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Original Articles

Age-Related Differences in Diagnostic Accuracy of Plasma Glial Fibrillary Acidic Protein and Tau for Identifying Acute Intracranial Trauma on Computed Tomography: A TRACK-TBI Study

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Abstract

Plasma tau and glial fibrillary acidic protein (GFAP) are promising biomarkers for identifying traumatic brain injury (TBI) patients with intracranial trauma on computed tomography (CT). Accuracy in older adults with mild TBI (mTBI), the fastest growing TBI population, is unknown. Our aim was to assess for age-related differences in diagnostic accuracy of plasma tau and GFAP for identifying intracranial trauma on CT. Samples from 169 patients (age <40 years [$n = 79$], age 40–59 years [$n = 60$], age 60 years+ [$n = 30$]), a subset of patients from the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot study who presented with mTBI (Glasgow Coma Scale score of 13-15), received head CT, and consented to blood draw within 24 h of injury, were assayed for hyperphosphorylated-tau (P-tau), total-tau (T-tau; both via amplification-linked enhanced immunoassay using multi-arrayed fiberoptics), and GFAP (via sandwich enzyme-linked immunosorbent assay). P-tau, T-tau, P-tau:T-tau ratio, and GFAP concentration were significantly associated with CT findings. Overall, discriminative ability declined with increasing age for all assays, but this decline was only statistically significant for GFAP (area under the receiver operating characteristic curve [AUC]: old 0.73 [reference group; ref] vs. young 0.93 [$p = 0.037$] or middle-aged 0.92 [$p = 0.0497$]). P-tau concentration consistently showed the highest diagnostic accuracy across all age-groups (AUC: old 0.84 [ref] vs. young 0.95 [$p = 0.274$] or middle-aged 0.93 [$p = 0.367$]). Comparison of models including P-tau alone versus P-tau plus GFAP revealed significant added value of GFAP. In conclusion, the GFAP assay was less accurate for identifying intracranial trauma on CT among older versus younger mTBI patients. Mechanisms of this age-related difference, including role of assay methodology, specific TBI neuroanatomy, pre-existing conditions, and anti-thrombotic use, warrant further study.

Keywords: biomarkers; CT; geriatric; traumatic brain injury

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Introduction

The highest and fastest rising incidence of traumatic brain injury (TBI)–related emergency department (ED) visits, hospitalizations, and deaths occur in older adults, largely due to low-level falls.[1] The vast majority of these injuries are classified as mild TBI (mTBI).[2] Among older adults presenting to EDs with mTBI and Glasgow Coma Scale (GCS) score of 13–15, up to 21% are found to have traumatic intracranial lesions on head computed tomography (CT), compared with only 5% of younger adults.[3–6] This surprisingly high prevalence of trauma-related CT findings is hypothesized to be due to aging-related changes in vessels and white matter rendering these structures more vulnerable to injury, attenuation of injury response mechanisms, weakening of musculature so that even low-level falls cannot be effectively braced by the body, and the increasing prevalence of anti-thrombotic use with increasing age.[7–9] While most current guidelines recommend head CT for all patients age >60 or >65 years presenting to an ED with mTBI,[4–6,10,11] older age is associated with longer delays in obtaining a head CT even after arrival to an ED.[12] In the pre-hospital setting, older adults are at high risk for being inappropriately triaged away from trauma centers,[13] leading to delays in definitive care and worse outcomes.[14,15] There is an urgent need for blood-based biomarkers, akin to a troponin level for the diagnosis of myocardial infarction, to aid in the rapid and reliable diagnosis of TBI in patients across the age spectrum.[16,17] In older adults, such a blood-based biomarker would be critical both in the pre-hospital setting to ensure appropriate triage to a trauma center, as well as in the hospital setting to identify patients in need of expedited head CTs and possible neurosurgical management.

Use of blood-based TBI biomarkers in the large and growing geriatric TBI population, however, requires further dedicated study: the neurobiological response to TBI may differ substantially in older versus younger patients due to all of the aging-related changes cited above, differences in the types of neurotrauma sustained,[18] and higher prevalence of medical and neurological comorbidities in older versus younger patients.[19] For example, 11% of adults admitted to hospitals for TBI have been found to have a pre-existing diagnosis of dementia.[19] These age-related differences, especially the higher prevalence of neurodegeneration, may lead to elevations in brain injury biomarkers at baseline, thus rendering these biomarkers less specific for TBI in older patients. To date, only one prior study has investigated the accuracy of a plasma proteomic biomarker for the diagnosis of TBI specifically in older adults.[20] This study reported that plasma S100B measured within 3 h of TBI was less specific for traumatic intracranial lesions on CT among older versus younger adults.[20]

Glial fibrillary acidic protein (GFAP) and its breakdown products (BDPs), hyperphosphorylated tau protein (P-tau), and the P-tau:total-tau (T-tau) ratio have shown great promise in distinguishing TBI patients with versus without CT evidence of intracranial trauma in studies that have pooled patients of all ages.[21–26] GFAP is an intermediate filament protein found in astrocyte cytoskeleton predominantly in the central nervous system. Following astrocyte injury, the normally insoluble GFAP is degraded into soluble GFAP-BDP (as a result of calpain activation), enters the interstitial fluid, is elevated in blood following TBI,[23] and can accurately identify TBI patients with trauma-related CT findings (area under the receiver operating curve [AUC] 0.79-0.88),[21–23,25] including in our prior studies of GFAP in pooled analyses of Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot study participants across the spectrum of age and TBI severity.[23,25] Tau protein is a microtubule associated protein found in neuronal axons. Abnormal accumulation and aggregation of tau has been identified neuropathologically in victims of severe TBI[27] as well as in several neurodegenerative tauopathies including Alzheimer's disease, in which it forms flame-shaped intraneuronal neurofibrillary tangles.[28] Elevations in various tau fragments have been identified in cerebrospinal fluid of patients with severe TBI[29] and in blood of concussed hockey players.[30] A unique pattern of P-tau accumulation is a pathological feature of chronic traumatic encephalopathy, a neurodegenerative disease associated with repetitive mTBI and sub-concussive head impacts.[31] Recently, Rubenstein and colleagues have shown that plasma P-tau and P-tau:T-tau ratio, but not T-tau alone, are highly sensitive and specific for distinguishing TBI patients with versus without CT findings (AUC P-tau 0.92, T-tau 0.65, P-tau:T-tau ratio 0.92) in a pooled cohort of patients across the spectrum of age and TBI severity from the TRACK-TBI Pilot study.[26]

