

<b>SUPPLEMENTARY INFORMATION</b>
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**Title:** Impact of Persistent Anemia on Mortality in Patients Hospitalized with Acute  
Pulmonary Embolism: a Retrospective Observational Study

**Short running title:** Persistent Anemia in Pulmonary Embolism

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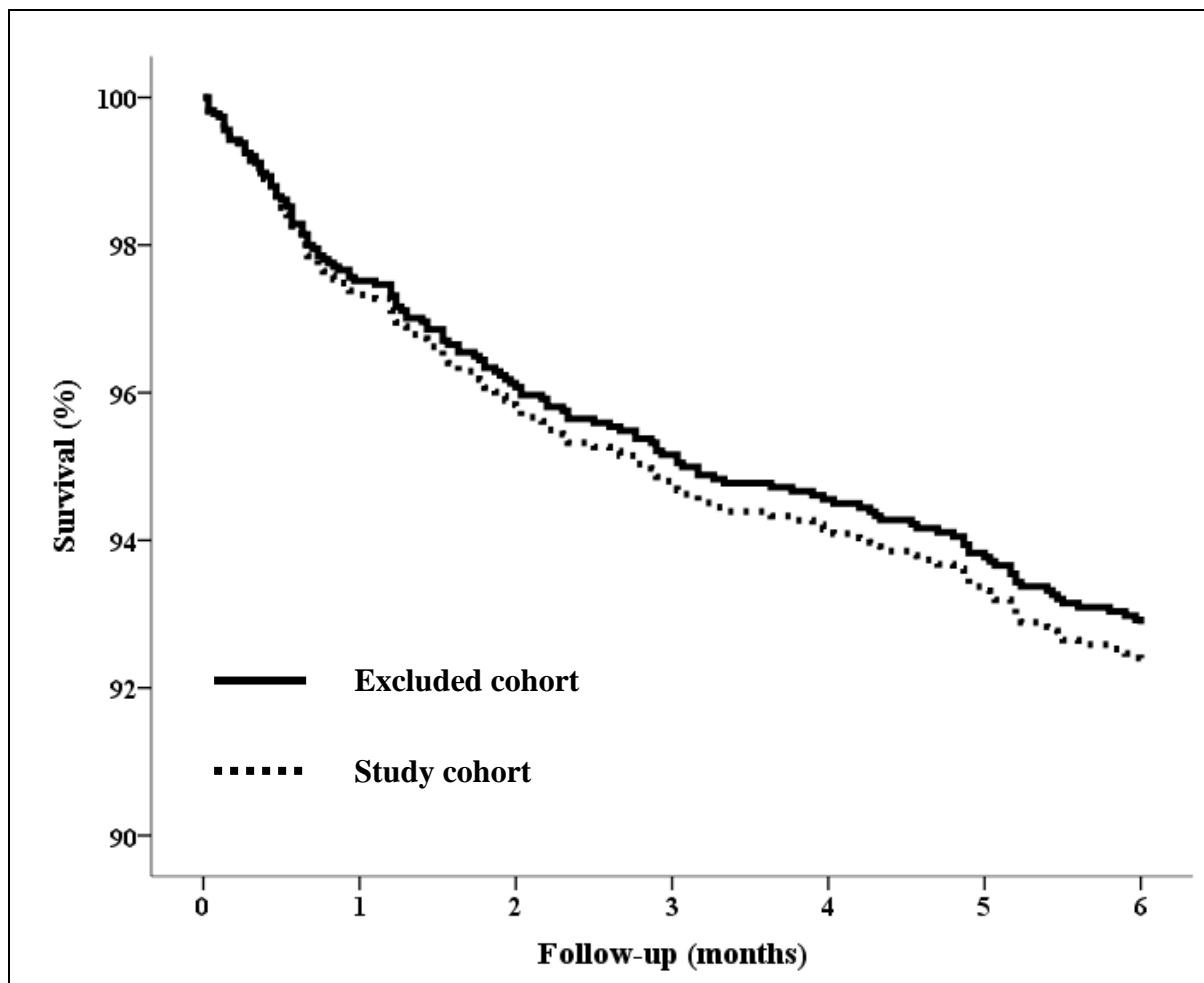
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**Figure S1: Adjusted survival curve analysis between excluded versus study patients**



