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ISSUES OF REHABILITATION AND RECOVERY

Cognition and Dementia

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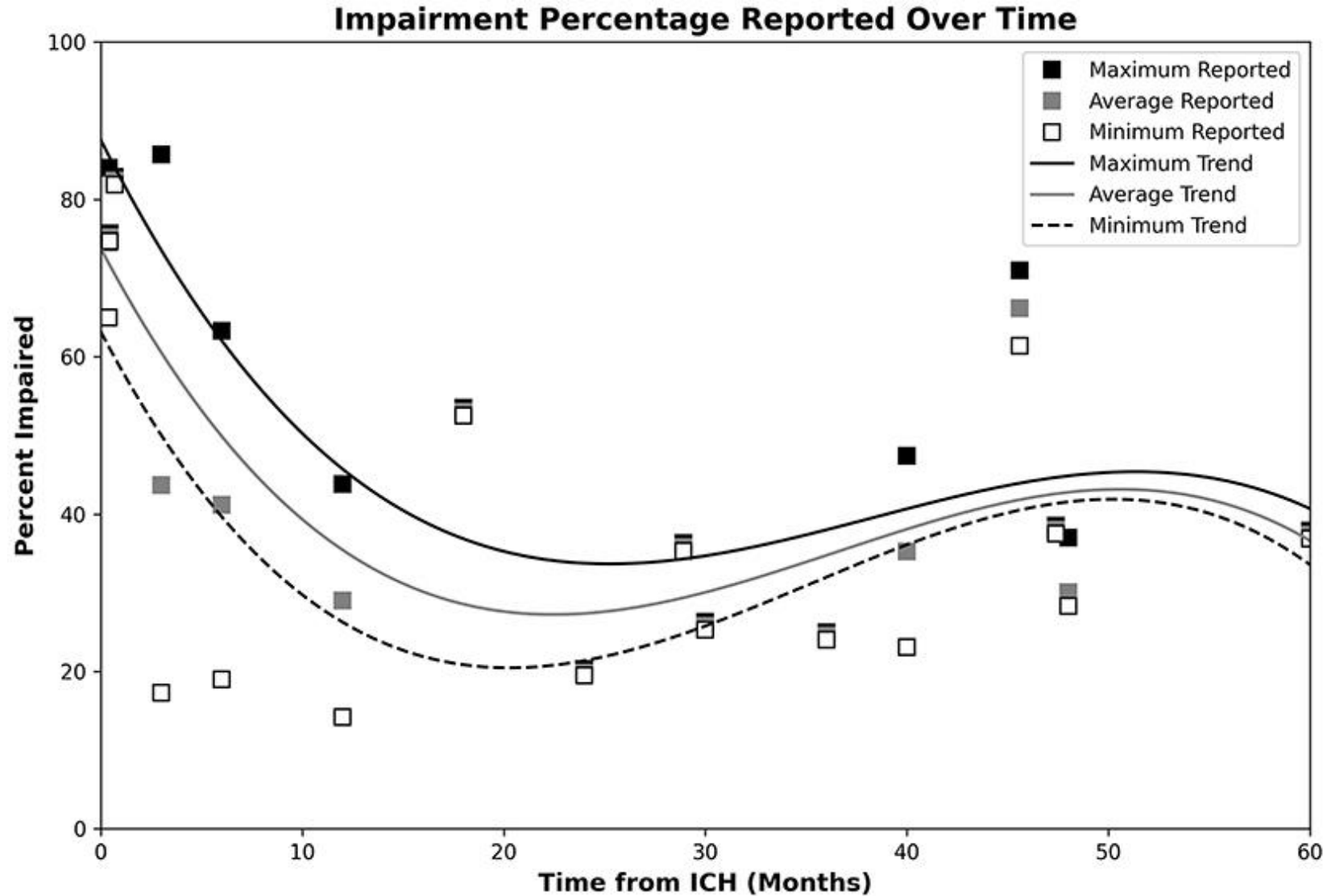
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2025.03.28

Disclosures

- Research grants from
 - Taiwan National Science and Technology Council
 - National Taiwan University Hospital

Dynamic course of cognitive impairment after ICH



(Variable) Incidence of post-ICH dementia

Study, year	Country	Design	Study period	Different Dx criteria	Early of delayed onset	Small sample size	Cumulative incidence of dementia
				Criteria for dementia diagnosis	Dementia onset	Sample size, <i>n</i>	
Barba et al., 2000 [34]	Spain	Prospective cohort*	1994–1995	DSM-IV criteria; NINDS-AIREN criteria for VaD	Early (within 3 months post-ICH)	29	27.6% at 3 months
Maduriera et al., 2001 [35]	Portugal	Prospective cohort	1995–1997	DSM-IV criteria; NINDS-AIREN criteria for VaD	Early (within 3 months post-ICH)	55	5.5% at 3 months
Altieri et al., 2004 [42]	Italy	Prospective cohort	1995–1997	ICD-10 criteria; NINCDS-ADRDA criteria for AD and NINDS-AIREN criteria for VaD	Delayed (≥ 6 months post-ICH)	4	25.0% at 4 years
Tang et al., 2004 [36]	Hong Kong	Prospective cohort	Not reported	DSM-IV criteria	Early (within 3 months post-ICH)	23	17.3% at 3 months
de Koning et al., 2005 [40]	Netherlands	Prospective cohort*	2000–2002	DSM-IV criteria; subclassified according to NINDS-AIREN criteria	Delayed (≥ 3 months post-ICH)	19	42.1% at 9 months
Ihle-Hansen et al., 2011 [41]	Norway	Prospective cohort	2007–2008	ICD-10 criteria	Anytime post-ICH	16	43.8% at 1 year
Arauz et al., 2014 [37]	Mexico	Prospective cohort	2005	DSM-IV criteria; NINDS-AIREN criteria for VaD	Early (within 3 months post-ICH)	14	14.3% at 3 months
Biffi et al., 2016 [4] [†]	USA	Prospective cohort	2006–2013	ICD-9 codes in electronic medical records and TICS-m score < 20	Early (within 6 months post-ICH)	738	19.0% at 6 months
Moulin et al., 2016 [5]	France	Prospective cohort	2004–2009	NIA-AA criteria for all-cause dementia	Delayed (≥ 6 months post-ICH)	218	32.0% at 5 years (5.8% yearly)
Planton et al., 2017 [44]	France	Prospective case-control	2012–2017	VASCOG criteria for major VCD	Delayed (≥ 3 months post-ICH)	40	14.2% at 1 year; 19.8% at 2 years; 24.5% at 3 years; 28.3% at 4 years
Xiong et al., 2019 [21]	USA	Prospective cohort	2006–2017	NIA-AA criteria for all-cause dementia	Delayed (≥ 6 months post-ICH)	97	2.5% at 4 months
Pendlebury et al., 2019 [6]	UK	Prospective cohort	2002–2012	MMSE score persistently < 24 or DSM-IV criteria	Anytime post-ICH	126	37.4% at 5 years
Dros et al., 2020 [38]	Poland	Prospective cohort	2015–2018	DSM-5 criteria	Anytime post-ICH	23	18.3% at 5 years
Pasi et al., 2021 [22] [†]	USA	Prospective cohort	1998–2017	ICD-9/10 codes in electronic medical records and TICS-m score < 20	Delayed (≥ 3 months post-ICH)	612	26.1% at 3 months; 45.5% at 1 year
Ismail et al., 2022 [43]	Hong Kong	Prospective cohort	2009–2010	DSM-IV criteria	Delayed (≥ 6 months post-ICH)	44	35.0% at 4 years
							6.8% at 5 years

Risk Factors Associated With Early vs Delayed Dementia After Intracerebral Hemorrhage

N=738

19.0% had delayed dementia (>6M)

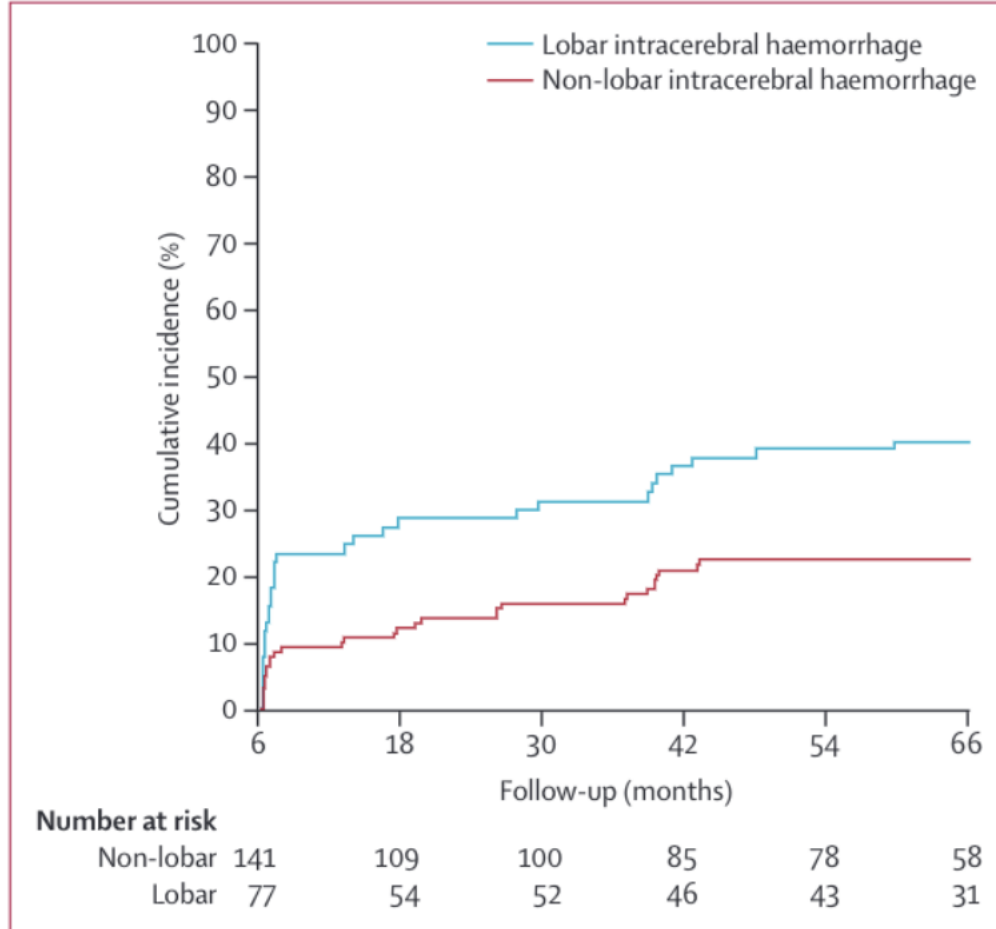
Alessandro Biffi, MD; Destiny Bailey, BS; Christopher D. Anderson, MD, MMSc; Alison M. Ayres, BA; Edip M. Gurol, MD; Steven M. Greenberg, MD, PhD; Jonathan Rosand, MD, MSc; Anand Viswanathan, MD, PhD