The performance of these acute TBI blood biomarkers specifically in older adults presenting with TBI and a GCS score of 13-15—the population who may be at highest risk for clinically silent intracranial trauma—is unknown.

Our aim in this study was to determine whether there are age-related differences in the diagnostic accuracy of GFAP and tau (P-tau, T-tau, and P-tau:T-tau ratio) for discriminating between mTBI (GCS score 13-15) patients with versus without CT evidence of intracranial trauma.

Methods

Study design, data source, and patient population

This is a cross-sectional cohort study using prospectively collected data from the TRACK-TBI Pilot study. The TRACK-TBI Pilot study protocol has been previously described in detail.[32] Briefly, the TRACK-TBI Pilot study was a prospective observational cohort study that enrolled 586 patients with TBI across the spectrum of age and TBI severity who presented to the emergency department (ED) of one of the three participating Level 1 trauma centers within 24 h of head trauma sufficient to warrant evaluation with a non-contrast head CT according to the American College of Emergency Physicians (ACEP)/Centers for Disease Control and Prevention (CDC) evidence-based joint practice guidelines.[33] Patients underwent extensive baseline assessments using National Institute for Neurological Disorders and Stroke TBI Common Data Elements (CDEs).[34] Additional inclusion criteria for TRACK-TBI Pilot included age 16 years and older and ability to provide informed consent either independently or via a proxy. Patients were excluded if they were non-English speaking, pregnant, in custody, undergoing psychiatric evaluation, had contraindications to magnetic resonance imaging (MRI), or had pre-existing medical or neurological conditions that would interfere with evaluation of TBI (such as pre-existing dementia or severe psychiatric illness). All patients or their legal authorized proxies provided written informed consent.

Of note, while TRACK-TBI Pilot enrolled 586 patients, only 183 patients had sufficient quantity of blood drawn within 24 hours of injury for measurement of the proteomic biomarkers analyzed in this study. Of these 183 patients, 169 presented with a GCS score of 13-15 and 14 ($n = 7$ age <40 years; $n = 5$ age 40–59 years; $n = 2$ age 60 years+) presented with a GCS score ≤12. Given the small number of patients with moderate-to-severe TBI (defined as a GCS score ≤12) that would have precluded investigation of the role of TBI severity on the performance of these proteomic biomarkers as well as our stated aim to investigate the performance of these assays in the population at highest risk for inappropriate triage and delays in care (e.g., older adults presenting with a GCS score of 13-15), we

excluded the 14 TRACK-TBI Pilot patients who presented with a GCS score ≤12 who otherwise had analyzable proteomic biomarker data. Thus, for the present analysis, a sub-set of TRACK-TBI Pilot participants were included if they: 1) presented with mTBI defined as a GCS score of 13-15 upon arrival to the ED; 2) consented to blood draw; and 3) had sufficient quantity of blood drawn within 24 h of injury for the measurement of the proteomic biomarkers analyzed in this study ($n = 169$). Compared with the 417 TRACK-TBI Pilot patients excluded from this study, the patients included in this study did not significantly differ in age, education, sex, race, or ethnicity. This study was approved by the University of California San Francisco committee for human research.

Baseline demographics and pre-existing medical conditions

Data about baseline patient characteristics were collected from the patient or proxy via a medical interview and chart review. These data included: patient age, years of education, sex, race, ethnicity, and baseline medical comorbidities (prior history of TBI before incident TBI, cardiovascular disease, cerebrovascular disease, diabetes, tobacco use, alcohol use, illicit drug use, depression/anxiety).

Characterization of TBI

GCS score was determined by a physician upon arrival to the ED. Additional details about mechanism of injury and whether the patient required a neurosurgical procedure while in the hospital were recorded by trained study staff in the ED via patient or proxy interview and chart review.

Head CT

A single board-certified neuroradiologist (ELY), blinded to demographic, socioeconomic, and clinical data (except age and sex), reviewed each head CT and scored evidence of acute intracranial trauma according to expert consensus recommendations of the TBI CDE Neuroimaging Working Group.[35] For this study, evidence of acute intracranial trauma (i.e., CT+) was defined as presence of at least one of the following: epidural hemorrhage (EDH), subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), brain contusion, intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), traumatic or diffuse axonal injury (TAI/DAI), midline shift >5 mm, partial or complete effacement of basal cisterns, or cerebral edema. CT- was defined as having none of these aforementioned findings. Additionally, intra-parenchymal injury was defined as contusion, ICH, TAI/DAI, or edema; extra-parenchymal injury, as EDH, SDH, SAH, or IVH.

Plasma assays

All blood samples were obtained within 24 h of injury. Details of sample collection, storage, and GFAP and tau assay performance have been described previously in detail.[23,26] Briefly, sample collection and storage at each site were performed according to the TBI CDE Biospecimens and Biomarkers Working Group Guidelines.[36] Whole blood was collected into K2-EDTA blood tubes. Plasma was extracted after centrifugation for 5 min at 3000 g, pipetted into 0.5-1.0 mL aliquots in polypropylene tubes, and stored at -80°C until they were shipped overnight via courier service to the biomarker analysis site. All samples were de-identified and thus all assays were performed blinded to patient characteristics and head CT findings.

