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Impact of persistent anaemia on mortality in patients hospitalised with acute pulmonary embolism: an Australian retrospective observational study

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ABSTRACT

Objectives Anaemia is associated with increased mortality in acute pulmonary embolism (PE) patients. However, prior studies have not examined the prognostic impact of trends in plasma haemoglobin during admission. This study investigates the impact of changes in haemoglobin level on mortality during hospital stay in acute PE.

Study design A retrospective observational study.

Setting Tertiary-referral centre in Australia.

Participants Consecutive patients from 2000 to 2012 admitted with confirmed acute PE were identified from a dedicated PE database. Haemoglobin levels on days 1, 3–4, 5–6 and 7 of admission were retrieved. Patients without both baseline haemoglobin and subsequent haemoglobin levels were excluded (n=327), leaving 1099 patients as the study cohort. Anaemia was defined as haemoglobin <130 g/L for men and <120 g/L for women. There were 576 patients without anaemia throughout admission, 65 with transient anaemia (anaemic on day 1, but subsequently normalised during admission), 122 with acquired anaemia (normal on day 1 but developed anaemia during admission) and 336 with persistent anaemia. A total of 71 patients received blood transfusion during admission.

Main outcome measure 6-month mortality was tracked from a state-wide death database and analysed using multivariable modelling.

Results After adjusting for transfusion, patietns with persistent anaemia had a significantly increased 6-month mortality risk (adjusted HR 1.97, 95% CI 1.26 to 3.09, p=0.003) compared with patients without anaemia. There was no difference in mortality between patients with transient or acquired anaemia and patients without anaemia.

Conclusion Among patients who had anaemia during their admission for acute PE, only the subgroup with persistent anaemia demonstrated worse outcomes.

Strengths and limitations of this study

- The present study included a large cohort of patients with confirmed acute pulmonary embolism (PE).
- Different haemoglobin fluctuation patterns were categorised for first time following acute PE.
- The independent prognostic impact of persistent anaemia post-acute PE was established, including adjustment for the effect of blood transfusion.
- Limitations of the present study include its retrospective single-centre study design.
- Not all confounders can be accounted for and no cause-specific mortality analysis.

INTRODUCTION

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death after coronary artery disease and stroke.[1] Anaemia as a predictor of mortality following acute PE has rarely been studied. Two studies have suggested that lower haemoglobin levels on the day of admission were associated with increased short-term mortality (30 days and 3 months) in acute PE.[2 3]

However, recent conflicting evidence suggests that a single measure of baseline haemoglobin on admission for acute PE may not be predictive of mortality after taking into account the impact of blood transfusions.[4] Haemoglobin fluctuations and variability have been explored in other diseases, such as chronic heart failure, end-stage renal failure and malignancy; these studies showed that persistent anaemia or declining haemoglobin trends were associated with poorer outcomes.[5–12] However, no study to date has investigated the pattern of haemoglobin fluctuation or determine the prognostic significance of persistent anaemia following acute PE.

This study investigated the impact of persistent anaemia during admission on 6 month mortality in a large cohort of patients hospitalised with confirmed acute PE.

PATIENTS AND METHODS

Study cohort

This study cohort was derived from a dedicated PE database of consecutive patients admitted with a primary confirmed diagnosis of acute PE between January 2000 and December 2012 to a tertiary-referral institution (Concord Hospital, Sydney, Australia). Outcomes from this database have been previously published.[13 14] Only the initial PE presentation was included in this study for patients with more than one episode of acute PE during study period. Patients who reside in other states were excluded to minimise incomplete tracking of outcomes.

The study was conducted in accordance with the Declaration of Helsinki. All patients' data were deidentified and analysed anonymously.

Patient and public involvement

There was no patient or public involvement in the development or design of this study.

Data sources

The Concord Hospital PE database records pertinent details of the patient's admission, including presenting haemodynamics, comorbidities, results of investigations and medications. The simplified Pulmonary Embolism Severity Index (sPESI) based on age, history of malignancy, heart failure or chronic pulmonary disease, heart rate (≥110 beats/min), systolic blood pressure (BP) (<100 mm Hg), and oxyhaemoglobin saturation (<90%) was calculated for each patient.[15] Blood transfusion records were collected from the hospital Blood Bank.

Haemoglobin levels on admission (day 1) and throughout the hospital stay (day 3/4, day 5/6 and day 7, if available) were retrieved from the database. If more than one assessment of plasma haemoglobin was performed over the day-range (eg, days 3 and 4), the average of the test results was recorded. From the main PE database, only patients who had both baseline haemoglobin recorded on admission (day 1) and at least one subsequent haemoglobin level assessment during admission were included as the study group of interest.

Study outcomes

The primary outcome was all-cause mortality at 6 months following admission for acute PE ascertained from a statewide death registry. A censored date of 31 October 2013 was predetermined to fulfil the minimum follow-up of 6 months for each patient.

Statistical analysis

Anaemia was defined according to the WHO criteria of serum haemoglobin level <130 g/L for men and <120 g/L for women.[16] The study cohort was then stratified into four groups: group 1, patients without anaemia at any time during admission; group 2, patients with transient anaemia (anaemic on presentation, then normalised during admission either spontaneously or after transfusion); group 3, patients with acquired anaemia (normal haemoglobin level on presentation, becoming anaemic during admission) and group 4, patients with persistent anaemia (anaemic on presentation and throughout admission, irrespective of transfusion).

