NYU Langone Health

CAI²R Center for Advanced Imaging Innovation and Research

Cerebral Microhemorrhages following Chronic Blast and Blunt-related Mild Traumatic Brain Injury – Imaging Findings

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Outline

- Definition of mTBI
- mTBI in the U.S
- mTBI in the military
- Clinical findings of mTBI
- Mechanisms of mTBI
- Imaging findings in mTBI
- Cerebral microhemorrhages in mTBI

Definition of TBI

- Multiple agencies have different definitions
- Common criteria:

	TBI SEVERITY		
Criteria	**Mild**	**Moderate**	**Severe**
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness	<30 minutes	30 minutes to 24 hours	>24 hours
Post traumatic amnesia	0–1 day	>1 and <7 days	>7 days
Glasgow Coma Scale score (best available score in 24 hours)	13–15	9–12	3–8

Poll#1: How big is the problem?

- How many emergency department (ED) TBI-related visits, hospitalizations, and deaths occur in the United States annually?

A. 0.5 million

B. 1 million

C. 3 million

D. 5 million

Traumatic Brain Injury in the U.S

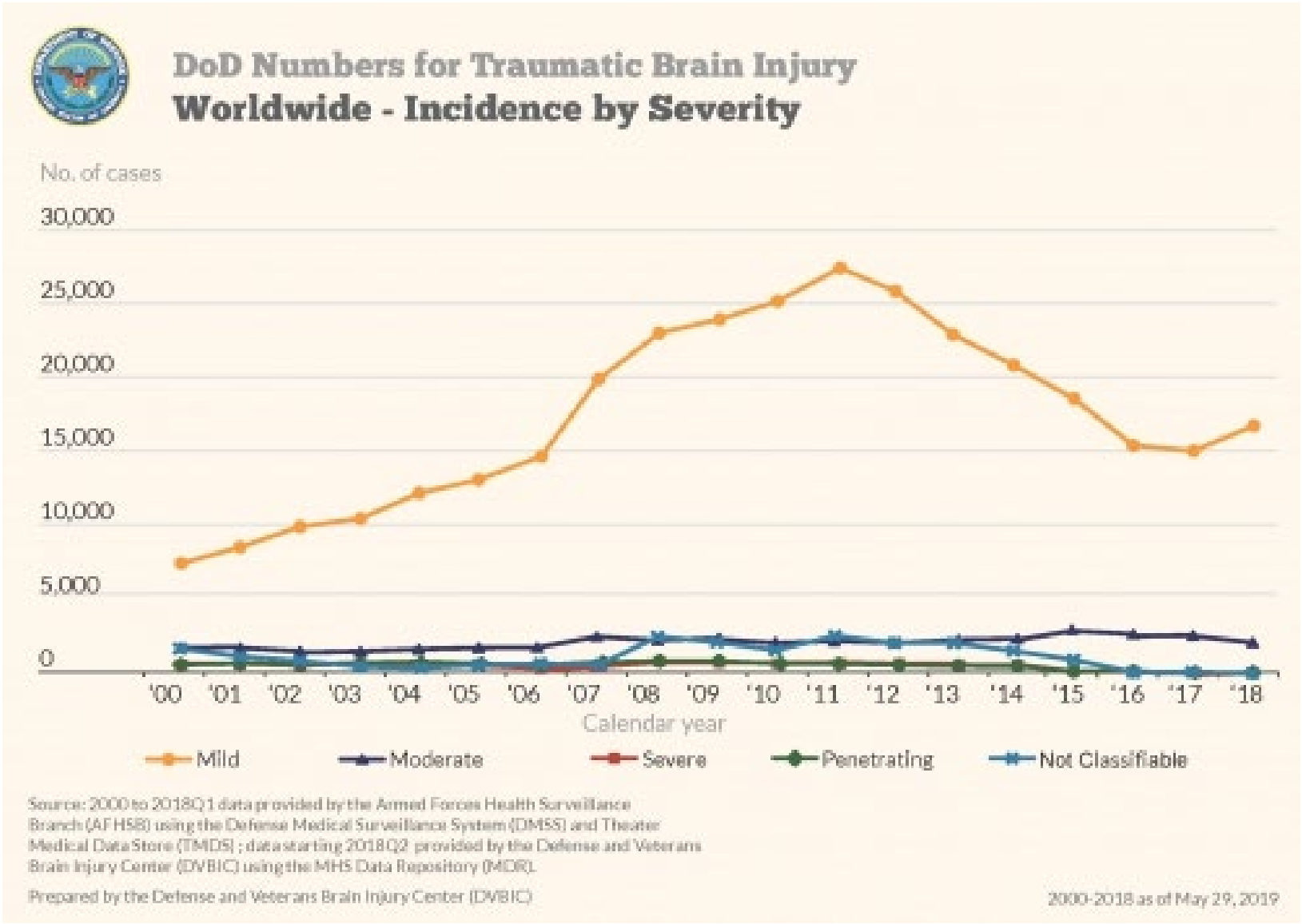
- In 2014, about 2.87 million TBI-related emergency department visits, hospitalizations (288,000), and deaths (56,800 people) occurred in the United States
- 5.3 million persons are currently living with a TBI-related disability

Centers for Disease Control and Prevention (2019). Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. https://www.cdc.gov/traumaticbraininjury/get_the_facts.html

Military TBI

- TBI is of considerable interest of the U.S. military especially following past operations Enduring Freedom, Iraqi Freedom and New Dawn (OEF/OIF/OND), and now including Operation Inherent Resolve (OIR) to defeat ISIS and Operation Freedom Sentinel (OFS) related to continued operations in Afghanistan
- The Armed Forces Health Surveillance Center reports that over 400 000 service members were diagnosed with TBI between 2000 and 2019

Defense and Veterans Brain Injury Center. DoD Worldwide Numbers for TBI. http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi.



https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi

Military TBI

- Incidence of TBI during the conflicts in Iraq and Afghanistan ranged from 12–35% with approximately 80% of the injuries involving blast exposure, usually more than one
- Soldiers who reported mTBI were younger males, more likely to be junior in rank, and with reported high combat intensity

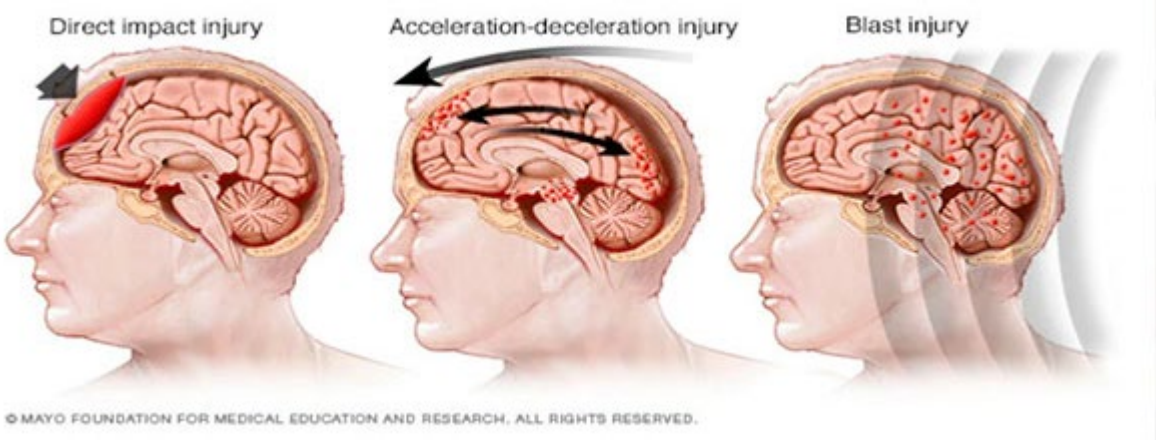
JOURNAL OF NEUROTRAUMA 34:S-44–S-52 (Supplement 1, 2017)

Clinical Findings in mTBI

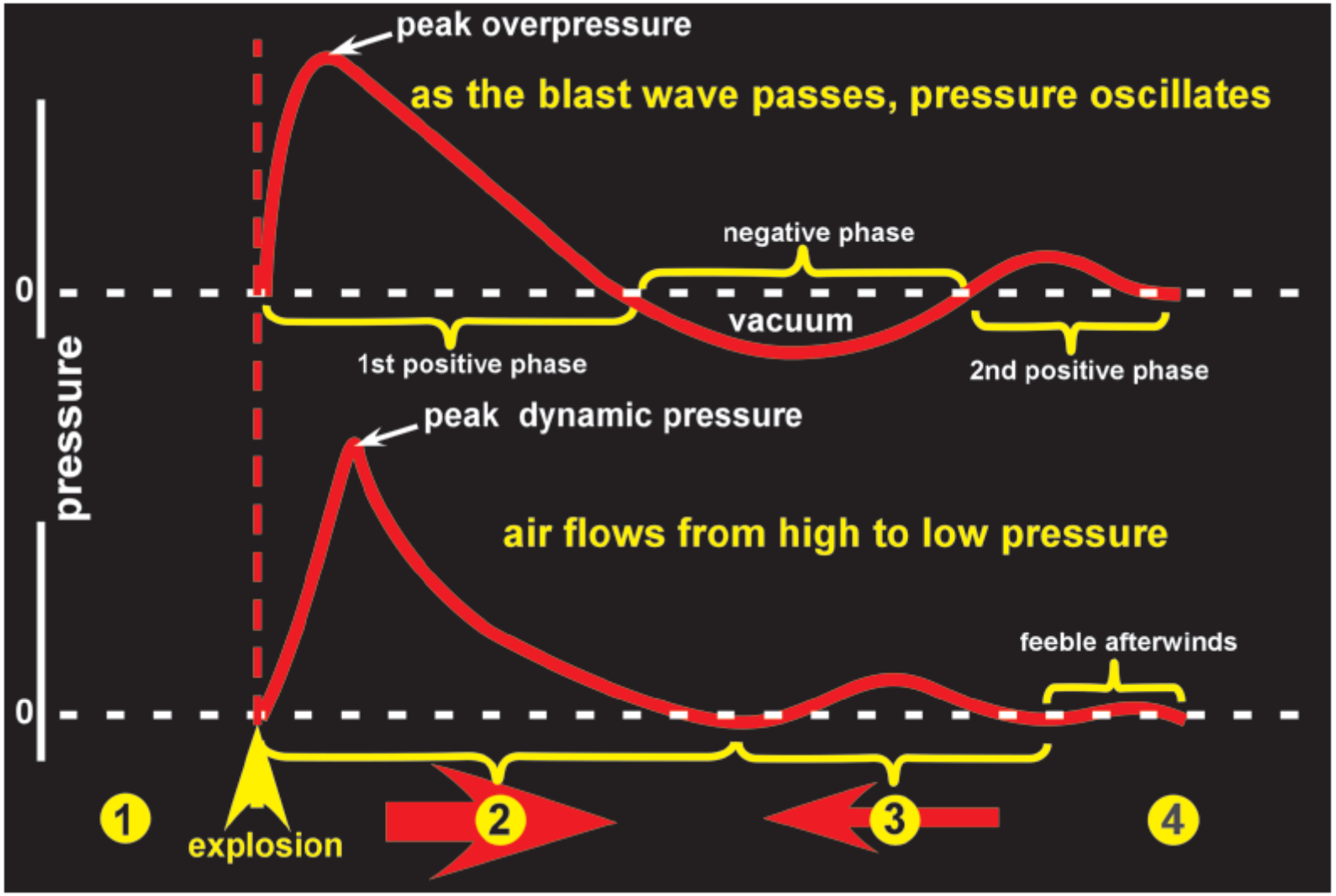
- mTBI symptoms are not limited to typical cognitive or motor deficits usually associated with more severe brain injuries
- A proportion of patients develop a chronic, complex combination of symptoms:
  - Mental health issues: PTSD, depression and impulsivity
  - Sensory defects: central processing deficits that affect perception and balance
  - Chronic headaches and pain
  - Sleep disorders
  - Metabolic and endocrine dysfunction

