

Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in HHT

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LEGENDS TO ONLINE SUPPLEMENTARY FIGURES:

Figure S1: Effect of PAVM severity:

A) Brain abscess and B) ischaemic stroke rates stratified by i) oxygen saturation standing SaO₂ and ii) size of largest PAVM feeding artery, severity increasing left-to-right: i) interquartile ranges: Q₁:59-88; Q₂:88-93; Q₃:93-96; Q₄:96-100%, ii) Q₁:0-3; Q₂:3-5; Q₃:5-6.5; Q₄:6.5-12mm. Error bars: standard error of the mean.

Figure S2: Anderson Gill proportional hazards models

(A) Proportional survival until first ischaemic stroke: overall $r^2 = 0.051$, Wald test $p=4.7 \times 10^{-5}$, Robust score $p=2.00 \times 10^{-2}$ (**for comparison, also presented in the text**).

(B) Proportional survival until first brain abscess: overall $r^2 = 0.017$, Wald test $p=6.3 \times 10^{-3}$, Robust score $p=9.50 \times 10^{-3}$.

Figure S3: Presentation pattern analyses

A) Pretreatment SaO₂; B) Age at PAVM diagnosis; C) Interval between PAVM diagnosis and treatment (**for comparison, also presented in the text**). RS: PAVM-related respiratory symptoms (dyspnoea and haemoptysis); Ix: incidental investigations; CNS: post stroke/abscess, HHT: via HHT screening programme. *P* values (ANOVA, Bonferroni post test corrections): *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ns: $p > 0.05$.

SUPPLEMENTARY TABLES

Table S1 : Univariate associations of non-PAVM variables with brain abscess

	N with/ without abscess	Event	Event-free group	P value*
Non-PAVM variables				
Gender, No. (%), % female	28/191	11 (39.3)	130 (67.7)	0.0054*
Hb, median (Q1, Q3), g/dl	27/186	15.1 (13.0, 16.4)	14.5 (12.8, 15.8)	0.35
Iron use, No. (%), %	28/175	12 (42.9)	61 (34.9)	0.41
Hormones, No. (%), %	22/180	2 (9.1)	37 (20.6)	0.26
Tranexamic acid, No. (%), %	26/187	1 (3.9)	7 (3.7)	0.99
Migraine, No. (%), %	28/189	8 (28.6)	82 (43.4)	0.16
Smoker§, No. (%), %	28/189	13 (46.4)	88 (46.6)	0.99
Hypertension, No. (%), %	28/189	3 (10.7)	33 (17.5)	0.59
Hypercholesterolaemia, No. (%), %	28/191	0 (0)	4 (2.1)	0.09
Diabetes, No. (%), %	28/188	0 (0)	7 (3.7)	0.99
Cardiac disease, No. (%), %	28/191	3 (10.7)	6 (3.2)	0.11
Atrial fibrillation, No. (%), %	27/188	1 (3.7)	6 (3.2)	0.99
FVIII:Ag, median (Q1, Q3), iu/l	17/90	1.85 (1.6, 3.0)	1.80 (1.52, 2.22)	0.44
PAP mean, median (Q1, Q3), mmHg	20/130	12.5 (10, 17)	13 (10.5, 16.0)	0.81
DVT/PE, No. (%), %	27/152	6 (22.2)	10 (6.8)	0.0186*

Legend: N = number of cases with/without abscess for which variable was measured. † more common in non-HHT patients ($p < 0.0001$, Fisher's exact test 2 sided p value). ‡ f.a.d. feeding artery diameter.

Table S2: Anderson Gill models for brain abscess

	N	df	R ²	Wald test P value	Robust score P value	Hazard ratio for variable (95% CI)	P value for variable in model
Model 1 (pre emb)	217	2	0.047	1.2×10^{-3}	1.76×10^{-2}		
Gender (male)						3.61 (1.58, 8.25)	2.4×10^{-3}
DVT						3.35 (1.32, 8.50)	0.011
Model 2 (pre+post emb)	392	1	0.017	6.3×10^{-3}	9.50×10^{-3}		
Gender (male)						3.49 (1.43, 8.33)	6.3×10^{-3}
Model 3 (pre emb)	316	3	0.03	0.015	0.029		
Gender (male)						4.55 (1.64, 12.5)	3.63×10^{-3}

SaO ₂ , %						0.95 (0.89, 1.00)	0.058
Largest PAVM f.a.d.						0.98 (0.82, 1.17)	0.79

Models 1 and 2: Best model for brain abscess in untreated patients, and all patients pre and post embolisation (for comparison, also **presented in the text**). Model 3 is presented in view of the clinical importance of the PAVM variable findings. N, number of datapoints, df degrees of freedom.