P-tau and T-tau levels in each sample were assayed in triplicate via enhanced immunoassay using multi-arrayed fiberoptics (EIMAF) conjugated with rolling circle amplification (a-EIMAF) as described previously in detail by Rubenstein and colleagues.[26] Intra-assay coefficient of variation (CV) for P-tau and T-tau were 3.5% and 5.5%, respectively. Inter-assay CV for P-tau and T-tau were 7.0% and 5.2%, respectively. Lower limit of detection (LLOD) for P-tau and T-tau are 0.00001 fg/mL and 0.0001 fg/mL, respectively. GFAP level in each sample was measured in duplicate using a sandwich enzyme-linked immunosorbent assay to GFAP-BDP that detected both whole GFAP molecules and GFAP-BDPs, thereby achieving a more complete measure of circulating GFAP levels[37] as previously described in detail by Okonkwo and colleagues.[23] Intra-assay CV for GFAP was 4.3-7.8%. Inter-assay CV for GFAP was 7.8-14.3%. Estimated LLOD for GFAP was 0.10 ng/mL; samples with undetectable levels were assigned a value of 0.03 ng/mL.[23,25]

Statistical analysis

Analyses were conducted using Stata 15. Patients were categorized as young (age <40 years), middle-aged (age 40–59 years), or older (age 60 years+). The definition of ''older adult'' varies widely in the published literature. We chose to define older adult as those age ≥60 years, rather than ≥65 years because there were only 16 patients age ≥65 years in our cohort.

Baseline demographics, pre-existing conditions (including prior TBI and anticoagulant use), TBI characteristics, and CT findings (e.g., acute intracranial trauma) were compared across age categories using summary statistics including chi-squared tests for categorical variables and analysis of variance for continuous variables. P-tau, T-tau, P-tau:T-tau ratio, and GFAP were not normally distributed. Correlations between assays were assessed using Spearman rank-order correlations, comparisons of assay levels across the three age categories were conducted using tests of trend, and comparisons of assay levels by CT findings were conducted using the non-parametric Mann-Whitney test. We used linear regression to assess for an association between each assay and age in both unadjusted models and models adjusted for CT findings and time from injury to blood draw.

We used logistic regression to assess the association of each assay with CT findings in the entire cohort. We determined whether an interaction with age category was present. We visualized receiver operating characteristic (ROC) curves for diagnostic accuracy of each assay individually, and of the tau assay with highest accuracy (by AUC) plus GFAP in combination, to identify CT findings by age category. We used chi-squared tests to assess for statistically significant differences in the AUC by age category. Based on the ROC curve for each assay for the entire pooled cohort, we identified the point on the ROC curve nearest to the point with perfect sensitivity and specificity [0,1] in order to estimate an optimal cut point for each plasma assay to discriminate patients with versus without intracranial trauma on CT. For each cut-point, 95% confidence intervals (CIs) were estimated using 100 bootstrap samples. We then determined the sensitivity and specificity of the identified optimal cut-point for each assay for diagnosis of CT findings for patients in each age category. Statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics, TBI characteristics, and CT findings of patients by age category are shown in Table 1. Age categories significantly differed on employment status and prevalence of cardiac disease, diabetes, developmental disorders, and anticoagulant use. While GCS score did not significantly differ across age categories, older adults had the highest prevalence of CT findings (especially SDH and SAH) and the highest prevalence of intensive care unit and stepdown admission. While all samples were collected less than 24 h post-injury, the time between injury and blood draw was longest among older patients.

Using Spearman rank-order correlations, a significant positive correlation was identified between all assays except T-tau vs. P-

