EARLY SERUM BIOMARKERS AS PREDICTORS OF BRAIN INJURY ON MRI AND NEURODEVELOPMENTAL OUTCOMES IN NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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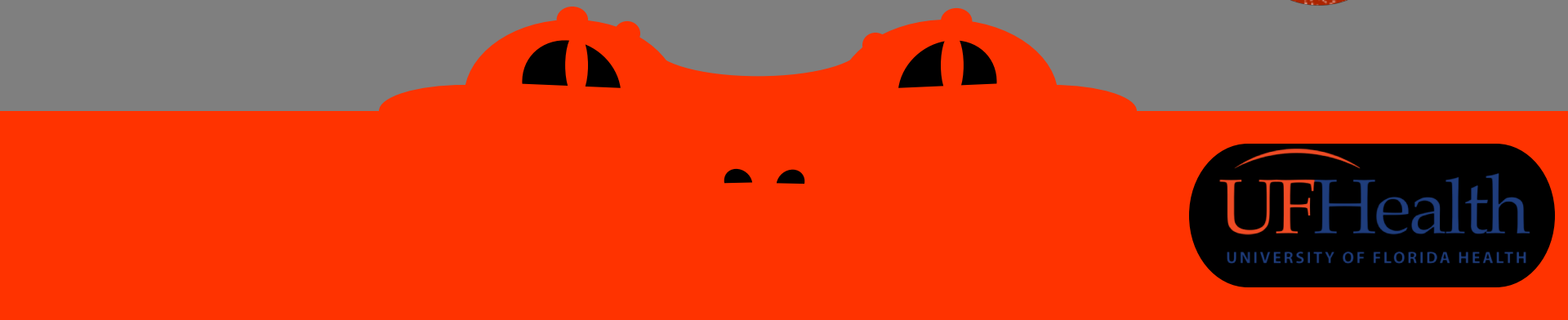

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Hypoxic Ischemic Encephalopathy

"Hypoxic"

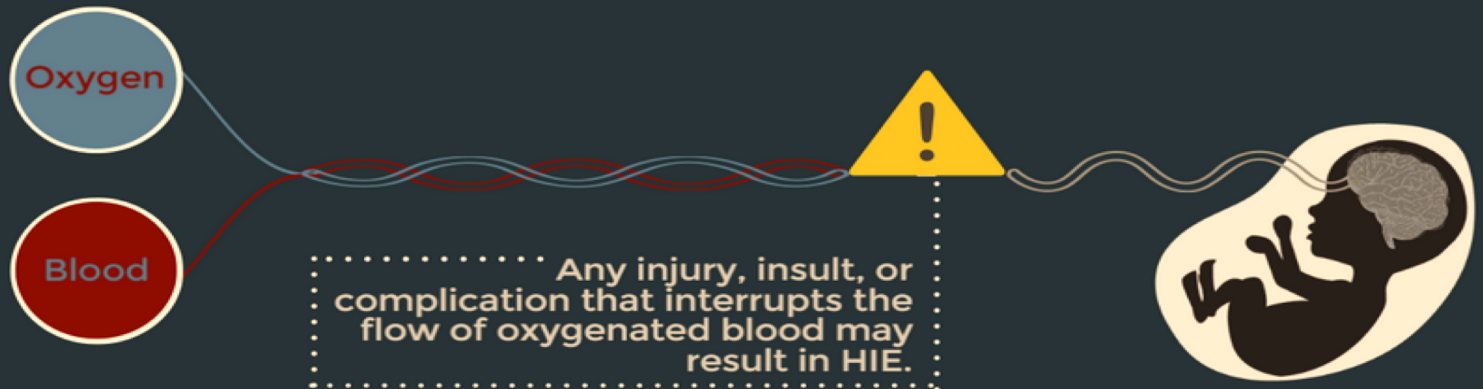
Hypoxia
A shortage of oxygen in the blood

"Ischemic"

Ischemia
A shortage of blood flow to the brain

"Encephalopathy"

