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## RESEARCH ARTICLE

# Blood biomarkers for cognitive decline and clinical progression in a Mexican American cohort

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## Abstract

**Introduction:** The clinical translation of biofluid markers for dementia requires validation in diverse cohorts. The study goal was to evaluate if blood biomarkers reflecting diverse pathophysiological processes predict disease progression in Mexican American adults. **Methods:** Mexican American adults (n = 745), 50 years of age and older, completed annual assessments over a mean of 4 years. Serum collected at baseline was assayed for total tau, neurofilament light (NFL), ubiquitin carboxyl-terminal hydrolase LI, glial fibrillary acidic protein (GFAP), soluble cluster of differentiation 14 (sCD14), and chitinase-3-like protein 1 (YKL-40). **Results:** Higher GFAP and NFL were associated with global cognitive decline. Only GFAP was associated with increased incident dementia risk (hazard ratio: 1.611 (95% confidence interval: 1.204-2.155)) and inclusion of additional biomarkers did not improve model fit. **Discussion:** Among a panel of six blood biomarkers previously associated with neurodegenerative disease, only

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GFAP predicted incident dementia in our cohort. The findings suggest that blood GFAP levels may aid dementia-risk prediction among Mexican American adults.

#### KEYWORDS

Alzheimer's disease, biomarkers, GFAP, Hispanic, Latinos, Mexican American, NFL, soluble CD14, total tau, UCHL-1, YKL-40

## 1 | INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative condition that gradually causes cognitive and functional decline, is a top contributor to mortality in the United States.<sup>1</sup> AD is a clinically and biologically heterogeneous disorder that develops insidiously over the span of decades.<sup>2</sup> Cerebral amyloid beta ( $A\beta$ ) deposition, followed by neurodegeneration and phosphorylated tau accumulation, are hallmarks of the disease.<sup>3</sup> In addition, growing research supports the central role of broader pathophysiological processes including neuroinflammation, glial dysfunction, synaptic loss, hypoperfusion, and metabolic alterations.<sup>2,4,5</sup> The complexity of the disease poses challenges to accurate diagnosis and therapeutic discovery. Biofluid markers, particularly in blood, hold the potential to aid early diagnosis, improve monitoring of disease progression, and foster individualized precision-medicine approaches to treatment.<sup>4</sup> Over the past decade, tremendous progress has been made in the validation of blood markers with diagnostic accuracy for AD and related dementias (ADRD), including neurofilament light (NFL), total tau (t-tau), and more recently, phosphorylated tau (p-tau) 181 and 217.<sup>6</sup>

Despite the substantial achievements in the field, advancements have not extended to all groups equitably. Ethnoracial minorities in the United States have elevated risk of ADRD,<sup>1</sup> yet the majority of blood biomarker research has focused primarily on non-Hispanic White populations. Emerging research suggests that ADRD biomarker levels may differ across ethnoracial groups, which may propagate further disparities in diagnostic accuracy, advanced care planning, and research engagement.<sup>7</sup> Several studies have reported lower t-tau and p-tau 181 levels in Black adults as compared to non-Hispanic White adults,<sup>8-11</sup> which may affect the sensitivity of cut-off values used for diagnosis.<sup>11</sup> Latinos of Mexican descent are the most populous ethnic group in the United States, yet remain highly understudied in ADRD biomarker research.<sup>12</sup> Prior proteomic research conducted by O'Bryant et al. reported significant differences in the plasma signature for ADRD between Mexican Americans and non-Hispanic Whites, with a stronger metabolic endophenotype among Mexican Americans.<sup>12,13</sup> Within a bi-ethnic cohort of Hispanics and non-Hispanic Whites, we previously reported that serum levels of NFL, glial fibrillary acidic protein (GFAP), and chitinase-3-like protein 1 (YKL-40) were associated with poorer cognition, but the associations were typically weaker among Hispanics.<sup>14</sup> It is notable that the ethnic differences were no longer significant when examining a demographically matched sub-sample of Hispanic and non-Hispanic White adults, highlighting the need to better understand how disparities across multidimensional determinants

of health may affect ADRD biomarker levels. Given the observed variances in biomarker performance across ethnoracial groups, the validation of ADRD biomarkers in diverse cohorts has been highlighted as a critical priority for the field.<sup>7</sup>