All continuous variables were expressed as either mean ±SD deviation or median (IQR) based on Shapiro-Wilk test of normality, with categorical variables as frequencies and percentages. Comparisons between groups were performed using Fisher's exact tests, Chi-square test, Student t-tests, one-way analysis of variance with post-hoc Bonferroni test, or Kruskal-Wallis test as appropriate. Outcomes of the study groups were compared using group 1 (no anaemia) as the control. Kaplan-Meier survival curves with log-rank tests were used to compare survival between groups. The prognostic significance of haemoglobin level fluctuations and other variables, including blood transfusion, were assessed using univariable Cox proportional hazards regression analyses. All continuous variables were dichotomised, with optimum levels derived from the Youden index.[17] The proportional hazards assumption was checked with log-minus-log plots. Significant variables (defined as $p<0.05$) were then included in the multivariable Cox regression analyses. To avoid significant co-linearity, only univariable predictors with a correlation coefficient ≤0.7 were chosen for the multivariable modelling. A separate sensitivity analysis was performed to determine if the prognostic impact of persistent anaemia persists when patients who had transfusion during admission were excluded. A two-tailed probability value <0.05 was considered statistically significant. All analyses were performed using SPSS v.22 (IBM, New York, NY, USA).

RESULTS

There were 1426 patients admitted with a confirmed diagnosis of PE between 2000 and 2012. Of these patients, 327 were excluded from further analysis due to the absence of a baseline haemoglobin level at admission (n=50) or lack of subsequent haemoglobin level assessment during admission (n=277). The final study cohort comprised 1099 patients representing all patients who satisfied the study's inclusion criteria of having both baseline haemoglobin recorded on admission (day 1) and at least one subsequent haemoglobin level assessment during admission (figure 1). There were no differences in survival at 6 months between excluded patients and study patients after adjusting for differences in baseline characteristics (online supplementary tables S1 and S2; figure S1).

Baseline characteristics

The final study cohort of 1099 patients was stratified into four groups according to patterns of haemoglobin fluctuation during their admission (figure 1): group 1 (no anaemia: n=576, 52%); group 2 (transient anaemia: n=65, 6%); group 3 (acquired anaemia: n=122, 11%) and group 4 (persistent anaemia: n=336, 31%). Patients who were anaemic on admission and who demonstrated transient normalisation of haemoglobin with recurrent

