

Relationship of ELF and PIIINP With Liver Histology and Response to Vitamin E or Pioglitazone in the PIVENS Trial

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Enhanced liver fibrosis score (ELF) and one of its components, amino-terminal propeptide of type III procollagen (PIIINP) are promising noninvasive biomarkers of liver histology in patients with nonalcoholic steatohepatitis (NASH). We evaluated the association of ELF and PIIINP with fibrosis stages at baseline and end of treatment (EOT) with vitamin E or pioglitazone in the PIVENS trial (Pioglitazone vs. Vitamin E vs. Placebo for the Treatment of Nondiabetic Patients With NASH) and characterized ELF and PIIINP changes and their associations with changes in the histological endpoints. ELF and PIIINP were measured at baseline and weeks 16, 48, and 96 on sera from 243 PIVENS participants. Baseline and EOT ELF were significantly associated with fibrosis stage ($P < 0.001$). The area under the curve for ELF's detection of clinically significant and advanced fibrosis in baseline biopsies was 0.74 and 0.79, respectively ($P < 0.001$). There was a significant drop in ELF score at weeks 48 and 96 in patients who achieved the NAFLD activity score (NAS)-based primary end point ($P = 0.007$) but not in those who experienced NASH resolution ($P = 0.24$) or fibrosis improvement ($P = 0.50$). Change in PIIINP was significantly associated with NASH resolution and improvement in NAS-based histological endpoint and fibrosis ($P < 0.05$ for all). Over the study period, both ELF and PIIINP significantly decreased with vitamin E ($P < 0.05$), but only PIIINP decreased with pioglitazone ($P < 0.001$). **Conclusion:** ELF is significantly associated with clinically significant and advanced fibrosis in patients with NASH, but its longitudinal changes were not associated with improvement in fibrosis or NASH resolution. PIIINP, one of its components, appears promising for identifying longitudinal histologic changes in patients with NASH and is worthy of further investigation. (*Hepatology Communications* 2021;0:1-12).

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of liver disease worldwide.⁽¹⁾ Identification of patients with the severe progressive NAFLD phenotype, nonalcoholic steatohepatitis (NASH), is clinically important, as progressive fibrosis in patients with NASH could lead to cirrhosis, liver failure, and increased risk for liver cancer.⁽²⁾ The

presence of fibrosis and especially advanced fibrosis is a strong predictor of liver-related outcomes in patients with NASH.⁽²⁻⁵⁾

Although liver biopsy is considered the “gold standard” for the diagnosis and staging of NASH,⁽²⁾ its invasive nature, cost, and sampling and interpretation variability are known limitations. These

Abbreviations: AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ELF, enhanced liver fibrosis score; EOT, end of treatment; HA, hyaluronic acid; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NASH-CRN, NASH Clinical Research Network; OR, odds ratio; PIIINP, amino-terminal propeptide of type III procollagen; PIVENS, Pioglitazone vs. Vitamin E vs. Placebo for the Treatment of Nondiabetic Patients With NASH trial; PPV, positive predictive value; TIMP-1, tissue inhibitor of metalloproteinases-1.

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limitations preclude the wide-scale use of liver biopsy in clinical practice to screen for clinically significant or advanced fibrosis, monitor disease progression, or evaluate response to therapy in patients with NAFLD. To address these unmet clinical needs, there has been an intense search for noninvasive, reproducible, and less costly biomarkers for assessing NAFLD severity, monitoring its progression, and response to therapy.⁽⁶⁻¹¹⁾

The enhanced liver fibrosis score (ELF) combines measurements of tissue inhibitor of metalloproteinases-1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP), and hyaluronic acid (HA) in an algorithm that incorporates a constant, correction factors, and natural logarithmic transformation of measurements of the analytes.⁽¹²⁾ Since its original derivation in patients with a range of different chronic liver diseases, ELF has subsequently been validated in patients with NAFLD and has shown good diagnostic accuracy for detecting advanced fibrosis using liver biopsy as the reference standard⁽¹³⁻²¹⁾ and for monitoring changes in fibrosis in response to treatment⁽²²⁾ or over time.⁽²³⁾ ELF is currently one of the serum markers recommended by the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity Clinical Practice Guidelines⁽²⁴⁾ and the United Kingdom's National Institute for Health and Clinical Excellence (NICE)⁽²⁵⁾ for

evaluating and monitoring disease severity of suspected NAFLD in patients with metabolic risk factors. PIIINP, one of the components of ELF, has previously been shown to be associated with severity of inflammation in NAFLD, independent from liver fibrosis staged with histology or measured by ELF.⁽²⁶⁾ Although ELF has been evaluated extensively in European and international studies, limited data exist on its performance in detecting various levels of hepatic fibrosis or correlating to severity of NAFLD histology in U.S. patients. Furthermore, although the NICE guidelines recommend ELF for initial assessment for advanced fibrosis, monitoring disease progression, and response to therapy in patients with NAFLD,⁽²⁵⁾ there are no data assessing its correlation with histological response to vitamin E or pioglitazone therapy.

The PIVENS trial (Pioglitazone vs. Vitamin E vs. Placebo for the Treatment of Nondiabetic Patients With NASH) was a multicenter, randomized controlled trial that compared the efficacy and safety of vitamin E and pioglitazone in patients with biopsy-proven NASH without cirrhosis.⁽²⁷⁾ Taking advantage of the paired liver biopsies that participants had at study entry and end of treatment (EOT) at 96 weeks, our aims were to assess the value of ELF in PIVENS participants at two levels: (1) cross-sectional, in which the diagnostic performance and association of ELF with stages of fibrosis and

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other NASH histological features are evaluated at baseline and EOT, and (2) longitudinal, in which the utility of ELF and PIIINP in monitoring response to vitamin E or pioglitazone therapy was assessed by evaluating dynamic changes in ELF and PIIINP from baseline at 16, 48, and 96 weeks in each therapy arm in relation to changes in histological endpoints of interest.