Table 1. Characteristics of Patients by Age Category

Mean ± SD (range) or n (%)	*Young (< 40 years)* n = *79*	*Middle-aged (40–59 years)* n = *60*	*Older (60 years +)* n = *30*	p
Demographics				
Age	25.8 ± 7.3 (16–39)	50.0 ± 5.9 (40–59)	68.0 ± 8.4 (60–93)	< 0.001
Female	21 (26.6)	20 (33.3)	11 (36.7)	0.516
Race				0.091
White	62 (78.5)	47 (78.3)	29 (96.7)	
Black	7 (8.9)	8 (13.3)	0 (0.0)	
Asian	5 (6.3)	2 (3.3)	0 (0.0)	
Other/unknown	5 (6.3)	3 (5.0)	1 (3.3)	
Hispanic	19 (24.1)	8 (13.3)	2 (6.7)	0.061
Education (years)	13.4 ± 2.9 (6–22)	14.0 ± 2.6 (8–20)	13.6 ± 2.9 (6–19)	0.373
Employment				< 0.001
Full-time	27 (34.2)	35 (58.3)	7 (23.3)	
Part-time	14 (17.7)	6 (10.0)	2 (6.7)	
Temporary	3 (3.8)	4 (6.7)	0 (0.0)	
Unemployed	24 (30.4)	10 (16.7)	1 (3.3)	
Unpaid	7 (8.9)	5 (8.3)	18 (60.0)	
Other/unknown	4 (5.1)	0 (0.0)	2 (6.7)	
Pre-existing conditions				
Prior TBI	46 (58.2)	26 (43.3)	13 (43.3)	0.155
Epilepsy	8 (10.1)	5 (8.3)	3 (10.0)	0.932
Migraine/headache	10 (12.7)	8 (13.3)	2 (6.7)	0.622
Psychiatric disease	22 (27.9)	22 (36.7)	7 (23.3)	0.355
Developmental disorder	15 (19.0)	4 (6.7)	0 (0.0)	0.007
Cardiac disease	7 (8.9)	19 (31.7)	20 (66.7)	< 0.001
Diabetes	1 (1.3)	3 (5.0)	8 (26.7)	< 0.001
Pulmonary disease	14 (17.7)	7 (11.7)	8 (26.7)	0.202
Anticoagulant medication	1 (1.3)	7 (11.7)	17 (56.7)	< 0.001
TBI features				
GCS				0.249
13	2 (2.5)	0 (0.0)	0 (0.0)	
14	16 (20.3)	10 (16.7)	2 (6.7)	
15	61 (77.2)	50 (83.3)	28 (93.3)	
Injury mechanism				< 0.001
Car	24 (30.4)	11 (18.3)	5 (16.7)	
Motorcycle	3 (3.8)	4 (6.7)	0 (0.0)	
Cyclist/pedestrian	15 (19.0)	14 (23.3)	1 (3.3)	
Fall	16 (20.3)	23 (38.3)	22 (73.3)	
Assault	17 (21.5)	6 (10.0)	0 (0.0)	
Struck by	2 (2.5)	2 (3.3)	1 (3.3)	
Other/unknown	2 (2.5)	0 (0.0)	1 (3.3)	
ED disposition				0.003
Discharge home	46 (58.2)	25 (41.7)	5 (16.7)	
Ward admission	12 (15.2)	9 (15.0)	3 (10.0)	
Stepdown admission	12 (15.2)	13 (21.7)	10 (33.3)	
ICU admission	8 (10.1)	12 (20.0)	12 (40.0)	
OR	1 (1.3)	1 (1.7)	0 (0.0)	
Neuro procedure	2 (2.5)	2 (3.3)	0 (0.0)	0.613
CT features				
Intracranial trauma				< 0.001
None	61 (77.2)	40 (66.7)	12 (40.0)	
Extra-parenchymal only	1 (1.3)	3 (5.0)	9 (30.0)	
Intra-parenchymal only	7 (8.9)	7 (11.7)	7 (23.3)	
Both	10 (12.7)	10 (16.7)	2 (6.7)	
EDH	4 (5.1)	3 (5.0)	0 (0.0)	0.455
SDH	8 (10.1)	12 (20.0)	11 (36.7)	0.006
SAH	8 (10.1)	13 (21.7)	10 (33.3)	0.014
IVH	1 (1.3)	0 (0.0)	2 (6.7)	0.070
Contusion	11 (13.9)	13 (21.7)	3 (10.0)	0.287
ICH	0 (0.0)	1 (1.7)	1 (3.3)	0.324
TAI/DAI	5 (6.3)	3 (5.0)	6 (20.0)	0.036
Edema	7 (8.9)	8 (13.3)	1 (3.3)	0.302
Sample collection				
Sample collection hours post-injury	8.6 ± 5.6 (1.0–23.9)	10.8 ± 6.9 (0.5–23.5)	13.6 ± 6.8 (2.1–23.5)	0.001

SD, standard deviation; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ED, emergency department; ICU, intensive care unit; OR, operating room; CT, computed tomography; EDH, epidural hemorrhage; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; TAI/DAI, traumatic or diffuse axonal injury.

tau:T-tau ratio (Supplementary Table 1; see online supplementary material at http://www.liebertpub.com). Using tests of trend, GFAP levels, P-tau levels, and P-tau:T-tau ratio were found to be significantly higher with increasing age group; T-tau levels were remarkably stable across age groups (Table 2). GFAP levels, P-tau levels, P-tau:T-tau ratio, and T-tau levels were significantly higher among those with versus without CT findings across all age groups (Table 3; Fig. 1). However, the magnitude of the difference in GFAP level was quite small for older adults (Table 3; Fig. 1).

In linear regression models of the entire pooled cohort, GFAP levels and T-tau levels were not associated with age in either unadjusted models ($p = 0.378$ and 0.774, respectively), models adjusted for time between injury and blood draw ($p = 0.914$ and 0.428, respectively), or models stratified by patients with ($p = 0.308$ and 0.338, respectively) versus without abnormal CT findings ($p = 0.590$ and 0.445, respectively). P-tau levels and P-tau:T-tau ratio, however, were significantly associated with age in unadjusted models ($p = 0.001$ and $p < 0.001$, respectively), models adjusted for time between injury and blood draw ($p = 0.032$ and 0.009, respectively), and models including only patients without CT findings ($p = 0.036$ and 0.016, respectively). Among patients with abnormal CT findings, however, P-tau and P-tau:T-tau ratio were not associated with age ($p = 0.641$ and 0.201, respectively).

In logistic regression analyses of the entire pooled cohort, all assays (GFAP, P-tau, T-tau, and P-tau:T-tau ratio) were significantly associated with CT findings in both unadjusted models and in models adjusted for time between injury and blood draw (all $p \leq 0.001$). The association between assay level and CT findings significantly differed across age groups for GFAP (interaction $p = 0.012$) and T-tau (interaction $p < 0.001$) but not for P-tau (interaction $p = 0.538$) or P-tau:T-tau ratio (interaction $p = 0.739$). These findings were unchanged even after adjustment for time between injury and blood draw.

In ROC analyses of the entire pooled cohort, the AUC (95% confidence interval [CI]) for diagnosis of CT findings for all assays was good to excellent, except for T-tau, which was fair: GFAP 0.88 (0.82-0.93), T-tau 0.71 (0.62-0.80), P-tau 0.93 (0.89-0.97) P-tau:T-tau ratio 0.92 (0.87-0.96). AUCs improved slightly when analyses were adjusted for time between injury and blood draw (AUC [95% CI]: GFAP 0.90 [0.86-0.95]; T-tau 0.83 [0.76-0.90]; P-tau 0.93 [0.90-0.98]; P-tau:T-tau ratio 0.93 [0.88-0.97]). To facilitate more concrete interpretation of results (but not for direct clinical application), optimal cut-points for each assay for diagnosing CT findings were estimated and age-specific sensitivity and specificity at this cut-point was determined (Table 4). Overall, accuracy was reduced among older versus young and middle-aged patients. P-tau had the most consistently high sensitivity across all age groups but showed dramatic reductions in specificity among older versus younger or middle-aged patients; T-tau had the lowest sensitivity and specificity across all age groups; and P-tau:T-tau ratio had the highest sensitivity and specificity among middle-aged and older patients but lower sensitivity and specificity (compared with P-tau) among younger patients. GFAP showed dramatic reductions in both sensitivity and specificity among older versus young and middle-aged patients.