Mechanism of Injury in mTBI

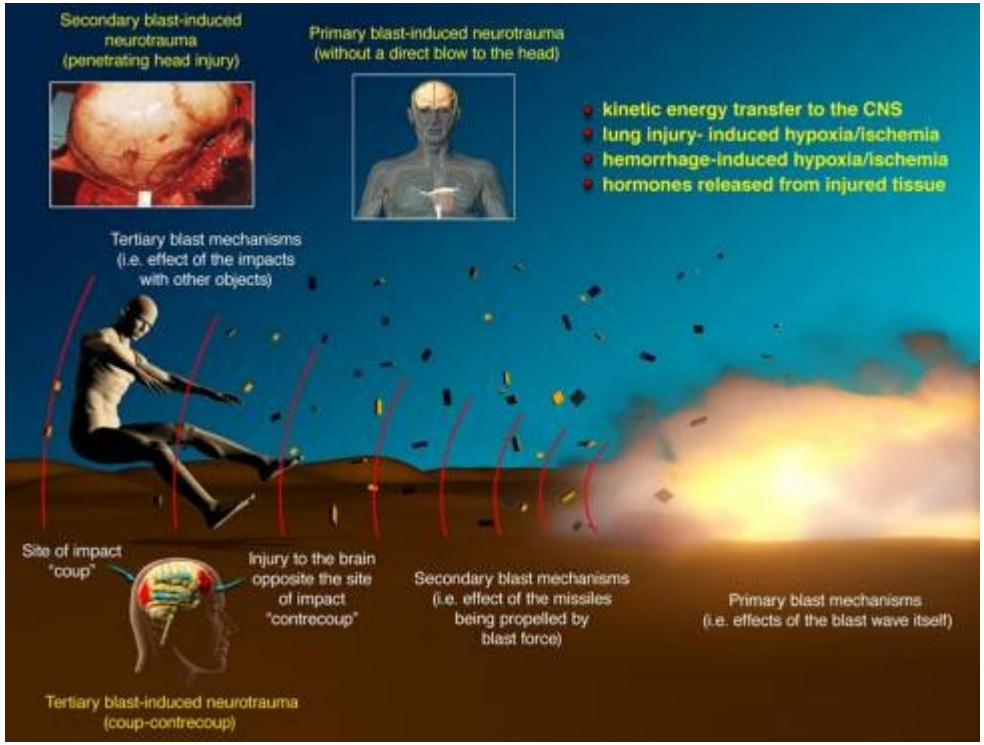
- Direct impact (blunt)
- Acceleration-deceleration
- Blast injuries
- It has been suggested that blast-related mTBI represents a unique injury mechanism distinct from blunt head trauma



Blast-related Forces



Taber KH, et al. J Neuropsychiatry Clin Neurosci. 2006;18:141-145.



Blast-related injury taxonomy

- **Primary**
  - Blast overpressure wave impacting the body
  - Examples: Blast lung, tympanic membrane rupture, non-blunt TBI
- **Secondary**
  - Damage from projectiles contacting the body
  - Examples: Penetrating ballistic or blunt injuries
- **Tertiary**
  - Physical displacement of the body and striking solid surfaces
  - Examples: Traumatic amputation, closed or open head injury, crush injuries
- **Quaternary**
  - Other "explosive products" effects
  - Examples: Burns, inhaled toxic fire gases
- **Quinary**
  - Clinical consequences of post detonation contaminants
  - Examples: Radiation poisoning, tissues reactions to fuels or metals

Cernak et al. J Cereb Blood Flow Metab. 2010; 30: 255-266

Bryden et al. J Exp Neurosci. 2019; 13: 1179069519872213

Neuroimaging of mTBI

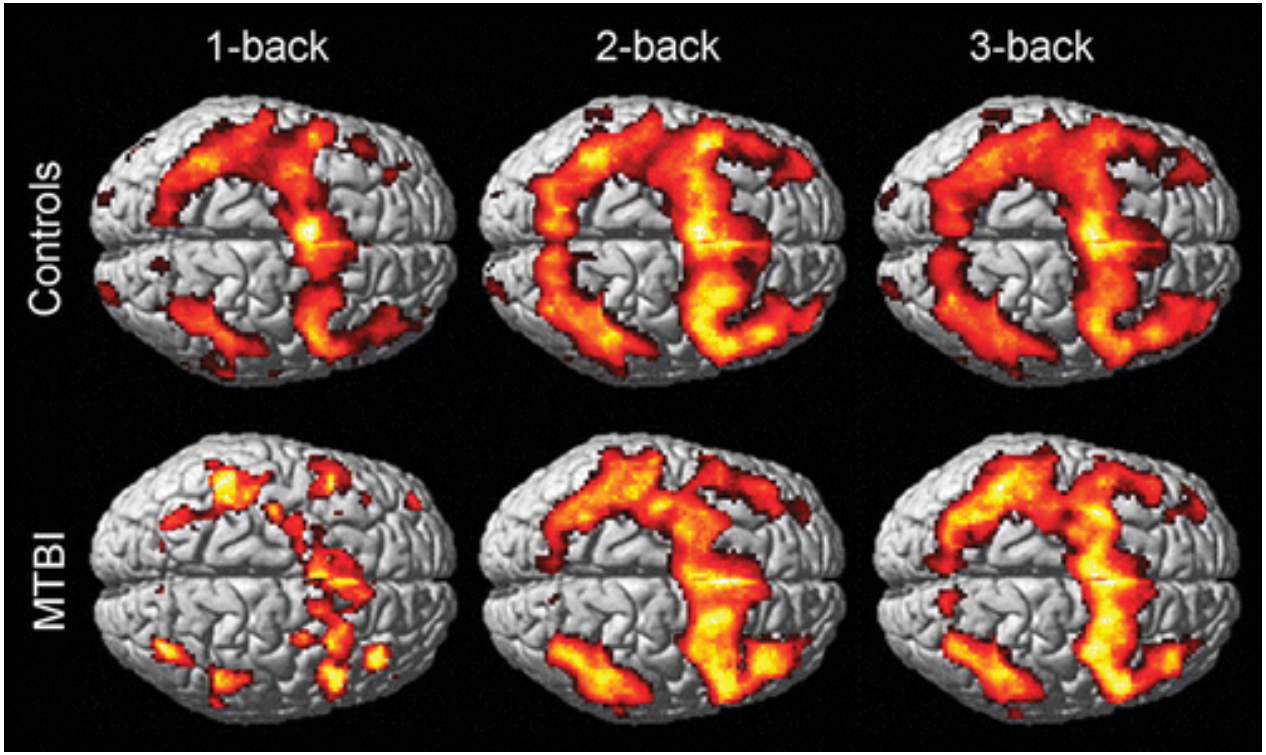
- CT is the standard of care for emergent evaluation and triage of acute TBI, regardless of severity
- MRI may prove useful as more sensitive modality, in case of negative initial or follow-up CT
- In assessing long-term outcome for mTBI, however, findings of conventional CT and MR imaging, are frequently normal in this setting

Neuroimaging of mTBI

- Several MR methods have shown promise in demonstrating evidence of subtle brain injury in mTBI not apparent at conventional imaging
- Three main categories:
  I. Structural MRI
  II. Functional MRI
  III. MR-Spectroscopy

Functional Imaging

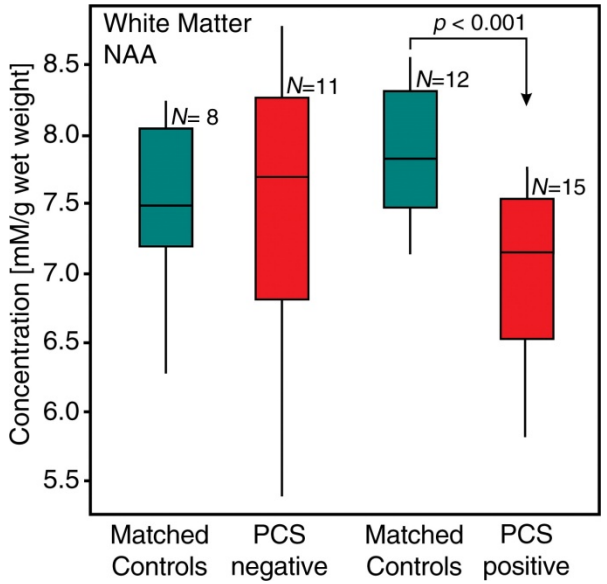
- Changes in Memory and Attention: Task-mediated Functional MR Imaging



Chen CJ, et al. Radiology 2012;264(3):844–851.

MR Spectroscopy - Metabolic Alterations

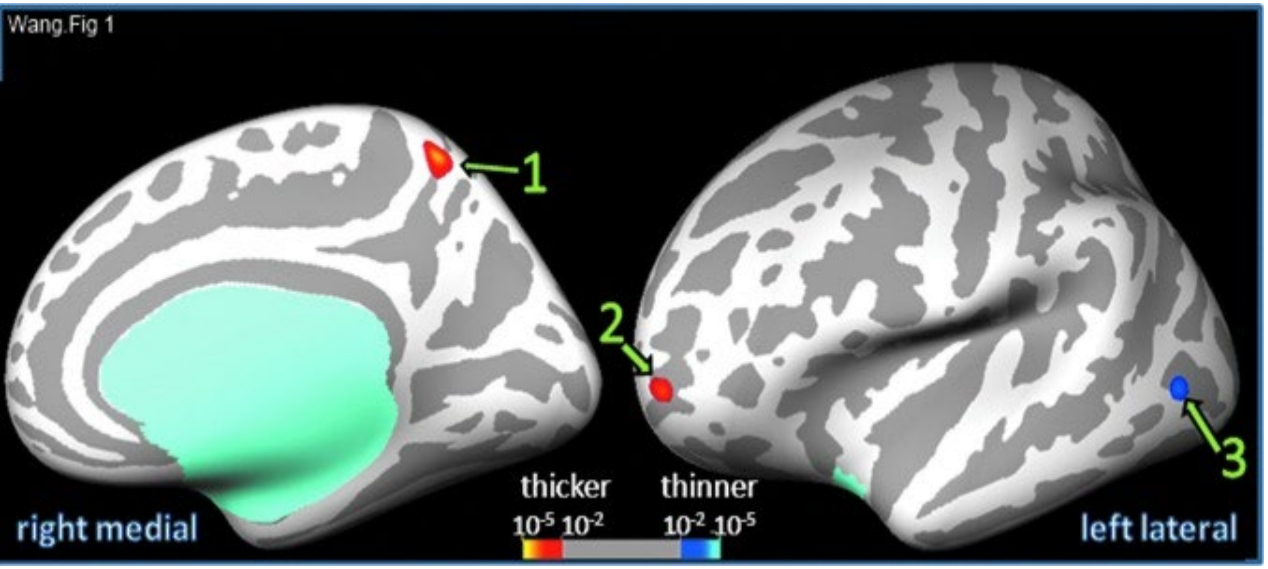
- Proton MR Spectroscopy, capable of reflecting mild neuronal injury
- MR spectroscopy metabolites in mTBI:
  - N-acetylaspartate (NAA) - marker of neuronal integrity
  - Creatine (Cr) - marker of energy consumption
  - Choline (Cho) - marker of cellular turnover