Risk Factor	Post-ICH Dementia Risk, HR (95% CI)				P Value for Heterogeneity
	Early	P Value	Delayed	P Value	
Model 1^a					
No. of patients	619		435		
Age	1.02 (1.00-1.04)	.03	1.01 (1.00-1.01)	.05	.78
Educational level (≥10 y)	0.89 (0.61-1.30)	.55	0.60 (0.40-0.89)	.01	<.001
African American race	1.22 (0.96-1.55)	.11	1.48 (1.09-2.02)	.01	.55
Incident mood symptoms	0.66 (0.04-11.11)	.77	1.29 (1.02-1.63)	.04	.01
ICH volume (per 10-mL increase)	1.47 (1.09-1.97)	.01	1.10 (0.70-1.73)	.68	<.001
Lobar ICH location	2.04 (1.06-3.91)	.03	1.33 (0.25-7.03)	.74	.02
CT-WMD severity	1.34 (0.23-7.76)	.74	1.70 (1.07-2.71)	.03	.04

Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study

PITCH cohort (2004-2009, N=560)

Solène Moulin, Julien Labreuche, Stéphanie Bombois, Costanza Rossi, Gregoire Boulouis, Hilde Hénon, Alain Duhamel, Didier Leys, Charlotte Cordonnier



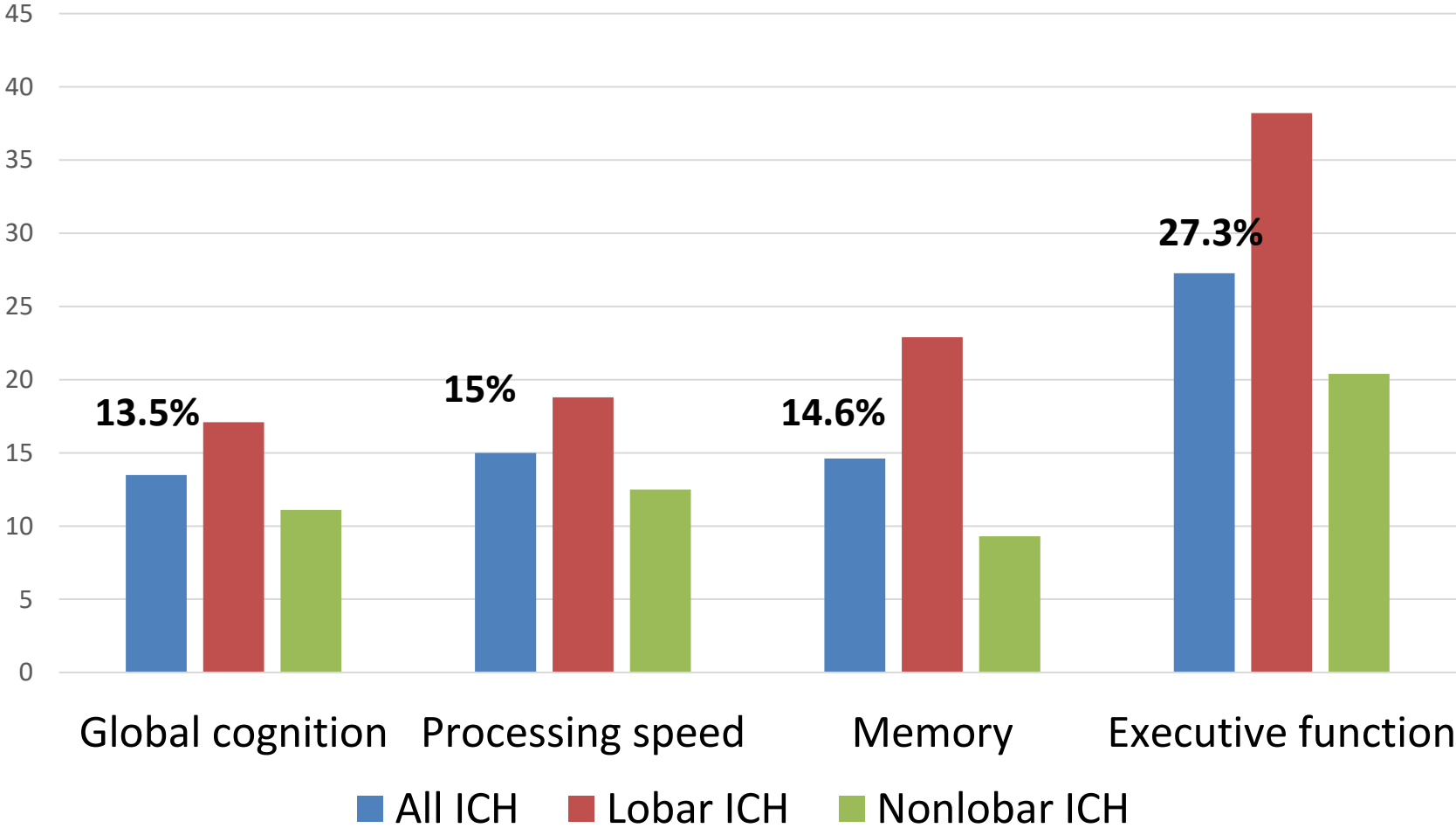
- **Incidence:**
 - 1-year post ICH: 14.2%
 - 2-year post ICH: 19.8%
 - 3-year post ICH: 24.5%
 - 4-year post ICH: 28.3%
- Age, previous stroke/TIA, NIHSS

	1 year post-intracerebral haemorrhage*	4 years post-intracerebral haemorrhage*
History of previous stroke or transient ischaemic attack		
No	14.6% (10.0–20.1)	21.8% (16.1–28.1)
Yes	15.2% (5.4–29.5)	45.5% (27.8–61.6)
Intracerebral haemorrhage location		
Lobar	23.4% (14.6–33.3)	35.1% (24.6–45.7)
Non-lobar	9.2% (5.1–14.7)	20.2% (14.0–27.3)

Cognitive profiles after ICH



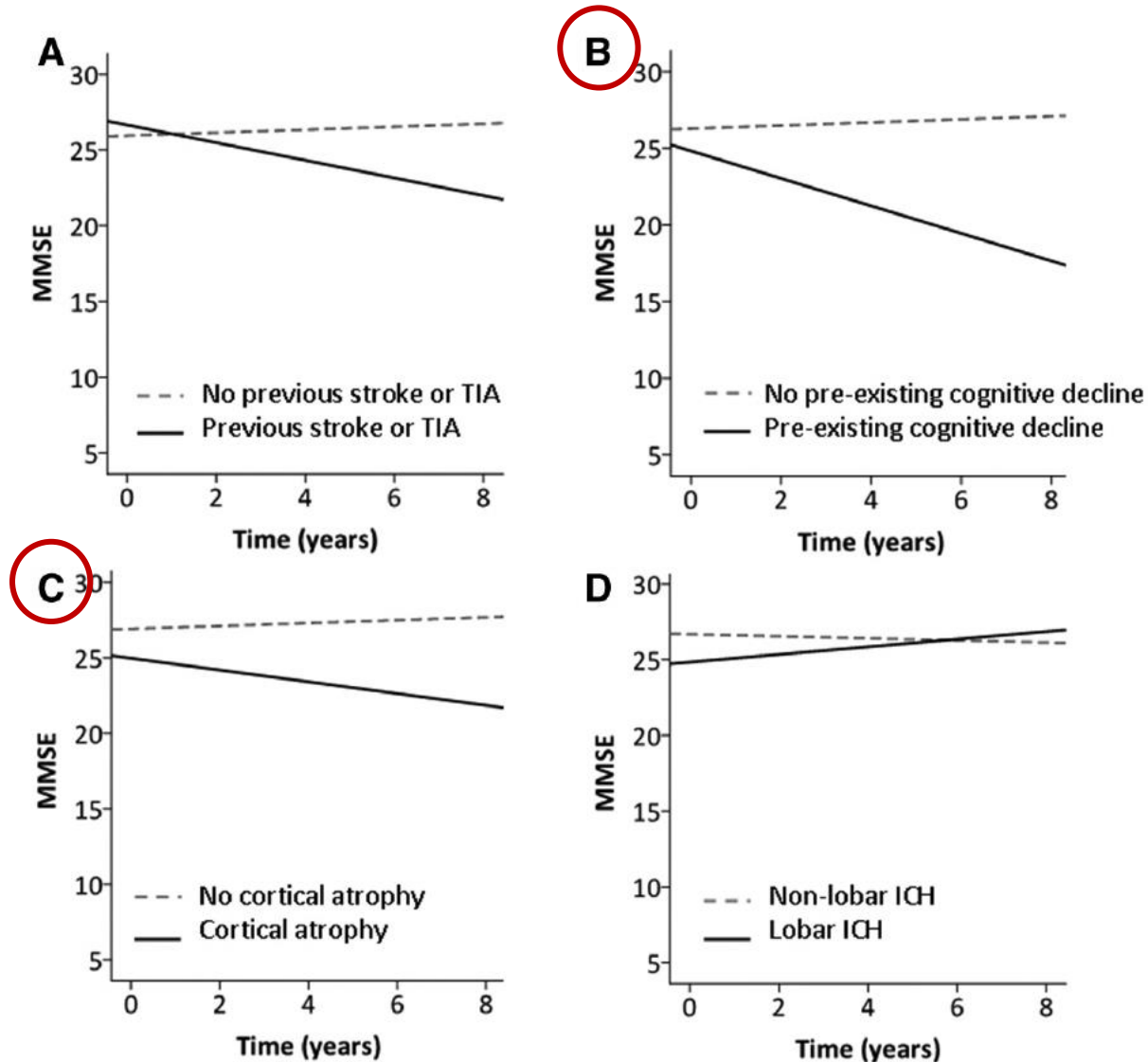
NTUH ICH-NPT cohort; N=89
Post ICH>1 Year