The resultant brain damage



HIE BURDEN

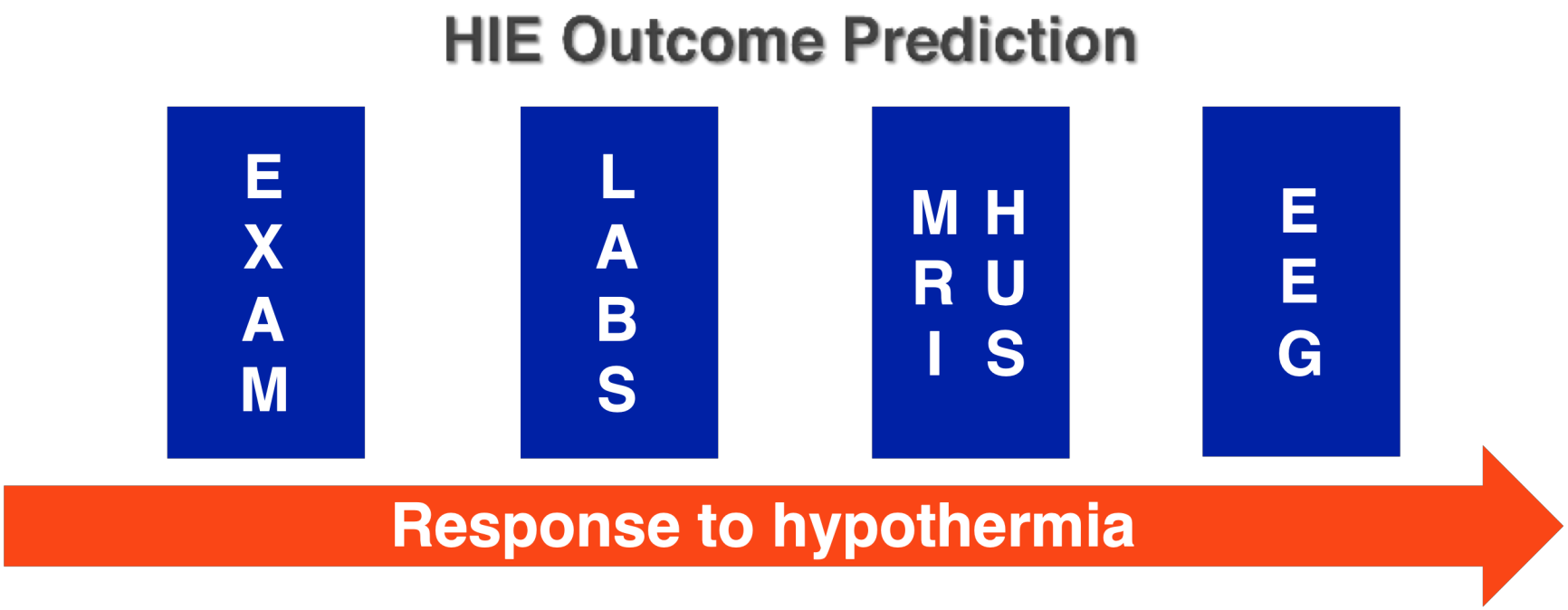
Incidence: 1-8/1,000 in live births

Mortality: 10-60%, morbidity- 25%

High cost: $161,000 per admission (FL)

Therapeutic hypothermia improves neurodevelopmental outcome in **1/8** infants (<6 hours)

TREATMENT/PROGNOSTIC PROBLEM



TREATMENT/PROGNOSTIC PROBLEM

We cannot accurately identify the neonate who will respond to hypothermia versus the non-responder

Barriers: sedatives administered and the effects of hypothermia itself

No objective algorithm for predicting the severity of brain injury and neurodevelopmental outcome

Need for development of simple, rapid, reliable, non-invasive, and objective prognostic tests

STUDY OBJECTIVE

https://hiehelpcenter.org/

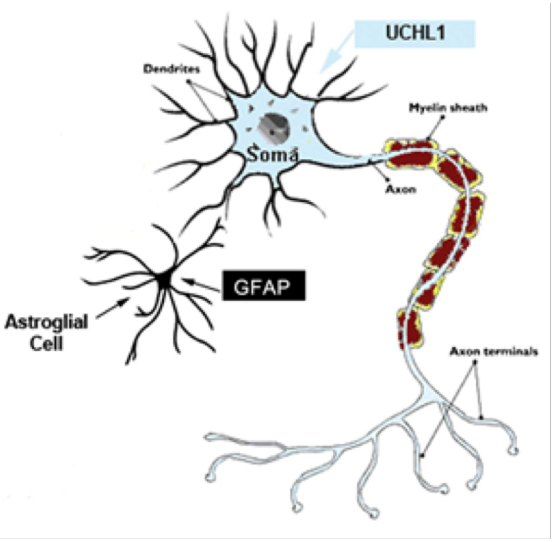
Evaluate associations between 2 serum biomarkers,

MRI injury and neurodevelopmental outcomes in neonates with HIE undergoing hypothermia.