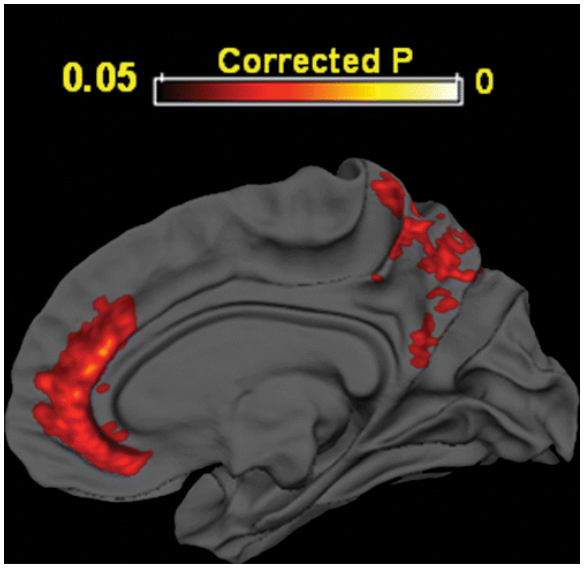


Kirov I, et al. J Neurotrauma 2013;30(13):1200–1204

Structural Imaging

- **Macrostructural Changes**:
  - Cortical thickening (acute settings)
  - Cortical thinning (more chronic settings)
  - WM and GM volume loss



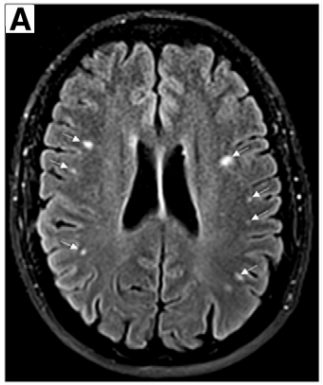


Wang X, et al. J Neurotrauma 2015;32:455–463.

Zhou Y, et al. Radiology 2013;267:880–890.

Structural Imaging

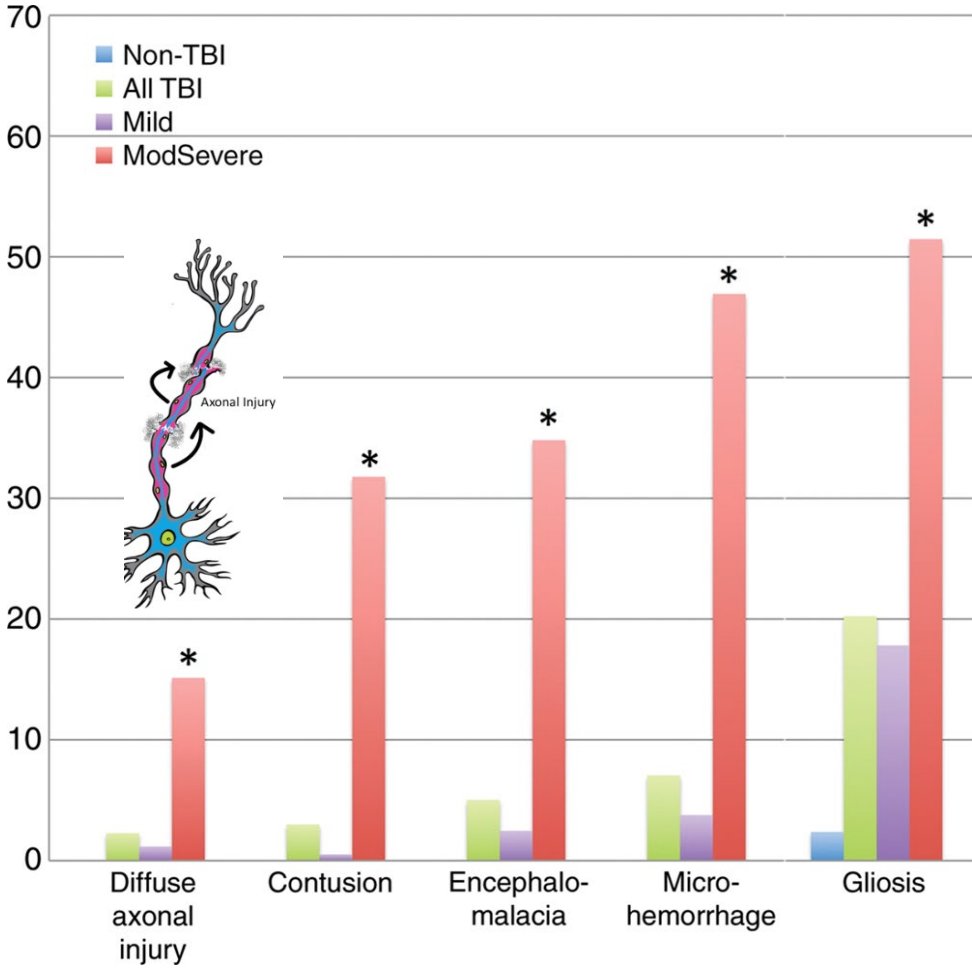
- **Microstructural Changes:**
  - Diffuse axonal injuries using Diffusion-Tensor Imaging (DTI)
  - Cerebral microhemorrhages (CMH) using Susceptibility-Weighted Imaging (SWI)



DAI

CMH

G. Trifan et al. / Magnetic Resonance Imaging 37 (2017) 243–251

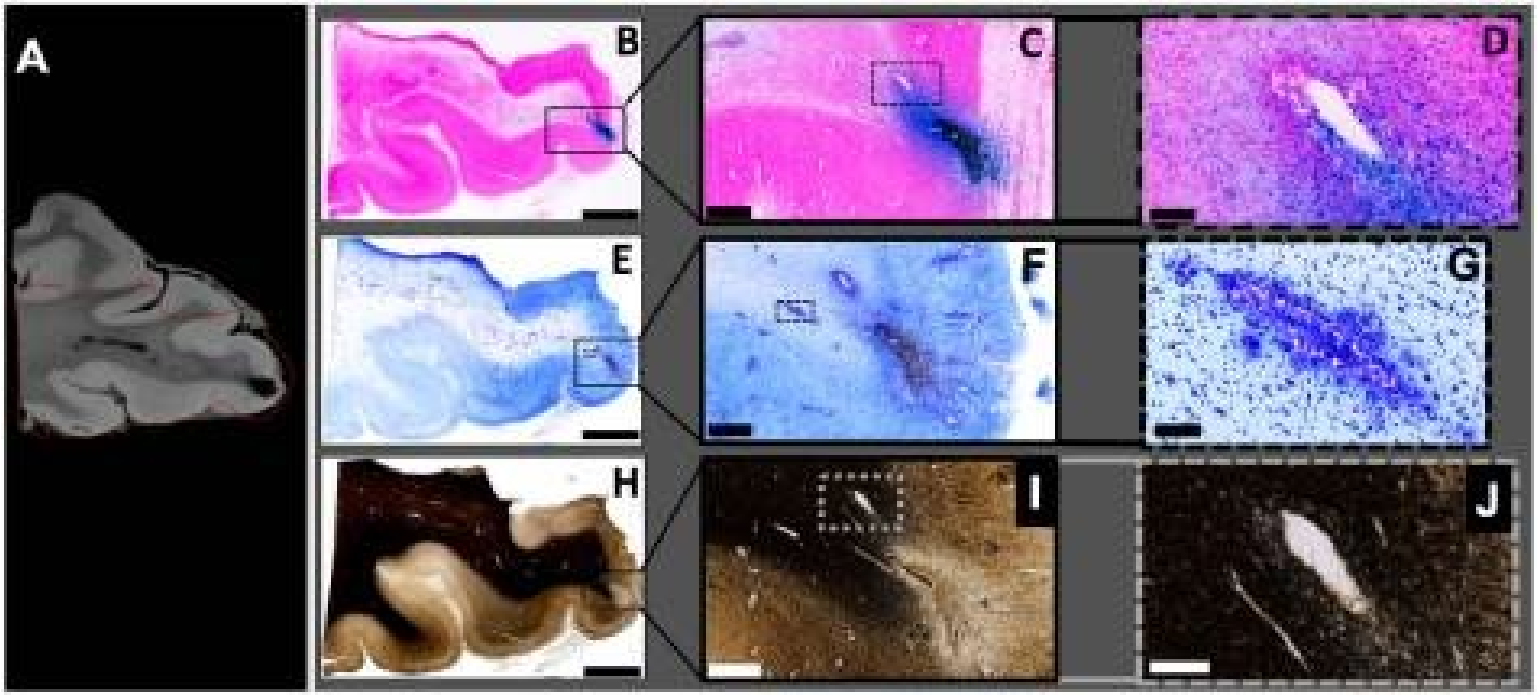


Riedy G. Published Online: December 15, 2015
https://doi.org/10.1148/radiol.2015150438

Radiology

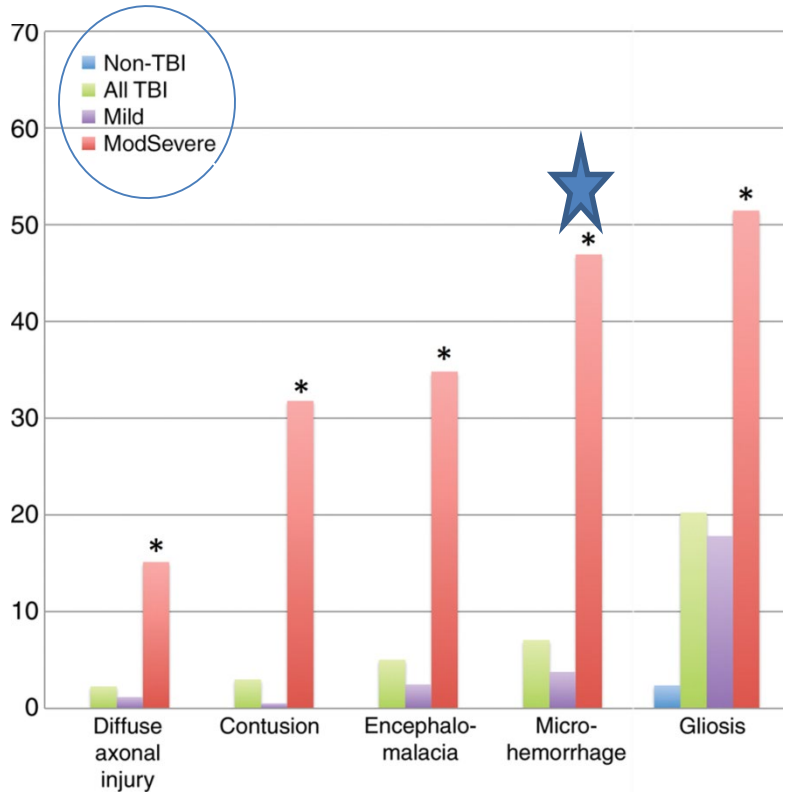
Traumatic microbleeds suggest vascular injury and predict disability in traumatic brain injury