Lobar ICH appears more cognitively impaired

Cognitive domains	Lobar ICH (n=35)	Non-lobar ICH (n=54)	P value
Global function			
MMSE<cut-off 24, n (%)	6/35(17.1%)	6/54(11.1%)	.416
MoCA ¹ <cut-off 26, n (%)	23/35(65.7%)	27/53(50.9%)	.171
Processing speed			
Processing Speed Index (PSI) ² of WAIS-IV at least -1.5 SD, n (%)	6/32(18.8%)	6/48(12.5%)	.443
Verbal memory			
Immediate Recall of WMS-III at least -1.5 SD, n (%)	3/35(8.6%)	7/54(13.0%)	.522
Delay Recall of WMS-III at least -1.5 SD, n (%)	8/35(22.9%)	5/54(9.3%)	.076
Executive function			
Categories completed of MWCST ¹ at least -1.5 SD, n (%)	13/34(38.2%)	11/54(20.4%)	.067
Perseverative errors of MWCST ¹ at least -1.5 SD, n (%)	7/34(20.6%)	5/54(9.3%)	.132
Categories fluency at least -1.5 SD, n (%)	11/35(31.4%)	18/54(33.3%)	.851
CDR-SB, mean (SD)	1.46(1.64)	1.21(1.54)	.478

Ongoing cognitive impairment when ICH occurs? PITCH cohort



- Previous stroke or transient ischemic attack (β [SE], -0.55 [0.23]; $P < 0.05$).
- **Preexisting cognitive impairment** (β [SE], -0.56 [0.25]; $P < 0.01$).
- **Severity of cortical atrophy** (β [SE], -0.50 [0.19]; $P < 0.01$).

OPEN

Cognitive Impairment Before Intracerebral Hemorrhage Is Associated With Cerebral Amyloid Angiopathy

Gargi Banerjee, BMBCh, MRCP; Duncan Wilson, MBChB; Gareth Ambler, PhD; Karen Osei-Bonsu Appiah, MSc; Clare Shakeshaft, MSc; Surabhika Lunawat, MSc; Hannah Cohen, PhD; Tarek Yousry, Dr Med Habil; Gregory Y.H. Lip, FRCP; Keith W. Muir, MD; Martin M. Brown, FRCP; Rustam Al-Shahi Salman, PhD; Hans Rolf Jäger, MD; David J. Werring, PhD; on behalf of the CROMIS-2 Collaborators*

- 166 patients with ICH
- Pre-existing cognitive impairment was determined using IQCODE

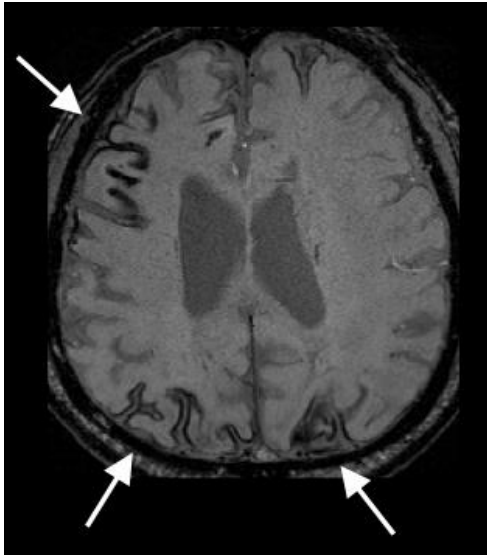
Table 2. Univariable and Adjusted Logistic Regression Models, Investigating Associations Between Cognitive Impairment Before ICH and Evidence of CAA

	Univariable OR (95% CI)	<i>P</i> Value	Adjusted OR (95% CI)	<i>P</i> Value
Meets modified Boston criteria for probable CAA	3.93 (1.72–8.96)	0.001	4.01 (1.53–10.51)	0.005
CAA score (per point increase)	1.45 (1.11–1.92)	0.007	1.42 (1.03–1.97)	0.033

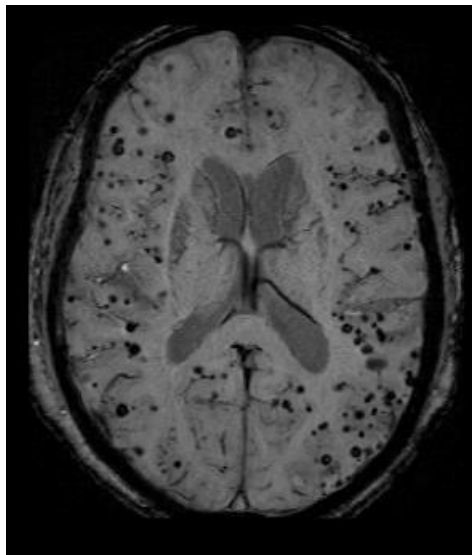
Neuroimaging risk factors for post-ICH cognitive impairment

Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study

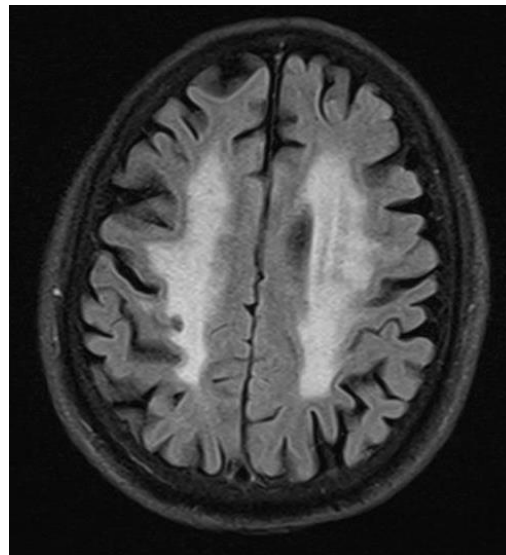
Solène Moulin, Julien Labreuche, Stéphanie Bombois, Costanza Rossi, Gregoire Boulouis, Hilde Hénon, Alain Duhamel, Didier Leys, Charlotte Cordonnier



cSS(+)



>5CMB

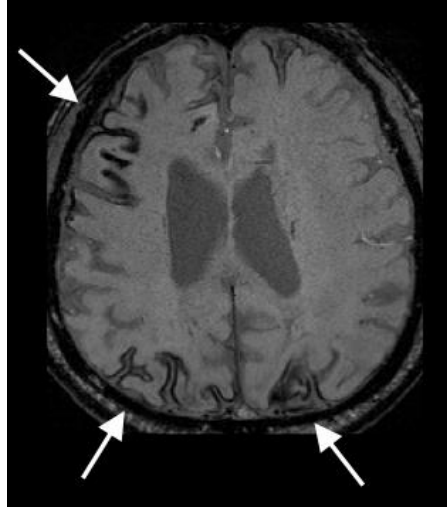
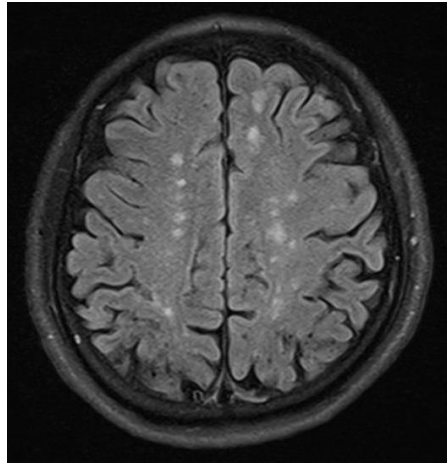


Severe WMH

	n (%)	Number of events	Subhazard ratio (95% CI)	p value
Fazekas score*			1.80 (1.17–2.75)*	0.007*
0	26 (14%)	2	1.00 (reference)	..
1	51 (27%)	8	1.37 (0.30–6.31)	0.69
2	68 (36%)	18	1.66 (0.36–7.55)	0.51
3	43 (23%)	24	4.09 (0.87–19.15)	0.074
Cortical atrophy score*			2.02 (1.28–3.19)*	0.002*
0	36 (19%)	2	1.98 (0.40–9.73)	0.40
1	67 (36%)	11	4.78 (0.96–23.96)	0.057
2+3†	85 (45%)	39	7.24 (1.10–47.74)	0.040
≥ 1 old lacunes	72 (38%)	26	1.48 (0.86–2.54)	0.16
≥1 old macrohaemorrhage	42 (22%)	19	2.90 (1.66–5.07)	0.0002
Superficial siderosis				
Any superficial siderosis	35 (19%)	17	2.31 (1.27–4.20)	0.006
Focal superficial siderosis	22 (12%)	6	0.98 (0.44–2.17)	0.96
Disseminated superficial siderosis	15 (8%)	12	4.10 (1.91–8.79)	0.0003
>5 cerebral microbleeds	46 (25%)	22	2.38 (1.39–4.09)	0.002

WMH burden and disseminated cSS are risks for post-ICH dementia in CAA

late post-ICH dementia conversion (occurred after 6 months)