The goal of the present study was to evaluate the ability of ADRD blood biomarkers to predict cognitive decline, clinical conversion, and disease progression in a cohort of Mexican American older adults followed over a mean of 4 years. Given the heterogeneity of ADRD,<sup>2</sup> we investigated a panel of blood markers reflecting diverse pathophysiological processes including neuronal/axonal injury (t-tau, NFL), ubiquitin protease system clearance (ubiquitin carboxyl-terminal hydrolase L1 [UCHL1]), and glial injury (soluble cluster of differentiation 14 (sCD14), YKL-40, GFAP). Based on prior research,<sup>14</sup> we hypothesized that markers of neuronal/axonal and glial injury would predict cognitive decline and clinical conversion in our cohort. As an exploratory aim, we further evaluated if the associations between biomarker levels and clinical outcomes were influenced by the presence of the apolipoprotein E (*APOE*)  $\epsilon$ 4 allele. Among non-Hispanic Whites, the *APOE*  $\epsilon$ 4 allele is the strongest known genetic risk factor for sporadic AD.<sup>15</sup> However, in Mexican Americans, the *APOE*  $\epsilon$ 4 allele has been found to display weaker and more inconsistent associations with cognitive impairment and dementia endophenotypes.<sup>16,17</sup> The impact of the *APOE*  $\epsilon$ 4 allele on ADRD blood biomarker levels remains unestablished among Mexican Americans.

## 2 | METHODS

### 2.1 | Participants

Stored serum biospecimens were obtained from participants completing the baseline visit of the Texas Alzheimer's Research and Care Consortium (TARCC) study. As described previously,<sup>18</sup> TARCC is a collaborative research effort to establish a consortium of Alzheimer's Disease Centers across 10 academic institutions, which was initially funded by the State of Texas in 1999. Annual assessment visits include a clinical examination, medical history, neuropsychological evaluation, and blood draw. Inclusion criteria for the TARCC study included age 50 years or older at the time of enrollment. For the current project, inclusion criteria additionally included Mexican American ethnicity, stored serum from the baseline visit, and completion of at least one annual follow-up visit. The six serum biomarkers assessed were available on all participants. The study was approved by the institutional review board at each enrolling institution and was conducted in adherence with The

Code of Ethics of the World Medical Association. Participants provided written informed consent prior to enrollment with appropriate legal representation for individuals lacking capacity to consent. Local institutional review board approval was obtained to process and analyze de-identified samples and clinical/demographic data.

## 2.2 | Neuropsychological evaluation

The neuropsychological evaluation was administered in English or Spanish in alignment with the participant's preference. The battery included measures of global cognition (Mini Mental Status Examination [MMSE]),<sup>19</sup> learning and memory (Wechsler Memory Scale, Third Edition [WMS-3] Logical Memory (LM) I and II<sup>20</sup>), attention/processing speed (Trail Making Test Part A<sup>21</sup>), executive function (Trail Making Test Part B<sup>21</sup>), and language (Animal Fluency<sup>22</sup>).

The Clinical Dementia Rating Scale (CDR) was also completed with participants and their study partners.<sup>23</sup>

## 2.3 | Consensus reviews

Clinical diagnoses were assigned at each site from a consensus review panel that included at least one physician, neuropsychologist, and research coordinator. National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were applied to assign diagnoses of possible or probable AD.<sup>24</sup> Mild cognitive impairment (MCI) subtypes (amnesic vs non-amnesic) were defined using established criteria by Petersen et al.<sup>25</sup>

## 2.4 | Blood draw and storage

TARCC collected and processed blood from participants in accordance with established guidelines for ADRD research.<sup>26</sup> Briefly, venipuncture with a 21 gauge needle was used to collect non-fasting blood in the morning. Serum tubes were allowed to clot for at least 30 minutes, while plasma tubes were inverted 5 to 10 times. Within 1 hour of collection, tubes were centrifuged for 10 minutes at 2000 xg. Next, 500 uL aliquots were transferred to polypropylene tubes and placed into -80° freezers within 2 hours of collection. APOE genotyping was performed with polymerase chain reaction (PCR) as described previously.<sup>18</sup> For the current project, samples were shipped to the Laboratory for Clinical Biochemistry at the University of Vermont for biomarker assays.

## 2.5 | Assays

The Simoa Neurology 4-Plex Kit Serum was used to quantify serum levels of t-tau, NFL, UCHL1, and GFAP using a Simoa HD-1 Analyzer (Quanterix, Lexington, MA). sCD14 and YKL-40 assays were performed using commercial enzyme-linked immunosorbent assays

### HIGHLIGHTS

- Higher baseline serum glial fibrillary acidic protein (GFAP) and neurofilament light (NFL) were associated with global cognitive decline
- Higher baseline serum GFAP, NFL, chitinase-3-like protein 1 (YKL-40), and soluble cluster of differentiation 14 (sCD14) associated with disease progression
- Serum GFAP, unlike total tau, NFL, UCHL-1, YKL-40, and sCD14, predicted incident dementia

### RESEARCH IN CONTEXT

1. **Systematic Review:** Emerging research suggests that biomarkers for Alzheimer's disease and related dementias may differ across ethnoracial groups, which may serve to further propagate health disparities in diagnosis and treatment if left unexamined. Latinos of Mexican descent are the fastest growing demographic group in United States, yet they remain highly understudied in biomarker research.
2. **Interpretation:** Study findings suggest that serum levels of neurofilament light (NFL), glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL-40), and soluble cluster of differentiation 14 (sCD14) were associated with worsening disease severity in Mexican American older adults. GFAP was the only biomarker significantly associated with increased risk of incident dementia risk and inclusion of additional biomarkers did not improve model fit.
3. **Future Directions:** Findings suggest that blood levels of GFAP may uniquely aid prediction of dementia risk among Mexican Americans. Further validation studies in Mexican American adults and other diverse cohorts are necessary for clinical translation.