**Legend**

The adjusted survival analysis factored in differences in baseline characteristics (see Supplementary Table 1). In addition to sex, it included the following variables with  $p < 0.10$ : computed-tomography pulmonary angiogram as imaging modality for diagnosis, concomitant deep vein thrombosis, ischemic heart disease, atrial fibrillation/flutter, neurodegenerative disease, simplified pulmonary embolism severity index (sPESI), day-1 sodium, INR (international normalized ratio), hemoglobin, and estimated glomerular filtration rate, and blood transfusion during admission. The unbroken line represents excluded cohort while the broken line represents the study cohort; there was no difference in survival ( $p=0.78$ ).

**Table S1: Baseline characteristics: Included versus Excluded Patients**

<b>Parameters</b>	<b>Study cohort (N=1099) *</b>	<b>Excluded cohort (N=327) *</b>	<b>p value</b>
Age, years	73 (60-81)	65 (52-75)	<0.001
Males	503 (46)	126 (39)	0.02
Concomitant DVT	239 (22)	45 (14)	0.001
Length of stay, days	7.0 (5-11)	3.0 (2-6)	<0.001
<b>Imaging modality</b>			
Ventilation-perfusion scintigraphy	818 (74)	257 (79)	0.14
CTPA	396 (36)	98 (30)	0.047
Both imaging modalities used	115 (10)	33 (10)	0.92
<b>Comorbidities</b> <sup>†</sup>			
Ischemic heart disease	201 (18)	35 (11)	0.001
Stroke	35 (3)	5 (2)	0.13
Heart failure	144 (13)	15 (5)	<0.001
Atrial fibrillation/flutter	174 (16)	23 (7)	<0.001
Valvular heart disease	25 (2)	9 (3)	0.68
<b>Cardiac risk factors</b>			
Hypertension	282 (26)	72 (22)	0.19
Hyperlipidemia	113 (10)	39 (12)	0.41
Diabetes	154 (14)	37 (11)	0.23
Current smoker	91 (8)	26 (8)	0.91
Ex-smoker	191 (17)	55 (17)	0.87
<b>Non-cardiac comorbidities</b>			
Malignancy	250 (23)	51 (16)	0.005
Chronic pulmonary disease	140 (13)	34 (10)	0.29
Neurodegenerative disease	73 (7)	9 (3)	0.007
Chronic renal disease	69 (6)	10 (3)	0.03
<b>Hemodynamic profile at admission</b>			
Heart rate, beats/minute	87 (74-102)	82 (71-94)	<0.001
Heart rate >110 beats/minute	149 (15)	23 (8)	0.001
Systolic BP, mm Hg	140 (122-157)	138 (123-152)	0.30
Systolic BP <100mmHg	35 (3)	9 (3)	0.86
Oxyhemoglobin saturation, %	96 (94-98)	97 (95-98)	0.006
sPESI score	1.0 (0.0-2.0)	0.0 (0.0-1.0)	<0.001
sPESI >0	706 (64)	132 (40)	<0.001
Shock index >0.7 <sup>‡</sup>	349 (35)	72 (24)	<0.001
<b>Blood profile during admission</b>			
Day-1 sodium, mmol/L	139 (137-141)	139 (137-141)	0.02
Day-1 eGFR, ml/min/1.73m <sup>2</sup>	75 (56-94)	81 (66-96)	<0.001
Day-1 INR	1.1 (1.0-1.2)	1.0 (1.0-1.1)	<0.001
Day-1 hemoglobin, g/L	130 (116-142)	136 (124-145)	<0.001
Blood transfusion during admission	71 (6)	4 (1)	<0.001
Blood transfusion (during Day 1-7)	60 (5)	4 (1)	0.001
<b>Admission medication use</b> <sup>§</sup>			
Aspirin	239 (24)	64 (21)	0.35
Clopidogrel	53 (5)	11 (4)	0.29
Thrombolysis	5 (0)	1 (0)	1.00

Warfarin	86 (9)	33 (11)	0.25
Enoxaparin	33 (3)	7 (2)	0.45
DOACs	0 (0)	1 (0)	0.23

Continuous variables expressed as median with interquartile range in brackets; all other categorical variables represent numbers of patients with values in brackets representing percentages.

