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The contribution of cardiovascular mortality to long term outcomes in a relatively young demographic following acute pulmonary embolism: A validation study

L. Hee [a,c,1], A.C.C. Ng [b,d,1], J. Huang [a,c,1], V. Chow [b,d,1], C. Mussap [a,c,1], L. Kritharides [b,d,1], L. Thomas [a,c,*,1]

[a] Cardiology Department, Liverpool Hospital, Sydney, NSW, Australia
[b] Cardiology Department, Concord Hospital, Sydney, NSW, Australia
[c] South Western Sydney Clinical School, The University of NSW, Sydney, NSW, Australia
[d] Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

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ABSTRACT

Background: Long-term studies following acute pulmonary embolism (PE) remain limited in the current era. A recent study from our collaborative group, in a contemporary adult population, showed substantially increased cardiovascular mortality following PE. We sought to evaluate the contribution of cardiovascular mortality to long-term outcomes in a different demographic that comprised of a significantly younger PE cohort.
Methods and results: Demographic and clinical characteristics were retrospectively collected for this cohort, and similar methods and outcome measures were applied as detailed in the original study. We compared a population from a different metropolitan area (LH: Liverpool Hospital) to that from the original study (CRGH: Concord Hospital) over a similar time period. A total of 815 patients comprised this cohort with mean 5.3 ± 3.8 year follow-up. There were similar demographics between the two cohorts, though the mean age was significantly younger in LH group (60 vs 68 years, $p < 0.001$). Prior history of cardiovascular disease in the LH group was half of that present in the CRGH cohort. The overall mortality was 7.4% per patient-year. Patients with underlying cardiovascular disease when presenting with an acute PE had a 2.3-fold increased risk of death during follow-up compared to those without. Multivariate analysis showed that older age, male gender, malignancy, diabetes, cardiovascular disease and chronic pulmonary disease were independent predictors of post-discharge mortality.
Conclusions: Despite our cohort being significantly younger with a lower incidence of pre-existing cardiovascular disease, cardiovascular disease was still a significant contributor to long-term outcomes and an important predictor of mortality following acute PE.

1. Introduction

Acute pulmonary embolism (PE) can potentially be a serious medical condition [1] with significant association with morbidity and mortality [2,3]. The interaction of extensive pulmonary artery obstruction with the presence of pre-existing cardiopulmonary co-morbidities may lead to significant right ventricular dysfunction, associated hemodynamic instability and in severe cases, death [4]. Of note, 25% of patients do not survive the first year after being diagnosed with a PE [5,6]; prospective cohort studies report acute case fatality rates for PE ranging from 7 to 11% [7]. Beyond 30 days however, underlying co-morbidities such as cancer, congestive heart failure, or lung disease are common causes of death [8,9].

Although individual complications of PE have been studied extensively, the combined risk for all adverse clinical events has not yet been reported. More importantly, long-term studies following acute PE are limited and such studies are particularly lacking in the current era. Knowledge of the long-term prognosis after acute PE is of importance as this could provide guidance on clinical decision-making regarding treatment regimes, specific preventive screening programmes, and mode and duration of follow-up for these patients.

A recent contemporary study from our collaborative group in an adult population showed that PE was associated with a substantially increased long-term mortality, of which nearly half was attributable to cardiovascular causes [10]. Accordingly, we derived a similar cohort from our hospital located in a different metropolitan area, and evaluated the clinical profile and outcomes of patients with confirmed acute PE to examine the effects of pre-existing cardiovascular disease. We sought to evaluate the long-term risk of cardiovascular mortality after acute

* Corresponding author at: Cardiology Department, Liverpool Hospital, Elizabeth Street, Liverpool, Sydney, NSW 2170, Australia. Tel.: +61 2 9828 3070; fax: +61 2 9828 3054.
E-mail address: l.thomas@unsw.edu.au (L. Thomas).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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PE, to ascertain if similar results of increased cardiovascular mortality would be observed.

2. Methods

2.1. Study population

The admission charts of all consecutive inpatients and outpatients diagnosed with acute PE between January 2000 and December 2010 at a single tertiary institution Liverpool Hospital (LH), Sydney, Australia were systematically retrieved for review, using standardised coding criteria for the diagnosis of acute PE as previously defined by Ng et al. at their institution (Concord Hospital [CRGH], Sydney, Australia) [10,11]; the same coding criteria were applied at both centres. In brief, confirmed PE required documented clinical diagnosis and/or treatment of acute PE by the attending physician together with an imaging study that confirmed the diagnosis (i.e. either an intermediate-high probability nuclear pulmonary ventilation–perfusion scintigraphy or computed-tomography pulmonary angiogram showing thrombus within pulmonary arterial circulation). Only patients with their first presentation of an acute PE were included in the study. This study was approved by the Institutional Human Research Ethics Committee.

2.2. Data collection

Detailed information was collected on study patients, including their admission history, demographic and clinical characteristics. Data on risk factors for PE were derived from the medical records and discharge summary of patients. History of cardiovascular diseases included ischemic heart disease, prior coronary artery bypass surgery, heart failure, valvular heart disease, prosthetic heart valves, arrhythmias including atrial fibrillation/flutter, peripheral vascular disease, and stroke. Neurodegenerative disease included dementia and/or Parkinson's disease. Hemodynamic profiles on admission (heart rate and systolic blood pressure) were available only for the CRGH cohort. The shock index (heart rate divided by systolic blood pressure) was assessed in this cohort, with a score > 0.7 signifying hemodynamic compromise [12].