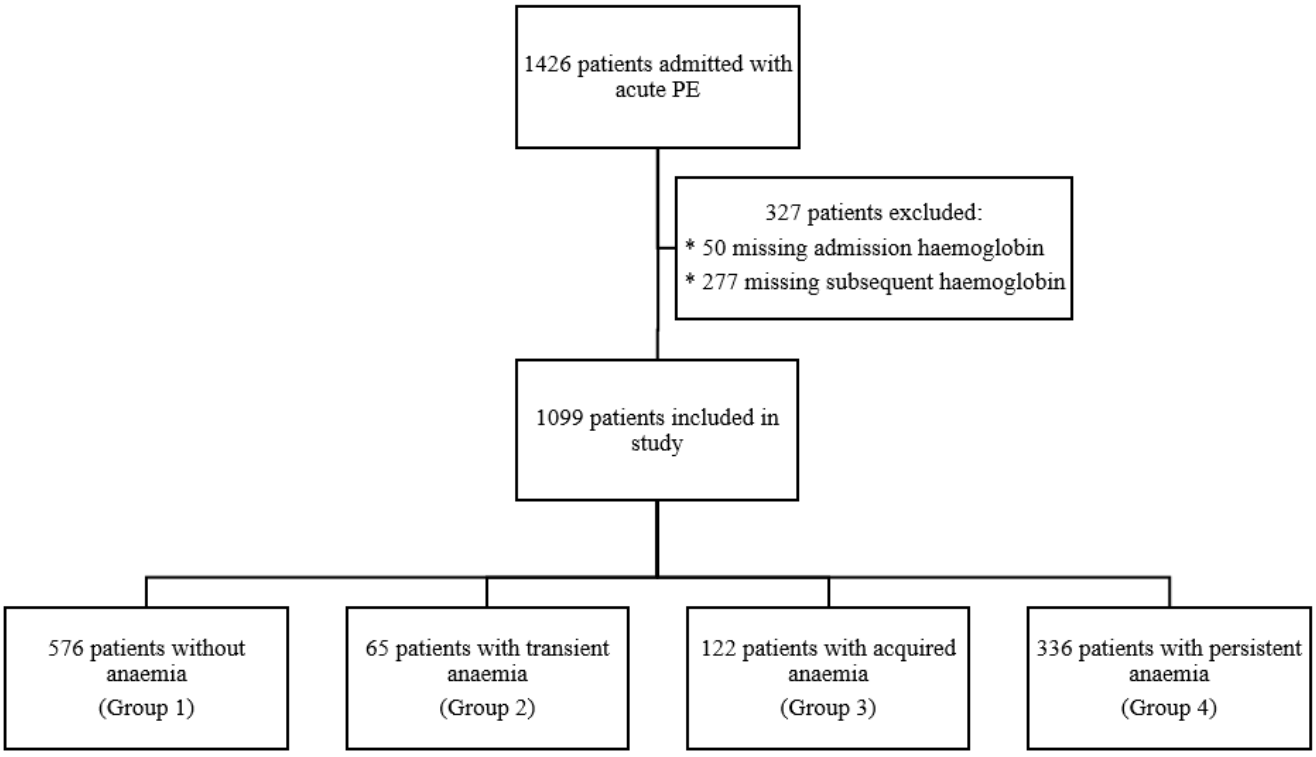

Figure 1 Study cohort derivation. Figure illustrates the derivation of the study cohort and the subsequent stratification into the four haemoglobin fluctuation pattern study groups. Group 1: normal (patients without anaemia on presentation and throughout admission); group 2: transient anaemia (anaemia on presentation, then normalised during admission); group 3: acquired anaemia (normal haemoglobin levels on presentation, then declined to levels below normal during admission); group 4: persistent anaemia (patients with persistent anaemia at baseline and throughout admission).

anaemia later in the admission (n=12) were categorised as having persistent anaemia.

Table 1 shows the baseline characteristics of the study cohort. Patients with persistent anaemia (group 4) were more likely to be a current smoker, have underlying diabetes and ischaemic heart disease compared with patients without anaemia (group 1). Furthermore, group 4 patients were more likely to be male and have underlying malignancy compared with all other groups, and more likely to have underlying hypertension and chronic renal disease compared with patients without anaemia (group 1) and acquired anaemia (group 3). Group 1 patients were younger, less likely to have underlying heart failure and chronic renal disease, compared with all the other groups.

Table 2 compares the haemodynamic, blood and medication profiles between the groups. While the median sPESI scores were the same among all four groups, the IQR distribution was higher in patients with acquired (group 3) and persistent anaemia (group 4) compared with patients without anaemia (group 1). Patients without anaemia had a higher median serum sodium level and estimated glomerular filtration rate on admission and lower median international normalised ratio (INR) compared with all other groups. Patients in groups 2 and 4 had the lowest median plasma day 1 haemoglobin levels on admission and were most likely to receive blood transfusion during admission. Thrombolysis was used only in patients in group 4; otherwise, there were no differences in the documented medications on admission between groups.

All-cause mortality

Overall, 140 of 1099 patients (12.7%) admitted with acute PE died within 6 months (online supplementary table S3). Unadjusted 6 month mortality was higher in both patients with acquired anaemia (group 3) and persistent anaemia patients (group 4) compared with patients without anaemia (group 1). Group 4 patients also fared worse at 6 months when compared with group 3 patients. At the 6 month time point, 27 out of 140 patients who died had received blood transfusions: 2 patients in group 2 and 25 patients in group 4. No patients who died in group 1 or 3 received blood transfusions.

Prognostic impact of persistent anaemia post-acute PE

Significant univariable predictors of 6 month mortality included sPESI, hypertension, hyperlipidaemia, malignancy, chronic pulmonary disease, day 1 serum sodium, INR, and blood transfusion during admission (online supplementary table S4). Acquired anaemia and persistent anaemia groups were also univariable predictors of mortality compared with patients without anaemia.

Table 1 Baseline characteristics of the study cohort

	Study cohort	Normal	Transient anaemia	Acquired anaemia	Persistent anaemia
	(n=1099)	Group 1 (n=576)	Group 2 (n=65)	Group 3 (n=122)	Group 4 (n=336)
Parameters					
Age, years	73 (60–81)	69 (54–79)	74 (63–85)*	76 (66–84)*	75 (67–83)*
Male	503 (46)	245 (43)	23 (35)	53 (43)	182 (54)*†‡
Concomitant DVT	239 (22)	117 (20)	13 (20)	40 (33)*	69 (21)‡
Length of stay, days	7 (5–11)	7 (5–9)	7 (6–11)	10 (6–13)	8 (6–13)
Imaging modality					
Ventilation-perfusion scintigraphy	818 (74)	443 (77)	51 (78)	87 (71)	237 (71)
CTPA	396 (36)	204 (35)	17 (26)	51 (42)	124 (37)
Both imaging modalities used	115 (10)	69 (12)	3 (5)	17 (14)	26 (8) *
Comorbidities§					
Cardiovascular disease					
Ischaemic heart disease	201 (18)	80 (14)	21 (32)*	23 (19) †	77 (23) *
Stroke	35 (3)	18 (3)	1 (2)	1 (1)	15 (4)
Heart failure	144 (13)	51 (9)	15 (23)*	21 (17)*	57 (17)*
Atrial fibrillation/flutter	174 (16)	85 (15)	16 (25)	18 (15)	55 (16)
Valvular heart disease	25 (2)	6 (1)	4 (6)*	6 (5)*	9 (3)
Cardiac risk factors					
Hypertension	282 (26)	134 (23)	18 (28)	26 (21)	104 (31)*‡
Hyperlipidaemia	113 (10)	61 (11)	12 (18)	8 (7)	32 (10)
Diabetes	154 (14)	58 (10)	11 (17)	19 (16)	66 (20)*
Current smoker	91 (8)	59 (10)	3 (5)	11 (9)	18 (5)*
Ex-smoker	191 (17)	96 (17)	9 (14)	23 (19)	63 (19)
Non-cardiac comorbidities					
Malignancy	250 (23)	77 (13)	14 (22)	33 (27) *	126 (38)*†‡
Chronic pulmonary disease	140 (13)	74 (13)	3 (5)	18 (15)	45 (13)
Neurodegenerative disease	73 (7)	33 (6)	6 (9)	11 (9)	23 (7)
Chronic renal disease	69 (6)	10 (2)	5 (8)*	7 (6)*	47 (14)*‡