BP, blood pressure, CTPA, computed tomography pulmonary angiography; DOACs, direct-acting oral anticoagulants including dabigatran, rivaroxaban, and apixaban; DVT, deep vein thrombosis;  $eGFR = 186 \times ([S_{CR}/88.4]^{-1.154}) \times (age)^{-0.203} \times (0.742 \text{ if female})$ , where  $eGFR$  = estimated glomerular filtration rate (ml/min/1.73m<sup>2</sup>),  $S_{CR}$  = serum creatinine concentration (μmol/L), and age is expressed in years; INR, international normalized ratio; sPESI = simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate  $\geq 110$  beats/minute, systolic BP  $< 100$  mmHg and oxyhemoglobin saturation  $< 90\%$ ).

\* The included study cohort incorporated all patients who had hemoglobin assessments on more than one day during admission. Excluded cohort were patients who had none or only one hemoglobin assessment during admission.

† Neurodegenerative disease includes dementia and Parkinson's disease.

‡ Shock index = heart rate divided by systolic BP (index  $> 0.7$  signify hemodynamic compromise).

§ Number of patients with missing data: Aspirin (Included cohort = 96; Excluded cohort = 24); Clopidogrel (Included cohort = 96; Excluded cohort = 24); Thrombolysis (Included cohort = 98; Excluded cohort = 25); Warfarin (Included cohort = 97; Excluded cohort = 24); Enoxaparin (Included cohort = 96; Excluded cohort = 24); DOACs (Included cohort = 96; Excluded cohort = 24).

**Table S2: Comparing all-cause mortality stratified by excluded versus study patients**

<b>All-cause mortality, no. (%) *</b>	<b>Study cohort (N=1099) †</b>	<b>Excluded cohort (N=327) †</b>	<b>Unadjusted p value</b>	<b>Adjusted p value ‡</b>
6-month	140 (12.7)	29 (8.9)	0.06	0.78

\* Cox proportional hazards regression was used to compare 6-month mortality.

† The study cohort included all patients who had hemoglobin assessments on more than one day during admission. The excluded cohort were patients who had none or only one hemoglobin assessment during admission.

‡ The adjusted survival analysis factored in differences in baseline characteristics (see Supplementary Table 1). In addition to sex, it included the following variables with  $p < 0.10$ : computed-tomography pulmonary angiogram as imaging modality for diagnosis, concomitant deep vein thrombosis, ischemic heart disease, atrial fibrillation/flutter, neurodegenerative disease, simplified Pulmonary Embolism Severity Index (sPESI), day-1 sodium, INR (international normalized ratio), hemoglobin, and estimated glomerular filtration rate, and blood transfusion during admission.

**Table S3: All-cause mortality outcome**

All-cause mortality	Study cohort	Normal	Transient anemia	Acquired anemia	Persistent anemia
no. (%) *	(N=1099)	Group 1 (N=575)	Group 2 (N=64)	Group 3 (N=124)	Group 4 (N=336)
6-month	140 (12.7)	38 (6.6)	8 (12.3)	17 (13.9) †	77 (22.9) †§

Group 1: Normal (patients without anemia on presentation and throughout admission); Group 2: Transient anemia (anemia on presentation, then normalized during admission); Group 3: Acquired anemia (normal hemoglobin levels on presentation, then declined to levels below normal during admission); Group 4: Persistent anemia (patients with persistent anemia at baseline and throughout admission).

\* Cox proportional hazards regression was used to compare 6-month mortality. Of the patients who died at the 6-month time-point, no patients who died received blood transfusion in Group 1 or Group 3, while 2 patients in Group 2, and 25 patients in Group 4 received blood transfusion during their index PE admission.