(ELISAs; R&D Systems, Minneapolis, MN). Analytical ranges and inter-assay coefficients of variance have been reported previously.<sup>14</sup> A certified laboratory-technician, who was blinded to demographic and clinical data, performed all assays between November and December 2019 using a single batch of reagents.

## 2.6 | Statistical analyses

All biomarker values, with the exception of sCD14, were skewed and were natural log transformed to normalize their distributions. The biomarker values were then standardized prior to analyses. To limit

data loss, t-tau values below the detection limit were set equal to the detection limit (0.09 pg/mL) prior to log transformation, since values were known to be at this level or below.<sup>14</sup> Differences in demographics and clinical characteristics across the diagnostic groups at baseline were assessed with the chi-square statistic for categorical variables or with Kruskal-Wallis tests for continuous variables. The association of each biomarker with cognitive decline was evaluated using separate generalized estimating equation (GEE) analyses, where mean cognitive change over time was modeled as a function of biomarker (standardized), time, time by biomarker, and covariates (age, sex, education, site, APOE  $\epsilon 4$  status [at least one  $\epsilon 4$  allele vs none], clinical diagnosis at baseline, body mass index [BMI], diabetes, systolic blood pressure). Cox proportional hazard models were used to evaluate the associations between serum biomarkers and incident MCI and dementia due to possible/probable AD with covariate adjustment for age, sex, education, site, APOE  $\epsilon 4$  status, BMI, diabetes, and systolic blood pressure. The GEE and cox proportional hazard models described above were repeated with stratification by APOE  $\epsilon 4$  carrier status (at least one  $\epsilon 4$  allele vs none). All statistical tests were two-sided. To adjust for multiple comparisons, the criterion for significance was set at an false discovery rate (FDR)-corrected  $P$ -value of  $<.05$ . The adjusted  $P$ -values are reported. Analyses were performed using SAS version 9.4.

## 3 | RESULTS

### 3.1 | Participant characteristics

The study sample included 745 Mexican American participants, mean age  $\pm$  SD ( $66 \pm 9$  years), of which 72% ( $n = 533$ ) were female. At the baseline examination, which was conducted between 2007 and 2017, approximately two-thirds of the sample was cognitively unimpaired, 28% ( $n = 207$ ) was diagnosed with MCI, and 8% ( $n = 59$ ) was diagnosed with dementia due to possible/probable AD (Table 1). The diagnostic groups differed across most demographic and clinical factors. In addition, all raw blood biomarker levels except NFL differed significantly across the diagnostic groups at baseline. Serum levels of GFAP were higher among APOE  $\epsilon 4$  carriers relative to non-carriers for the overall sample, MCI, and dementia groups at baseline (Table S1). In addition, serum NFL was higher among APOE  $\epsilon 4$  carriers within the MCI group, and UCHLI levels were lower among APOE  $\epsilon 4$  carriers within the cognitively unimpaired group. Over the study interval, 29% ( $n = 138$ ) of individuals who were cognitively unimpaired at baseline converted to MCI and 7% ( $n = 50$ ) of 686 participants without dementia at baseline converted to dementia due to possible/probable AD.

### 3.2 | Serum biomarkers, longitudinal cognitive decline, and clinical progression

Higher baseline serum NFL and GFAP levels were associated with worsening global cognition over time (Table 2). In addition, higher baseline levels of GFAP, as well as t-tau, predicted accelerated decline on

measures of learning and memory. Higher baseline levels of NFL, GFAP, YKL-40, and sCD14 were associated with ADRD disease progression as evaluated by the CDR Sum of Boxes (Table 3).

Stratified analyses by APOE  $\epsilon 4$  carrier status indicated associations between baseline NFL, GFAP, and YKL-40 levels with worsening global cognition among  $\epsilon 4$  carriers (Table S2). NFL and YKL-40 were associated with faster immediate recall decline and t-tau was associated with faster semantic fluency decline among  $\epsilon 4$  carriers. Among APOE  $\epsilon 4$  non-carriers, only t-tau was associated with accelerated memory decline. NFL, GFAP, and YKL-40 were associated with ADRD progression among APOE  $\epsilon 4$  carriers, whereas as no significant associations emerged for  $\epsilon 4$  non-carriers (Table S3).