Allison D. Griffin,[1,2] L. Christine Turtzo,[2] Gunjan Y. Parikh,[3,4] Alexander Tolpygo,[5] Zachary Lodato,[1,5] Anita D. Moses,[1,2] Govind Nair,[6] Daniel P. Perl,[1,7] Nancy A. Edwards,[8] Bernard J. Dardzinski,[1,7] Regina C. Armstrong,[1,7] Abhik Ray-Chaudhury,[8] Partha P. Mitra[5] and Lawrence L. Latour[1,2]



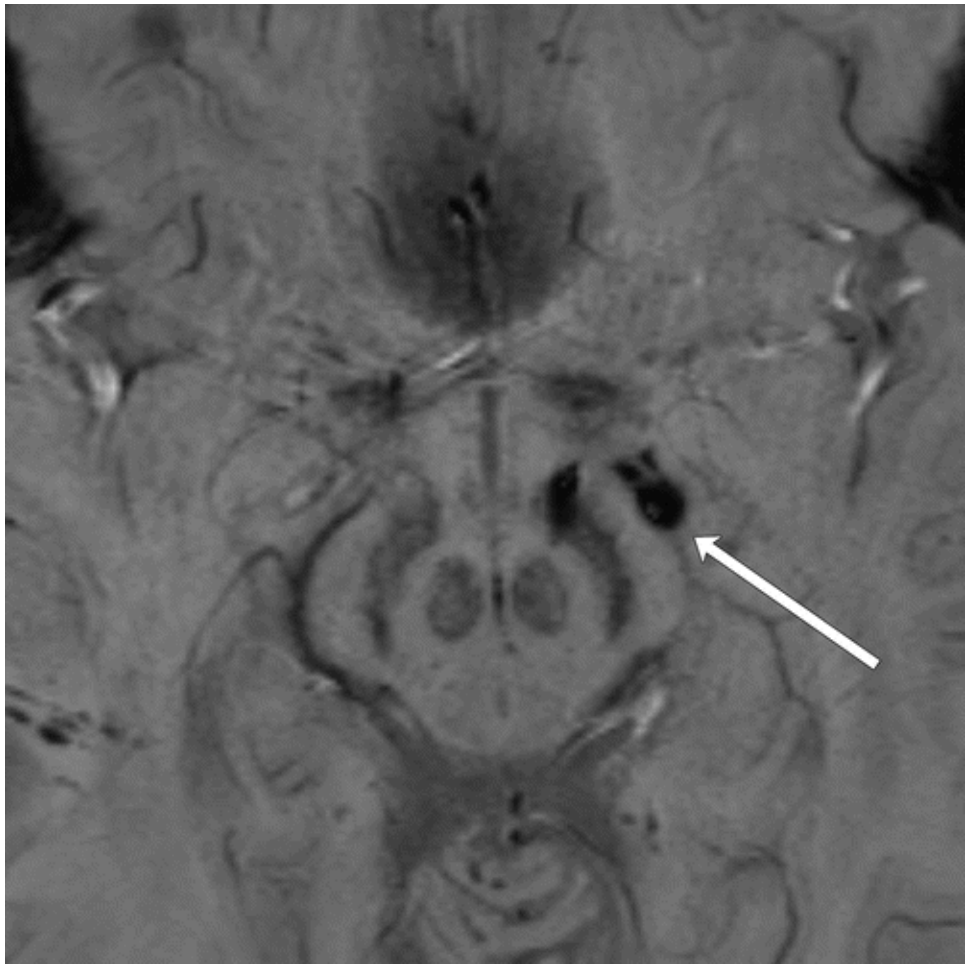
Cerebral Microhemorrhages

- In the appropriate clinical settings CMH could be considered a marker for TBI
- Detection of CMH in TBI correlates with injury severity and can explain focal neurologic deficits



Riedy G. Published Online: December 15, 2015
https://doi.org/10.1148/radiol.2015150438
Radiology

40-year-old female bicyclist with mTBI
Present with right visual field homonymous hemianopsia



Wu X. Published Online: May 16, 2016
https://doi.org/10.1148/radiol.16142535

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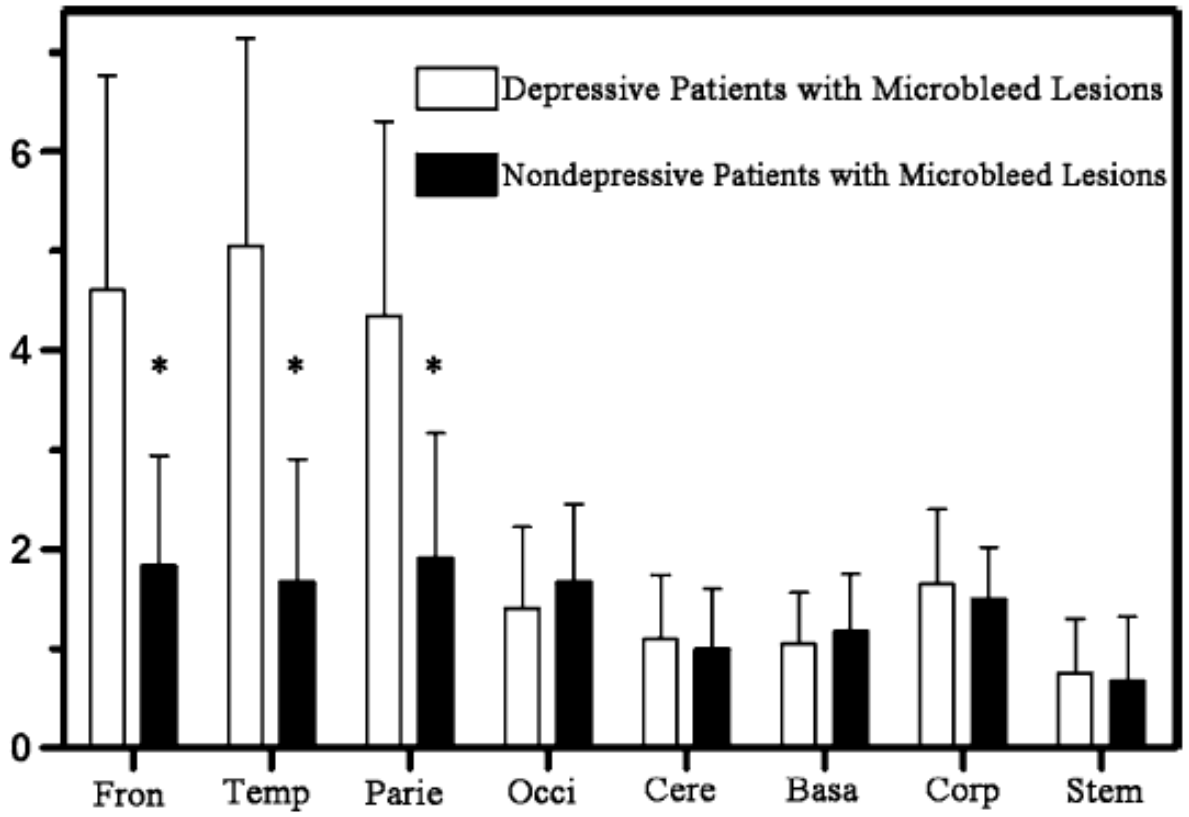
Supplemental Table 3: Logistic Regression Analysis of Demographic and Clinical Predictors of Outcome

Logistic Regression Analysis of Demographic and Clinical Predictors of Outcome				
	Univariate Analysis		Logistic Regression	
Predictors	OR (95%)	*P*-Value	OR (95%)	*P*-Value
Trauma Level	0.280 (0.165 – 0.476)	0.001	3.140 (1.799 – 5.480)	0.001
Presence of Both: Linear & Punctate TMBs	0.398 (0.208 – 0.761)	0.005	1.423 (1.196 – 4.908)	0.014
Time from Injury to Research MRI		0.001[a]	0.969 (0.948 – 0.989)	0.003



Neurol Sci (2014) 35:1533–1539

Table 4 Neuropsychological performance in patients with mTBI

	Negative finding (n = 85)	Microbleeds (+) (n = 26)	p Value
Digit span (scaled)			
Total	23.1 ± 3.8	21 ± 5.0	0.017[a]
Forward	14.3 ± 1.8	13.6 ± 2.7	0.065
Backward	8.7 ± 2.7	7.4 ± 3.2	0.025[a]
CPT			
Omissions	65.0 ± 46.2	61.2 ± 43.8	0.359
Commissions	51.7 ± 7.7	53.8 ± 10.4	0.181
Hit reaction time	56.4 ± 8.7	56.7 ± 9.8	0.451

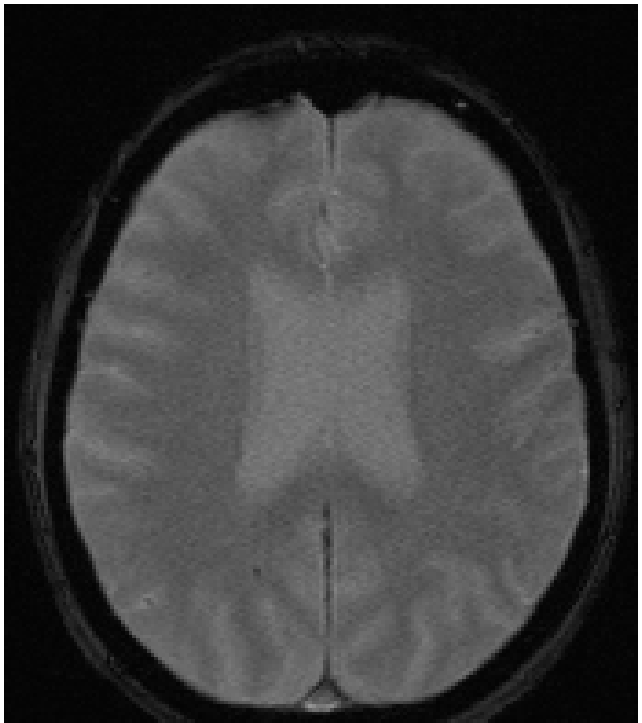
Abbreviations: CPT = continuous performance test; mTBI = mild traumatic brain injury.
Data are mean ± SD.
[a] Significant values.

Huang YL, et al. Susceptibility-weighted MRI in mild traumatic brain injury. Neurology. 2015;84:580-585.