† p<0.05 compared to Group 1

‡ p<0.05 compared to Group 2

§ p<0.05 compared to Group 3

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**Table S4: Univariable predictors for all-cause 6-month mortality**

Univariable analysis	Clinical parameters *	HR (95% CI)	p value
6-month death	sPESI score ( $\geq 1$ )	8.90 (4.53-17.5)	<0.001
	Male	1.35 (0.97-1.88)	0.08
	Concomitant DVT	1.06 (0.71-1.57)	0.77
	Ischemic heart disease	1.12 (0.74-1.70)	0.59
	Stroke	2.06 (1.01-4.20)	0.05
	Heart failure	1.52 (0.98-2.34)	0.06
	Atrial fibrillation/flutter	1.01 (0.64-1.58)	0.98
	Valvular disease	1.63 (0.67-3.99)	0.28
	Hypertension	0.58 (0.37-0.90)	0.02
	Hyperlipidemia	0.37 (0.16-0.84)	0.02
	Diabetes	0.89 (0.54-1.46)	0.65
	Current/ex-smoker	1.07 (0.74-1.55)	0.73
	Malignancy	7.01 (4.96-9.89)	<0.001
	Chronic pulmonary disease	1.74 (1.15-2.65)	0.01
	Neurodegenerative disease	1.45 (0.82-2.56)	0.20
	Chronic renal disease	1.04 (0.53-2.05)	0.90
	Day-1 sodium ( $\leq 138.5$ mmol/L)	2.42 (1.72-3.42)	<0.001
	Day-1 INR ( $\geq 1.2$ )	2.65 (1.86-3.78)	<0.001
	Blood transfusion during admission	4.09 (2.69-6.23)	<0.001
	Thrombolysis	0.05 (0.00-9791)	0.63
	Normal hemoglobin	1.00 (reference)	
	Transient anemia	1.88 (0.88-4.03)	0.10
	Acquired anemia	2.20 (1.24-3.89)	0.007
	Persistent anemia	3.80 (2.58-5.61)	<0.001

BP, blood pressure; CI, confidence interval; DVT, deep vein thrombosis; HR, hazards ratio; INR, international normalized ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate  $\geq 110$  beats/minute, systolic BP  $< 100$  mmHg and oxyhemoglobin saturation  $< 90\%$ ).

**Table S5: Univariable predictors for all-cause 6-month mortality (non-transfused cohort, N=1028)**

Univariable analysis	Clinical parameters *	HR (95% CI)	p value
6-month death	sPESI score ( $\geq 1$ )	7.53 (3.81-14.9)	<0.001
	Male	1.34 (0.93-1.94)	0.12
	Concomitant DVT	1.06 (0.68-1.65)	0.81
	Ischemic heart disease	1.22 (0.78-1.92)	0.39
	Stroke	2.21 (1.03-4.74)	0.04
	Heart failure	1.98 (1.26-3.10)	0.003
	Atrial fibrillation/flutter	1.25 (0.78-2.02)	0.35
	Valvular disease	2.02 (0.82-4.95)	0.13
	Hypertension	0.68 (0.43-1.08)	0.10
	Hyperlipidemia	0.46 (0.20-1.05)	0.07
	Diabetes	0.99 (0.58-1.68)	0.97
	Current/ex-smoker	1.09 (0.72-1.65)	0.69
	Malignancy	6.07 (4.18-8.82)	<0.001
	Chronic pulmonary disease	1.69 (1.05-2.72)	0.03
	Neurodegenerative disease	1.71 (0.94-3.11)	0.08
	Chronic renal disease	1.13 (0.53-2.44)	0.75
	Day-1 sodium ( $\leq 138.5$ mmol/L)	2.62 (1.78-3.85)	<0.001
	Day-1 INR ( $\geq 1.2$ )	2.35 (1.58-3.48)	<0.001
	Thrombolysis	0.05 (0-1133581)	0.73
	Normal hemoglobin	1.00 (reference)	
	Transient anemia	1.53 (0.65-3.61)	0.34
	Acquired anemia	2.26 (1.28-4.00)	0.005
	Persistent anemia	3.08 (2.02-4.67)	<0.001

BP, blood pressure; CI, confidence interval; DVT, deep vein thrombosis; HR, hazards ratio; INR, international normalized ratio; sPESI, simplified Pulmonary Embolism Severity Index (sPESI score incorporates age, history of malignancy, heart failure/chronic lung disease, heart rate  $\geq 110$  beats/minute, systolic BP  $< 100$  mmHg and oxyhemoglobin saturation  $< 90\%$ ).