### 3.3 | Serum biomarkers and clinical conversion

No serum biomarker values were associated with incident MCI (Table 4) or with further stratification by amnesic and non-amnesic MCI subtypes (Table S4). Across the six biomarkers examined, only higher levels of baseline GFAP predicted incident dementia (Table 4, Figure 1). In nested models that examined incremental improvement of discriminating dementia risk with NFL and t-tau (biomarkers with the second and third largest effect sizes) added to GFAP (largest effect size), only GFAP was significant (hazard ratio [HR]: 1.440, 95% confidence intervals [CI]: 1.010 to 2.054, adjusted  $P$ -value: 0.04), and C-statistics were similar in all models (range: 0.8726 to 0.8739).

In stratified analyses by APOE  $\epsilon 4$  carrier status, there were no associations between serum biomarkers and incident MCI (Table S5). Among APOE  $\epsilon 4$  non-carriers, serum GFAP levels were associated with incident dementia. There were no significant associations between serum biomarkers and incident dementia among APOE  $\epsilon 4$  carriers.

## 4 | DISCUSSION

The current study examined the efficacy of established and exploratory ADRD blood biomarkers for predicting cognitive decline, clinical conversion, and disease progression in a cohort of Mexican American older adults. Consistent with prior literature conducted primarily in non-Hispanic White cohorts,<sup>27-30</sup> we found that higher baseline t-tau, NFL, and GFAP levels were associated with accelerated cognitive decline. In addition, NFL and GFAP, along with less-established markers, YKL-40 and sCD14, were associated with more rapid ADRD disease progression as evaluated by the CDR Sum of Boxes. Stratified analyses indicated stronger associations between blood biomarkers with cognitive decline and ADRD progression among APOE  $\epsilon 4$  carriers relative to non-carriers. Of the six biomarkers examined, only higher baseline levels of GFAP were linked to increased risk of incident dementia due to possible/probable AD. No additional biomarkers were significant when included in the model, suggesting that GFAP alone provided important information relevant to incident dementia in our cohort of Mexican American older adults.

**TABLE 1** Demographic and clinical characteristics by baseline clinical diagnosis

	Cognitively Unimpaired N = 479	Mild Cognitive Impairment N = 207	Dementia N = 59	P-value
Age, years	63 ± 7	71 ± 8	74 ± 8	<.001*
Female, no. (%)	354 (74%)	140 (68%)	39 (66%)	.15
Education, years	11 ± 4	11 ± 4	11 ± 4	.57
Body mass index, m/kg <sup>2</sup>	31 ± 6	31 ± 6	29 ± 5	.50
Blood pressure, mm Hg				
Systolic	137 ± 20	138 ± 19	144 ± 19	.023*
Diastolic	78 ± 12	76 ± 10	75 ± 9	.002*
Diabetes, no. (%)	160 (33%)	77 (37%)	23 (39%)	.018*
Presence of APOE ε4 allele, no. (%)	99 (21%)	45 (22%)	24 (41%)	.009*
Raw serum t-tau, median (Quartile 1, Quartile 3), pg/mL	0.28 (0.13, 0.42)	0.29 (0.14, 0.44)	0.32 (0.19, 0.58)	<.001*
Raw serum NFL, median (Quartile 1, Quartile 3), pg/mL	15 (11, 21)	19 (15, 28)	26 (20, 36)	.088
Raw serum GFAP, median (Quartile 1, Quartile 3), pg/mL	136 (102, 189)	179 (123, 261)	223 (160, 391)	<.001*
Raw serum UCHL1, median (Quartile 1, Quartile 3), pg/mL	26 (22, 36)	29 (22, 39)	29 (24, 40)	<.001*
Raw serum YKL-40, median (Quartile 1, Quartile 3), pg/mL	53506 (33701, 97333)	62291 (39586, 103909)	89030 52979, 47139079)	.013*
Raw serum sCD14, median (Quartile 1, Quartile 3), pg/mL	1301 (1150, 1456)	1318 (1172, 1554)	1295 (1178, 1536)	<.001*
Average follow-up length, years	4 ± 2	4 ± 2	3 ± 2	0.29
Cognitive scores at baseline				
MMSE	28 ± 2	27 ± 2	23 ± 4	<.001*
WMS LM I	35 ± 9	28 ± 9	22 ± 12	<.001*
WMS LM II	21 ± 7	16 ± 7	10 ± 8	<.001*
Animal Fluency	16 ± 4	14 ± 4	12 ± 4	<.001*
Trails A, time to completion (seconds)	45 ± 19	55 ± 29	79 ± 38	<.001*
Trails A, time to completion (seconds)	118 ± 59	171 ± 80	237 ± 81	<.001*
Average annualized change in cognitive scores				
MMSE	0.01 ± 0.66	-0.18 ± 0.85	-0.86 ± 1.45	<.001*
WMS LM I	0.84 ± 2.27	0.54 ± 2.49	-0.27 ± 2.93	<.001*
WMS LM II	0.84 ± 1.75	0.66 ± 1.89	0.28 ± 2.05	.006*
Animal Fluency	0.01 ± 1.22	-0.23 ± 1.30	-0.63 ± 1.48	<.001*
Trails A, time to completion (seconds)	0.00 ± 5.57	0.93 ± 7.86	3.79 ± 12.75	<.001*
Trails A, time to completion (seconds)	2.86 ± 16.41	1.32 ± 18.59	5.74 ± 23.04	.034*