Materials and Methods

The PIVENS trial was conducted by the NASH Clinical Research Network (NASH-CRN). Its design, methods, and results were previously published.^(27,28) Briefly, 247 adults with biopsy-proven NASH without cirrhosis or diabetes were randomized to receive pioglitazone (30 mg daily, 80 subjects), vitamin E (800 IU daily, 84 subjects), or placebo (83 subjects) for 96 weeks. Eligibility for study entry was determined based on local pathology read of liver biopsy, whereas final analysis of histology was based on central read of deeper cuts of baseline and 96-week liver biopsies. The central read was performed by the NASH-CRN Pathology Committee according to the NASH-CRN scoring system.⁽²⁹⁾ The primary outcome was improvement in histology defined as improvement by ≥ 1 point in ballooning score, no increase in the fibrosis score, and either a decrease in the NAFLD activity score (NAS) to ≤ 3 points or a decrease in NAS of ≥ 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score. Statistical significance was set at 0.025.

Subsequent ancillary studies, including this study, on archived biosamples were permitted under the original informed consent that participants provided before enrollment in PIVENS.

Serum samples used in the current study were aliquots (0.5 mL) from the original samples, in which blood from fasting participants was collected into serum separator tubes, allowed to clot for at least 30 minutes at room temperature, and centrifuged at 1800g for 15 minutes at 4°C. Aliquots of serum were immediately frozen at -80°C. Processing was completed within 2 hours, and samples were free of hemolysis.

Of the 247 adult patients with NASH who participated in PIVENS, 243 had serum samples from baseline, 213 had samples from week 16, 219 had samples from week 48, and 219 had samples from

week 96 available for the current study. ELF (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) and the individual components of ELF were measured on an Advia Centaur XP (Siemens Healthcare Diagnostics Inc.) according to the manufacturer's instructions.⁽³⁰⁾

Statistical Methods

Descriptive statistics were used to compare histologic features by the categorical ELF result, defined as mild (< 7.7), moderate (7.7-9.8), or severe (≥ 9.8) fibrosis as per manufacturer's recommendations,⁽³⁰⁾ and by the continuous ELF score, at baseline and after 96 weeks of treatment. *P* values for the associations between histologic features and categorical ELF result were derived from the Mantel-Haenszel chi-square test for trend; for associations between histologic features and continuous ELF score, *P* values were derived from linear regressions of the rank of the ELF score on the histologic feature.

The performance of individual biomarkers comprising the ELF score (HA, PIIINP, and TIMP-1) was compared with that of the ELF score for detecting four fibrosis outcomes: any fibrosis (F1, F2, F3, F4 vs. F0), clinically significant fibrosis (F2, F3, F4 vs. F0, F1), and advanced fibrosis (F3, F4 vs. F0, F1, F2). For these comparisons, odds ratios (ORs) and 95% confidence intervals (CIs) were determined from logistic regression models of the fibrosis outcome on the specified biomarker. Area under the receiver operating characteristic curves (AUROCs) and 95% CIs were used to compare the individual biomarkers to the ELF score. The association between untransformed PIIINP levels and baseline NAS was determined from a logistic regression analysis, in which the outcome (baseline NAS) was dichotomized as ≥ 5 versus < 5 , and regressed on the baseline PIIINP value.

The ELF score and change in ELF score from baseline are presented for each time point (baseline, 16, 48, and 96 weeks) by treatment group. *P* values comparing the means and mean changes were derived from multiple linear regression models with two indicator variables for the effect of treatment versus placebo. For the mean change in scores, *P* values were calculated with multiple linear regression models with two indicator variables for the effect of treatment versus placebo, adjusting for the baseline value of the outcome.

Multiple logistic regression analysis was used to measure the association between improvement in

histology and decrease in ELF, as well as the association of fibrosis improvement and decrease in each ELF component (HA, PIIIP, and TIMP-1) over 96 weeks. Measures of histologic improvement included (1) overall histological improvement (defined as a 2+ point decrease in the NAS and no worsening of fibrosis); (2) resolution of steatohepatitis (defined as a diagnosis of borderline or definite steatohepatitis at baseline and a diagnosis of not NAFLD or nonalcoholic fatty liver only at 96 weeks); (3) improvement in fibrosis stage (defined as a decrease by one or more stage, with change from stage 1b to 1a also considered improvement); (4) improvement in the individual components of the NAS (i.e., steatosis, lobular inflammation, and ballooning grades) (defined as a decrease in grade of 1+ points; and (5) improvement in the NAS (defined as a 1+ point decrease in score over 96 weeks). ORs and 95% CIs were determined from logistic regressions of change in histologic improvement on change in ELF, adjusting for the baseline value of ELF and assigned PIVENS treatment group (two splines). Similarly, regressions to determine estimates for association of the fibrosis improvement and change in each component of ELF were adjusted for the baseline biomarker and treatment group. Changes in ELF and PIIINP at each time point are also presented graphically by histologic improvement outcome (overall histologic improvement, resolution of steatohepatitis, and fibrosis improvement); unadjusted mean changes are plotted, whereas *P* values are adjusted for the baseline ELF and PIIINP and treatment group. The association between PIIINP and change in NAS over 96 weeks was determined from a linear regression analysis of continuous change in NAS on PIIINP, adjusting for baseline NAS and treatment group. Similar linear regression models were run separately by treatment group.