BIOMARKERS

GFAP - type III intermediate filament that forms part of the cytoskeleton of mature astrocytes and other glial cells, not found outside the CNS

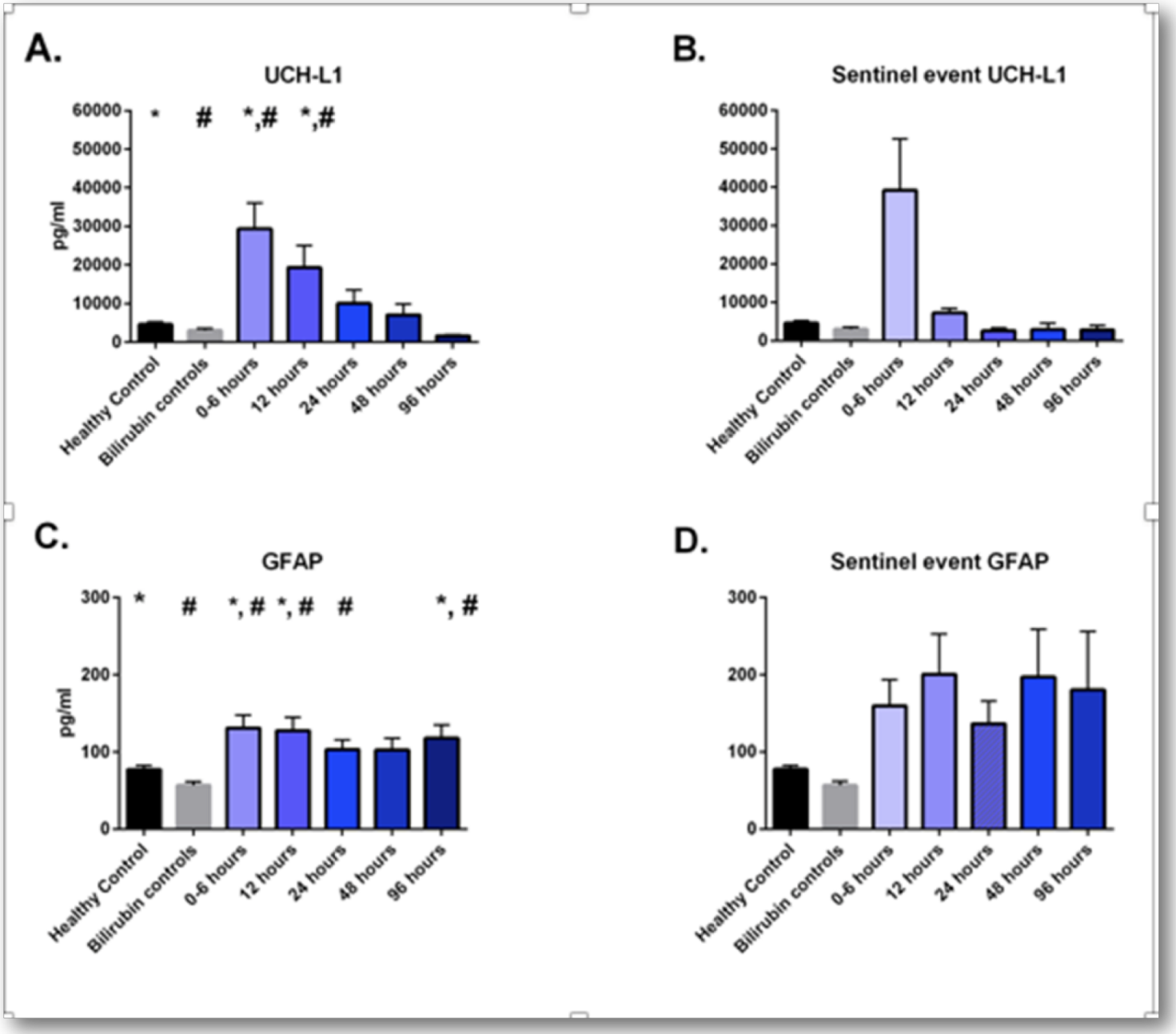
UCH-L1 - highly abundant neuronal protein, critical role in cellular protein degradation during normal and pathological conditions



Both are elevated in neonates with HIE vs controls

Approved by the FDA as diagnostics for mild and moderate TBI in adults

GFAP- biomarker for CNS injury in children s/p ECMO.



Serum UCH-L1 and GFAP serum in healthy and bilirubin controls compared with 40 neonates with HIE (A and C). Neonates with HIE are represented by shades of blue at the various sampling time points (*$p<0.05$, #$p<0.05$). B and D demonstrate the concentration of UCH-L1 and GFAP in neonates with sentinel events.

BIOMARKERS

Lancet Neurol. 2018 Sep;17(9):782-789. doi: 10.1016/S1474-4422(18)30231-X. Epub 2018 Jul 24.

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study.

Bazarian JJ[1], Biberthaler P[2], Welch RD[3], Lewis LM[4], Barzo P[5], Bogner-Flatz V[6], Gunnar Brolinson P[7], Büki A[8], Chen JY[9], Christenson RH[10], Hack D[11], Huff JS[12], Johar S[13], Jordan JD[14], Leidel BA[15], Lindner T[15], Ludington E[16], Okonkwo DO[17], Ornato J[18], Peacock WF[19], Schmidt K[20], Tyndall JA[21], Vossough A[22], Jagoda AS[23].