Microhemorrhages and Iron Detection

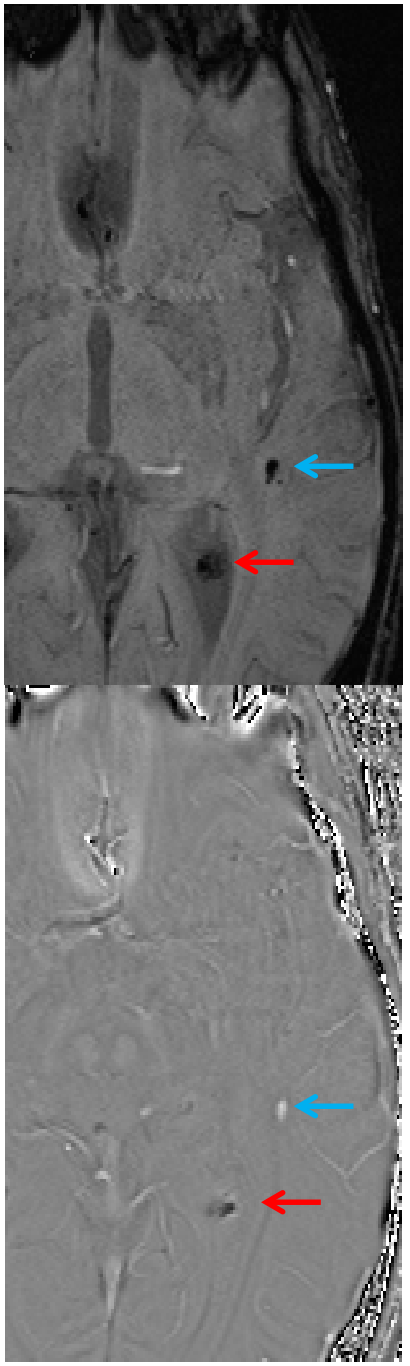
- High iron concentration of hemosiderin, allows detection by MRI because of its paramagnetic properties

Gradient Echo (T2*GRE)



Susceptibility-weighted Imaging (SWI)

- SWI sensitive to subtle CMH
- Phase map may be helpful
- Calcification (diamagnetic) vs Hemorrhagic blood products (paramagnetic)



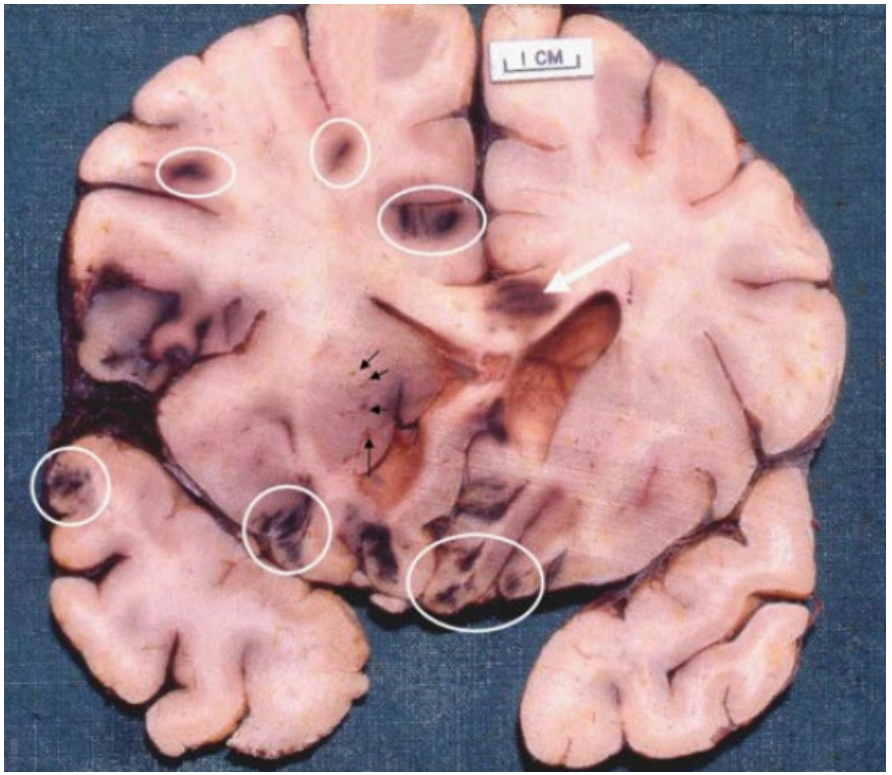
SWI

Phase

Courtesy of Dr. Yvonne Lui

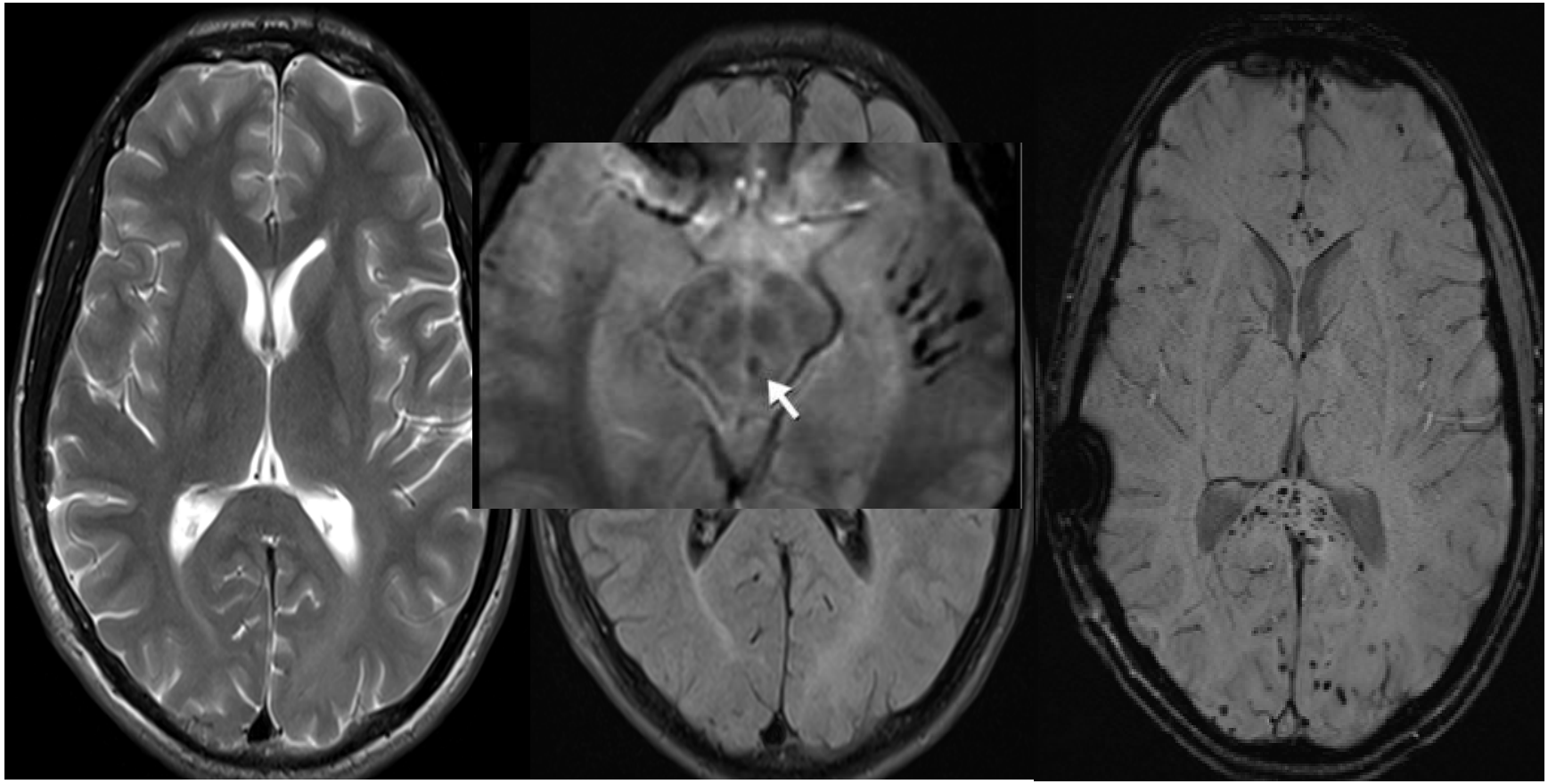
Poll#2: Typical locations of CMH?

- Corpus callosum (especially the splenium)
- Gray-white matter junction (especially the frontal and temporal lobes)
- Dorsal brainstem
- All above



Brain Imaging and Behavior (2012) 6:108–136

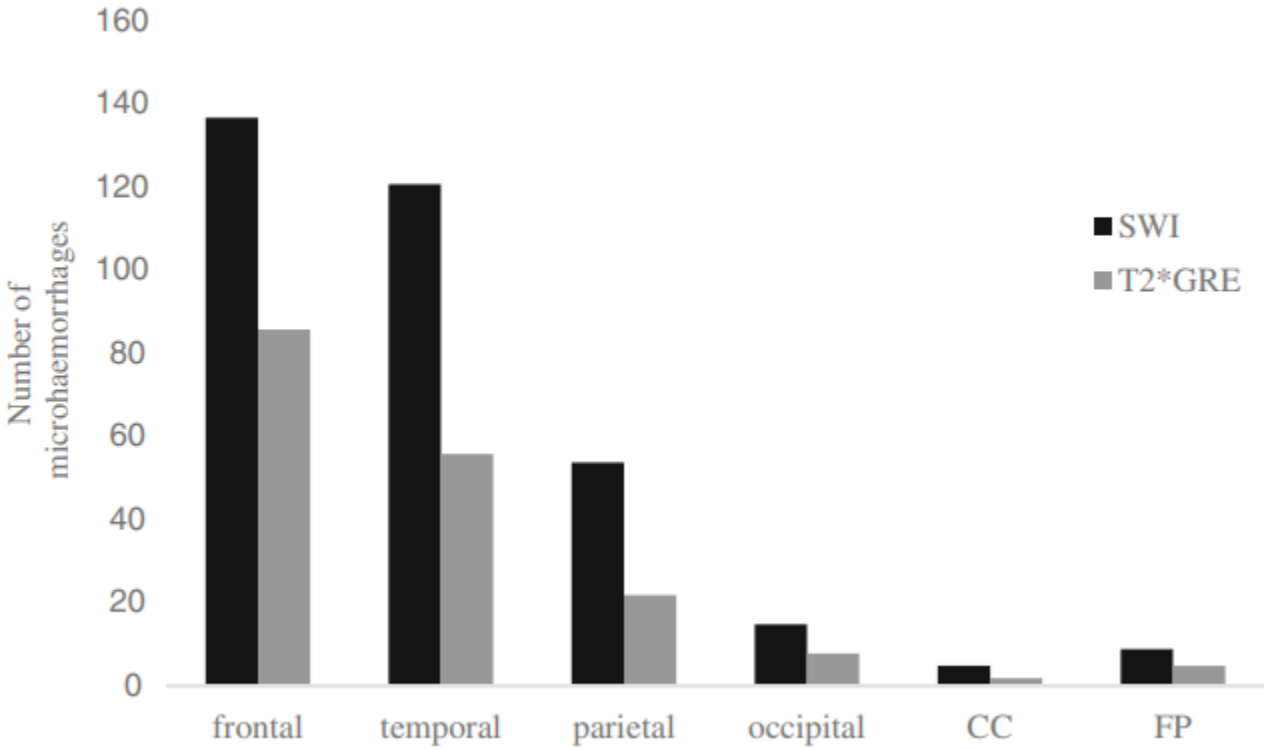
25yo M: HA, dizziness, ringing in ears s/p MVA 6 months ago