Nominal two-sided *P* values were considered significant if *P* < 0.05. Analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC) and Stata (release 15.1; StataCorp, College Station, TX).

Results

PIVENS TRIAL

The results of the PIVENS trial were previously published.⁽²⁷⁾ Briefly, compared with placebo,

significantly more patients achieved the primary endpoint of NAS-based overall histological improvement with vitamin E but not with pioglitazone (19% vs. 43% vs. 34%, respectively). Compared with placebo, vitamin E was not significantly associated with higher rate of NASH resolution, although pioglitazone was (21% vs. 36% vs. 47%, respectively). Compared with placebo, significantly more patients on vitamin E and pioglitazone had improvement in steatosis (31% vs. 54% vs. 69%, respectively), lobular inflammation (35% vs. 54% vs. 60%, respectively), hepatocellular ballooning (29% vs. 50% vs. 44%, respectively), and reduction in NAS (-0.5 vs. -1.9 vs. -1.9, respectively), but neither vitamin E nor pioglitazone was significantly associated with fibrosis improvement (31% vs. 41% vs. 44%, respectively). Supporting Table S1 summarizes the baseline characteristics of the 243 participants included in this analysis.

CROSS-SECTIONAL ASSOCIATION ELF, FIBROSIS STAGE, AND OTHER HISTOLOGICAL SUBPHENOTYPES AT BASELINE AND EOT

At baseline, the overall mean ELF score was 8.9 (1.1), with 20 (8%) categorized as mild, 185 (76%) as moderate, and 38 (16%) as severe fibrosis. Histograms of ELF score by study visit are shown in Supporting Fig. S1. Baseline and EOT (96 weeks) ELF category and score were significantly associated with fibrosis stages (all *P* < 0.001), with more severe ELF category and higher ELF scores associated with worse fibrosis (Table 1, Supporting Table S2, and Supporting Fig. S2).

ELF category or score was also significantly and consistently associated with the severity of hepatocellular ballooning, portal and lobular inflammation, Mallory-Denk bodies, and diagnosis of definite NASH at baseline and EOT (Table 1 and Supporting Table S2).

Regression analyses were performed to determine whether the observed associations between ELF and histologic features of NAFLD (lobular inflammation, hepatocellular ballooning, and portal inflammation) were independent of fibrosis stage. Adjustment for fibrosis yielded similar associations between ELF and each histologic feature as those measured without adjustment, but with attenuation of the effect size and loss of significance for some features, suggesting that ELF is primarily a measure of fibrosis in NAFLD (Supporting Table S3).

TABLE 1. DISTRIBUTION OF ELF BY HISTOLOGICAL FEATURE AT BASELINE

	ELF Category			P Value*	ELF Score	P Value†
	Mild (<7.7)	Moderate (7.7-9.7)	Severe (≥9.8)			
Number	20	185	38		243	
Fibrosis stage‡:				<0.0001		<0.0001
None	10 (50%)	30 (16%)	1 (3%)		8.28 ± 0.89	
Mild	7 (35%)	82 (45%)	6 (16%)		8.57 ± 0.69	
Moderate	3 (15%)	45 (24%)	9 (24%)		8.95 ± 0.86	
Bridging	0 (0%)	26 (14%)	18 (47%)		9.73 ± 1.21	
Cirrhosis	0 (0%)	1 (1%)	4 (11%)		11.07 ± 1.52	
Steatosis grade:				0.47		0.29
≤33%	5 (25%)	60 (32%)	16 (42%)		9.04 ± 1.16	
34%-66%	10 (50%)	70 (38%)	11 (29%)		8.72 ± 0.95	
>66%	5 (25%)	55 (30%)	11 (29%)		8.87 ± 1.05	
Lobular inflammation:				0.03		0.04
<2 foci	13 (65%)	70 (38%)	12 (32%)		8.69 ± 1.03	
≥2 foci	7 (35%)	115 (62%)	26 (68%)		8.98 ± 1.06	
Hepatocellular ballooning:				<0.0001		<0.0001
None	7 (35%)	42 (23%)	2 (5%)		8.54 ± 0.75	
Few	8 (40%)	67 (36%)	5 (13%)		8.45 ± 0.82	
Many	5 (25%)	76 (41%)	31 (82%)		9.31 ± 1.16	
Portal inflammation:				<0.0001		<0.0001
None	6 (30%)	37 (20%)	1 (3%)		8.37 ± 0.74	
Mild	14 (70%)	116 (63%)	23 (61%)		8.82 ± 1.05	
More than mild	0 (0%)	32 (17%)	14 (37%)		9.50 ± 1.06	
Mallory-Denk bodies:				<0.0001		<0.0001
Absent/rare	17 (85%)	142 (77%)	12 (32%)		8.59 ± 0.84	
Many	3 (15%)	43 (23%)	26 (68%)		9.52 ± 1.23	
Acidophils:				0.34		0.40
Absent/rare	14 (70%)	119 (64%)	22 (58%)		8.80 ± 0.96	
Many	6 (30%)	66 (36%)	16 (42%)		9.00 ± 1.21	
Steatohepatitis diagnosis:				0.003		0.06
NAFLD, not NASH	3 (15%)	22 (12%)	1 (3%)		8.68 ± 0.81	
Borderline, suspicious	7 (35%)	32 (17%)	3 (8%)		8.50 ± 0.94	
Definite NASH	10 (50%)	131 (71%)	34 (90%)		8.99 ± 1.10	

* *P* values (two-sided) for the association of histological feature and the categorical ELF result derived from Mantel-Haenszel chi-square test for trend (exact test used for those with small numbers).