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Glial Fibrillary Acidic Protein as a Biomarker for Periventricular White Matter Injury

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Linda Papa, MDCM, MSc[1]; Gretchen M. Brophy, PharmD[2,3]; Robert D. Welch, MD, MS[4]; et al

Glial fibrillary acidic protein as a brain injury biomarker in children undergoing extracorporeal membrane oxygenation

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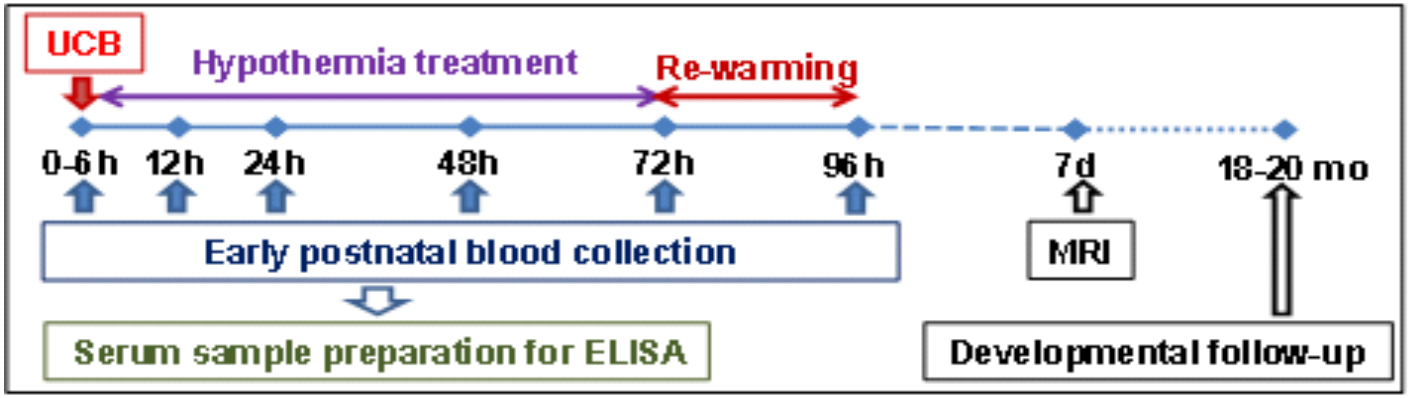
STUDY CRITERIA

Table 1. Inclusion and exclusion criteria

HIE neonates	
Inclusion Criteria	***Exclusion Criteria***
1. Gestational age ≥ 36 weeks **AND** birth weight ≥ 1.8 kg **AND** ≤ 6 hours from insult **AND** 2. Seizures **OR** 3-of-6 of the clinical signs of HIE (Table 1) 3. **ONE OR MORE** of the following predictors of severe HIE: • pH ≤ 7.0 with base deficit ≥16 on arterial blood gas • pH7.01-7.15, base deficit 10-15.9 or no blood gas available and acute perinatal event (cord prolapse, heart rate decelerations, uterine rupture) and either • Apgar score ≤ 5 at 10 min or • Assisted ventilation at birth for ≥10 min	• Lethal chromosomal abnormalities **OR** • Severe intrauterine growth restriction **OR** • Significant intracranial hemorrhage (Grade III or intra-parenchymal echodensity (Grade IV)) • Sepsis evaluation with clinical signs and symptoms consistent with meningitis



MRI was performed between **4-12 days** of age when the individual subjects were stable enough for transport.

3T scanner with a 32-channel head coil. Analysis focused on the T1-weighted, T2-weighted, and diffusion weighted imaging (DWI) abnormalities.

MRIs were interpreted by a single blinded subspecialty board-certified neuroradiologist using the **Barkovich scoring system**

The Barkovich scoring system scores injury in different brain regions using a scale with increasing values representing worsening injury.

Individual brain regions scored: **basal ganglia and thalamus** (BG) (0-4) and the cortex/white matter or **watershed score**(W) (0-5) and finally, a **combined basal ganglia/ watershed** (BG/W) score was also used.

Infants with scores of **0-2** in any region were categorized as no/mild injury and infants with scores **greater than 3** in any region were coded as moderate/severe injury.

The strength of associations between the MRI variables and biomarkers was assessed using logistic regression

METHODS

Analysis focused on ability of UCH-L1 and GFAP to predict moderate/severe brain MRI injury (3 or higher) (n=36)

GFAP/UCH-L1 ratio was examined at 12 hours post birth and compared to the total volume of injury represented as a percent of the total brain on MRI

Bayley III exam was performed between 17-24 months of age (n=20)

Individual developmental domains (motor, cognitive and language) on the Bayley III including were analyzed

Logistic regressions used to relate the binary responses to the biomarkers: good outcome (>85) or a poor outcome (< 85)