Continuous variables are expressed as medians with IQR in brackets; all other categorical variables represent numbers of patients with values in brackets representing percentages.
Group 1: normal (patients without anaemia on presentation and throughout admission); group 2: transient anaemia (anaemia on presentation, then normalised during admission); group 3: acquired anaemia (normal haemoglobin levels on presentation, then declined to levels below normal during admission); group 4: persistent anaemia (patients with persistent anaemia at baseline and throughout admission). In this study, anaemia is defined as haemoglobin level <130 g/L for men and <120 g/L for women.
*p<0.05 compared with group 1.
†p<0.05 compared with group 2.
‡p<0.05 compared with group 3.
§Neurodegenerative disease includes dementia and Parkinson's disease.
CTPA, CT pulmonary angiography; DVT, deep vein thrombosis.

The independent prognostic impact of haemoglobin fluctuations on all-cause mortality at 6 months is shown in table 3, with accompanying full multivariable analysis results shown in table 4. The composite sPESI (which accounts for significant comorbidities including age, heart failure/chronic lung disease, malignancy, heart rate, systolic BP and oxyhaemoglobin) was used to avoid overfitting the multivariable models. Model 1, which includes the whole study cohort (n=1099), showed persistent anaemia was a significant independent predictor of 6 month mortality (adjusted HR (aHR) 1.97, 95% CI 1.26–3.09, p=0.003) compared with patients without anaemia during admission even after adjusting for blood transfusion. Transient and acquired anaemia were not independent predictors of 6 month mortality (aHR: 1.16, 95% CI 0.51 to 2.66, p=0.72; aHR: 1.03, 95% CI 0.53 to 2.01, p=0.92, respectively). Adjusted survival curves comparing the study groups are shown in figure 2.

In a separate sensitivity analysis to negate the impact of blood transfusion on mortality, we included only patients who did not receive blood transfusion during admission (n=1028). In this cohort, acquired anaemia

Table 2 Haemodynamic, blood and medication profiles of study cohorts during admission

Parameters	Study cohort (n=1099)	Normal Group 1 (n=576)	Transient anaemia Group 2 (n=65)	Acquired anaemia Group 3 (n=122)	Persistent anaemia Group 4 (n=336)
Haemodynamic profile at admission					
Heart rate, beats/min	87 (74–102)	87 (74–101)	76 (66–95)*	92 (80–108)*†	88 (75–100)†‡
Heart rate >110 beats/min	149 (15)	73 (13)	7 (12)	25 (22)	44 (15)
Systolic BP, mm Hg	140 (122–157)	141 (127–159)	139 (120–157)	135 (120–158)*	134 (118–154)*
Systolic BP<100 mm Hg	35 (3)	10 (2)	1 (2)	7 (6)*	17 (6)*
Oxyhaemoglobin saturation, %	96 (94–98)	96 (94–98)	96 (94–98)	96 (94–98)	96 (93–98) *
sPESI score	1.0 (0–2)	1.0 (0–1)	1.0 (0–2)	1.0 (1–2)*†	1.0 (1–2)†
sPESI>0	706 (64)	308 (53)	42 (65)	92 (75)*	264 (79)*†
Shock index>0.7§	347 (35)	176 (32)	15 (26)	47 (41)	109 (38)
Blood profile during admission					
Day 1 sodium, mmol/L	139 (137–141)	139 (137–141)	139 (135–140)*	139 (137–141)*	138 (135–141)*
Day 1 eGFR, mL/min/1.73 m^2	75 (56–94)	80 (64–97)	73 (54–95)*	70 (48–86)*	66 (43–90)*
Day 1 INR	1.1 (1.0–1.2)	1.1 (1.0–1.1)	1.1 (1.0–1.2)*	1.1 (1.0–1.2)*	1.1 (1.0–1.3)*
Day 1 haemoglobin, g/L	130 (116–142)	141 (133–149)	117 (111–124)*	132 (126–138)*†	109 (99–116)*†‡
Last or day 7 haemoglobin, g/L	128 (115–141)	139 (132–150)	129 (124–135)*	119 (114–125)*†	108 (101–116)*†‡
Blood transfusion during admission	71 (6)	0 (0)	6 (9)*	3 (2)*	62 (18)*‡
Blood transfusion during day 1 to 7	60 (5)	0 (0)	6 (9)*	2 (2)*†	52 (15)*‡
Admission medication use¶					
Aspirin	239 (24)	117 (21)	16 (28)	30 (26)	76 (26)
Clopidogrel	53 (5)	25 (5)	4 (7)	5 (4)	19 (7)
Thrombolysis	5 (0)	0 (0)	0 (0)	0 (0)	5 (2)*
Warfarin	86 (9)	43 (8)	8 (14)	9 (8)	26 (9)
Enoxaparin	33 (3)	13 (2)	1 (2)	5 (4)	14 (5)
DOACs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Continuous variables expressed as median with IQR in brackets; all other categorical variables represent numbers of patients with values in brackets representing percentages.
Group 1: normal (patients without anaemia on presentation and throughout admission); group 2: transient anaemia (anaemia on presentation, then normalised during admission); group 3: acquired anaemia (normal haemoglobin levels on presentation, then declined to levels below normal during admission); group 4: persistent anaemia (patients with persistent anaemia at baseline and throughout admission). In this study, anaemia is defined as haemoglobin level <130 g/L for men and <120 g/L for women.
*p<0.05 compared with group 1.
†p<0.05 compared with group 2.
‡p<0.05 compared with group 3.
§Shock index=heart rate divided by systolic BP (index >0.7 signify haemodynamic compromise).
¶The admission medication use represents pre-existing medications patients were already taking at time of PE presentation, except for thrombolysis which was treatment given at the time of patient's index PE admission. Number of patients with missing data: aspirin (group 1=31; group 2=9; group3=8; group 4=48); clopidogrel (group 1=31; group 2=9; group 3=8; group 4=48); thrombolysis (group 1=32; group 2=9; group 3=8; group 4=49); warfarin (group 1=31; group 2=9; group 3=8; group 4=49); Enoxaparin (group 1=31; group 2=9; group 3=8; group 4=48); DOACs (group 1=38; group 2=9; group 3=12; group 4=60).
BP, blood pressure; DOACs, direct-acting oral anticoagulants including dabigatran, rivaroxaban, and apixaban; eGFR, 186 x ([SCR/88.4]–1.154) x (age)–0.203 x (0.742 if female), where eGFR is estimated glomerular filtration rate (mL/min/1.73 m^2), SCR is serum creatinine concentration (µmol/L) and age is expressed in years; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic BP <100 mm Hg and oxyhaemoglobin saturation <90%).