† *P* values (two-sided) for the association of histological feature and ELF score were derived from linear regression of the rank of the ELF score on the histological feature.

‡ One patient was missing fibrosis score at baseline due to insufficient trichrome.

Bold values indicate statistical significance.

PERFORMANCE OF ELF AND ITS INDIVIDUAL COMPONENTS FOR DISCRIMINATION OF DIFFERENT FIBROSIS STAGES AT BASELINE

ELF score and its individual components had AUROC = 0.623–0.681 (*P* < 0.05) for discriminating

patients with any stage of fibrosis, AUROC = 0.680–0.727 (*P* < 0.001) for discriminating patients with clinically significant fibrosis, and AUROC = 0.705–0.787 (*P* < 0.001) for discriminating patients with advanced fibrosis (Table 2). ELF score had significantly higher AUROC than its individual components for detection of these different stages of fibrosis.

TABLE 2. COMPARISON OF THE BASELINE VALUES OF SERUM HA, PIIINP, TIMP-1, AND ELF SCORE FOR DISCRIMINATION OF FIBROSIS STAGES IN PATIENTS WITH NASH IN THE PIVENS TRIAL

Biomarker Performance by Baseline Fibrosis*	Odds Ratio (95% CI) [†]	P Value [†]	AUROC (95% CI)
Any fibrosis:			
HA (per SD ng/mL)	13.5 (1.9, 96.2)	0.01	0.668 (0.577, 0.759)
PIIINP (per SD ng/mL)	1.9 (1.1, 3.2)	0.02	0.623 (0.525, 0.721)
TIMP-1 (per SD ng/mL)	2.9 (1.6, 5.3)	<0.001	0.670 (0.587, 0.754)
ELF (per SD score)	2.5 (1.6, 4.1)	<0.001	0.681 (0.588, 0.773)
Clinically significant fibrosis:			
HA (per SD ng/mL)	9.9 (3.6, 27.3)	<0.001	0.698 (0.631, 0.765)
PIIINP (per SD ng/mL)	3.0 (2.0, 4.6)	<0.001	0.708 (0.643, 0.773)
TIMP-1 (per SD ng/mL)	2.4 (1.6, 3.4)	<0.001	0.680 (0.612, 0.749)
ELF (per SD score)	2.9 (2.0, 4.2)	<0.001	0.727 (0.662, 0.792)
Advanced fibrosis:			
HA (per SD ng/mL)	9.5 (3.9, 23.1)	<0.001	0.762 (0.682, 0.842)
PIIINP (per SD ng/mL)	3.2 (2.1, 4.9)	<0.001	0.781 (0.707, 0.854)
TIMP-1 (per SD ng/mL)	2.6 (1.8, 3.7)	<0.001	0.705 (0.623, 0.787)
ELF (per SD score)	3.6 (2.4, 5.4)	<0.001	0.787 (0.713, 0.862)

Note: A total of 242 baseline levels of ELF and three components from the PIVENS trial participants were used in the analyses.

* Fibrosis categories were defined as any fibrosis = F1, F2, F3, F4 versus F0; clinically significant fibrosis = F2, F3, F4 versus F0, F1; and advanced fibrosis = F3, F4 versus F0, F1, F2.

[†] ORs and associated 95% CIs were determined from a logistic regression model of fibrosis on the specified biomarker. ORs given in the table are standardized and represent the odds of fibrosis categories per SD change in the biomarker. *P* values (two-sided) were determined from a Wald test.

ASSOCIATION BETWEEN CHANGES IN ELF SCORE AT 16, 48, AND 96 WEEKS FROM BASELINE AND HISTOLOGICAL PHENOTYPES AT EOT

Next, we evaluated changes in ELF in response to therapy received in each study arm. There were no significant changes in mean ELF score at the 16-week, 48-week, and 96-week specific time points from baseline with vitamin E or pioglitazone versus placebo (Table 3). However, for the overall trend over the entire study period, ELF score significantly decreased with vitamin E ($P = 0.04$) but not with pioglitazone ($P = 0.2$) (Fig. 1A). As Fig. 1A shows, in the vitamin E group, ELF decreased at 48 weeks and remained at this level at 96 weeks, whereas the change in ELF score in the placebo group was very close to 0 over time.

At 96 weeks, 118 (54%) participants achieved any decrease in ELF, 56 (25.8%) had at least a 0.5-unit drop in ELF, and 20 (9.2%) had a one-unit drop in ELF (Supporting Fig. S3A). In a model constructed

to predict improvement in histology per unit decrease in ELF score after 96 weeks of treatment (Table 4), one unit drop was significantly associated with overall NAS-based histological improvement (OR 1.59 [1.03, 2.45], $P = 0.04$) and improvement in NAS (OR 1.57 [1.01, 2.44], $P = 0.04$), but not with improvement in fibrosis, NASH resolution, or other NAFLD histological features. Supporting Fig. S3B shows the distribution of change in NAS by change in ELF at 96 weeks.

In total, 82 patients with fibrosis improvement had a mean change in ELF at week 96 by -0.15 units ($-0.33, 0.03$), whereas 132 patients without fibrosis improvement had a mean change in ELF at week 96 by -0.06 units ($-0.19, 0.07$) ($P = 0.14$). When we constructed a model to predict improvement in fibrosis per unit decrease in ELF score for individual components after 96 weeks of treatment (Table 5), a unit drop in PIIINP (OR 1.23 [1.07, 1.42], $P = 0.004$) and TIMP-1 (OR 1.01 [1.00, 1.02], $P = 0.005$), but not HA (OR 1.00 [1.00, 1.00], $P = 0.70$), were significantly associated with higher likelihoods of improvement in fibrosis.