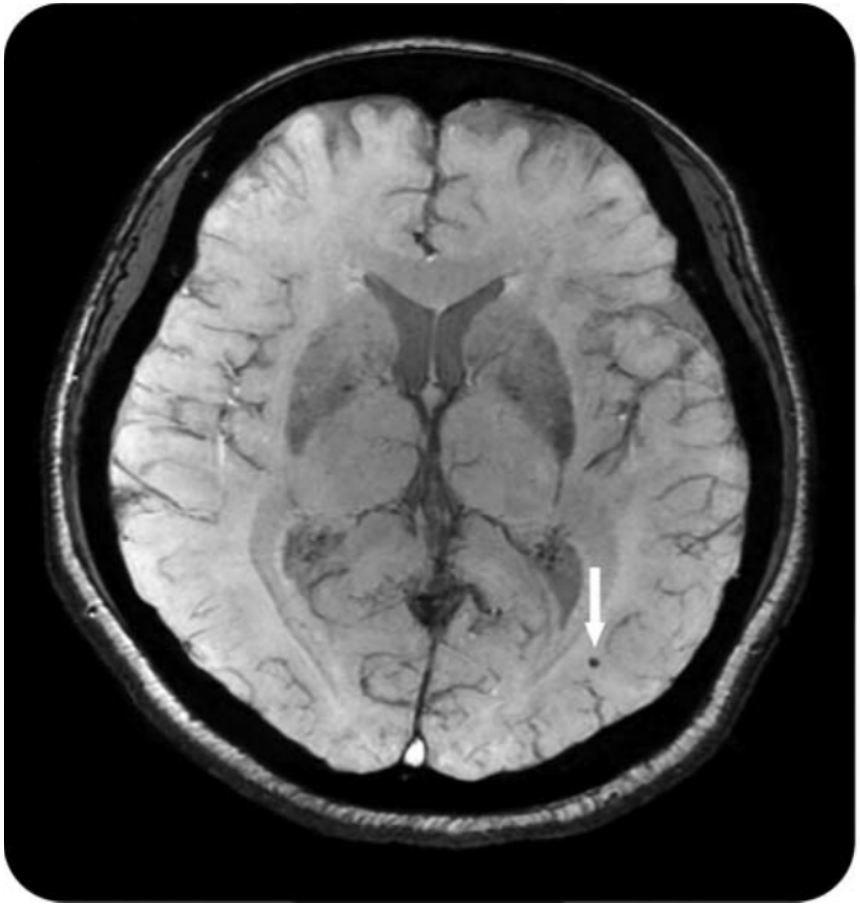
T2 FLAIR SWI

Courtesy of Dr. Yvonne Lui

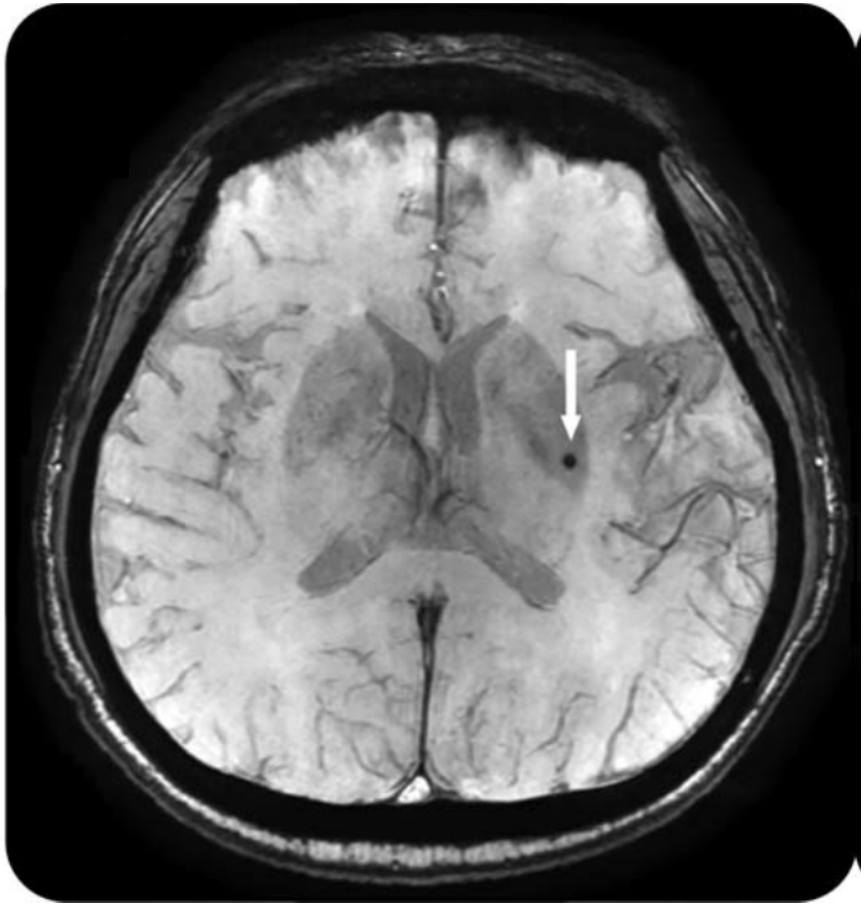
Distribution of CMH on SWI and T2*GRE



Neuroradiology (2017) 59:963–969



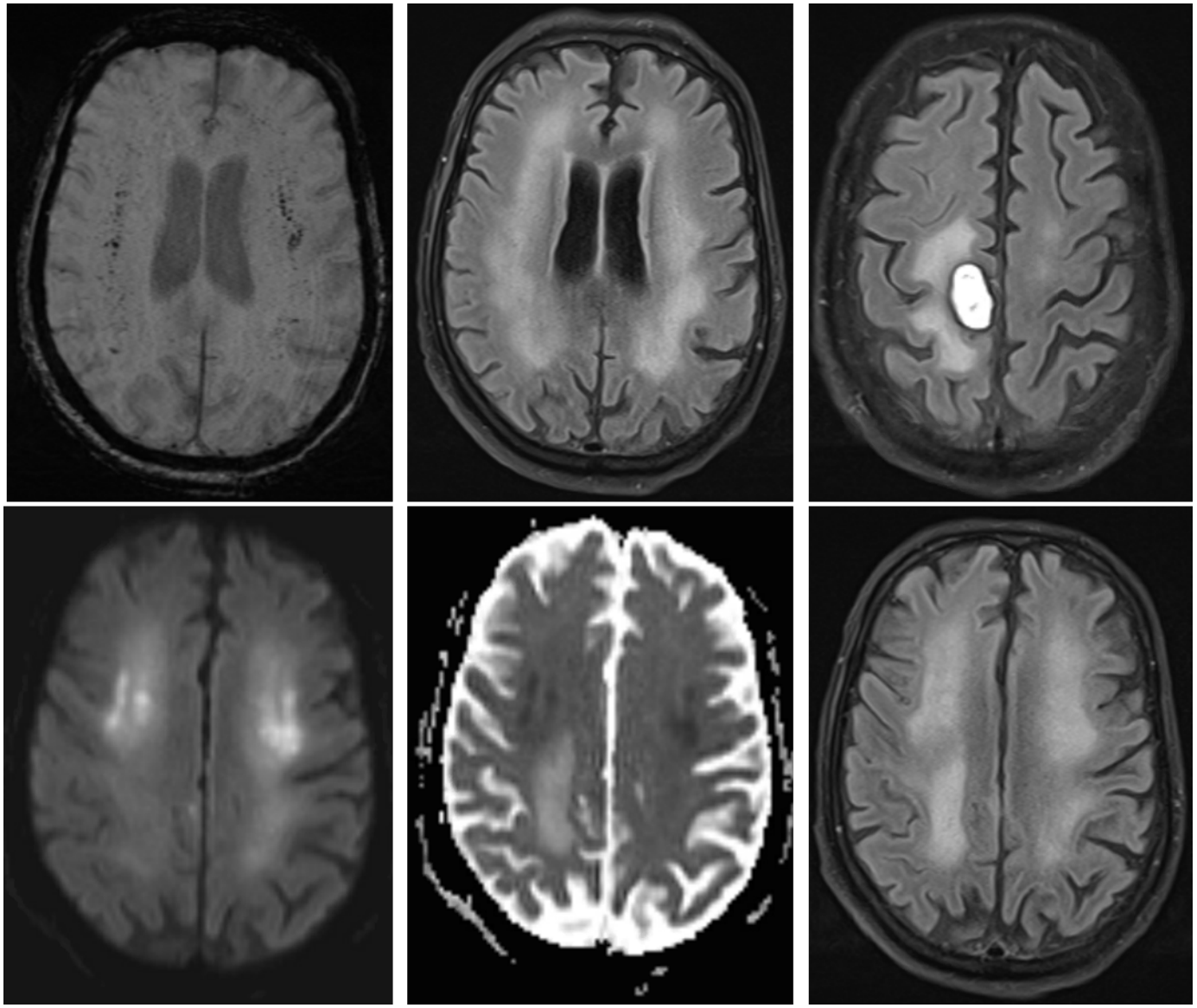
S/P trauma



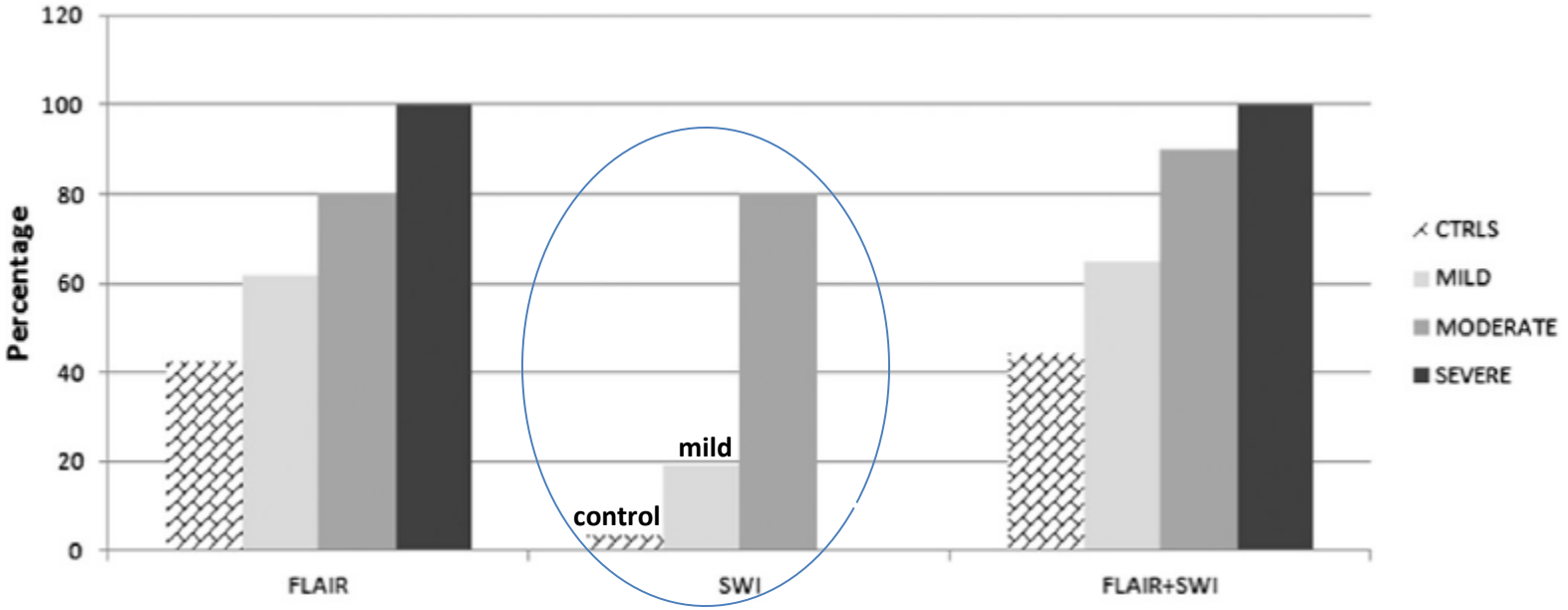
Volunteer

Huang YL, et al. Susceptibility-weighted MRI in mild traumatic brain injury. Neurology. 2015;84:580-585.