Similarly, comparison of ROCs across age categories for each assay revealed worse diagnostic accuracy among older patients (Fig. 2), which was statistically significant for GFAP (AUC, 95% CI: old 0.73, 0.54-0.91 [reference group; ref] vs. young 0.93, 0.88–0.99 [$p = 0.037$] or middle-aged 0.92, 0.86–0.99 [$p = 0.0497$]) but not for T-tau (AUC, 95% CI: old 0.74, 0.54-0.93 [ref] vs. young 0.68, 0.52–0.84 [$p = 0.694$] or middle-aged 0.74, 0.59–0.89 [$p = 0.968$]), P-tau (AUC, 95% CI: old 0.84, 0.66-1.00 [ref] vs. young 0.95, 0.89–1.00 [$p = 0.274$] or middle-aged 0.93, 0.87–0.99 [$p = 0.367$]), or P-tau:T-tau ratio (AUC, 95% CI: old 0.77, 0.53-1.00 [ref] vs. young 0.95, 0.89–1.00 [p = 0.165] or middle-aged 0.91, 0.83–0.99 [$p = 0.268$]). Overall, P-tau showed the greatest accuracy (by AUC) both in the pooled cohort and in age-stratified analyses for diagnosing intracranial trauma on CT. Findings were similar after adjustment for time between injury and blood draw, with evidence for consistently worse diagnostic accuracy among older patients across all assays and for P-tau showing greatest accuracy (by AUC) both in the pooled cohort and in age-stratified analyses.

ROC analyses comparing models including the best tau assay (P-tau) alone versus P-tau plus GFAP identified significant added value of GFAP (AUC, 95% CI: P-tau alone 0.93, 0.89-0.97 vs. P-tau plus GFAP 0.96, 0.93-0.99 [$p = 0.008$]). This pattern of added value in models including P-tau plus GFAP versus P-tau alone was apparent even after stratification by age, though differences between models were no longer statistically significant (Supplementary Figure 1; see online supplementary material at http://www.liebertpub.com). Findings were similar after adjustment for time between injury and blood draw, with persistent evidence for added value of P-tau plus GFAP versus P-tau alone.

Discussion

In this study of 169 adults presenting within 24 h of mTBI, we identified novel age-related differences in diagnostic accuracy of all plasma assays studied for distinguishing patients with versus without CT evidence of intracranial trauma that was statistically significant for GFAP level only. Specifically, GFAP level showed decreasing accuracy (e.g., AUC), sensitivity, and specificity with increasing age. While P-tau level also showed slightly decreasing accuracy (e.g., AUC) and decreasing specificity with increasing age, these differences were not statistically significant, and P-tau level maintained high accuracy even among older adults. Performance of T-tau and P-tau:T-tau ratio, while not significantly worse

Table 2. Plasma Assay Concentration by Age Category

Median (IQR)	*Young* n = *79**	*Middle-aged* n = *60**	*Older* n = *30**	p
GFAP, ng/mL	0.15 (0.03–0.65)	0.28 (0.12–1.03)	0.46 (0.17–0.79)	0.032
T-tau, fg/mL	79.22 (73.35–85.09)	78.24 (73.35–85.09)	79.22 (75.31–84.11)	0.802
P-tau, fg/mL	1.49 (1.28–2.50)	2.00 (1.36–2.92)	2.92 (1.56–3.11)	< 0.001
P-tau:T-tau ratio × 100	1.87 (1.65–2.98)	2.65 (1.83–3.55)	3.50 (2.14–3.86)	< 0.001

*There was insufficient remaining plasma for tau assays in 15 of the 169 patients. Thus, for all tau assays, sample size is as follows: 70 young, 57 middle-aged, and 27 older.

IQR, interquartile range; GFAP, glial fibrillary acidic protein; T-tau, total-tau protein; P-tau, hyperphosphorylated-tau protein.

Table 3. Plasma Assay Concentration by Age Category and CT Evidence of Intracranial Trauma

	Young (< 40 years) n = *79**			*Middle-aged (40–59 years)* n = *60**			*Older (60 years+)* n = *30**		
Median (IQR)	CT–	CT+	*p*	CT–	CT+	*p*	CT–	CT+	*p*
GFAP, ng/mL	0.11 (0.03–0.26)	1.55 (0.56–3.23)	< 0.001	0.15 (0.03–0.29)	2.22 (0.81–3.26)	< 0.001	0.22 (0.07–0.49)	0.67 (0.20–1.32)	0.038
T-tau, fg/mL	77.26 (73.35–84.11)	84.11 (77.26–89.00)	0.026	76.77 (71.39–80.20)	85.09 (78.24–89.98)	0.003	76.77 (73.35–80.20)	80.20 (79.22–86.06)	0.044
P-tau, fg/mL	1.33 (1.21–1.56)	3.00 (2.68–3.11)	< 0.001	1.53 (1.31–2.00)	2.95 (2.75–3.25)	< 0.001	1.50 (1.39–2.84)	3.03 (2.86–3.11)	0.004
P-tau:T-tau ratio × 100	1.81 (1.55–2.02)	3.45 (3.19–3.83)	< 0.001	1.97 (1.71–2.65)	3.58 (3.47–3.76)	< 0.001	1.94 (1.82–3.62)	3.51 (3.44–3.86)	0.021

Because levels of GFAP and P-tau are not normally distributed, data are summarized using median and interquartile range (25th percentile – 75th percentile). *There was insufficient remaining plasma for tau assays in 15 of the 169 patients. Thus, for all tau assays, sample size is as follows: 70 young, 57 middle-age, and 27 older.