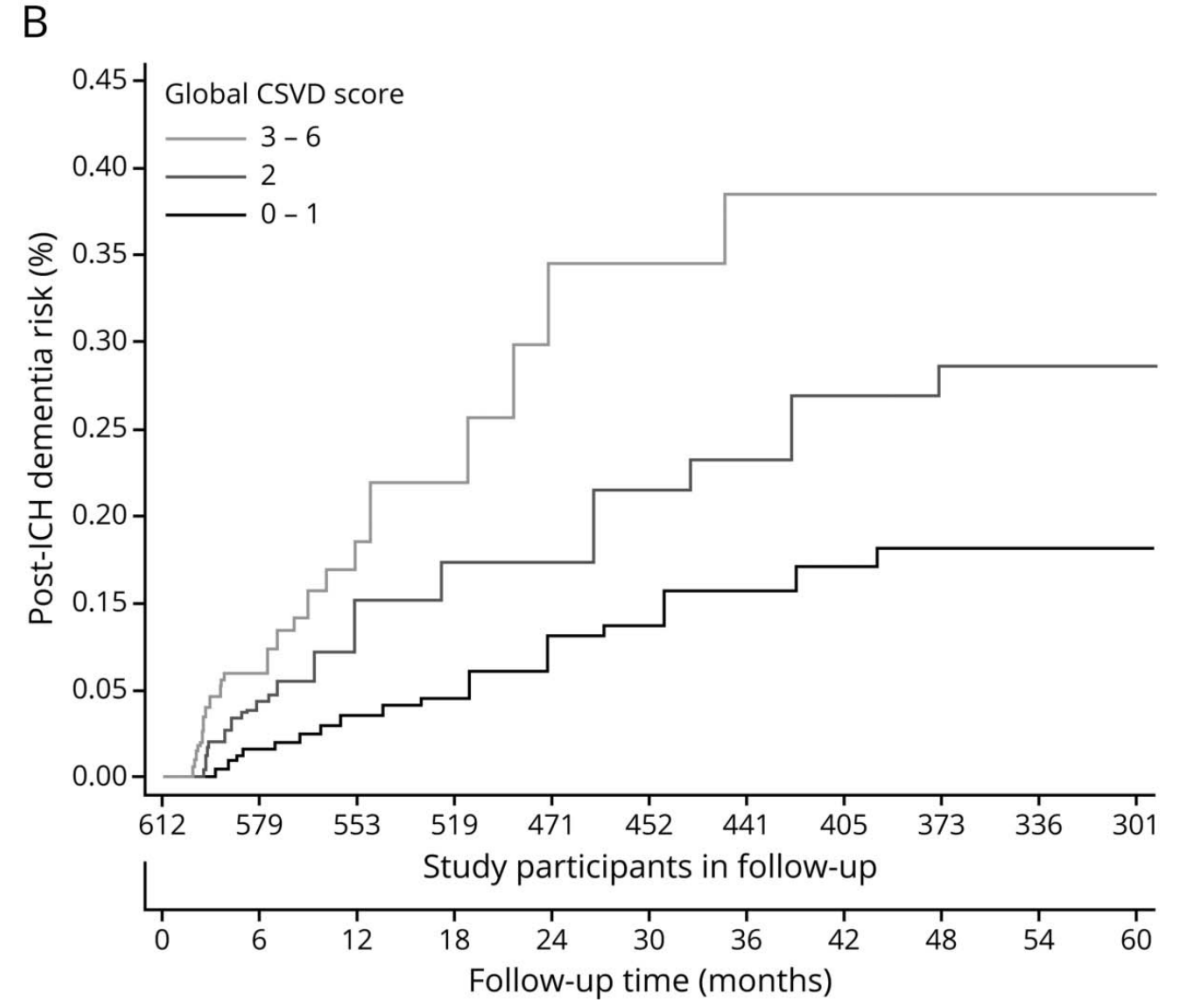
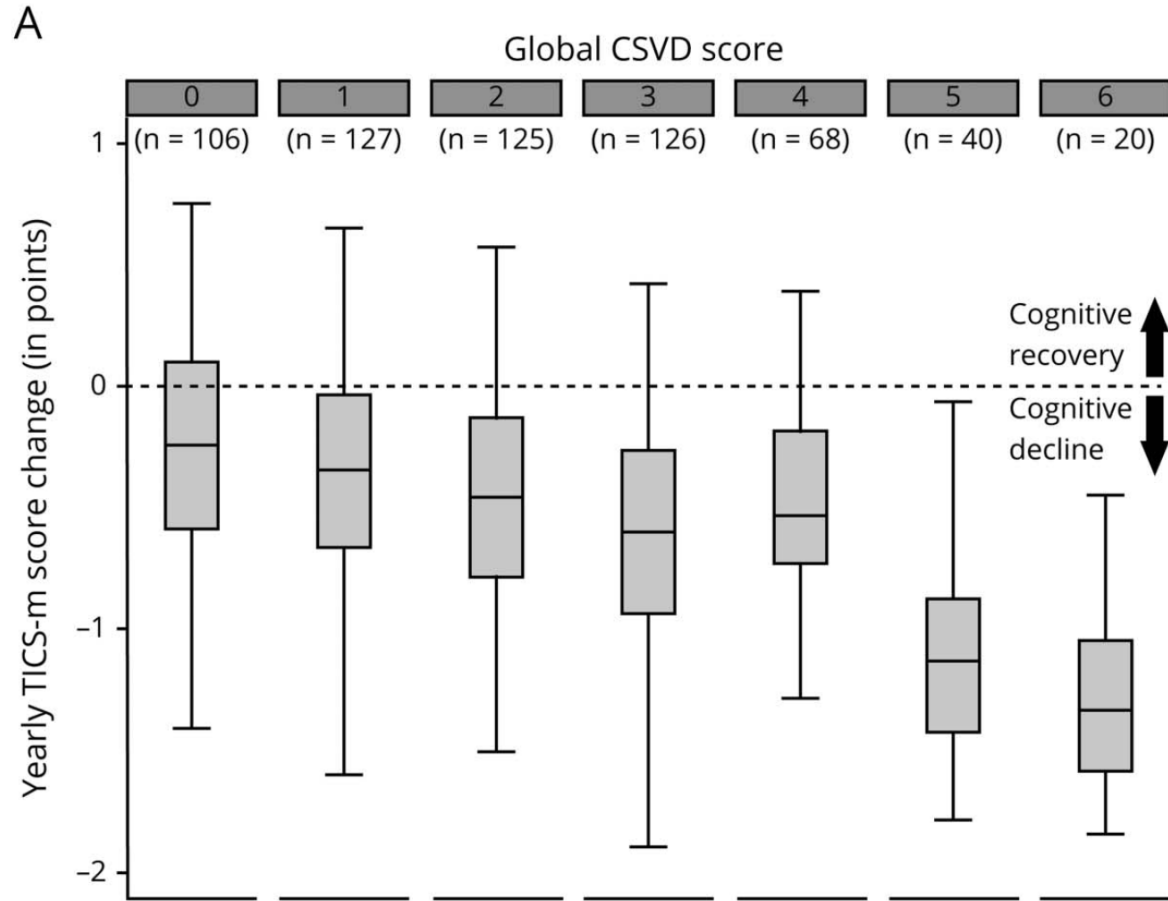
Multivariable analysis of risk factors for delayed post-ICH dementia conversion in patients with probable CAA

Variables	HR	95% CI	p
<i>Model 1 (demographic factors)</i>			
Age (per year)	1.042	0.989–1.098	0.123
Education (score)	0.66	0.361–1.208	0.178
MCI (yes versus no)	4.617	1.848–11.536	0.001*
<i>Model 2 (neuroimaging factors)</i>			
Disseminated cSS (yes versus no)	3.115	1.030–9.424	0.044*
WMH (Fazekas score)	1.439	1.036–2.001	0.03*
Lobar CMBs ≥ 5	1.105	0.431–2.834	0.835
WMH/TBV (%) [#]	1.480	1.157–1.891	0.002*
<i>Model 3 (sensitivity analysis: factors combined)</i>			
MCI (yes versus no)	5.880	2.250–15.367	<0.001*
Disseminated cSS (yes versus no)	3.275	1.129–9.499	0.029*
WMH (Fazekas score)	1.427	1.057–1.927	0.02*
WMH/TBV (%) [#]	1.426	1.112–1.830	0.005*
<i>Model 4 (sensitivity analysis: factors combined)</i>			
MCI (yes versus no)	6.043	2.401–15.212	<0.001*
SVD score for CAA ≥ 3	2.961	1.278–6.861	0.011*

Model 1 and model 2 included demographic factors and neuroimaging factors separately, and factors survived from model 1 and model 2 were then included in model 3. Model 4 used SVD score for CAA to replace individual neuroimaging markers. [#]WHM/TBV (%) was included in the model to replace WHM Fazekas score. * with statistical significance. HR, hazard ratio; MCI, mild cognitive impairment; CMBs, cerebral microbleeds; WMH, white matter hyperintensity; cSS, cortical superficial siderosis; SVD, small vessel disease; CAA, cerebral amyloid angiopathy.