Abbreviations: APOE = apolipoprotein E, MMSE = Mini Mental Status Examination, WMS LM = Weschler Memory Scale Logical Memory, Trails = Trail Making Test, t-tau = total tau; NFL = neurofilament light, GFAP = glial fibrillary acidic protein, UCHL1 = ubiquitin carboxyl-terminal hydrolase L1, YKL-40 = chitinase-3-like protein 1, sCD14 = soluble cluster of differentiation.

\* $P < 0.05$ . Group differences were assessed with Kruskal-Wallis tests for continuous variables and the chi-square test for categorical variables. All values represent mean ± standard deviation unless otherwise noted.

In alignment with prior research conducted primarily within non-Hispanic White populations,<sup>27,28,30</sup> higher levels of t-tau, NFL, and GFAP were associated with accelerated cognitive decline over time. Cerebral tau is considered a core biological marker of AD and closely correlates with cognitive decline.<sup>31</sup> Within the blood, t-tau levels are

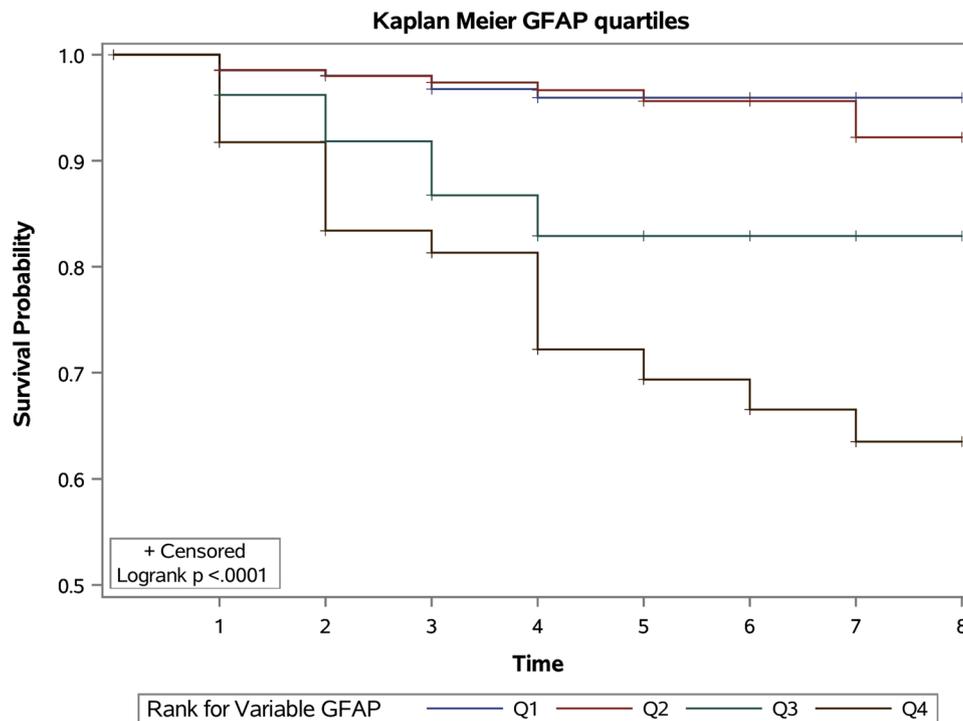
presumed to reflect neuronal injury.<sup>27</sup> Blood t-tau levels have been associated with multi-domain cognitive decline in numerous cohort studies of neurodegenerative disease,<sup>27,32</sup> as well as in association with other neurological conditions.<sup>33</sup> In addition to t-tau, higher baseline NFL was associated with faster global cognitive decline in