Table 3 Impact of persistent anaemia on 6 month all-cause mortality

Multivariable analysis*	Model 1 aHR (95% CI)	P value	Model 2 aHR (95% CI)	P value
Normal haemoglobin (Group 1)	1.00 (reference)	–	1.00 (reference)	–
Transient anaemia (Group 2)	1.16 (0.51 to 2.66)	0.72	1.06 (0.41 to 2.73)	0.90
Acquired anaemia (Group 3)	1.03 (0.53 to 2.01)	0.92	1.10 (0.56 to 2.15)	0.78
Persistent anaemia (Group 4)	1.97 (1.26 to 3.09)	0.003	1.90 (1.21 to 2.99)	0.005

Group 1: normal (patients without anaemia on presentation and throughout admission); group 2: transient anaemia (anaemia on presentation, then normalised during admission); group 3: acquired anaemia (normal haemoglobin levels on presentation, then declined to levels below normal during admission); group 4: persistent anaemia (patients with persistent anaemia at baseline and throughout admission).
*Cox proportional hazards regression method was used for multivariable analysis. Model 1 includes the whole study cohort (n=1099). Only univariables with p<0.05 (including haemoglobin groups, hypertension, hyperlipidaemia, sPESI, day 1 serum sodium and INR, and blood transfusion during admission) were included in the multivariable analysis (see online supplementary table S4 and table 4 for full univariable and multivariable analyses results). Model 2 included only patients who did not receive blood transfusion during admission (n=1028). Univariables with p<0.05 (including haemoglobin groups, stroke, sPESI, day 1 serum sodium and INR) were included in the multivariable analysis (see online supplementary table S5 and table 5 for full univariable and multivariable analyses results).
aHR, adjusted HR; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic blood pressure <100 mm Hg and oxyhaemoglobin saturation <90%).

Table 4 Multivariable independent predictors for 6 month all-cause mortality

Variables*	Adjusted hazard ratio (95% CI)	P value
Hypertension	0.55 (0.34 to 0.90)	0.02
Hyperlipidaemia	0.58 (0.23 to 1.47)	0.25
sPESI score (≥1)	5.56 (2.79 to 11.1)	<0.001
Day 1 sodium (≤138.5 mmol/L)	2.19 (1.50 to 3.18)	<0.001
Day 1 INR (≥1.2)	1.76 (1.21 to 2.54)	0.003
Blood transfusion during admission	1.79 (1.10 to 2.91)	0.02
Normal haemoglobin (Group 1)	1.00 (reference)	–
Transient anaemia (Group 2)	1.16 (0.51 to 2.66)	0.72
Acquired anaemia (Group 3)	1.03 (0.53 to 2.01)	0.92
Persistent anaemia (Group 4)	1.97 (1.26 to 3.09)	0.003

*Only univariables with p<0.05 were included during multivariable modelling (see online supplementary table S4 for univariable analysis).
BP, blood pressure; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic BP <100 mm Hg and oxyhaemoglobin saturation <90%).

and persistent anaemia remained significant univariable predictors of mortality compared with patients without anaemia (online supplementary table S5). In multivariable analysis (Model 2 in table 3 with full multivariable analysis results shown in table 5), persistent anaemia remained an independent predictor of 6 month mortality (aHR: 1.90, 95% CI 1.21 to 2.99, p=0.005) compared with patients without anaemia. Neither transient nor acquired anaemia were independent predictors of 6 month mortality. Adjusted survival curves comparing study groups excluding transfused patients are shown in figure 3.