CT, computed tomography; IQR, interquartile range; CT-, no evidence of intracranial trauma on head CT; CT+, evidence of intracranial trauma on head CT; GFAP, glial fibrillary acidic protein; P-tau, hyperphosphorylated tau protein.

among older adults, was not as high (by AUC) as that of P-tau. While there was a significant correlation between GFAP level and P-tau level, this correlation was only moderate, suggesting that these assays are measuring slightly different aspects of injury. This hypothesis is further supported by the model combining both GFAP and P-tau level that showed improved accuracy over the model containing P-tau alone.

Our findings build upon the one prior human study that identified reduced specificity of plasma S100B for diagnosis of intracranial trauma on CT among older versus younger patients with TBI.[20]

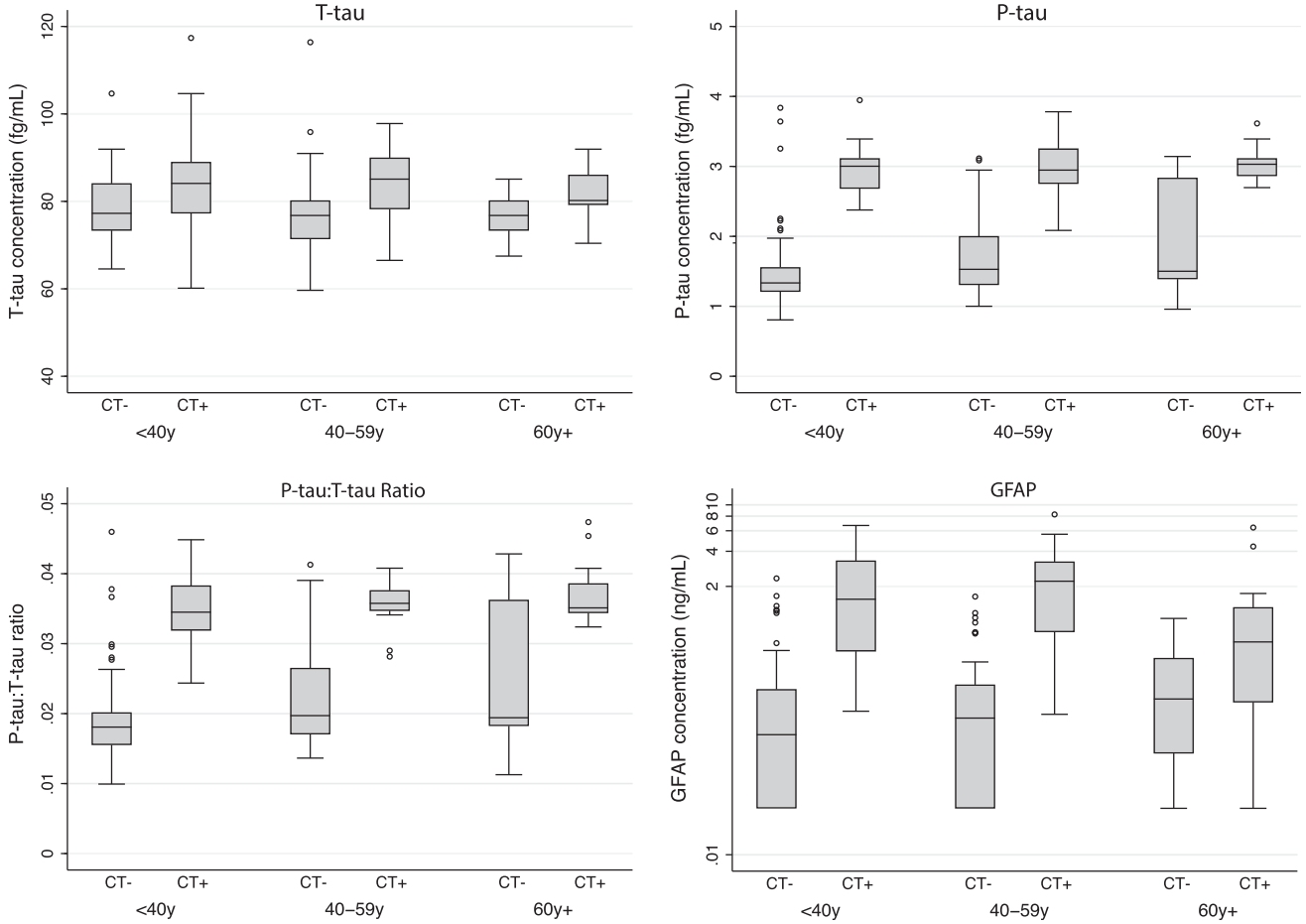

FIG. 1. Total-tau (T-tau), hyperphosphorylated-tau (P-tau), P-tau:T-tau ratio, and glial fibrillary acidic protein (GFAP) plasma concentration by age and computed tomography (CT) evidence of neurotrauma. The distribution of T-tau protein, P-tau, P-tau:T-tau ratio, and fibrillary acidic protein breakdown products (GFAP) plasma concentration are shown by age category and CT evidence of neurotrauma (CT- vs. CT+). GFAP is shown on the log scale for improved visualization of group differences at very low concentrations approaching zero. All others are shown on a linear scale. The shaded box depicts the interquartile range (75th percentile [upper hinge], median [central line], and 25th percentile [lower hinge]). The upper and lower whiskers depict the upper and lower adjacent values. Hollow circles depict outliers falling outside of the upper and lower adjacent values. There is marked overlap in the distribution of T-tau concentration among patients with versus without CT evidence of neurotrauma across all age groups. With increasing age, there is increasing overlap in the distribution of P-tau concentration, P-tau:T-tau ratio, and GFAP concentration among patients with versus without CT evidence of neurotrauma.