**TABLE 2** Results of generalized estimating equation analyses displaying associations between serum biomarkers and longitudinal cognitive outcomes

	t-tau	NFL	GFAP	UCHL1	YKL-40	sCD14
MMSE	$\beta = -0.031$ , SE = 0.040, p = 0.65	$\beta = -0.103$ , SE = 0.041, P = .034*	$\beta = -0.141$ , SE = 0.053, P = .034*	$\beta = -0.030$ , SE = 0.033, P = .65	$\beta = -0.099$ , SE = 0.034, P = .79	$\beta = -0.009$ , SE = 0.036, P = .79
WMS LM I	$\beta = -0.344$ , SE = 0.120, P = .024*	$\beta = -0.170$ , SE = 0.122, P = .22	$\beta = -0.330$ , SE = 0.129, P = .032*	$\beta = -0.011$ , SE = 0.098, P = .84	$\beta = -0.154$ , SE = 0.116, P = .22	$\beta = -0.244$ , SE = 0.120, P = .083
WMS LM II	$\beta = -0.390$ , SE = 0.088, P < .001*	$\beta = -0.113$ , SE = 0.089, P = .30	$\beta = -0.260$ , SE = 0.100, P = .027*	$\beta = -0.092$ , SE = 0.080 P = .30	$\beta = -0.115$ , SE = 0.088, P = .30	$\beta = -0.080$ , SE = 0.089, P = 0.37
Animal Fluency	$\beta = -0.142$ , SE = 0.056, P = .05	$\beta = -0.075$ , SE = 0.057, P = .28	$\beta = -0.164$ , SE = 0.069, P = .05	$\beta = -0.034$ , SE = 0.067, P = .73	$\beta = -0.113$ , SE = 0.053, P = .07	$\beta = -0.002$ , SE = 0.007, P = 0.98
Trails A	$\beta = 0.408$ , SE = 0.385, P = .42	$\beta = 0.656$ , SE = .397, P = .17	$\beta = 0.955$ , SE = .435, P = .17	$\beta = 0.768$ , SE = .410, P = .18	$\beta = 0.334$ , SE = 0.356, P = .42	$\beta = 0.183$ , SE = 0.363, P = .61
Trails B	$\beta = 0.273$ , SE = 0.882, p = 0.91	$\beta = 1.347$ , SE = 0.841, p = 0.40	$\beta = 1.550$ , SE = 1.030, p = 0.40	$\beta = 0.510$ , SE = 0.891, p = 0.85	$\beta = 0.748$ , SE = 0.814, p = 0.72	$\beta = -0.036$ , SE = 0.833, p = 0.97

Abbreviations: t-tau = total tau, NFL = neurofilament light, GFAP = glial fibrillary acidic protein, UCHL1 = ubiquitin carboxyl-terminal hydrolase L1, YKL-40 = chitinase-3-like protein 1, sCD14 = soluble cluster of differentiation 14, MMSE = Mini Mental Status Examination, WMS LM = Weschler Memory Scale Logical Memory, Trails = Trail Making Test.

\*FDR-corrected  $P < 0.05$ . Generalized estimating equation models with longitudinal cognitive data regressed on age, sex, ethnicity, APOE  $\epsilon 4$  status, education, site, clinical diagnostic group, body mass index, systolic blood pressure, diabetes, and serum biomarkers (modeled separately).  $\beta$  = coefficient associated with time by standardized biomarker interaction.

**FIGURE 1** Serum glial fibrillary acidic protein (GFAP) and incident dementia: Kaplan-Meier curve derived from a cox proportional hazard model evaluating the association between serum GFAP and incident dementia due to possible/probable Alzheimer's disease with adjustment for age, sex, education, site, apolipoprotein E (APOE)  $\epsilon 4$  status, body mass index, diabetes, and systolic blood pressure

**TABLE 3** Results of generalized estimating equation models displaying associations between serum biomarkers and longitudinal clinical progression

	CDR Sum of Boxes N = 745
t-tau	$\beta = 0.033$ , SE = 0.025, $P = .18$
NFL	$\beta = 0.099$ , SE = 0.026, $P < .001^*$
GFAP	$\beta = 0.125$ , SE = 0.036, $P = .001^*$
UCHL1	$\beta = 0.038$ , SE = 0.024, $P = .14$
YKL-40	$\beta = 0.044$ , SE = 0.016, $P = .010^*$
sCD14	$\beta = 0.036$ , SE = 0.017, $P = .048^*$

Abbreviations: t-tau = total tau, NFL = neurofilament light, GFAP = glial fibrillary acidic protein, UCHL1 = ubiquitin carboxyl-terminal hydrolase L1, YKL-40 = chitinase-3-like protein 1, sCD14 = soluble cluster of differentiation 14.