DISCUSSION

The present study is the first to investigate whether haemoglobin fluctuation during admission has any impact on outcomes following acute PE. We found that persistent anaemia throughout admission was an independent predictor of long-term mortality, which remained significant after adjusting for blood transfusions. Furthermore, there were no differences in mortality between patients with transient or acquired anaemia and patients without anaemia.

Jiménez and colleagues first demonstrated that low baseline haemoglobin level on admission day, categorised by quartiles, was an independent predictor of 3 month mortality following acute PE.[2] This observation was later confirmed by Donze *et al* in a large multicenter observational study, which showed that anaemia at presentation was independently associated with increased 30 day mortality.[3] Our patients had comparable baseline characteristics, and our 6 month mortality rate of 13% is in keeping with the previously published mortality rates at 30 days (2%) and 3 months (14%).[2 3] However, authors of both studies acknowledged the inability to account for the impact of blood transfusions as an important limitation. We recently demonstrated that blood transfusion administration independently predicted 30 day and 6 month mortality, with haemoglobin losing its prognostic significance when blood transfusions were accounted for.[4] The adverse effects of blood transfusion have been well documented, including risk of blood-borne infections, transfusion-related circulatory overload, acute lung injury, induction of a prothrombotic state,[18 19] and increased postoperative mortality.[20–22] Therefore, this study adds significantly to the existing literature by separating the effect of anaemia from the adverse effects of blood transfusion. The present study also suggested that changes in haemoglobin level over time following acute PE had more prognostic importance than a single measurement of plasma haemoglobin.

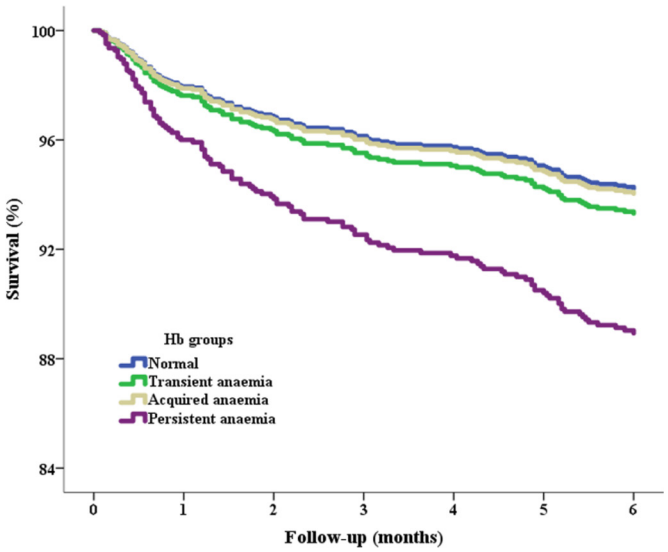

Figure 2 Adjusted survival curve analysis based on haemoglobin groups (Model 1). Figure shows the adjusted survival analysis of the study cohort (n=1099), stratified into the four haemoglobin fluctuation pattern groups. The survival analysis is adjusted for hypertension, hyperlipidaemia, sPESI, day 1 serum sodium, INR and whether patients received blood transfusion during admission (based on multivariable Model 1 in table 5). Compared with the control group (group 1: patients without anaemia on presentation and throughout admission), the persistent anaemia group (group 4: patients with persistent anaemia at baseline and throughout admission) survival was significantly worse at 6 months (HR 1.97, 95% CI 1.26 to 3.09, p=0.003). Hb, haemoglobin; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic blood pressure <100 mm Hg and oxyhaemoglobin saturation <90%).