TABLE 4. SENSITIVITY, SPECIFICITY, AND CLASSIFICATION ACCURACY OF EACH ASSAY FOR DIAGNOSIS OF CT EVIDENCE OF INTRACRANIAL TRAUMA AT CUT-POINT (NEAREST TO [0,1] ON ROC CURVE)

		Young n = *79**			*Middle-aged* N = *60**			*Older* n = *30**		
	Cut-point (95% CI)	Sens	Spec	% correctly classified	Sens	Spec	% correctly classified	Sens	Spec	% correctly classified
GFAP, ng/mL	0.43 (0.25-0.60)	83.3	83.6	83.5	90.0	77.5	81.7	66.7	66.7	66.7
T-tau, fg/mL	79.71 (77.74-81.67)	75.0	55.6	60.0	73.7	65.8	68.4	58.8	60.0	59.3
P-tau, fg/mL	2.45 (2.30-2.59)	100.0	94.4	95.7	94.7	81.6	86.0	100.0	50.0	81.5
P-tau: T-tau ratio × 100	2.96 (2.69-3.24)	87.5	90.7	90.0	94.7	84.2	87.7	100.0	60.0	85.2

*There was insufficient remaining plasma for tau assays in 15 of the 169 patients. Thus, for all tau assays, sample size is as follows: 70 young, 57 middle-age, and 27 older.

CT, computed tomography; ROC, receiving operating characteristic; CI, confidence interval; Sens, sensitivity; Spec, specificity; GFAP, glial fibrillary acidic protein; T-tau, total tau protein; P-tau, hyperphosphorylated tau protein.

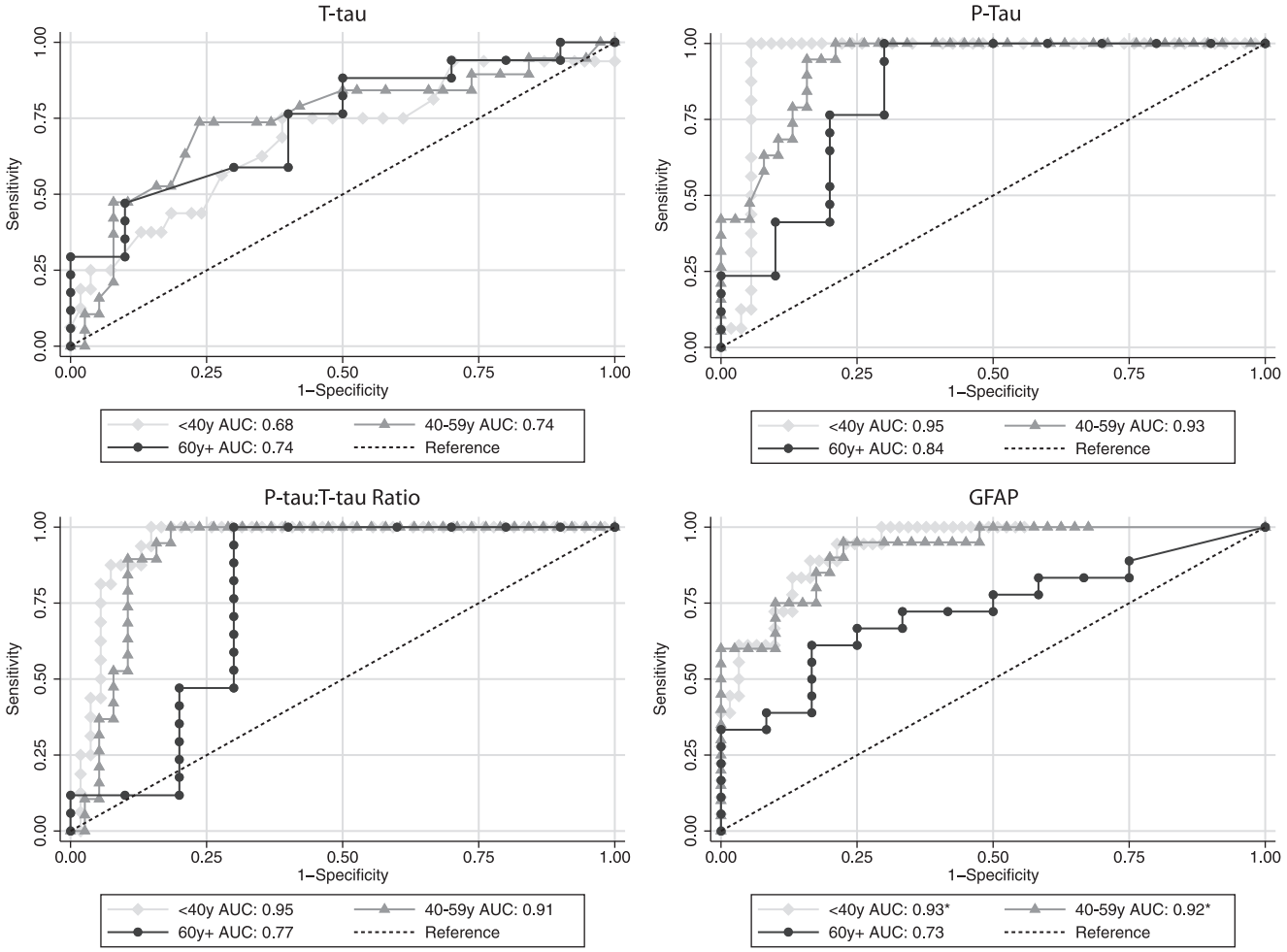

FIG. 2. Comparison of receiver operating characteristic curves for each assay by age group for distinguishing patients with versus without computed tomography (CT) evidence of intracranial trauma. Accuracy of each assay for diagnosis of CT evidence of intracranial trauma among patients presenting with mild traumatic brain injury and Glasgow Coma Scale score of 13-15 is represented here as the area under the receiver operating characteristic curve (AUC). AUC for glial fibrillary acidic protein (GFAP), hyperphosphorylated-tau (P-tau), and P-tau: total-tau (T-tau) ratio is lower among older patients versus young or middle-aged patients. This difference is statistically significant for GFAP only. The *p* values are calculated using patients age 60 years+ as the reference value (*$p < 0.05$ vs. 60 years+).

