to more imaging and a consequent identification of less clinically significant pulmonary emboli. The detailed analysis in this paper and our previous work, however, makes this potential explanation less likely. When analysed by clot type, the effect of obesity on incidence of PE was found to be limited to unprovoked PE (OR 4.6; p<0.001) compared to a slight reduction in pulmonary emboli provoked by causes other than COVID (OR 0.7; p=0.048) in the obese versus healthy weight patients.[8] By contrast, in this paper, the reduction in mortality for the obese group was isolated to the provoked groups (Adjusted HR 0.31; p<0.001) whereas in the unprovoked clots obesity had no significant effect on mortality.

Alternative possible explanations include:

1. A confounding effect whereby the provoking co-morbidity is responsible for both the low BMI and the risk of mortality. This association is clear in cancer patients but also likely in frail

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patients at risk of PE from immobility or falls resulting in lower limb fracture or surgery.

2. The theory of metabolically healthy obese individuals found frequently in modern societies.[9]
3. The influence of factors that cannot be controlled for in this study including, for example, the widespread use of long-term anticoagulation in the unprovoked group (which has a higher representation of obese patients) compared to the provoked groups where there are fewer overweight and obese patients.

Further work is required to tease out these possibilities but, given our findings, it is crucial to analyse by clot type in any future studies.

Inherent strengths of this study are the detailed and complete data on consecutive PE patients and that is it real world audit data aimed at improving a clinical service rather than a selected research cohort. Capture of patients through an established PE pathway which encourages referral of all patients in order to ensure appropriate follow up has seen annual numbers of PE patients in line with the expected numbers from epidemiological studies. The minority not seen in clinic because of death, attendance in haematology-obstetric clinics or failure to attend were identified by audit of the referrals themselves. A sample of over 500 CTPA and VQ scans on patients performed in the time-frame of the study identified only a small number of individuals with positive scans who had not been referred giving assurance that case capture was very high. Of 1650 total patients included in the audit, all had sex and age data, only 2 were missing postcode data and 39 had no BMI measurement recorded at the time of diagnosis. Data was, therefore, comprehensive and allowed accurate logistic regression analysis to control for potential confounders. Information on whether the PEs were provoked or not came from records at diagnosis for all and were checked at a 3 month review in a specialist clinic for the majority.

Weaknesses include the fact that this was a single-centre study based on an audit database and, a larger, prospective, multi-centre data collection would provide more conclusive data. We believe, however, that this work helps provide justification for such a study. As a secondary care audit of PE patients, there was incomplete data on medical cause of death limiting a detailed analysis of this to cases where cause of death was available from hospital records.

These results highlight important, clinically-relevant messages and should prompt a careful and holistic assessment before discharge focussing in particular on patients with high sPESI, with provoked PEs particularly in 'healthy' or underweight individuals and on those with negative scans to ensure that any treatable comorbidities are identified and addressed.

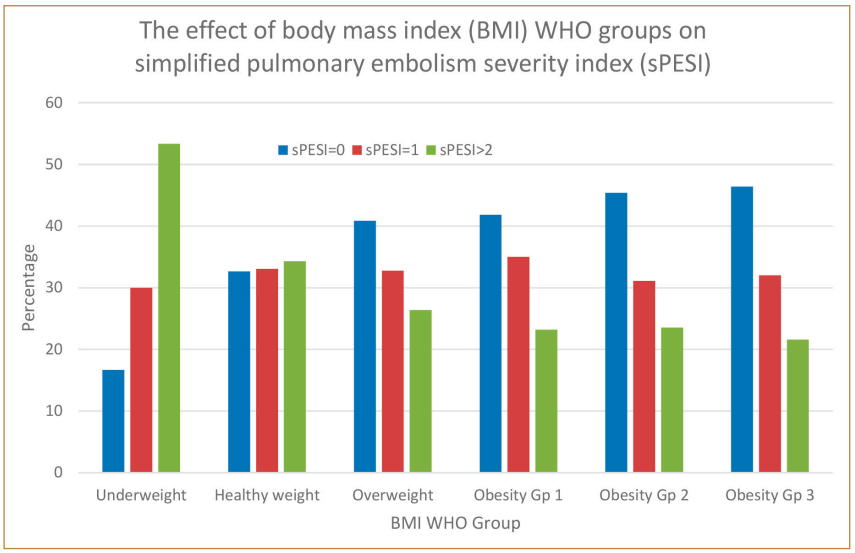


Figure 1.

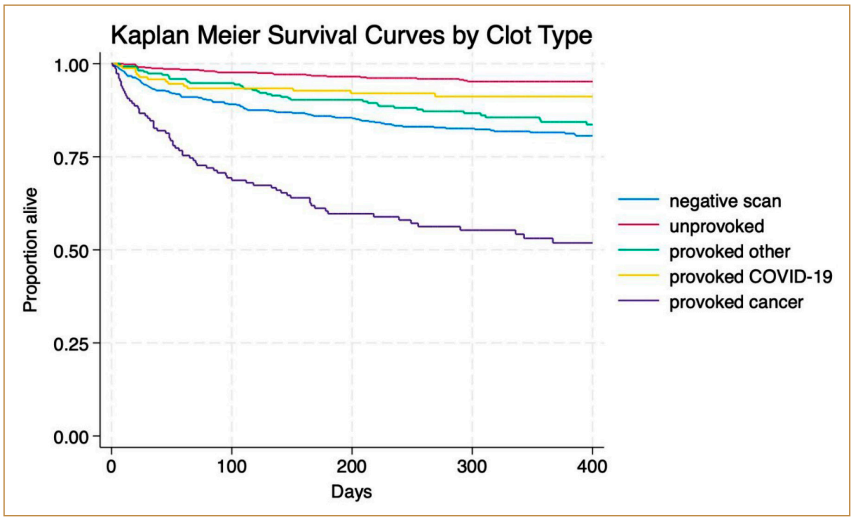


Figure 2.

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Competing Interests

There are no competing interests for any author

Contributor statement

Ivan Le Jeune contributed to planning, data collection, analysis and reporting of findings. Richard Hubbard contributed to planning, data analysis and reporting of findings.

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