TABLE 3. ELF SCORE AT BASELINE, 16, 48, AND 96 WEEKS OF FOLLOW-UP, AND CHANGE FROM BASELINE BY TREATMENT GROUP

	PIVENS Trial Treatment Group				P Value*	
	Placebo	Vitamin E	Pioglitazone	Total	Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Baseline, n	82	83	78	243		
ELF score, mean (95% CI)	8.80 (8.57, 9.03)	8.91 (8.68, 9.14)	8.89 (8.66, 9.13)	8.87 (8.73, 9.00)	0.51	0.58
Week 16, n	73	74	66	213		
ELF score, mean (95% CI)	8.85 (8.62, 9.09)	9.03 (8.80, 9.26)	8.98 (8.73, 9.23)	8.95 (8.82, 9.09)	0.29	0.46
ELF score, mean change from baseline (95% CI)	0.02 (-0.11, 0.15)	0.11 (-0.02, 0.24)	0.06 (-0.08, 0.20)	0.06 (-0.01, 0.14)	0.35	0.70
Week 48, n	73	78	68	219		
ELF score, mean (95% CI)	8.72 (8.48, 8.97)	8.70 (8.46, 8.94)	8.63 (8.37, 8.88)	8.68 (8.54, 8.83)	0.90	0.59
ELF score, mean change from baseline (95% CI)	-0.06 (-0.21, 0.08)	-0.23 (-0.38, -0.09)	-0.23 (-0.38, -0.07)	-0.17 (-0.26, -0.09)	0.10	0.13
Week 96, n	74	77	68	219		
ELF score, mean (95% CI)	8.82 (8.58, 9.06)	8.70 (8.47, 8.94)	8.84 (8.59, 9.09)	8.78 (8.65, 8.92)	0.47	0.92
ELF score, mean change from baseline (95% CI)	-0.01 (-0.17, 0.15)	-0.22 (-0.38, -0.06)	-0.04 (-0.21, 0.13)	-0.09 (-0.19, 0.00)	0.06	0.79
Overall					0.04	0.20

* For the means of outcome measures, *P* values were derived from multiple linear regression models with two indicator variables for the effect of treatment versus placebo. For the mean change in scores, means are adjusted for the baseline value of the outcome; *P* values were calculated with multiple linear regression models using two indicator variables for the effect of treatment versus placebo, adjusting for the baseline value of the outcome.

CHANGES IN ELF SCORE IN PATIENTS WHO ACHIEVED IMPROVEMENT IN MAJOR HISTOLOGICAL ENDPOINTS

In patients who achieved overall NAS-based histological improvement, there was a significant drop in ELF score compared with those who did not achieve histological improvement over the 96-week study period (*P* = 0.007) (Fig. 1B). Of note, the mean drop in ELF associated with overall NAS-based histological improvement was small both at 48 (-0.21 units [-0.34, -0.08]) and 96 (-0.23 units [-0.40, -0.07]) weeks and did not exceed 0.4-unit drop in the ELF score. Importantly, the change in ELF in participants who achieved these endpoints varied by treatment received. At week 96, some patients on pioglitazone experienced an increase in ELF despite histological improvement (+0.08 units [-0.18, 0.35] vs. -0.45 units [-0.71, -0.18] for vitamin E) and NAS improvement (-0.01 units [-0.23, 0.21] vs. -0.35 units [-0.55, -0.15] for vitamin E).

No significant change in ELF score was observed at 48 or 96 weeks in patients who experienced NASH resolution (Fig. 1C).

ELF SCORE AND CHANGES IN FIBROSIS

No significant change in ELF score was observed at 48 or 96 weeks in patients who experienced fibrosis improvement (Fig. 1D). In patients who achieved fibrosis improvement, the mean drop in ELF was small both at 48 weeks (-0.23 [-0.38, -0.08]) and 96 weeks (-0.15 [-0.33, 0.03]). In patients who experienced fibrosis worsening, the mean change in ELF also showed a small drop at 48 weeks (-0.24 [-0.46, -0.02]) and 96 weeks (-0.06 [-0.30, 0.19]) weeks (Supporting Table S4). By comparison, those without worsening of fibrosis had a larger, but not statistically significant, drop in ELF at 96 weeks (-0.10 [-0.22, 0.02], *P* = 0.43).

Of note, 9 patients who maintained stable low stages of fibrosis had low ELF scores throughout the trial. The 5 patients with no fibrosis at baseline had no fibrosis at 96 weeks; the 3 patients with 1a fibrosis at baseline had either 1a fibrosis (2 of 3) or no fibrosis (1 of 3) at 96 weeks, and the 1 patient with grade 2 fibrosis at baseline had no fibrosis at 96 weeks.