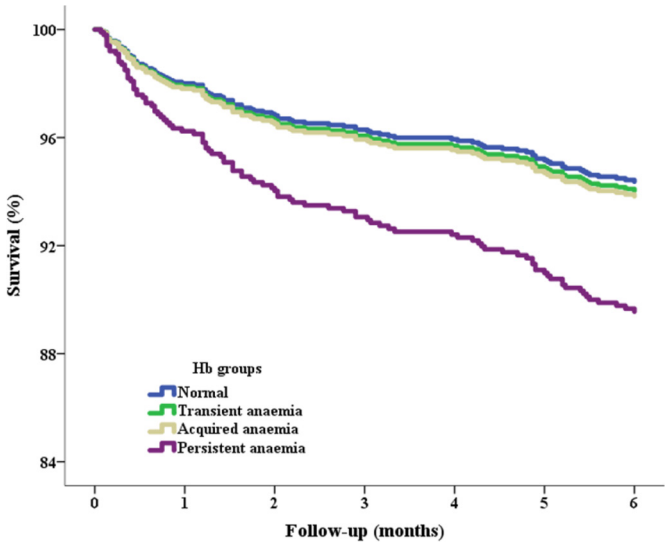

Figure 3 Adjusted survival curve analysis based on haemoglobin groups (Model 2). Figure shows the adjusted survival analysis stratified into the four haemoglobin fluctuation pattern groups, excluding all patients who received transfusion during admission (n=1028). The survival analysis is adjusted for stroke, sPESI, day 1 serum sodium and INR (based on multivariable Model 2 in table 5). Compared with the control group (group 1: patients without anaemia on presentation and throughout admission), the persistent anaemia group (group 4: patients with persistent anaemia at baseline and throughout admission) survival was significantly worse at 6 months (HR 1.90, 95% CI 1.21 to 2.99, p=0.005). Hb, haemoglobin; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic blood pressure <100 mm Hg and oxyhaemoglobin saturation <90%).

Table 5 Multivariable independent predictors for 6 month all-cause mortality (non-transfused cohort, n=1028)

Variables*	Adjusted hazard ratio (95% CI)	P value
Stroke	1.38 (0.60 to 3.19)	0.45
sPESI score (≥1)	5.02 (2.51 to 10.0)	<0.001
Day 1 sodium (≤138.5 mmol/L)	2.37 (1.56 to 3.61)	<0.001
Day 1 INR (≥1.2)	1.71 (1.14 to 2.57)	0.01
Normal haemoglobin (Group 1)	1.00 (reference)	–
Transient anaemia (Group 2)	1.06 (0.41 to 2.73)	0.90
Acquired anaemia (Group 3)	1.10 (0.56 to 2.15)	0.78
Persistent anaemia (Group 4)	1.90 (1.21 to 2.99)	0.005

*Only univariables with p<0.05 were included during multivariable modelling (see online supplementary table S5 for univariable analysis).
BP, blood pressure; INR, international normalised ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate ≥110 beats/min, systolic BP <100 mm Hg and oxyhaemoglobin saturation <90%).

To ensure a robust assessment in separating the effects of blood transfusion-related changes in haemoglobin from spontaneous haemoglobin changes, we performed two separate multivariable modelling analyses. The first model adjusted for the effects of blood transfusion on mortality, while the second model removed patients receiving transfusion (n=71) in a sensitivity analysis. In both cases, persistent anaemia was associated with an approximately twofold increased risk in 6 month mortality compared with patients without anaemia. Moreover, our study demonstrated that both transient anaemia (group 2) and acquired anaemia (group 3) during admission had better prognosis compared with patients with persistent anaemia.

The prognostic impact of trends in haemoglobin level has been studies in other conditions. Diez-Lopez *et al*[5] and Tang *et al*[7] both demonstrated that persistent anaemia predicted increased mortality in patients with chronic heart failure. Declining haemoglobin levels over time were also associated with poor prognostic outcomes in heart failure patients.[5 23 24] Similarly, there was an association between the duration of anaemia and increased mortality in hemodialysis-dependent patients,[8 9] with

suggestions that a chronic anaemic state may correlate with increased disease severity.[25] Consistently, low haemoglobin or decreasing haemoglobin levels measured over time have also been associated with increased mortality and poorer regional control of various cancers.[10–12] This may be relevant to the increased mortality shown in the persistently anaemic group following PE, who were also more likely to have malignancy compared with all other groups. The overall rate of malignancy in our study cohort was 23%, consistent with other published PE cohorts (19%–23% with malignancy) and with similarly higher rates of malignancy (43%) in the subgroups of patients with anaemia and acute PE.[2 3] The present study demonstrates for the first time that even after accounting for the impact of malignancy on mortality, patients with acute PE and persistent anaemia had increased mortality compared with other groups.

Our study addresses a gap in the literature by identifying increased mortality in chronic, rather than transient anaemia following acute PE. We propose three possible explanations that are in line with our findings. First, chronic anaemia may affect mortality due to secondary haemodynamic adaptations, including neurohormonal activation, myocardial remodelling and hypertrophy, and eventual right ventricular failure and death.[26] Second, persistent anaemia may be a marker of ongoing bleeding. Anaemia on admission has been shown to be an independent risk factor for major bleeding in patients with venous thromboembolism on anticoagulant therapy, leading to increased mortality.[27] We believe that our study's findings will help direct future research in establishing the causal links between persistent anaemia and post-PE mortality. Third, chronic anaemia may be a marker of serious comorbidity. In the present study, patients with persistent anaemia were more likely to have renal failure or malignancy compared with all other groups. Although these conditions were adjusted in our multivariable models, it is possible that other unrecognised comorbidities contributed to ongoing anaemia and adverse outcomes.