CSVD burden predicts risks of post-ICH dementia

CSVD scores ≥ 2 : sensitivity 83%; specificity 91%

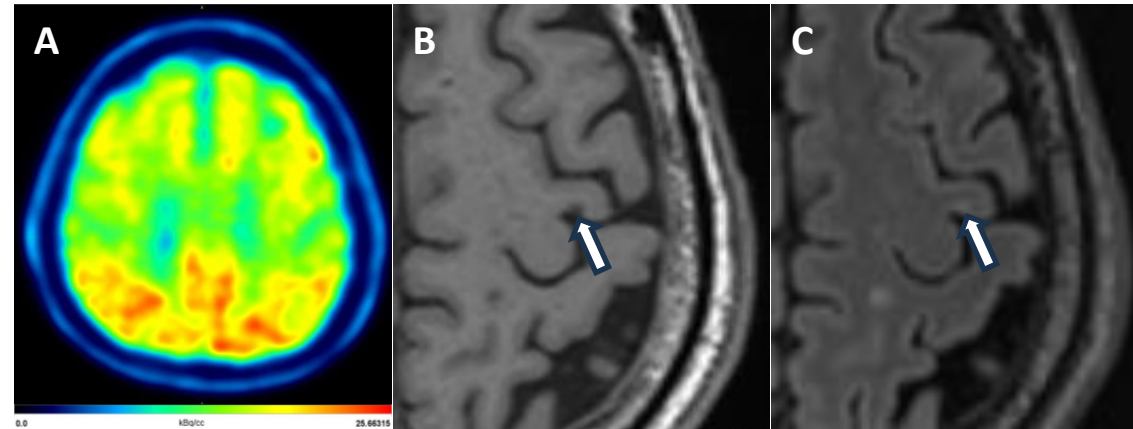


Cortical microinfarct and cognitive decline in ICH survivors

37.2%

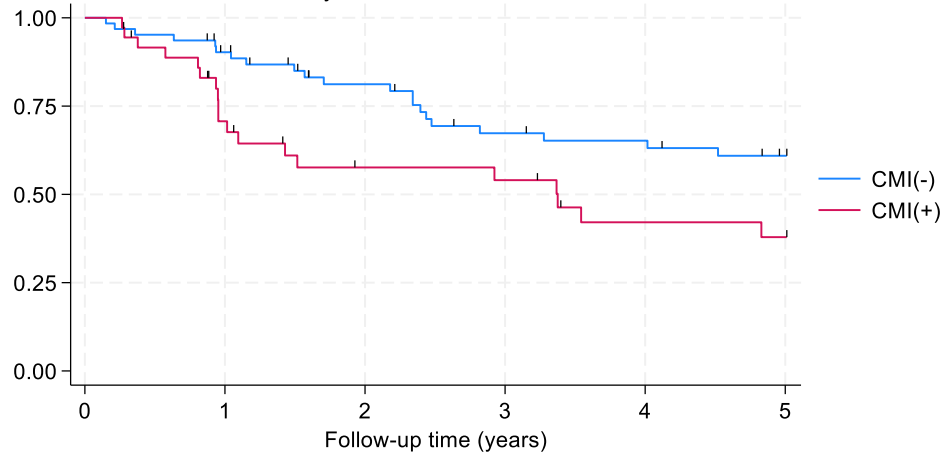
CMI is associated with

- Probable CAA (OR 2.3)
- cSS (OR 2.4)
- Amyloid load (OR 1.2)



Pu-Tien Chiang, MD

Kaplan–Meier Estimates of Cognitive Decline Over 5 Years
Stratified by Presence vs. Absence of CMI

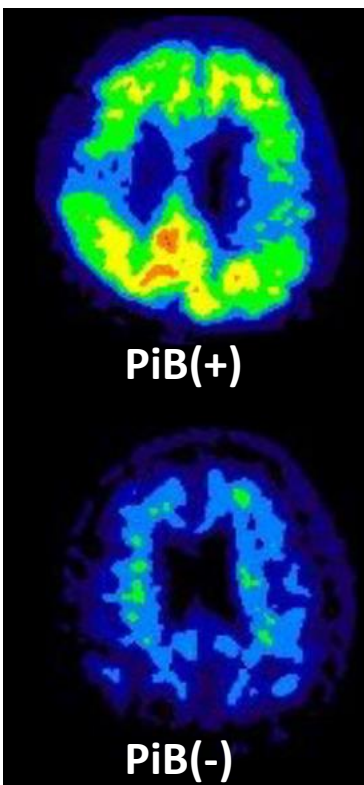


Follow-up time (years)	0	1	2	3	4	5
CMI(-)	63	53	42	33	31	26
CMI(+)	36	23	16	15	10	9

Risk factors	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
CMI	2.02 (1.08-3.76)	0.027	2.11 (1.11-4.00)	0.022	2.63 (1.28-5.37)	0.008
Age			1.10 (1.06-1.14)	< 0.001	1.08 (1.03-1.12)	< 0.001
Female			1.95 (1.00-3.83)	0.051	2.40 (1.13-5.07)	0.022
Education (years)			1.05 (0.97-1.13)	0.245	1.06 (0.98-1.14)	0.150
Probable CAA					1.14 (0.51-2.56)	0.749
Mean cortical thickness*					0.20 (0.03-1.37)	0.100
Total cSVD score					1.34 (0.92-1.95)	0.133

Cerebral amyloid deposition predicts long-term cognitive decline in hemorrhagic small vessel disease

Ya-Chin Tsai¹ | Hsin-Hsi Tsai^{2,3}  | Chia-Ju Liu⁴ | Sheng-Sian Lin² | Ya-Fang Chen⁵ | Jiann-Shing Jeng² | Li-Kai Tsai^{2,6} | Ruoh-Fang Yen⁴



Ya-Chin Tsai, MD, MSc



N = 68
Median follow-up 3.8 years

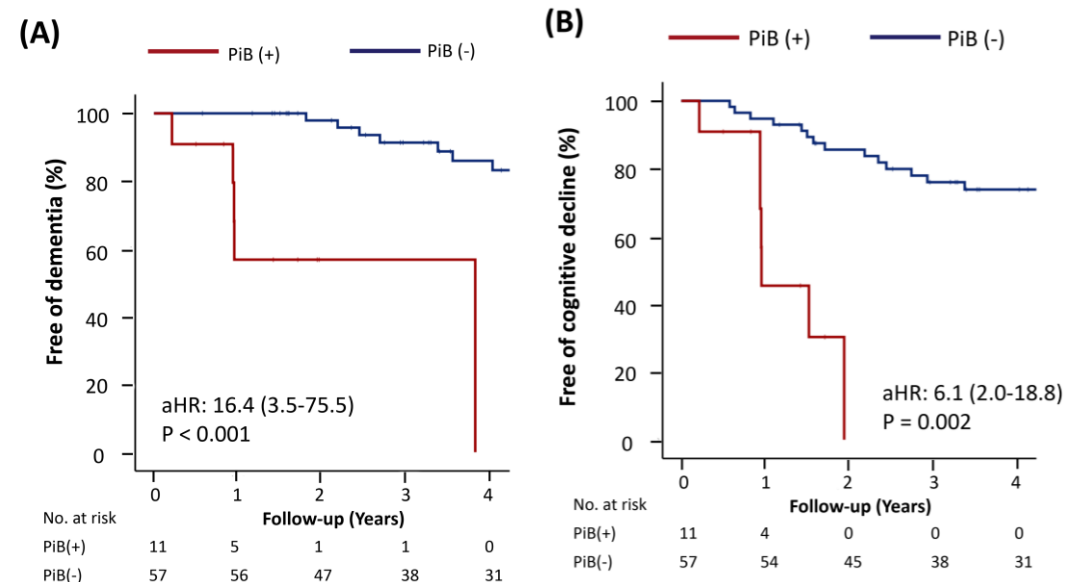
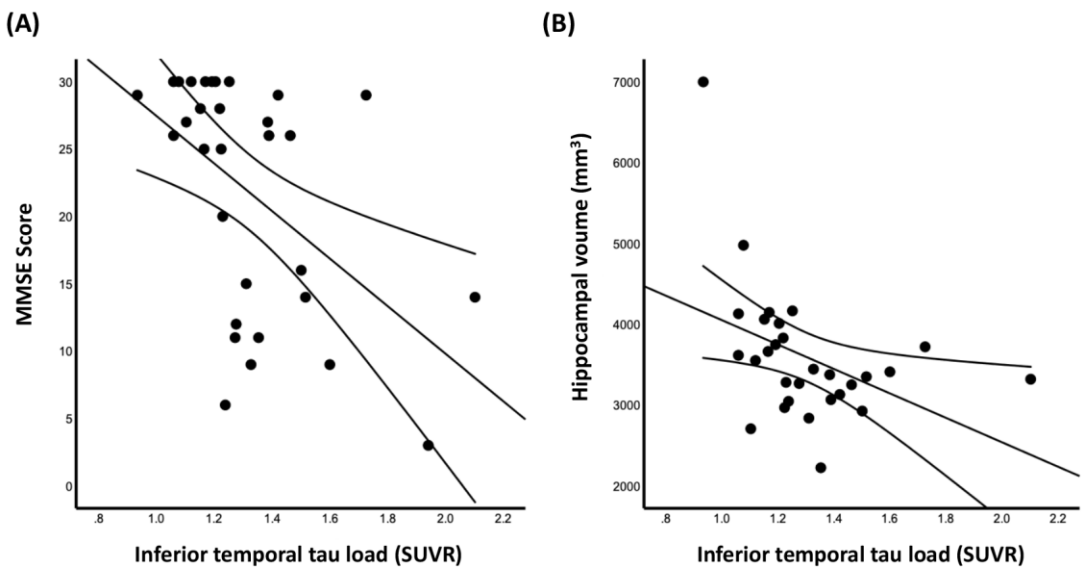
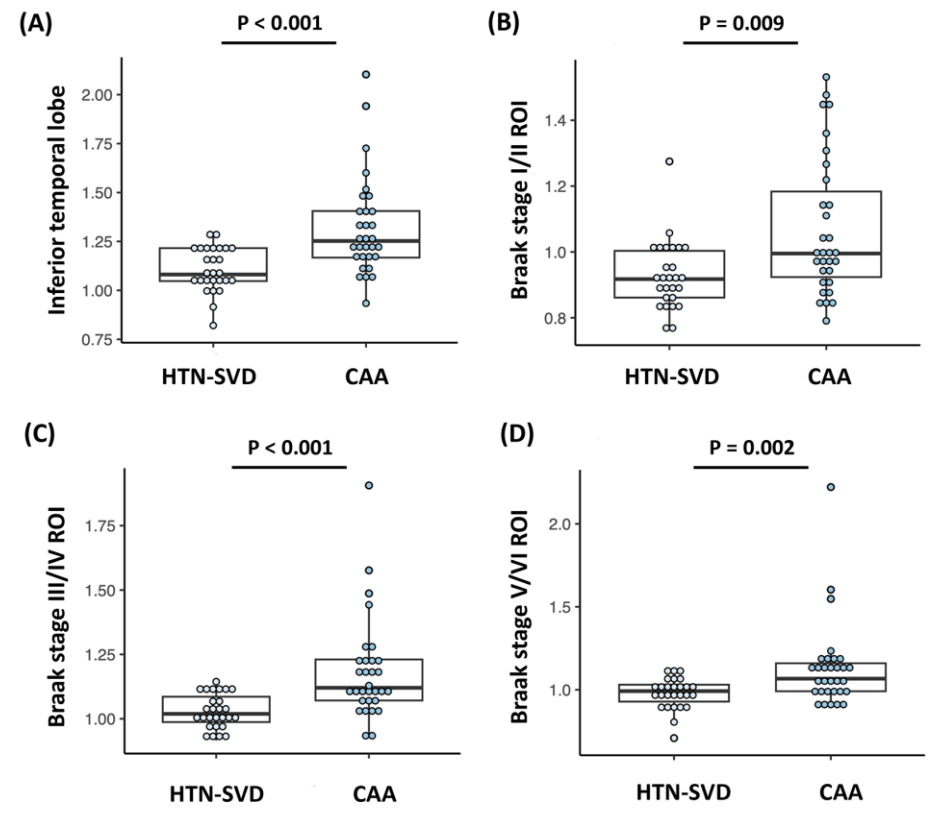
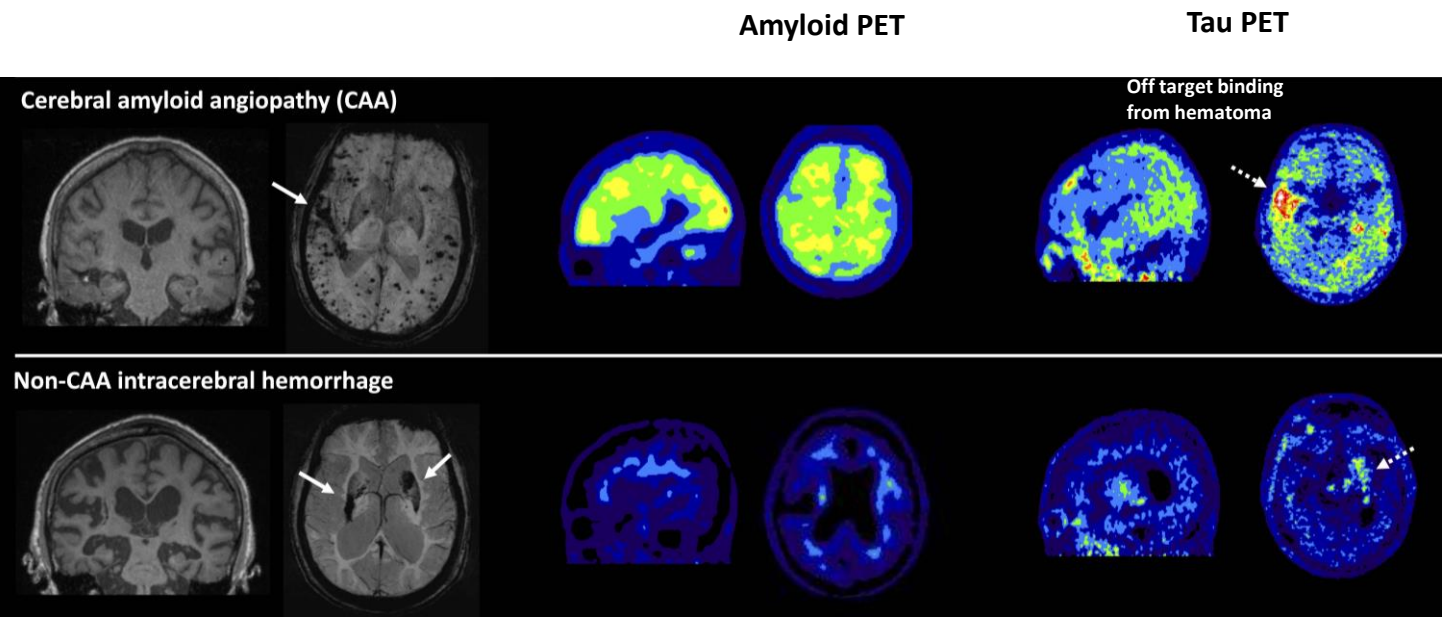