Table S3 Bacteriological cultures and potential precipitating events in patients with brain abscesses

	Cases	Positive microbiology
Treatment/condition		
Scale and polish	3	<i>Streptococcus milleri</i> (2 cases)
Dental plates	1	<i>Bacteroides</i> , <i>Propionibacterium</i> , <i>Actinomyces meyeri</i>
Dental work & fillings	3	<i>Porphyromona</i> , <i>Gemella</i> , <i>Peptostreptococcus</i> (1 case)
Dental abscess	1	G+ve cocci, G+ve rods
Extraction	2	nil
Dental checks	1	nil
Poor dentition	2	G+ve rods
Oral radiotherapy	1	nil
Nasal cautery	1	nil
Venous access	1	<i>MRSA</i> , <i>enterococcus</i>
Otitis media	1	nil

Legend: There were no data on interventional events in the 8-10 weeks prior to brain abscess in the other patients, four of whom had *Streptococcus milleri*, *Actinomyces israelii* or *bacteroides spp.* cultured from their abscess.

Table S4: Univariate analyses of ischaemic stroke

	N with/without stroke	Event	Event-free group	P value*
PAVM-associated variables				
RS presentation, No. (%), %	30/186	8 (26.7)	39 (21)	0.48
SaO ₂ , median (Q1, Q3), %	25/157	93 (85, 96)	94(88.5, 96)	0.3
R-L, median (Q1, Q3), %	24/105	11.0 (7.1, 19.5)	8.8 (4.7, 20.0)	0.32
Single PAVMs†, No. (%), %	29/181	7 (24.1)	44 (24.3)	0.99
Largest f.a.d. ‡, median (Q1, Q3), mm	28/158	5.5 (4.0, 7.5)	5 (3.0, 6.0)	0.087
Small (f.a.d.≤3mm), No. (%), %	29/187	24 (82.8)	137 (73.3)	0.36
Non PAVM-associated variables				
Gender, No. (%), % female	30/189	22 (73.3)	119 (63.0)	0.36
Hb, median (Q ₁ , Q ₃), g/dl	30/183	14.2 (12.6, 16.1)	14.6 (12.9, 15.8)	0.67
Iron use, No. (%), %	29/172	15 (51.7)	57 (33.1)	0.063
Hormones, No. (%), %	28/172	7 (25)	30 (17.4)	0.43

Tranexamic acid, No. (%), %	29/182	0 (0)	8 (4.4)	0.6
Migraine, No. (%), %	30/185	9 (30)	80 (43.2)	0.23
Smoker§, No. (%), %	30/185	14 (46.7)	86 (46.5)	0.99
Hypertension, No. (%), %	30/185	8 (26.7)	28 (15.1)	0.12
Atrial fibrillation, No. (%), %	30/183	2 (6.7)	5 (2.7)	0.25
Hypercholesterolaemia, No. (%), %	30/187	2 (6.7)	2 (1.1)	0.09
Diabetes, No. (%), %	30/184	1 (3.3)	6 (3.3)	0.99
Cardiac disease, No. (%), %	30/187	3 (10)	6 (3.3)	0.11
FVIII:Ag, median (Q_1 , Q_3), iu/l	15/90	2.01 (1.74, 2.76)	1.79 (1.54, 2.22)	0.12
PAP mean, median (Q_1 , Q_3), mmHg	24/126	12 (10, 14.5)	13.0 (10.5, 16.0)	0.49
DVT/PE, No. (%), %	28/149	3 (10.7)	13 (8.8)	0.86

Legend: N = number of cases with/without ischaemic stroke for which variable was measured * significant values at false discovery rate FDR=0.05 level³⁷, § current or former smoker

Table S5: Anderson Gill models for ischaemic stroke

	N	df	R ²	Wald test P value	Robust score P value	Hazard ratio for variable (95% confidence intervals)	P value for variable in model
Model 4 (pre emb)	178	1	0.036	6.1x10 ⁻⁴	3.20x10 ⁻³		
PAP mean, mmHg						0.89 (0.83, 0.95)	6.2x10 ⁻⁴
Model 5 (pre +post emb)	250	4	0.051	4.7x10 ⁻⁵	2.00x10 ⁻²		
PAP mean, mmHg						0.85 (0.79, 0.92)	5.0x10 ⁻⁵
Hb, g/dl						0.95 (0.72, 1.27)	0.75
Embolisation						5751.6 (2.5, 1.3x10 ⁷)	0.028
Hb, g/dl x Embolisation						1.84 (1.1, 3.07)	0.021
Model 6 (pre emb)	347	2	0.001	0.75	0.75		
SaO ₂ , %						0.95 (0.89, 1.00)	0.058
Largest PAVM f.a.d.						0.98 (0.82, 1.17)	0.79

Models 4 and 5: Best models for ischaemic stroke in untreated, and all patients pre and post embolisation (for comparison, also **presented in the text**). Model 6 is presented in view of the clinical importance of the PAVM variable findings. N, number of datapoints, df degrees of freedom.