Our study has several methodological limitations. First, it is a single-centre study, thus, susceptible to sampling bias. While our findings remain robust due to a large cohort, this should be confirmed in a multicenter study. Second, not all confounders can be accounted for, including parameters such as haematocrit levels, pre-admission treatments for known existing anaemia such as iron or vitamin B12 supplements, use of erythropoietin, or the impact of long-term PE therapy on outcomes. In addition, the retrospective nature of our study design meant that the grouping of patients was limited by the availability of haemoglobin levels at various time points of admission. Third, we were not able to determine the aetiology of anaemia in our patients, and we did not have information regarding rates of bleeding or cause of mortality. The aetiology of anaemia may be of particular relevance in postoperative patients and those with malignancy.[28 29] Fourth, the majority of our study cohort have submassive PE given their stable haemodynamic profiles and the low use of thrombolysis, limiting the generalisability of the results. Finally, we were unable to explore the impact of other treatments in our cohort, including intravenous fluids resuscitation, inotropic use, iron infusion or erythropoietin supplementation. These limitations provide direction for future studies, ideally in the form of prospective registries, to further explore the aetiology and management of anaemia in patients with acute PE, in order to determine their impact on outcomes.

In summary, persistent anaemia appears to be an independent predictor of 6 month mortality in patients hospitalised with acute PE even after adjusting for the effects of blood transfusion.

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REFERENCES

1. Giuntini C, Di Ricco G, Marini C, *et al*. Pulmonary embolism: epidemiology. *Chest* 1995;107:3S–9.
2. Jiménez D, Escobar C, Martí D, *et al*. Association of anaemia and mortality in patients with acute pulmonary embolism. *Thromb Haemost* 2009;102:153–8.
3. Donzé J, Labarère J, Méan M, *et al*. Prognostic importance of anaemia in patients with acute pulmonary embolism. *Thromb Haemost* 2011;106:289–95.
4. Wong CCY, Chow WWK, Lau JK, *et al*. Red blood cell transfusion and outcomes in acute pulmonary embolism. *Respirology* 2018;23:935–41.
5. Díez-López C, Lupón J, de Antonio M, *et al*. Hemoglobin kinetics and long-term prognosis in heart failure. *Rev Esp Cardiol* 2016;69:820–6.
6. Peterson PN, Magid DJ, Lyons EE, *et al*. Association of longitudinal measures of hemoglobin and outcomes after hospitalization for heart failure. *Am Heart J* 2010;159:81–9.
7. Tang WH, Tong W, Jain A, *et al*. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 2008;51:569–76.
8. Gilbertson DT, Ebben JP, Foley RN, *et al*. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol* 2008;3:133–8.
9. Ishani A, Solid CA, Weinhandl ED, *et al*. Association between number of months below K/DOQI haemoglobin target and risk of hospitalization and death. *Nephrol Dial Transplant* 2008;23:1682–9.
10. Cetin B, Afsar B, Deger SM, *et al*. Association between hemoglobin, calcium, and lactate dehydrogenase variability and mortality among metastatic renal cell carcinoma. *Int Urol Nephrol* 2014;46:1081–7.
11. Gao J, Hu JY, Xia YF, *et al*. Continuous fall in hemoglobin level is a poor prognostic factor in patients with nasopharyngeal carcinoma treated with radiotherapy. *Chin J Cancer* 2010;29:561–6.

12. Rutkowski T, Suwinski R, Idasiak A. The prognostic value of hemoglobin concentration in postoperative radiotherapy of 835 patients with laryngeal cancer. *Int J Radiat Oncol Biol Phys* 2007;69:1018–23.
13. Ng AC, Chung T, Yong AS, *et al*. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circ Cardiovasc Qual Outcomes* 2011;4:122–8.
14. Ng AC, Chow V, Yong AS, *et al*. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. *Respiration* 2013;85:408–16.
15. Jiménez D, Aujesky D, Moores L, *et al*. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383–9.
16. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1968;405:5–37.
17. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biom J* 2005;47:458–72.
18. Goodnough LT. Blood management: transfusion medicine comes of age. *Lancet* 2013;381:1791–2.
19. Aung HH, Tung JP, Dean MM, *et al*. Procoagulant role of microparticles in routine storage of packed red blood cells: potential risk for prothrombotic post-transfusion complications. *Pathology* 2017;49:62–9.
20. Ferraris VA, Davenport DL, Saha SP, *et al*. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. *Arch Surg* 2012;147:49–55.
21. Schwann TA, Habib JR, Khalifeh JM, *et al*. Effects of blood transfusion on cause-specific late mortality after coronary artery bypass grafting-less is more. *Ann Thorac Surg* 2016;102:465–73.
22. Murphy GJ, Reeves BC, Rogers CA, *et al*. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;116:2544–52.
23. Anand IS, Kuskowski MA, Rector TS, *et al*. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* 2005;112:1121–7.
24. Komajda M, Anker SD, Charlesworth A, *et al*. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006;27:1440–6.
25. Weinhandl ED, Peng Y, Gilbertson DT, *et al*. Hemoglobin variability and mortality: confounding by disease severity. *Am J Kidney Dis* 2011;57:255–65.
26. Anand IS, Chandrashekhar Y, Ferrari R, *et al*. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J* 1993;70:357–62.
27. Ruíz-Giménez N, Suárez C, González R, *et al*. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008;100:26–31.
28. Khalafallah AA, Kirkby BE, Wong S, *et al*. Venous thromboembolism in medical patients during hospitalisation and 3 months after hospitalisation: a prospective observational study. *BMJ Open* 2016;6:e012346.
29. Caine GJ, Stonelake PS, Lip GY, *et al*. The hypercoagulable state of malignancy: pathogenesis and current debate. *Neoplasia* 2002;4:465–73.