TABLE 3 Multivariable Cox regression models of factors that predict cognitive outcomes among survivors of intracerebral hemorrhage.

	Dementia conversion			MMSE decline ≥ 2		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Age, per 10 years	2.2	.9-5.0	.066	2.2	1.3-3.8	.003
PiB PET (+)	15.8	2.6-95.4	.003	5.7	1.6-.3	.008
>5 Lobar CMBs	1.5	.3-6.2	.604	2.2	.8-5.5	.113
Presence of lacunes	.6	.1-5.4	.653	2.3	.8-7.0	.136
High-degree CSO-PVS	.8	.1-12.4	.899	2.1	.8-5.7	.133

Tau pathology can be concomitant in CAA



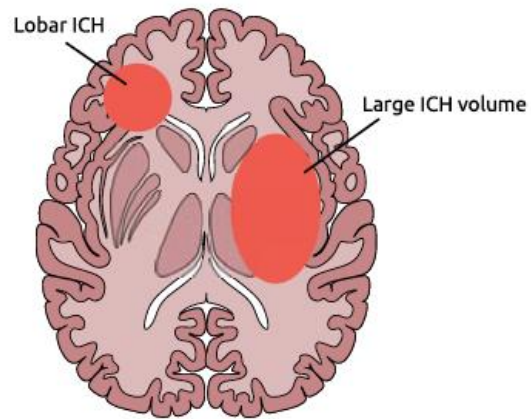
	Model 1 (Univariable)		Model 2 (Age-adjusted)		Model 3 (Age- and PiB SUVR-adjusted)	
Parameter	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
PiB whole cortex SUVR	0.11 (0.02-0.19)	0.02	0.11 (0.00-0.21)	0.055	-	-
Lobar CMB number	0.06 (-0.16-0.14)	0.114	0.07 (-0.01-0.16)	0.067	-	-
Total cSS score	0.11 (0.05-0.18)	0.002	0.13 (0.06-0.21)	0.001	0.11 (0.05-0.16)	<0.001
WMH volume	0.06 (-0.07-0.19)	0.335	0.04 (-0.10-0.18)	0.555	-	-
CSO-PVS grade	0.04 (-0.06-0.15)	0.385	0.04 (-0.08-0.16)	0.500	-	-
CAA score	0.13 (0.05-0.22)	0.003	0.14 (0.05-0.24)	0.006	0.12 (0.02-0.21)	0.015

Spontaneous ICH as a precipitating insult

Reported incidence of post-ICH dementia ranges from 5.5% to 45.5%

Primary brain injury






- Mass effect and hematoma expansion
- Risk factors include:
 - Lobar ICH location
 - Larger ICH volume
 - Stroke severity (NIHSS score)



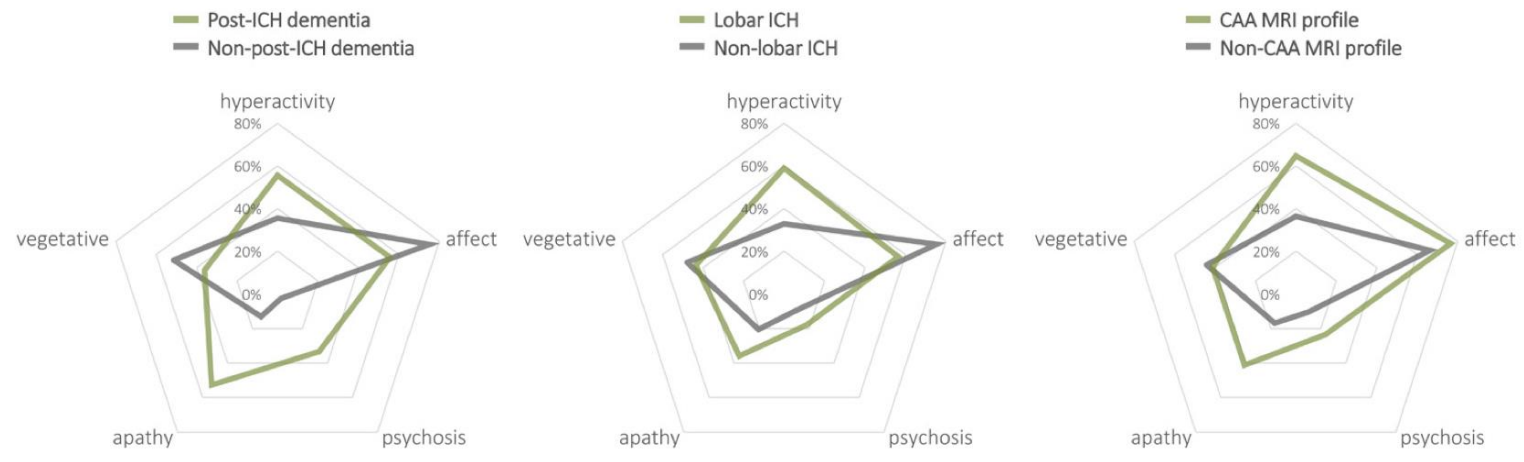
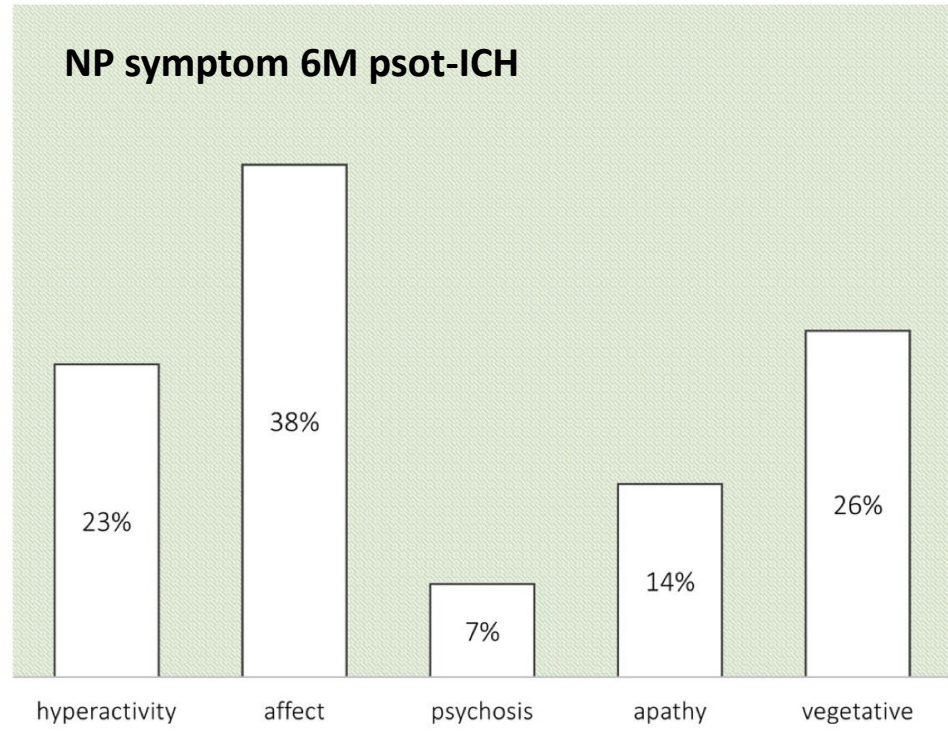
Secondary brain injury