BIOMARKERS AND MRI INJURY

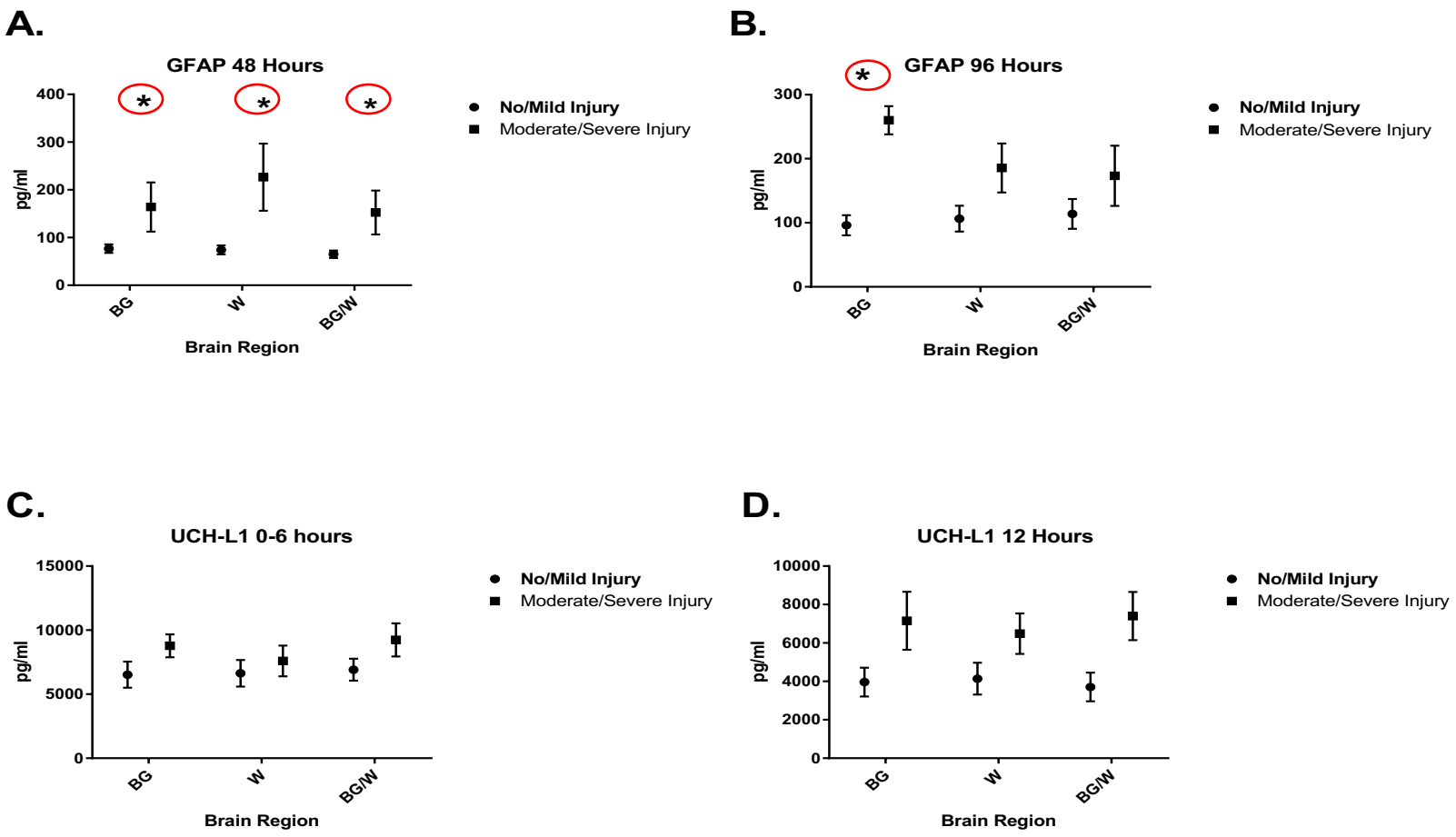


Figure 1. Serum concentrations of UCH-L1 and GFAP compared with the injury score on MRI. The brain regions are basal ganglia (BG), cortex watershed (W) and basal ganglia/white matter (BG/W).