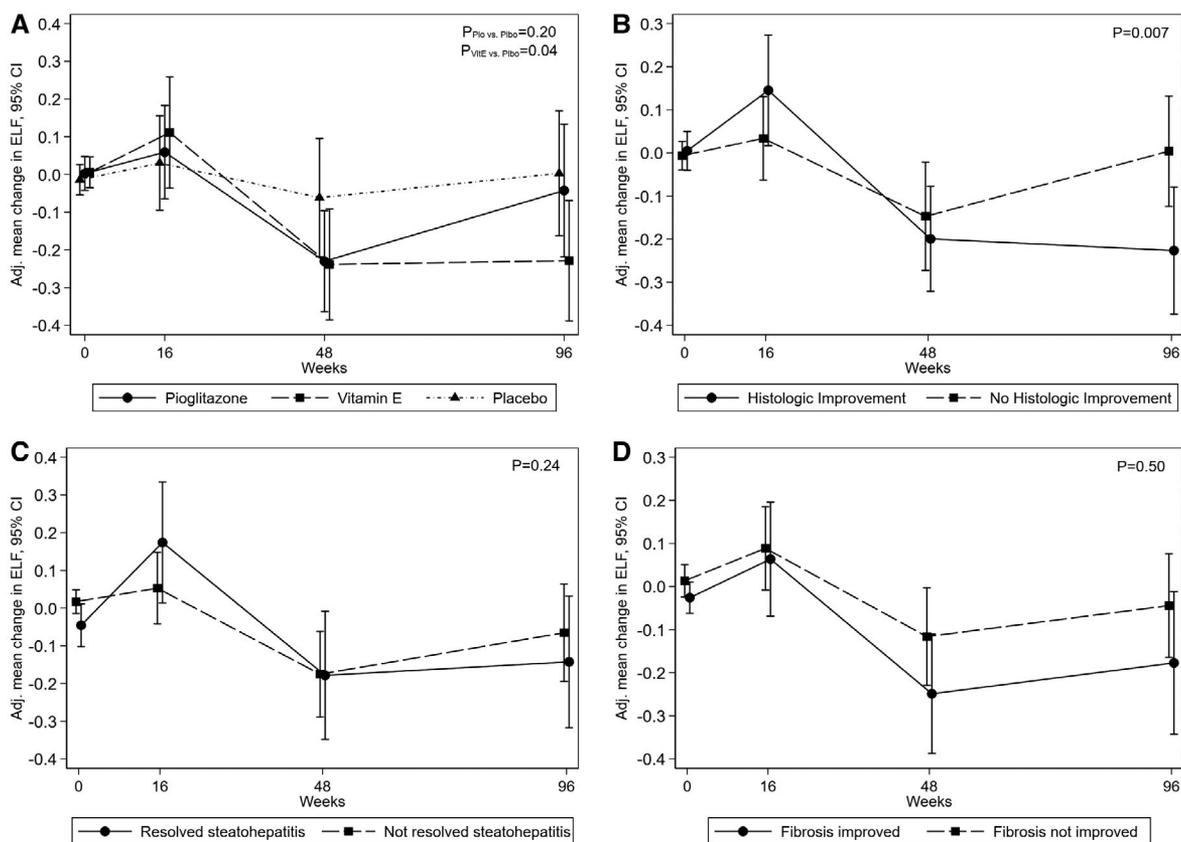


FIG. 1. Changes in serum ELF score in the PIVENS trial. (A) Changes in serum ELF score in three treatment groups (placebo, pioglitazone, and vitamin E). The adjusted mean values of changes from baseline in serum ELF score during treatment with pioglitazone, vitamin E, or placebo over 96 weeks are shown. Error bars show 95% CIs. *P* values for the overall treatment effects (pioglitazone vs. placebo and vitamin E vs. placebo) on change in ELF score over time were derived from generalized estimating equation linear regression, modeling change as a function of treatment group indicators, visit code indicators, baseline ELF score, and treatment group by visit code interaction terms. (B) Changes in serum ELF score in adults who achieved NAS-based histologic endpoint compared with those who did not achieve that histologic endpoint. The adjusted mean values of changes from baseline in serum ELF score over 96 weeks are shown. Error bars show 95% CIs. *P* values for the overall association between histologic improvement and change in ELF score over time were derived from generalized estimating equation linear regression, modeling change as a function of histologic improvement, visit code indicators, baseline ELF score, treatment group indicators, and histologic improvement by visit code interaction terms. (C) Changes in serum ELF score in adults with and without resolution of NASH. The adjusted mean values of changes from baseline in serum ELF score over 96 weeks are shown. Error bars show 95% CIs. *P* values for the overall association between resolution of NASH and change in ELF score over time were derived from generalized estimating equation linear regression, modeling change as a function of resolution of NASH, visit code indicators, baseline ELF score, treatment group indicators, and resolution of NASH by visit code interaction terms. (D) Changes in ELF score in adults with or without ≥ 1 -point improvement in fibrosis (biopsies with no fibrosis at baseline counted as not improved). The adjusted mean values of changes from baseline in serum ELF score over 96 weeks are shown. Error bars show 95% CIs. *P* values for the overall association between fibrosis improvement and change in ELF score over time were derived from generalized estimating equation linear regression, modeling change as a function of fibrosis improvement, visit code indicators, baseline ELF score, treatment group indicators, and fibrosis improvement by visit code interaction terms.

To detect ≥ 1 -stage improvement in fibrosis, the sensitivity, specificity, and positive predictive value (PPV) for a drop of ELF by ≥ 0.5 unit were 2%, 97% and 62%, respectively; for ≥ 0.75 -unit decrease, the PPV was 10%, 95% and 63% respectively; and for ≥ 1.0 -unit decrease, the PPV was 11%, 92% and 63%, respectively (Supporting Table S5).