\*FDR-corrected  $P < 0.05$ , Generalized estimating equation models with longitudinal clinical progression data (Clinical Dementia Rating Scale Sum of Boxes) regressed on age, sex, ethnicity, APOE  $\epsilon 4$  status, education, site, clinical diagnostic group, body mass index, systolic blood pressure, diabetes, and serum biomarkers (modeled separately).  $\beta$  = coefficient associated with time by standardized biomarker interaction.

our Mexican American cohort. NFL is an intermediate filament protein found in myelinated axons.<sup>34</sup> Within blood, NFL levels are considered a marker of axonal/neuronal damage.<sup>35</sup> NFL levels in blood closely correlate with CSF levels,<sup>28</sup> suggesting that blood may serve as a viable proxy for the extent of axonal/neuronal damage in the CNS. Individual and meta-analytic studies have reported that NFL predicts cognitive decline in AD,<sup>28,29,32</sup> as well as in broader neurological conditions

including multiple sclerosis and vascular dementia.<sup>36</sup> Finally, higher baseline levels of serum GFAP were associated with accelerated cognitive decline across the domains of global cognition, learning, and memory in our cohort. GFAP is an intermediate filament found in the cytoskeletons of mature astrocytes.<sup>37</sup> It is considered a putative marker of astroglial injury and has higher expression in the brains of individuals with AD relative to controls.<sup>38</sup> In the blood, GFAP levels have been found to predict incident cognitive decline even among individuals without cognitive impairment,<sup>30,39</sup> suggesting that elevations occur early in the disease process. Similar to t-tau and NFL, GFAP is not specific to neurodegenerative disease and has been found to change in the context of multiple neurological conditions and acute CNS injury.<sup>40</sup>

In addition to cognitive decline, we evaluated the associations between biomarkers and ADRD clinical progression based on the CDR Sum of Boxes, a gold standard tool for evaluating interval change in cognition and functional status.<sup>23</sup> In alignment with our cognitive findings, higher baseline levels of serum GFAP and NFL were associated with worsening disease severity. Although serum t-tau was associated with cognitive decline in our sample, it surprisingly did not predict changes in disease progression. A prior study by Rajan et al. reported that plasma GFAP and NFL predicted incident AD over a period of 4 to 8 years prior to clinical diagnosis, whereas t-tau was only associated with AD 8 to 16 years prior to diagnosis.<sup>29</sup> Therefore, the 4-year longitudinal follow-up period in our study may have been too short to appreciate associations between t-tau and clinical progression.

In our study, higher baseline levels of sCD14 and YKL-40, which are considered putative markers of glial injury and neuroinflammation, were also associated with advancing disease progression over time. sCD14 is a glycoprotein found in monocytes and neutrophils with integral role in governing innate immunity and inflammatory cascades.<sup>41</sup> YKL-40 is a glycoprotein expressed in numerous bodily tissues, including within astrocytes and microglia in the CNS.<sup>42</sup> Consistent with our findings, previous studies have reported associations between blood sCD14 and YKL-40 levels and ADRD.<sup>43,44</sup> In our sample, sCD14 and

**TABLE 4** Results of cox proportional hazard models displaying for incident mild cognitive impairment and dementia

	MCICases = 138/479	DementiaCases = 50/686
t-tau	HR = 1.037, 95% CI = 0.867-1.241, $P = .69$	HR = 1.399, 95% CI = 1.032-1.896, $P = .07$
NFL	HR = 0.932, 95% CI = 0.770-1.129, $P = .57$	HR = 1.360, 95% CI = 1.024-1.805, $P = .07$
GFAP	HR = 0.901, 95% CI = 0.724-1.120, $P = .57$	HR = 1.611, 95% CI = 1.204-2.155, $P = 0.008^*$
UCHL1	HR = 1.065, 95% CI = 0.915-1.238, $P = .57$	HR = 1.106, 95% CI = 0.826-1.432, $P = .75$
YKL-40	HR = 1.075, 95% CI = 0.903-1.279, $P = .57$	HR = 0.980, 95% CI = 0.708-1.356, $P = .90$
sCD14	HR = 0.936, 95% CI = 0.784-1.116, $P = .57$	HR = 0.968, 95% CI = 0.714-1.313, $P = .90$

Abbreviations: t-tau = total tau, NFL = neurofilament light, GFAP = glial fibrillary acidic protein, UCHL1 = ubiquitin carboxyl-terminal hydrolase L1, YKL-40 = chitinase-3-like protein 1, sCD14 = soluble cluster of differentiation 14.

\*FDR-corrected  $P < 0.05$ , Cox proportional hazard models for incident mild cognitive impairment and dementia with adjustment for age, sex, ethnicity, APOE  $\epsilon 4$  status, education, site, clinical diagnostic group, body mass index, systolic blood pressure, diabetes, and serum biomarkers (modeled separately).