GLIAL/NEURONAL INJURY

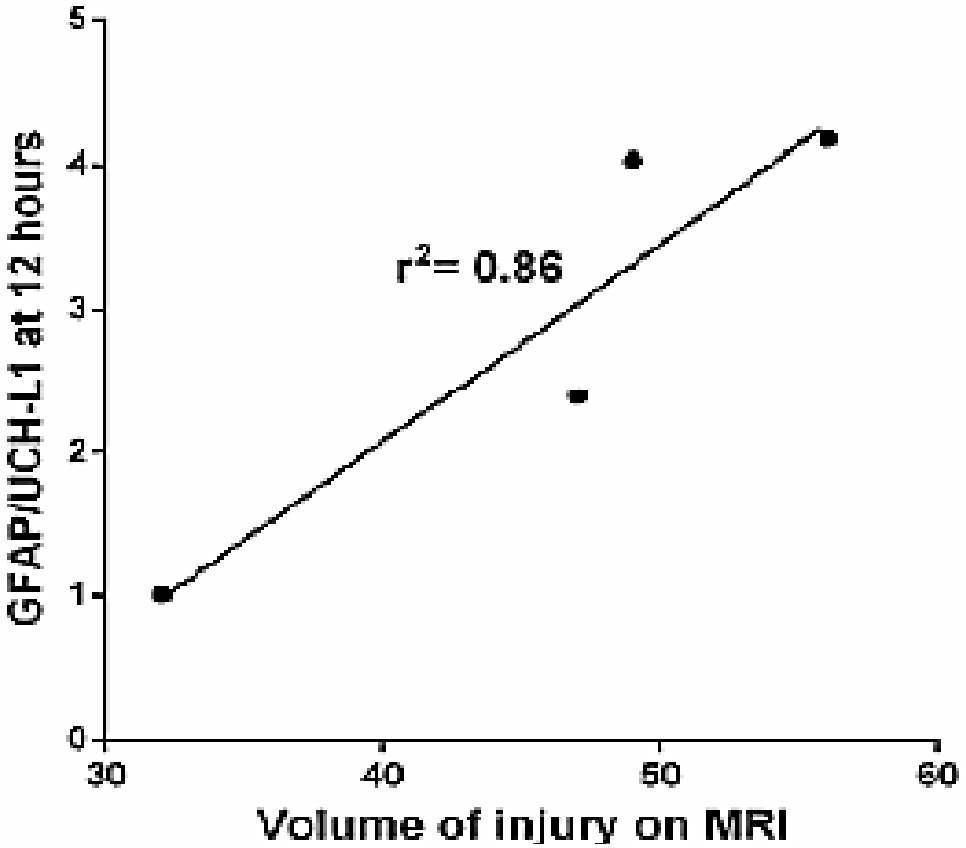


Figure 2. The **GFAP/UCH-L1 ratio** was examined at 12 hours post birth and compared to the total volume of injury represented as a percent of the total brain on MRI.