61 y.o male with Covid-19



Prevalence of CMH in Blunt mTBI



Lesion findings by imaging modality and severity.

Clinical Severity	FLAIR N	FLAIR (%)	SWI N	SWI (%)	FLAIR + SWI N	FLAIR + SWI (%)
Mild (150)	67	(45)	26	(17)	78	(52)
Moderate (22)	18	(81)	17	(77)	20	(91)
Severe (8)	8	(100)	7	(87.5)	8	(100)

MR imaging findings in mild traumatic brain injury with persistent neurological impairment

Magnetic Resonance Imaging 37 (2017) 243–251

Gabriela Trifan [a], Ramtilak Gattu [b], Ewart Mark Haacke [b,c], Zhifeng Kou [b,c], Randall R. Benson [a,*]

Prevalence of CMH in mTBI

- Prevalence of CMBs in blunt-related mTBI patients is around 20%

Table 3: Prevalence of CMH in civilian and military populations

Authors	Population	Mechanism of mTBI	Prevalence of CMH	Time since mTBI	MRI	Voxel Size (mm)
van der Horn et al (2017)[24]	Civilian	Blunt	15/54 (28%)	33 days	SWI (3T)	0.9 × 0.9 × 2
Trifan et al (2017)[34]	Civilian	Blunt	26/150 (17%)	29 months	SWI (3T)	0.5 × 0.5 × 2
Toth et al (2018)[35]	Civilian	Blunt	1/13 (8%)	2 years	SWI (3T)	1.0 × 0.9 × 1.5
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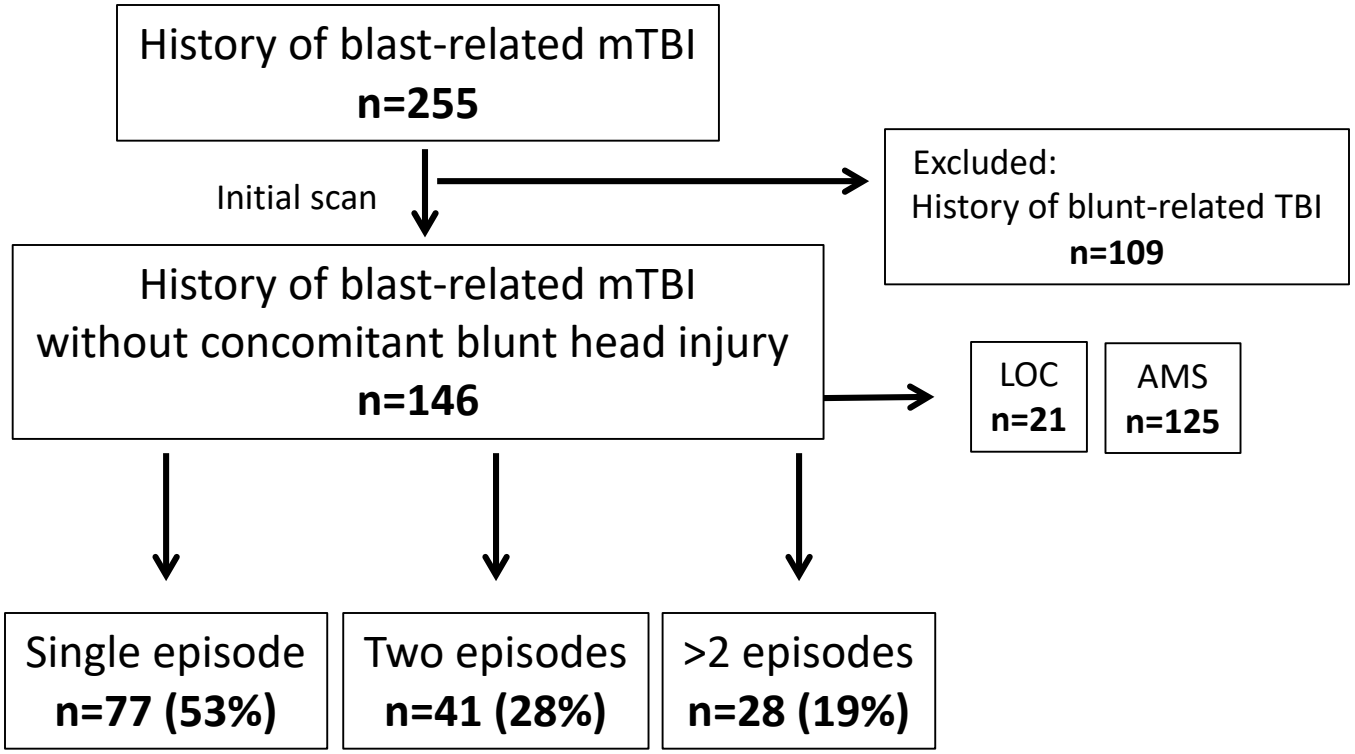
Yuh et al (2013)[21]	Civilian	Blunt	23/98 (23%)	12 days	T2*-weighted GRE (1.5/3T)	NA
Topal et al (2008)[36]	Civilian	Blunt	4/40 (10%)	<1 day	T2*-weighted GRE (1.5T)	NA
Tate et al (2017)[26]	Military members	Mixed blunt and blast	9/77 (12%)	309 days	SWI (3T)	1.0 × 0.9 × 1.5
Liu et al (2016)[25]	Military members	Mixed blunt and blast	18/559 (3%)	1325 days	SWI (3T)	0.5 × 0.9 × 1.5
Riedy et al (2016)[3]	Military members	Mixed blunt and blast	29/768 (4%)	1381 days	SWI (3T)	0.5 × 0.9 × 1.5
Current study (2018)	Military members	Blast	0/146 (0%)	9 years	SWI (3T)	0.5 × 0.6 × 2

Prevalence of Cerebral Microhemorrhage following Chronic Blast-Related Mild Traumatic Brain Injury in Military Service Members Using Susceptibility-Weighted MRI

AJNR Am J Neuroradiol 39:1222–25 Jul 2018
E. Lotan, C. Morley, J. Newman, M. Qian, D. Abu-Amara, C. Marmar, and Y.W. Lui



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No cerebral microhemorrhages were identified in any subject

Possible Explanations

1. Blast mechanism of injury
2. Chronicity of injury

Table 2: Demographic and clinical characteristics ($N = 146$)[a]

Variable	Mean	SD
Time since mTBI (yr)	9.4	6.2
Deployment time (yr)	5.7	3.5
WASI-II IQ (standard score)	106.6	13.3
HIT-6 score	45.8	9.3
CSI	12.5	14.0

Note:—WASI-II indicates Wechsler Adult Intelligence Scale, 2nd ed; IQ, intelligence quotient; HIT-6 = Headache Impact Test-6; CSI = Concussion Symptom Inventory.
[a] The maximum CSI and HTI-6 score is 72, indicating maximum symptom severity.

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Chronicity of injury

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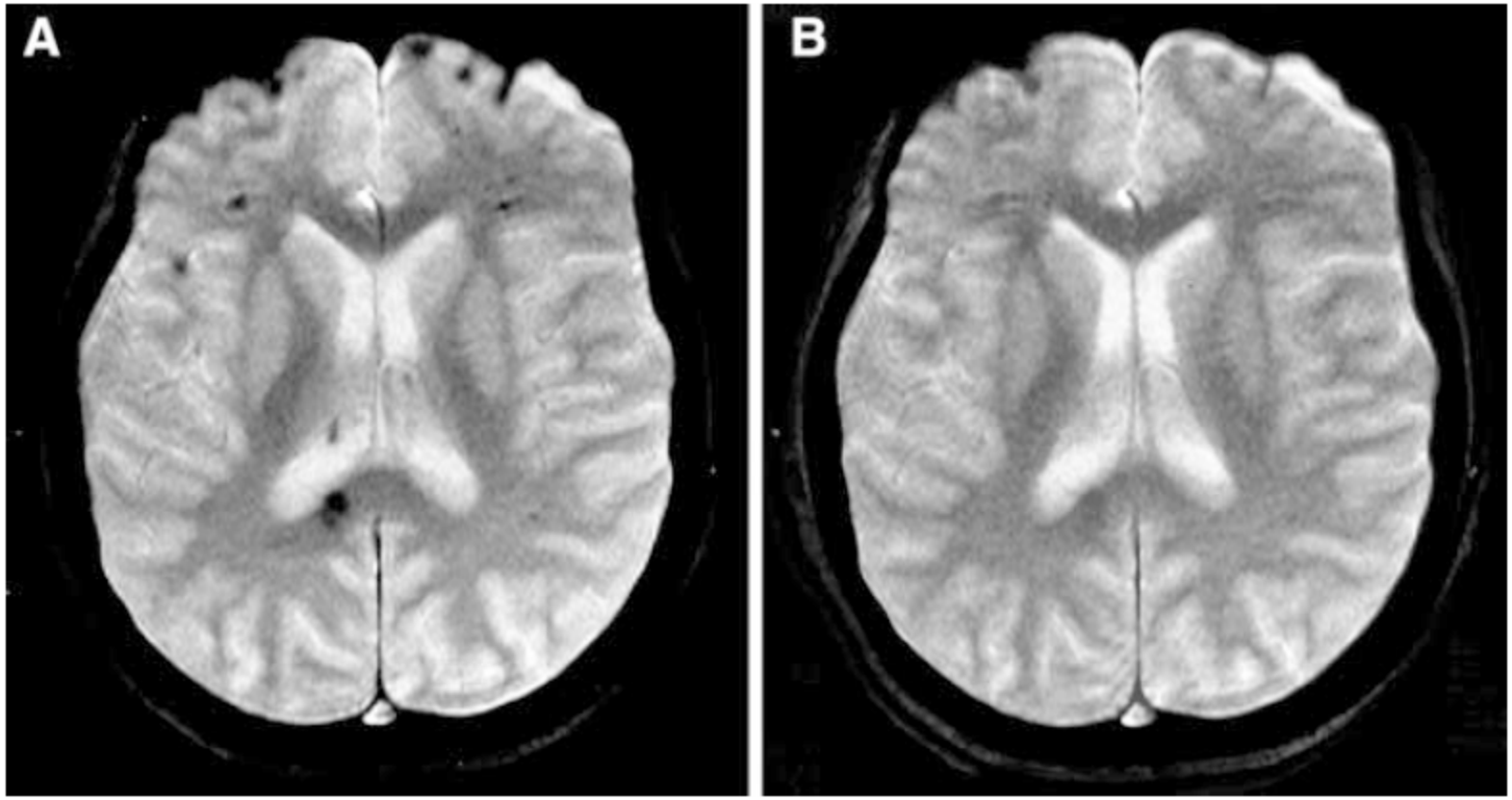
Is haemosiderin visible indefinitely on gradient-echo MRI following traumatic intracerebral haemorrhage?