- Increased ICP and cerebral hypoperfusion
- NVU dysfunction and BBB disruption
- Inflammation, oxidative stress, neurotoxicity

Long-term neuropsychiatric symptoms in spontaneous intracerebral haemorrhage survivors

Giuseppe Scopelliti ¹, Barbara Casolla,¹ Grégoire Boulouis ², Gregory Kuchcinski,² Solène Moulin,¹ Didier Leys ¹, Hilde Henon,¹ Charlotte Cordonnier ¹, Marco Pasi ¹

- 202 patients survived 6M after ICH
- 55% had NP symptoms
- Higher prevalence in post-ICH dementia and CAA-ICH



Predictors of affective disturbances and cognitive impairment following small spontaneous supratentorial intracerebral hemorrhage

Qiuyi Jiang^{1,2} | Chunyang Liu^{1,2} | Hongli Zhang^{1,2} | Rui Liu^{1,2} | Jian Zhang^{1,2} | Jinyi Guo^{1,2} | Enzhou Lu^{1,2} | Shouyue Wu^{1,2} | Jianda Sun^{1,2} | Yan Gao^{1,2} | Qiunan Yang^{1,2} | Guangyao Shi^{1,2} | Chao Yuan^{1,2} | Yanchao Liang^{1,2} | Huan Xiang^{1,2} | Lu Wang³ | Guang Yang^{1,2} 

- 1,563 ICH survivors (mostly deep)
- 52.8% with depressive symptoms
- 39.4% exhibited anxiety symptoms

Modifiable factor?

Variables	Cognitive impairment		Depressive symptoms		Anxiety symptoms	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age	1.46 (1.26, 1.69)	<0.001	1.32 (1.16, 1.51)	<0.001	1.19 (1.05, 1.36)	0.008
Male	1.65 (1.20, 2.28)	0.002	1.58 (1.19, 2.10)	0.002	0.80 (0.60, 1.05)	0.112
Alcohol intake	0.73 (0.55, 0.97)	0.029	1.56 (1.20, 2.03)	<0.001	1.48 (1.14, 1.93)	0.003
Hospitalization days	1.04 (0.91, 1.18)	0.592	1.16 (1.03, 1.30)	0.015	1.17 (1.04, 1.31)	0.009
Systolic blood pressure	0.43 (0.36, 0.51)	<0.001	0.85 (0.73, 0.99)	0.036	1.11 (0.95, 1.29)	0.191
Diastolic blood pressure	1.10 (0.93, 1.32)	0.273	1.07 (0.92, 1.26)	0.376	0.72 (0.61, 0.84)	<0.001
Hematoma volume	0.67 (0.59, 0.77)	<0.001	1.56 (1.38, 1.76)	<0.001	0.84 (0.75, 0.95)	0.005
Anatomical distribution						
Deep location		Ref.		Ref.		Ref.
Lobar location	0.31 (0.22, 0.43)	<0.001	1.00 (0.73, 1.36)	0.986	1.13 (0.83, 1.54)	0.424

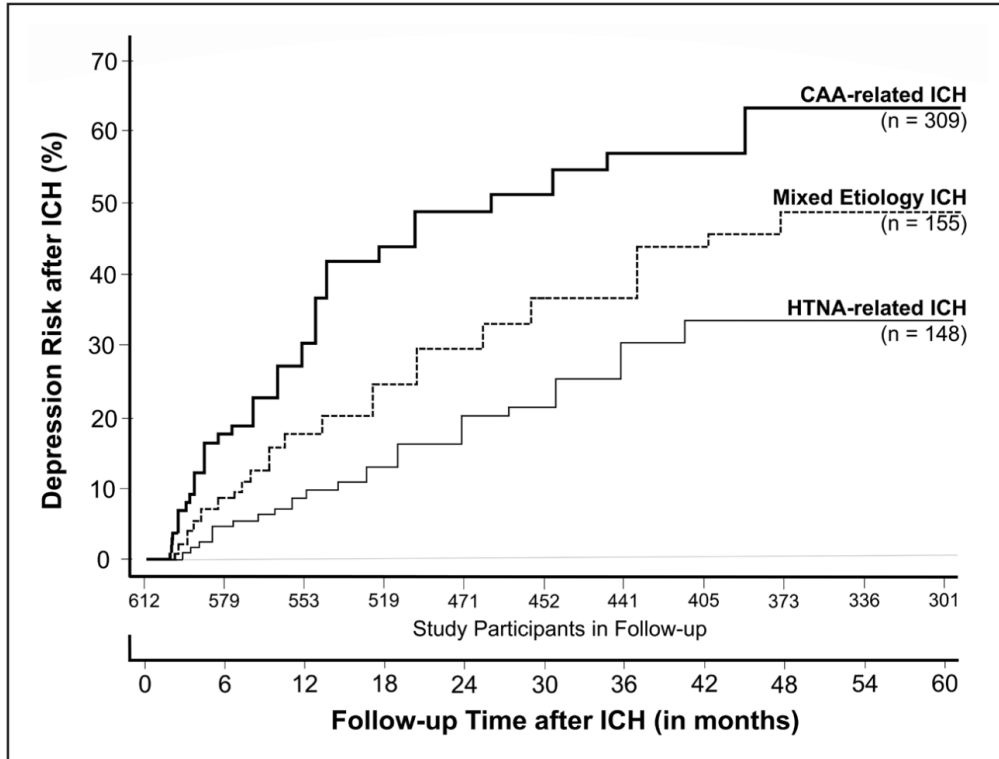
The contribution of CSVD on post-ICH depression

Stroke

CLINICAL AND POPULATION SCIENCES

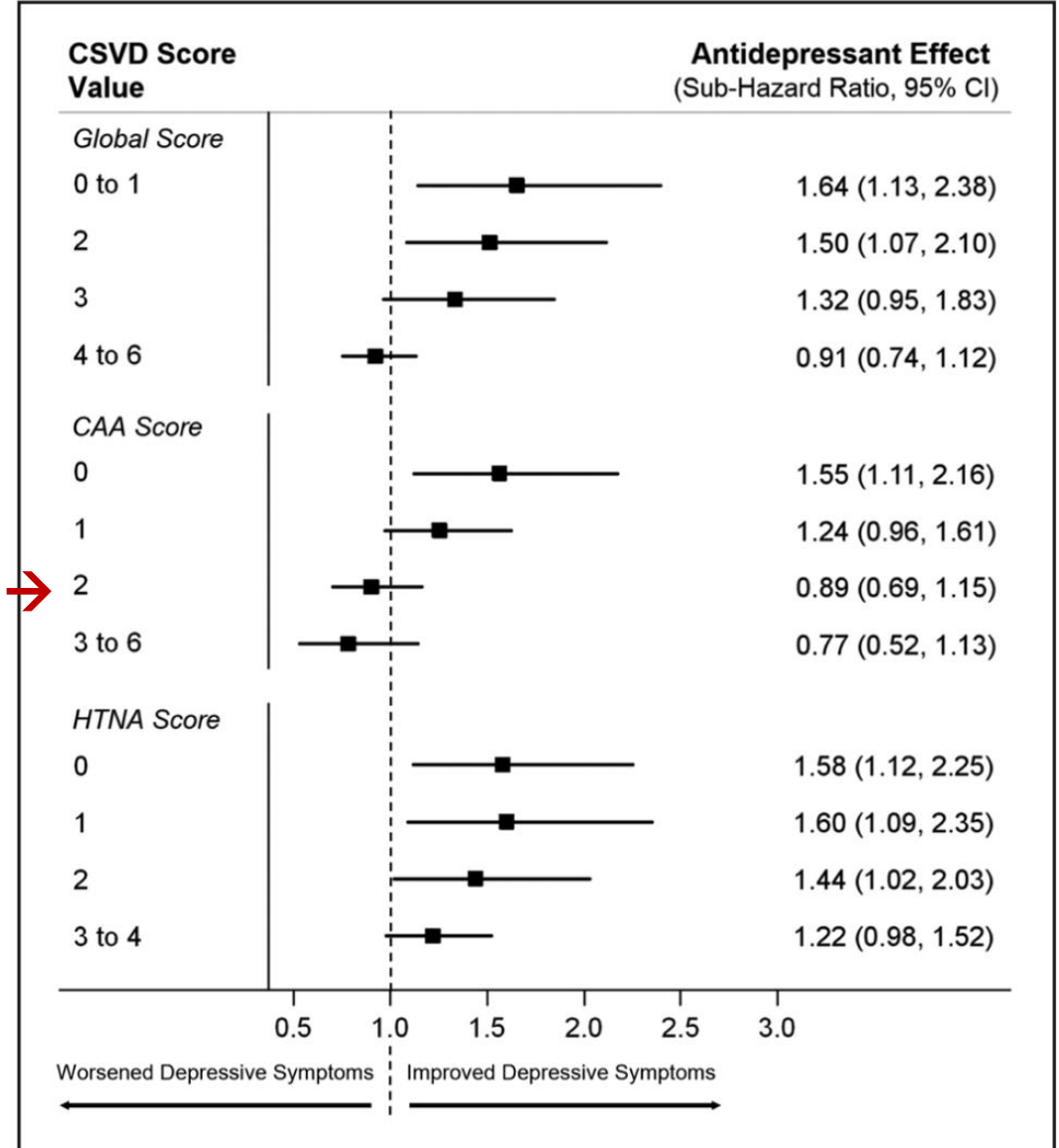
Cerebral Small Vessel Disease and Depression Among Intracerebral Hemorrhage Survivors