UCH-L1 AND NEURODEVELOPMENT

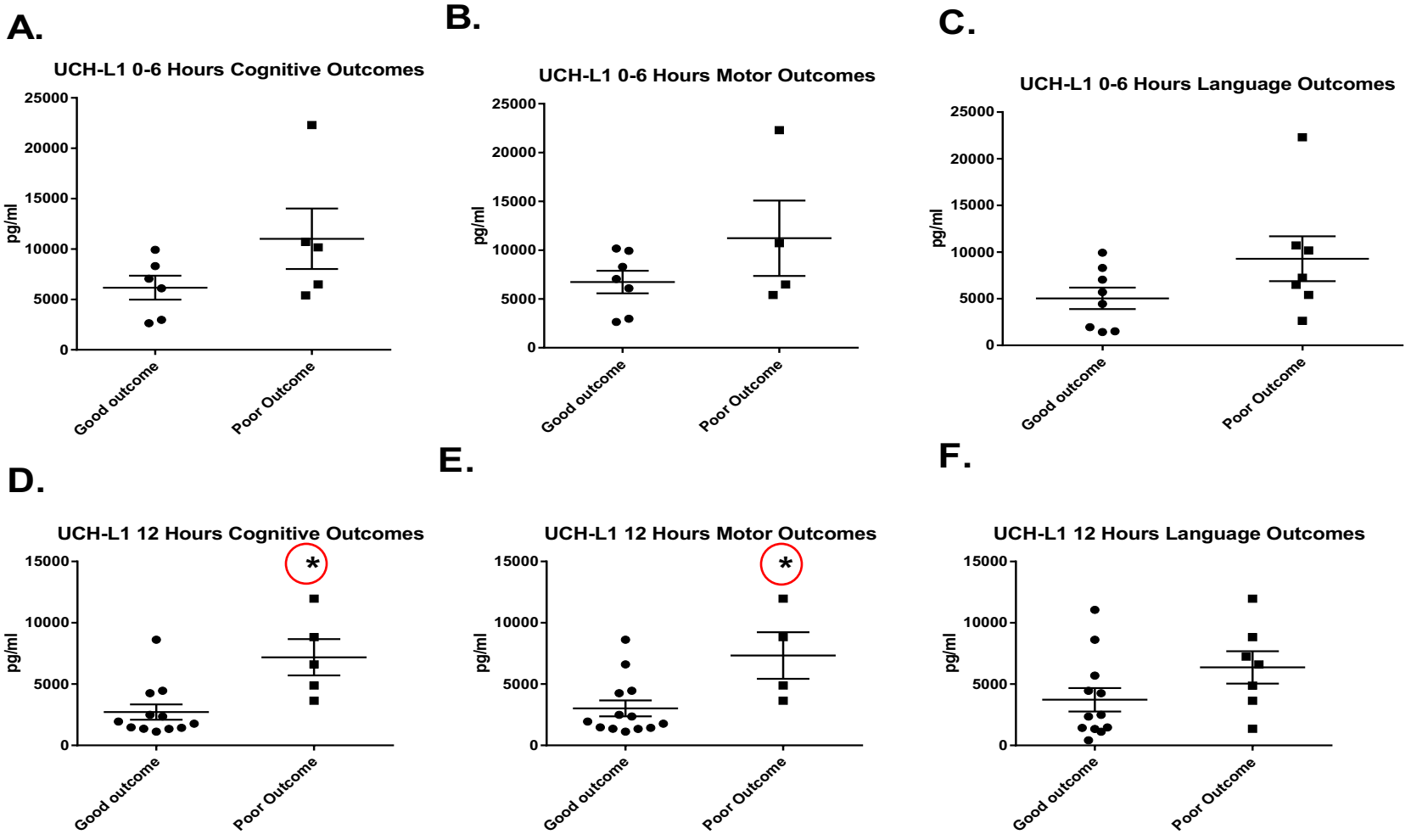


Figure 3. UCH-L1 and Bayley scores at 17-24 months of age.
Trends were noted at 0-6 hours of age with UCH-L1 with higher serum concentrations in neonates with poor outcomes (**Panels A-C**). At 12 hours, increased concentrations of UCH-L1 correlated with poor cognitive and motor outcomes (**Panels D and E**, *$p<0.05$).