Neuroradiology (2003) 45: 881–886

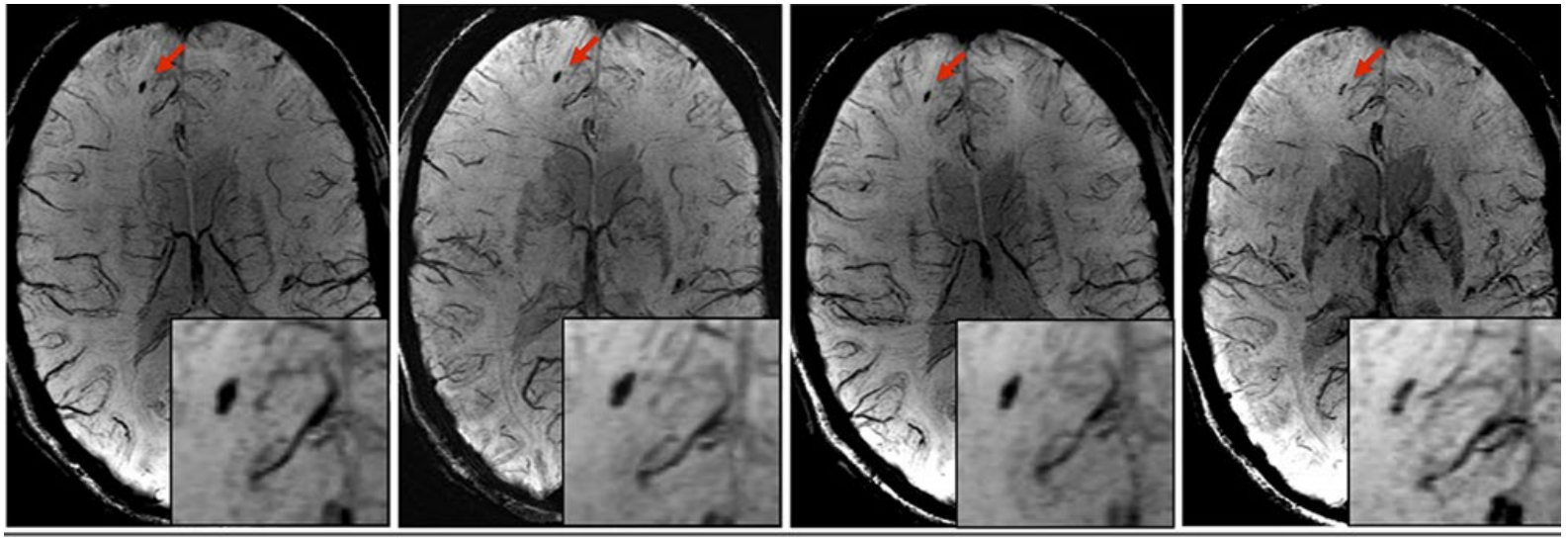
Of 1235 CMH on T2*GRE images at 4– 6 months, 248 (20.1%) were not detected at 24-month

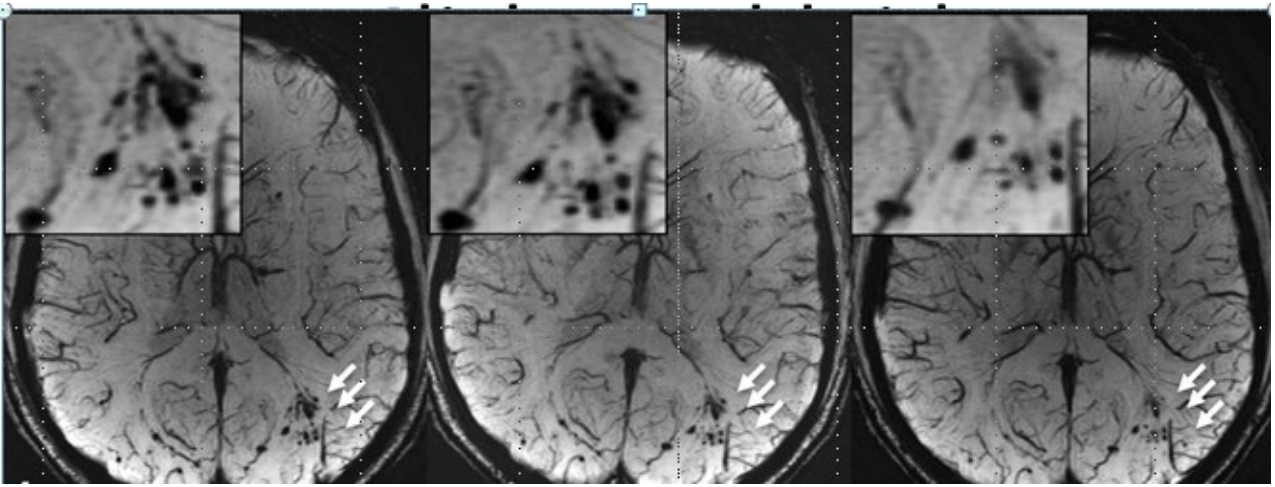


4 months

2 years after trauma

3 months 8 months 12 months 36 months





6 months 12 months 36 months

Time Since Injury	Percentage of Patients with CMH
<3 mo	24.0
3–6 mo	18.4
6–12 mo	7.6
>1 y	5.2
Total	7.1

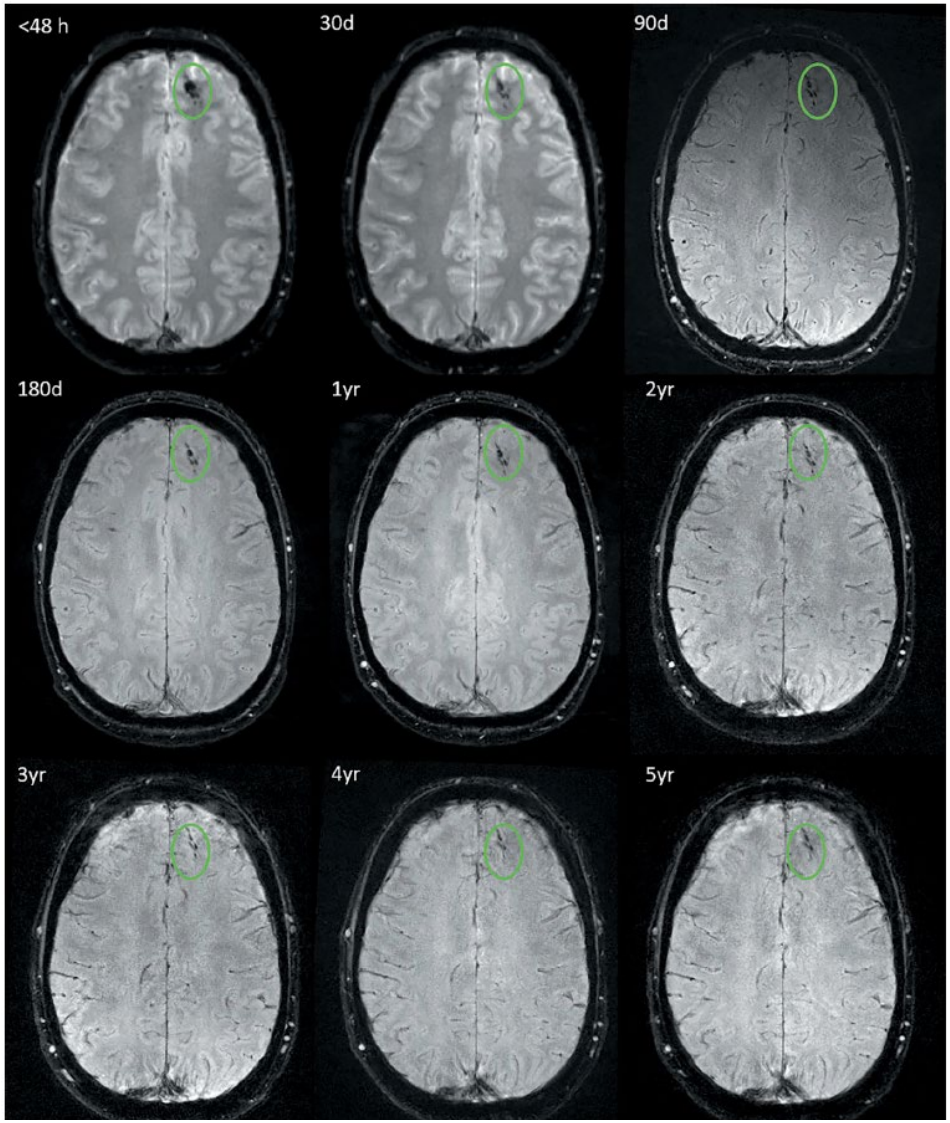
Liu W, Soderlund K, Senseney JS et al. Imaging Cerebral Microhemorrhages in Military Service Members with Chronic Traumatic Brain Injury. Radiology (2015).

Patient No.	Changes in CMH Volume (mm^3 per day)
1	−0.26
2	−2.36
3	−0.57
4	−5.71
5	−0.28
6	−0.24
7	−0.42
8	−0.07
9	−0.11
10	−0.01
11	−0.09
12	−0.84
13	−0.07
Mean*	−0.85 ± 1.59†

Patient No.	No. of CMHs at SWI	
	Baseline	Follow-up
1	6	3
2	18	10
3	14	3
4	73	59
5	4	3
6	14	12
7	14	13
8	7	6
9	1	1
10	13	12
11	2	2
12	45	21
13	15	4
Mean*	17.4 ± 20.1	11.5 ± 15.4‡

Liu W, Soderlund K, Senseney JS et al. Imaging Cerebral Microhemorrhages in Military Service Members with Chronic Traumatic Brain Injury. Radiology (2015).

15 out of 18 patients showed persistent low signal related to microhemorrhage following blunt related TBI over 5 years timespan



Traumatic microbleeds persist for up to five years following traumatic brain injury despite resolution of other acute findings on MRI

Theresa Rizk[a], L. Christine Turtzo[b], Martin Cota[c], Andre J. Van Der Merwe[c], Lawrence Latour[b,c], Mark D. Whiting[c], and Leighton Chan[a,c]

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Conclusions

- CMH is more common finding in patients with TBI at the acute stage and in blunt-related TBI
- Despite the long-standing idea that brain hemosiderin remains in clusters of iron-laden macrophages in perivascular spaces for the long term, there may be evolution of blood products
- The ability to monitor the evolution of microhemorrhages could provide important information regarding disease progression or recovery with implication for patient care

Thank you!!!