Additional prior studies of TBI biomarkers in aged versus younger rodents have identified age-related differences in TBI-associated proteomic signatures,[38] including differences is GFAP and S100B levels, with aged animals having higher basal (pre-injury) levels of GFAP and S100B.[39] While prior studies have reported that GFAP is most sensitive to focal high density lesions rather than diffuse injuries, metrics for assigning lesion type in these studies is rudimentary and thus findings must be considered inconclusive.[40,41] Potential explanations for reduced accuracy (including both reduced sensitivity and specificity) of GFAP among older patients in this study include reduced production of GFAP and GFAP-BDP in response to injury in older adults, higher baseline levels of GFAP due to other pre-existing conditions in older versus younger patients, or differences in types of neurotrauma sustained in older versus younger patients. Interestingly, we found that among patients with CT findings, GFAP levels were surprisingly low (median <1 ng/mL) in older adults despite having the highest prevalence of mass lesions such as SDH. Thus, whether the specific type of lesion (e.g., intraparenchymal hemorrhage such as ICH vs. extraparenchymal hemorrhage such as SDH or SAH) impacts GFAP level, as has been reported for different stroke sub-types,[42] deserves further study. For example, among all patients with intracranial trauma on CT in our cohort, 94% of young patients had at least some parenchymal injury versus only 50% of older patients.

The trend toward reduced specificity of P-tau among older patients in our study likely reflects higher prevalence of baseline elevations of P-tau with increasing age: a hypothesis supported by our finding that P-tau levels were significantly associated with age even after adjusting for CT findings. Higher baseline plasma levels of P-tau, unrelated to TBI, may be due to aging or neurodegenerative disease.[43] Approximately 70% of adults in their 60s have at least low-grade (Braak stage I – II) tau-containing neurofibrillary tangle pathology on brain autopsy[44] and 11% of adults admitted to hospitals for TBI may have a pre-existing diagnosis of dementia.[19] Because our study specifically excluded patients with known dementia, baseline elevations of P-tau in this cohort may reflect either normal aging or pre-clinical neurodegeneration. Further research is needed on the diagnostic accuracy of P-tau in geriatric TBI patients with pre-existing dementia, who make up a substantial minority of older adults presenting to hospitals with TBI.[19] Despite these age-related differences in both GFAP and P-tau, our analyses of both markers together identified excellent diagnostic accuracy even among older patients (AUC of 0.88), suggesting that combining several plasma biomarkers may be a useful strategy for increasing overall accuracy[25] and mitigating some of the age-related reductions in diagnostic accuracy we identified.

Strengths of this study include the collection of plasma within 24 h of injury in a well-characterized cohort of patients with mTBI across the adult age spectrum. Prior studies have found that plasma GFAP levels are maximal within 10 h of injury, remain stable until 24 h,[45] then decline to near-control levels by Day 30,[46] while tau levels also appear to be maximal within 24 h of injury and then decline more gradually reaching near-control levels by Day 90.[46] Additional strengths include the use of highly sensitive assays, scoring of head CTs according to consensus TBI CDEs, and comparison of two biomarkers across three age categories.

Limitations include the relatively small sample size, exclusion of patients with known dementia, inability to evaluate the role of pre-existing conditions or anti-thrombotic therapy, and the use of CT as the gold-standard for defining intracranial trauma. While head CT is considered the standard of care for ruling out signs of intracranial trauma in the acute setting, it is increasingly recognized as a crude measure that frequently misses clinically important traumatic lesions that may be detected on more sensitive imaging modalities such as MRI.[47]

Generalizability of our findings may be limited by the high prevalence of CT abnormalities in our population that is representative of an mTBI population presenting to Level 1 trauma centers who meet ACEP/CDC criteria for TBI (the recruitment pool for TRACK-TBI Pilot). Our population may not be representative of patients presenting to other types of settings or to patients presenting to emergency departments with an ambiguous head injury history not meeting ACEP/CDC criteria for TBI. Additionally, the GFAP assay sensitivity of ng/mL versus fg/mL for P-tau may have contributed to the relatively worse accuracy of GFAP versus P-tau and we cannot exclude the possibility that GFAP level might be more accurate among geriatric patients if a more sensitive assay—such as Quanterix SIMOA[46] or a-EIMAF—were used. Because our focus was on discriminating mTBI patients with versus without intracranial trauma on CT (a question of great importance in the geriatric population who frequently harbor clinically silent traumatic lesions), this study did not address the separate question of discriminating TBI patients from non-TBI controls, which should be addressed in future larger studies with sufficient elderly controls. An additional important area for future study is how the basic kinetics of these assays may change with age, polypharmacy, or pre-existing conditions, such as renal or hepatic impairment.

In conclusion, in this study of 169 adult patients with mTBI, we report that plasma GFAP level has significantly lower accuracy, and P-tau level may have slightly lower specificity but still has high overall accuracy, for identifying intracranial trauma on CT among older versus younger adults. Use of several biomarkers together, however, may mitigate these age-related reductions in diagnostic accuracy. Whether these differences are due to aging related changes such as dampened astrocytic activation, incipient neurodegeneration, or basic differences in the types/anatomical locations of injuries sustained in older versus younger patients or are due to assay-specific or imaging-modality sensitivity will require further study in larger samples.

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