RELATIONSHIP BETWEEN PIINP, NAS, AND RESPONSE TO THERAPY

At baseline, higher PIINP was associated with higher likelihood of NAS ≥ 5 (OR 1.2 [1.1, 1.3], $P < 0.001$, AUROC = 0.69 [0.65, 0.72]). In a linear regression model, the beta coefficient was 0.10 (SEM

TABLE 4. RELATIVE ODDS OF IMPROVED HISTOLOGY PER UNIT DECREASE IN ELF SCORE OVER 96 WEEKS IN PIVENS TRIAL PARTICIPANTS

Histological Change Over 96 weeks	Relative Odds (95% CI) of Improved Histology per Unit Decrease in ELF Over 96 Weeks (n = 217)*	PValue [†]	AUROC (95% CI)
Overall histological improvement [‡]	1.59 (1.03, 2.45)	0.04	0.68 (0.61, 0.75)
Resolution of steatohepatitis [§]	1.22 (0.77, 1.95)	0.40	0.69 (0.62, 0.77)
Improvement of at least 1 point:			
Fibrosis stage [¶]	1.36 (0.90, 2.06)	0.14	0.59 (0.52, 0.67)
Steatosis grade	1.40 (0.92, 2.11)	0.11	0.69 (0.62, 0.76)
Lobular inflammation	1.39 (0.93, 2.08)	0.11	0.65 (0.58, 0.73)
Hepatocellular ballooning	1.35 (0.90, 2.04)	0.14	0.62 (0.54, 0.69)
NAS	1.57 (1.01, 2.44)	0.04	0.70 (0.62, 0.78)

* Participants with paired ELF scores (baseline and 96 weeks) and paired histology were included in the analyses.

[†] P value determined from logistic regression of change in histological feature on change in ELF, controlling for baseline value of ELF and assigned PIVENS treatment group (two splines).

[‡] Overall histological improvement response was defined as a decrease in NAS score by 2 or more points and no worsening of fibrosis.

[§] Resolution of steatohepatitis was defined as a diagnosis of borderline or definite steatohepatitis at baseline and a diagnosis of not NAFLD or NAFLD only at 96 weeks; n = 204 with borderline/definite steatohepatitis at baseline; n = 59 with resolution of steatohepatitis.

[¶] Fibrosis improvement defined as a decrease by one or more stage, with change from stage 1b to 1a also considered improvement.

Bold values indicate statistical significance.

TABLE 5. RELATIVE ODDS OF FIBROSIS IMPROVEMENT PER UNIT DECREASE IN ELF COMPONENTS OVER 96 WEEKS IN PIVENS TRIAL PARTICIPANTS

	Relative Odds (95% CI) of Fibrosis Improvement per Unit Decrease in Biomarker Over 96 Weeks (n = 214)*	PValue	AUROC (95% CI)
HA (ng/mL)	1.00 (1.00, 1.00)	0.70	0.59 (0.51, 0.67)
PIIINP (ng/mL)	1.23 (1.07, 1.42)	0.004	0.62 (0.55, 0.70)
TIMP-1 (ng/mL)	1.01 (1.00, 1.02)	0.005	0.64 (0.56, 0.71)

* Adjusted for baseline biomarker and treatment group.

Abbreviations: HA, hyaluronic acid; PIIINP, amino-terminal propeptide of type III procollagen; TIMP-1, tissue inhibitor of metalloproteinases-1.

0.02, $P < 0.001$), indicating that for every 1-unit increase in baseline PIIINP, the expected mean NAS increases by 0.1 point ($P < 0.001$).

PIIINP levels dropped significantly from baseline with vitamin E beginning at week 48 ($P < 0.001$) and with pioglitazone beginning at week 16 ($P < 0.001$) (Supporting Table S6). The overall decrease in PIIINP over the entire study period was significant with both vitamin E and pioglitazone compared with placebo, as shown in Fig. 2A.

Beginning at week 16, an early and significant decrease in PIIINP was observed in participants with ≥ 2 -point decrease in NAS ($P < 0.001$) as well as those who achieved NASH resolution ($P = 0.01$) and fibrosis improvement ($P = 0.003$) (Fig. 2B-D).

When the 96-week change in NAS was regressed on the 96-week change in PIIINP, adjusting for baseline NAS and treatment group, the beta coefficient was

0.12 (SEM 0.03) ($P < 0.001$). Thus, for every 1-unit decrease in 96-week change in PIIINP, there is a 0.12 decrease in 96-week change in NAS. Among those in the vitamin E treatment group, for every 1-unit decrease in 96-week change in PIIINP, there was a 0.34 decrease in 96-week change in NAS, adjusted for baseline NAS and baseline PIIINP ($P < 0.001$). Among those in the pioglitazone treatment group, for every 1-unit decrease in 96-week change in PIIINP, there was a 0.21-unit decrease in NAS, adjusted for baseline NAS and baseline PIIINP ($P = 0.03$).

Discussion

This *post hoc* analysis makes several important observations. First, it confirms that ELF performs reasonably well in identifying clinically significant and advanced