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P = 0.037 →

Response to antidepressant



Long-term affective symptoms are common in ICH survivors

Median f/u: 5.7 year (N=95)

Figure 1 the prevalence of NPS subsyndrome in chronic-phase ICH patients

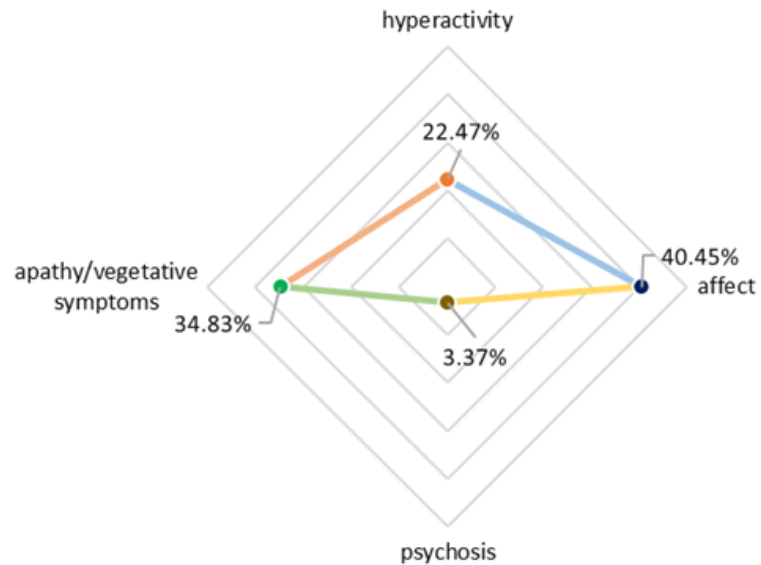
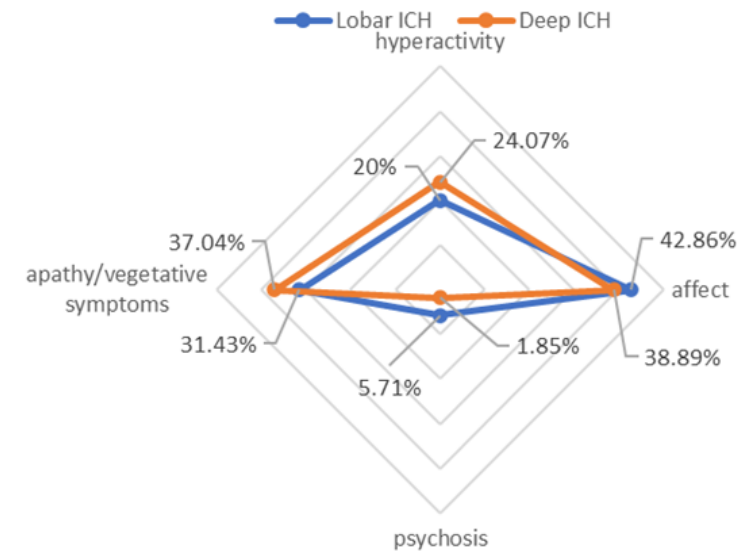
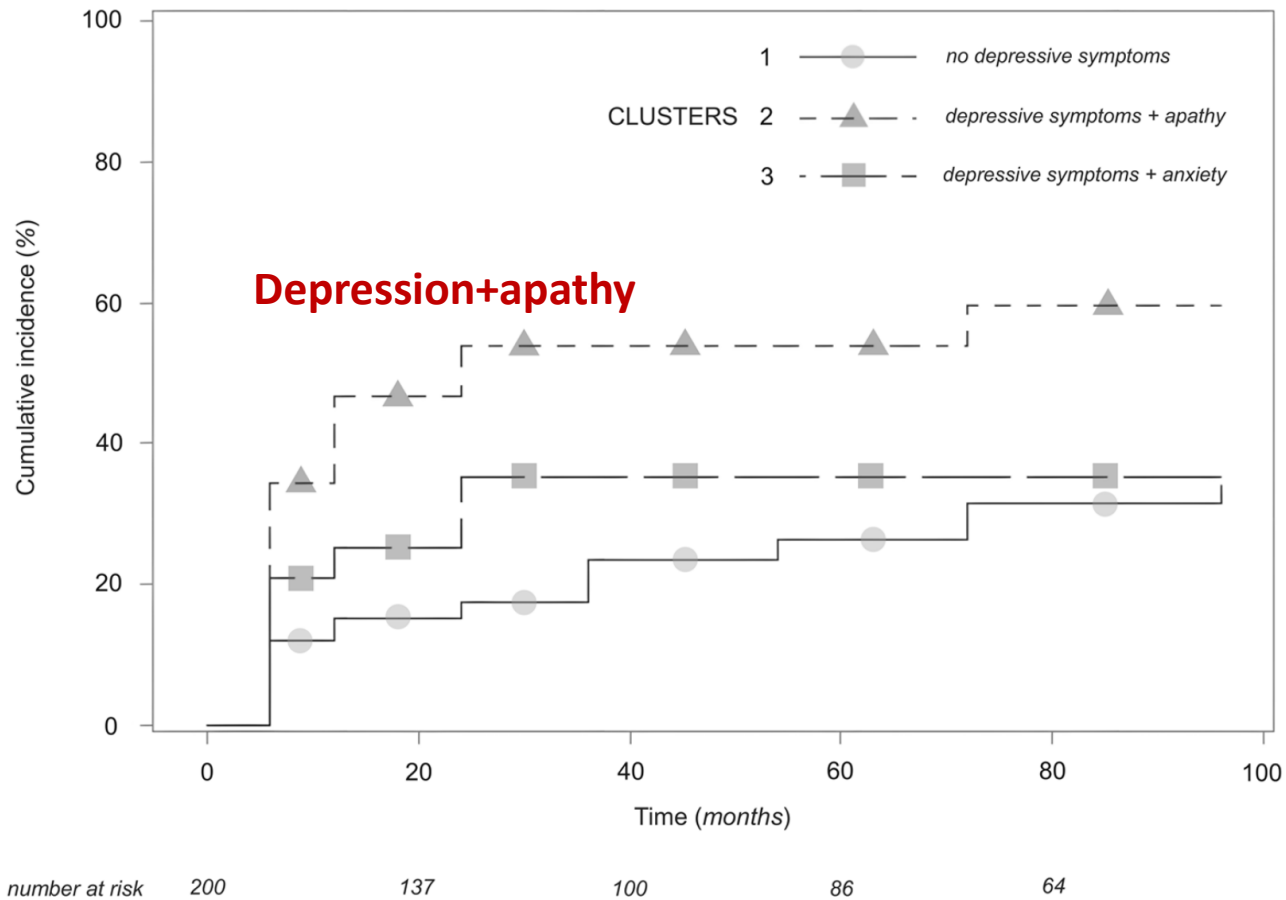


Figure 2 the prevalence of NPS subsyndrome in Lobar ICH versus Deep ICH



- Those with long-term affective symptoms were more cognitively impaired ($p < 0.001$)
- Deep CMBs is independently associated with long-term depression and anxiety (OR=1.2, $p=0.02$)

Screening of NPS in ICH survivors (Depression, apathy)



3 depressive symptom profiles were identified:

- No significant depressive symptoms
n = 152
- Depressive symptoms with predominant **apathy**
n = 41
- Depressive symptoms with predominant **anxiety**
n = 28

N = 221 ICH survivors

vs.

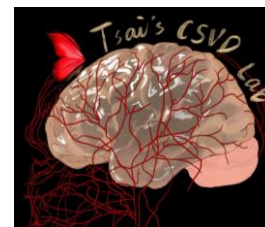
- ↑↑ cerebral atrophy**
(adj. OR=2.4, 95% CI=1.4-4.2)
- ↑↑ long-term dementia risk**
(HR=2.2, 95% CI=1.3-3.8)

vs.

- ↑↑ diabetes**
(adj. OR=3.1, 95% CI 1.1-8.6)
- ≈ cerebral atrophy**
- ≈ long-term dementia risk**

Summary and Take Home Messages

- Cognitive impairment is common among post-ICH survivors (>**10%** 1 year post-ICH).
- Risk factors include **lobar ICH**, **preexisting cognitive impairment**, **CSVD burden** and types (**CAA**).
- Long-term cognitive profile: Decreased **executive function** and impaired memory.
- Post-ICH cognitive impairment is highly associated with **neuropsychiatric symptoms**, especially in **affective** domain (depression, anxiety, apathy).
- Screening of cognitive function and neuropsychiatric symptoms are important measures in managing long-term consequences of ICH survivors.



Thank you.
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