YKL-40 were not significantly associated with cognitive decline, which may be partially attributable to the enhanced utility of considering both cognitive and functional outcomes when using the CDR. This is particularly relevant for diverse ethn racial groups given inherent biases in cognitive tests due to variances in educational quality, linguistic background, and culture.<sup>7,45</sup>

In our sample, none of the blood biomarkers were associated with incident MCI. Individuals with MCI have variable long-term outcomes, spanning from improvement or stability to progression to dementia.<sup>46</sup> The heterogeneity of the underlying cause of the diagnosis makes the identification of accurate biomarkers challenging. Furthermore, our cohort lacks broader biomarker data, including brain magnetic resonance imaging (MRI), CSF, and positron emission tomography (PET) imaging outcomes, which can be used to further improve discrimination of underlying disease etiology.<sup>31</sup>

Across the six biomarkers examined, only baseline GFAP levels were associated with increased risk of incident dementia in our Mexican American cohort. Although blood GFAP levels have been less extensively examined in AD RD research relative to t-tau and NFL, growing literature indicates its strong predictive utility.<sup>29,30,39</sup> In addition, previous studies have reported that core AD biomarkers such as tau and amyloid beta may have poorer discriminability for AD RD in some diverse ethn racial groups.<sup>11,13</sup> Within a cohort of Mexican American adults, O'Bryant et al. reported that plasma A $\beta$ 42 and t-tau were less important for classifying dementia relative to their utility in non-Hispanic Whites, whereas inflammatory and metabolic markers had stronger predictive value.<sup>13</sup> These results, coupled with our findings, highlight the potential value of examining biomarkers beyond the traditional A $\beta$  and tau pathways, particularly among Mexican American cohorts.

As an exploratory aim, we examined associations between blood biomarkers with cognitive decline and clinical progression with stratification by APOE  $\epsilon$ 4 status. For cognitive decline and AD RD progression, significant associations were typically only observed among APOE  $\epsilon$ 4 carriers. For incident dementia, the association with GFAP was only significant among APOE  $\epsilon$ 4 non-carriers, which may be attributable to the smaller sample size and more limited power within the APOE  $\epsilon$ 4 carrier group. Although some previous studies conducted in predominately non-Hispanic White populations have not found APOE-related differences in biomarker levels,<sup>47,48</sup> there is some evidence that markers of astrogliosis, such as CSF YKL-40 levels, may be higher among APOE  $\epsilon$ 4 carriers within the early disease stage.<sup>49</sup> The results of more robust associations between blood biomarkers and interval cognitive change among APOE  $\epsilon$ 4 carriers within our cohort is somewhat surprising, as prior studies have reported weaker associations between the APOE  $\epsilon$ 4 allele and cognitive outcomes among Mexican Americans as compared to non-Hispanic Whites.<sup>16,17</sup> A study of adults of diverse Hispanic backgrounds reported that Amerindian ancestry may be protective against the risk for cognitive decline conferred by APOE  $\epsilon$ 4 allele.<sup>16</sup> Mexican Americans present with diverse genetic admixtures,<sup>50</sup> as well as variability in environmental and lifestyle exposures, that may modulate risk. Future research with large, well-characterized Mexican American cohorts is necessary to understand the associations more fully

between APOE  $\epsilon$ 4 carrier status and AD RD biomarker levels within this ethnic group.

Our study has several strengths including a sizable Mexican American cohort with well-characterized clinical and cognitive profiles, longitudinal monitoring, and inclusion of multiple established and more novel blood biomarkers. However, the findings of the study must also be considered in the context of the limitations. It is important to note that our study lacks available brain MRI, CSF, and PET imaging outcomes, preventing further confirmation of suspected diagnostic etiology.<sup>31</sup> That being said, our study employs routine clinical and cognitive assessments for dementia workup, making the findings relevant to the clinical setting, particularly in underserved communities with more limited access to neuroimaging. Another potential limitation is that our study included biospecimens that were collected across multiple institutions over the course of many years, which may lead to variability in biomarker values.<sup>4</sup> In addition, the annualized rate of cognitive decline was small and only a small percentage of individuals converted to dementia, which may have limited our power for detecting significant associations. Furthermore, the participants enrolled in TARCC were recruited from academic institutions for the purpose of developing a consortium of AD Centers, which may pose limits to generalizability. Finally, our study was solely comprised of Mexican Americans and aimed to advance the identification of biomarkers that are most predictive of incident dementia risk within this ethnic group. Future studies with well-matched samples, harmonized protocols, and adequate representation of multiple diverse groups are critically needed to evaluate ethn racial differences in biomarker values,<sup>7</sup> as well as to establish the multidimensional determinants of health that may contribute to observed variances.

In summary, our study examined both established and more novel AD RD blood biomarkers reflecting diverse pathophysiological processes in a cohort of Mexican American older adults. We found that higher baseline levels of t-tau, NFL, and GFAP were associated with accelerated cognitive decline. In addition, NFL and GFAP, as well as sCD14 and YKL-40, were associated with disease progression over time, highlighting the important role of neuroinflammatory processes. Finally, we found that only baseline levels of serum GFAP were associated with increased risk of dementia in our sample. With further validation, GFAP, potentially in combination with blood biomarkers beyond those included in our study, may optimize dementia risk prediction in Mexican American older adults, providing avenues for earlier diagnosis, more accurate prognosis, and improved risk stratification for clinical trials.

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#### SUPPORTING INFORMATION

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