GFAP AND NEURODEVELOPMENT

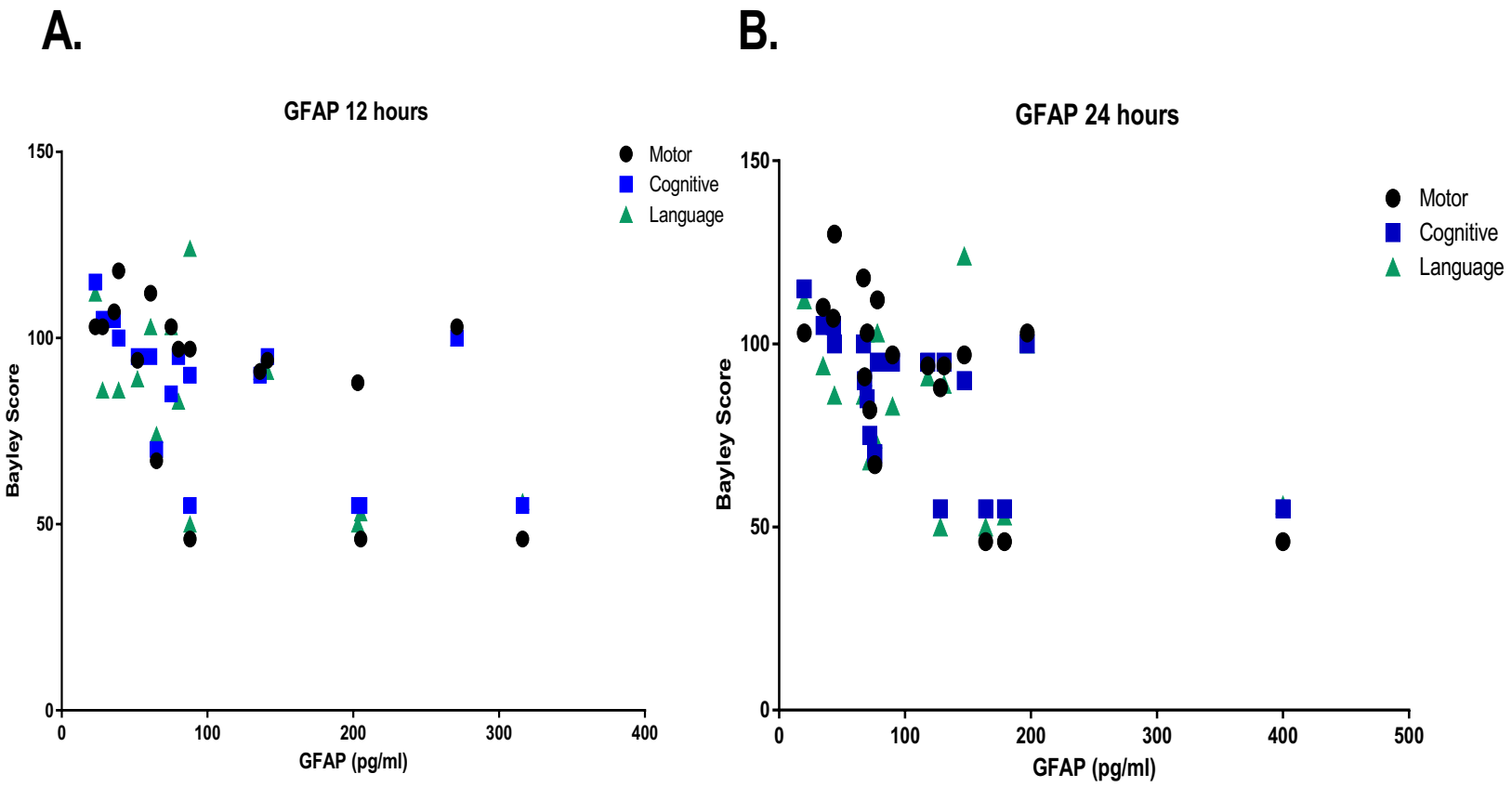


Figure 4. GFAP and Bayley scores at 17-24 months of age.
At 12 (**Panel A**) and 24 hours (**Panel B**) of age, GFAP serum concentrations demonstrated a significant negative correlation with motor, cognitive and language scores on the Bayley III exam ($p<0.05$). (Motor-black circle, Cognition-blue square, Language-green triangle)

CONCLUSIONS

Statistically significant positive association was observed for GFAP and correlations appeared to exist between UCH-L1 and MRI severity of injury

GFAP/UCH-L1 ratio indicated that both neurons and astrocytes are affected in more extensive injury

At 12 hours, increased concentrations of UCH-L1 correlated with poor cognitive and motor outcomes.

GFAP serum concentrations at 12 and 24 hours showed significant negative correlation with motor, cognitive and language scores

Potential to employ a more personalized medical approach for neonates affected by HIE

FUTURE DIRECTIONS

Analyze additional 90 subjects MRIs and compare the results with the biomarker concentrations

Developmental outcomes and therapies used

MRI volumetric analysis, ADC maps

Possible alternatives biomarkers: αll-spectrin breakdown products (SBDPs)-MAP2 and pNF-H

ACKNOWLEDGMENTS

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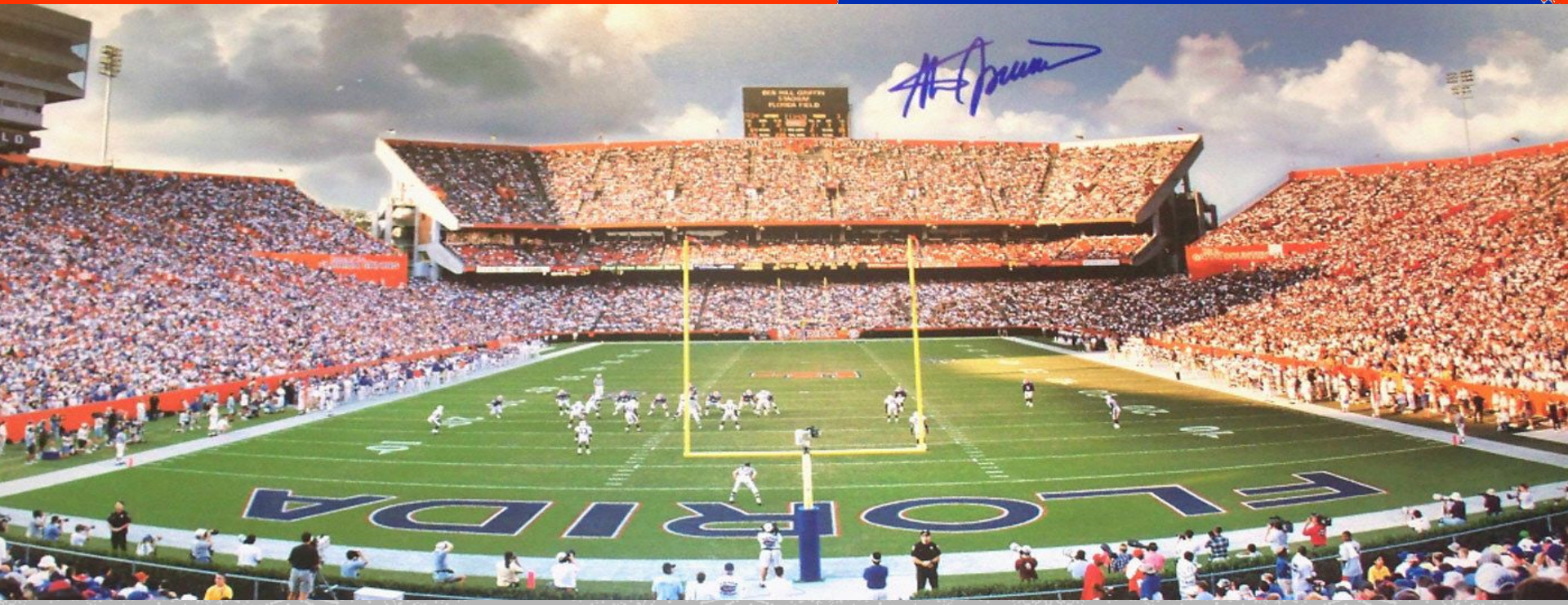

QUESTIONS?