2.3. Study outcomes

The same outcomes described in CRGH study [10] were adopted for this current study in the LH patients. In brief, long-term mortality for each patient was tracked using a state-wide death registry database and each death was coded. The Australian Institute of Health and Welfare (AIHW) uses data from the registry to compile tables of age and sex-specific causes of death in the General Record of Incidence of Mortality (GRIM) reports, which are classified according to the International Classification of Diseases (ICD)10-Australian Modification [1]. A censored date of June 30, 2013 was pre-determined or the occurrence of the primary outcome of the study, which all-cause mortality. All death certificates, or the pathology report from autopsy, were examined to determine the cause of death. In instances of ambiguity, cause of death was verified with the treating physician or general practitioner. The cause of death for each patient was coded independently by 2 investigators (JH and LT), blinded to details of the patients background and co-morbid conditions. All surviving patients were followed up by mail or phone, to obtain data on recurrence of adverse events, and this was corroborated with information on their medical history and clinical condition.

The secondary outcome of the study was the rate of both cardiovascular and non-cardiovascular death. Cardiovascular death was defined as in the CRGH study as death from PE, acute myocardial infarction, heart failure, stroke, cardiac arrest, and cardiac-related causes (when more than one cardiac cause of death was recorded). Non-cardiovascular deaths included those due to malignancy, sepsis, and dementia. Patients with potentially multiple causes of death were classified as 'undefined' or unexplained death for the purpose of the present study.

2.4. Comparator cohort

A validation study of the previously reported derivation CRGH cohort [10] was performed, to verify the risk of cardiovascular mortality and the event-free survival in patients with a confirmed acute PE. We compared a population from a different metropolitan area of New South Wales, serviced by Liverpool Hospital, over a similar time period as previously examined and reported by Ng et al. [10]. The study cohort was stratified into the same age groups as described in CRGH cohort, and the annual all-cause mortality rate in each age group was compared between the two cohorts.

2.5. Statistical analysis

SPSS, version 21 (SPSS Inc., Chicago, IL) was used for all analyses. All analyses were based on two-sided tests with significance level stated at $\alpha = 0.05$. Duration of follow-up is reported as mean (± standard deviation [SD]). All patients were followed from the index event to the date of death or up till June 30, 2013, whichever came first. The

Table 1
Baseline characteristics comparison between LH and CRGH cohorts.

Parameters	LH (n = 815)	CRGH (n = 1023)	*p* value
Mean age (SD), years	60.1 (17.4)	68.1 (16.3)	<0.001
Males, n (%)	362 (44.4)	457 (44.7)	0.913
Race, n (%)			
Asian	38 (4.7)	54 (5.3)	0.547
Non-Asian	783 (95.3)	969 (94.7)	
Documented deep vein thrombosis during admission, n (%)	119 (14.6)	184 (18.0)	0.052
Admitting physician specialty, n (%)			
Internal medicine specialties	800 (97.4)	999 (97.6)	0.079
Surgical specialties	21 (2.6)	19 (1.9)	
Hemodynamic profile on admission			
Mean heart rate (SD), beats/min	–	88 (21)	
Mean systolic blood pressure (SD), mm Hg	–	141 (25)	
Shock index[a] > 0.7, n (%)	–	231 (22.6)	
Length of hospital stay, days			
Median (inter-quartile range)	6 (5–10)	7 (5–10)	0.251
Echocardiogram during admission, n (%)	119 (14.6)	381 (37.2)	<0.001
Imaging modality			
Ventilation–perfusion scintigraphy, n (%)	362 (44.4)	860 (84.1)	<0.001
Computed tomography pulmonary angiogram, n (%)	402 (49.3)	257 (25.1)	<0.001
Both imaging modalities used, n (%)	47 (5.8)	102 (10.0)	0.008
Co-morbid conditions			
Cardiovascular disease[b], n (%)	192 (23.6)	451 (44.1)	<0.001
Cardiac risk factors, n (%)			
Hypertension	221 (27.1)	316 (30.9)	0.077
Hyperlipidemia	103 (12.6)	142 (13.9)	0.436
Diabetes	122 (15)	158 (15.4)	0.778
Current smoker	166 (20.4)	86 (8.4)	<0.001
Ex-smoker	142 (17.4)	177 (17.3)	0.946
Malignancy, n (%)	149 (18.3)	229 (22.4)	0.031
Chronic pulmonary disease, n (%)	102 (12.5)	144 (14.1)	0.329
Neurodegenerative disease, n (%)	69 (8.5)	66 (6.5)	0.100
Chronic renal disease, n (%)	67 (8.2)	59 (5.8)	0.146

[a] Shock index = heart rate divided by systolic blood pressure (index > 0.7 signify hemodynamic compromise).
[b] Cardiovascular disease includes history of ischemic heart disease, stroke, heart failure, peripheral vascular disease, valvular heart disease (with or without prosthetic valve) and/or atrial fibrillation/flutter. Neurodegenerative disease includes dementia and Parkinson disease.