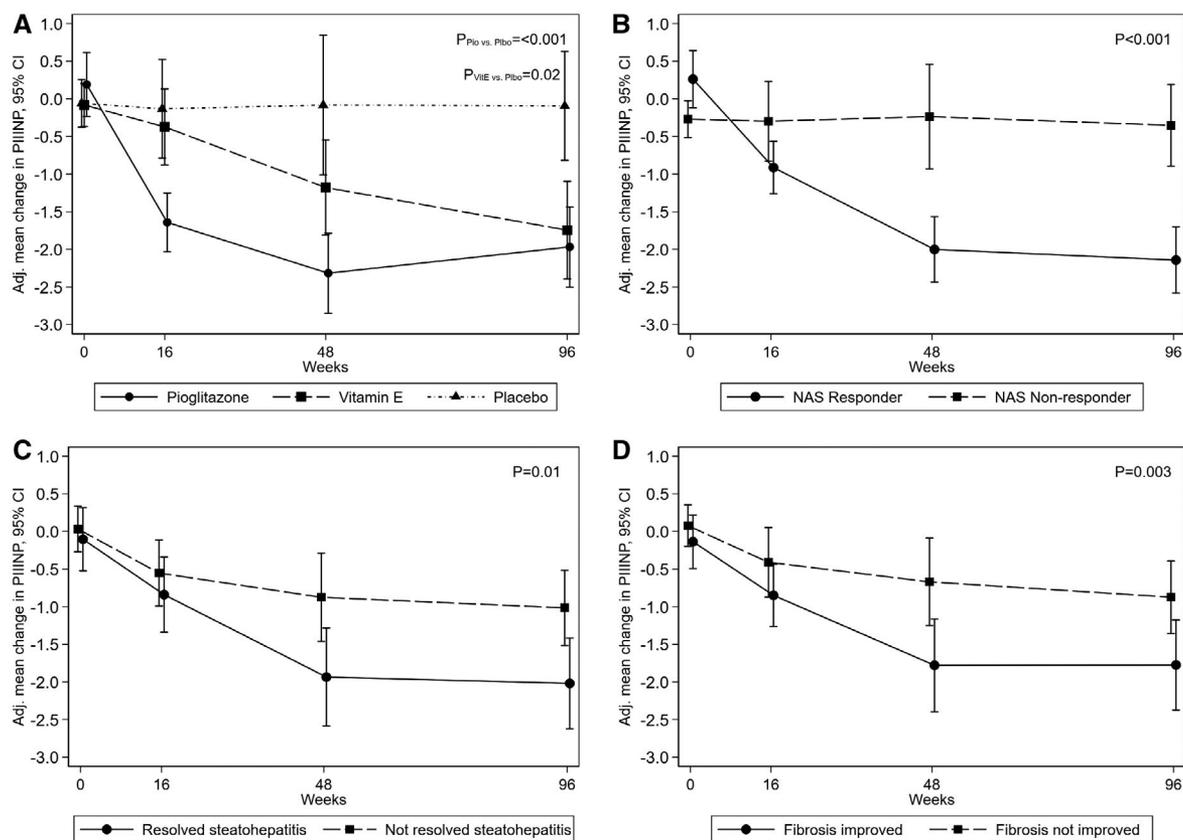


FIG. 2. PIIINP change per treatment arm and histological endpoints in the PIVENS trial. (A) Change in PIIINP by treatment group. (B) Change in PIIINP by NAS responder versus nonresponder. (C) Changes in PIIINP in adults with and without resolution of NASH. (D) Changes in PIIINP in adults with or without ≥ 1 -point improvement in fibrosis (biopsies with no fibrosis at baseline counted as not improved). NAS responder was defined as ≥ 2 -point decrease in NAS from baseline to 96 weeks.

fibrosis in adults with biopsy-proven NASH. Although ELF significantly correlates with other histological features of NASH, their strength of association diminished when controlled for fibrosis, suggesting that ELF is primarily an indicator of hepatic fibrosis. Second, longitudinal change in ELF score, while significantly associated with improvement in NAS and NAS-based histologic primary endpoint, did not relate to improvement in fibrosis or NASH resolution. Third, any longitudinal treatment effect on ELF in this trial was only limited to the vitamin E arm, which showed a steady and significant decline relative to the placebo group. Finally, PIIINP had more dynamic longitudinal changes as it relates to changes in liver histology. Change in PIIINP significantly correlated with NASH resolution and improvement in NAS and fibrosis. Furthermore, its levels significantly declined in both the vitamin E and pioglitazone groups, relative to the placebo.

We are discouraged that change in ELF score was not associated with change in fibrosis in this data set, but we speculate that PIVENS—with no significant change in fibrosis at the end of treatment in the placebo, vitamin E, or pioglitazone groups—is perhaps not best suited for assessing this relationship. Sanyal et al. recently presented the results from a *post hoc* analysis of over 1,000 patients with Child class A NASH cirrhosis, who participated in simtuzumab and selonsertib clinical trials.⁽³¹⁾ Investigators noted that change in ELF was significantly associated with fibrosis regression ($P = 0.0076$). Similar observations were reported in the paper by Harrison et al., in which NGM282, an engineered FGF19 analogue, administered for 12 weeks was associated with fibrosis improvement, and drop in ELF was significantly associated with histological improvements.⁽³²⁾

We find it interesting that PIIINP was more dynamic longitudinally than ELF as it relates to

vitamin E and pioglitazone treatment. Although ELF showed a decline only with vitamin E treatment, PIIINP showed a decrease in either vitamin E or pioglitazone treated individuals, suggesting that it may be better suited for monitoring for response to therapy in patients with NASH. This discordance between ELF and PIIINP relative to treatments, in addition to PIIINP response to other therapeutic agents under investigation, must be verified in future studies.

Some potential limitations of this analysis deserve further discussion. First, PIVENS was completed and published in 2010, raising the possibility that ELF tested on samples stored for such a lengthy duration may not provide accurate results. ELF was measured on serum samples in 2012–2013, but *post hoc* data analyses were done much later. Second, PIVENS eligibility was restricted to patients without diabetes and without cirrhosis (with NASH) who met strict histologic criteria; thus, our observations from this study may not be generalizable to other populations. Third, although the PIVENS design included a follow-up visit at 24 weeks at EOT, we did not measure ELF at this time point and therefore missed an opportunity to assess for changes once pharmacological agents were discontinued. These limitations notwithstanding, we believe our study adds incremental knowledge to a growing body of literature surrounding the utility of circulating hepatic matrix proteins in the cross-sectional and longitudinal assessment of liver histology in NAFLD.

In conclusion, ELF is significantly associated with clinically significant and advanced fibrosis in patients with NASH, but its longitudinal changes are not associated with improvement in fibrosis. PIIINP, one of its components, appears promising for identifying longitudinal histologic changes in patients with NASH, and is worthy of further investigation.

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