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ORIGINAL RESEARCH

Determinants and Clinical Interpretation of Circulating Transthyretin in ATTR Amyloidosis

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ABSTRACT

BACKGROUND Transthyretin (TTR) amyloidosis (ATTR) ranges from localized to systemic disease, but the clinical interpretation of circulating TTR remains uncertain.

OBJECTIVES The objective of the study was to characterize serum TTR in ATTR and identify longitudinal determinants, including disease-modifying therapies.

METHODS In a single-center cohort, 134 patients with ATTR were enrolled. Serum TTR was measured at baseline (91 treatment-naive patients) and longitudinally during follow-up (347 measurements). Linear mixed-effects models were used to identify clinical and therapeutic determinants of circulating TTR.

RESULTS Baseline TTR levels declined across clinical stages, from isolated carpal tunnel syndrome to symptomatic heart failure (27 vs 20 mg/dL). In longitudinal mixed-effects analyses, older age ($\beta = -0.310$, $P < 0.001$), inflammation ($\log_{10}$[C-reactive protein+0.1], $\beta = -6.011$, $P < 0.001$), and cardiac stress ($\log_{10}$BNP, $\beta = -1.460$, $P = 0.033$) were independently associated with lower TTR levels, whereas albumin was positively associated ($\beta = 3.041$; $P < 0.001$). Wild-type ATTR showed higher TTR levels than variant ATTR ($\beta = 6.766$; $P < 0.001$). Tetramer stabilizers increased TTR ($\beta = 8.095$; $P < 0.001$), whereas small-interfering RNA therapy reduced TTR levels ($\beta = -13.456$; $P < 0.001$). Following stabilizer initiation, median TTR increased from 21.5 mg/dL to 32.2 mg/dL after >730 days of therapy.

CONCLUSIONS Circulating TTR reflects the integrated effects of systemic status and therapeutic interventions and should not be interpreted as a simple surrogate of ATTR disease severity. (JACC Adv. 2026;■:103047) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ATTR = transthyretin amyloidosis

BNP = brain natriuretic peptide

CRP = C-reactive protein

CTS = carpal tunnel syndrome

DMT = disease-modifying therapy

eGFR = estimated glomerular filtration rate

GLS = global longitudinal strain

HF = heart failure

LVEF = left ventricular ejection fraction

siRNA = small interfering RNA

TTR = transthyretin

Transthyretin (TTR) amyloidosis (ATTR) encompasses a spectrum of disease ranging from localized deposition, such as carpal tunnel syndrome (CTS), to progressive cardiomyopathy leading to symptomatic heart failure (HF).[1,2] Although circulating TTR is synthesized predominantly in the liver and is routinely measurable in serum,[3] its clinical interpretation in the context of ATTR remains unclear.

TTR is a negative acute-phase reactant, and its synthesis can be suppressed by inflammation, cytokine activation, and malnutrition—conditions commonly observed in chronic HF.[4-7] Low plasma TTR concentrations predict a higher risk of developing HF in general population[8,9] and in ATTR amyloidosis patients.[10,11] Conversely, stabilization of the TTR tetramer by disease-modifying therapies (DMTs) increase TTR concentrations,[12,13] while small interfering RNA (siRNA)-based therapies markedly reduce serum TTR by suppressing hepatic synthesis.[14] Thus, serum TTR concentration may represent the net balance of synthesis, degradation, and tetramer stability. Despite these considerations, few studies have addressed circulating TTR across the clinical spectrum of ATTR or identified the major determinants of serum TTR receiving contemporary DMTs. Therefore, we investigated serum TTR concentration in a cohort of patients with ATTR amyloidosis, including those with isolated CTS, subclinical disease and symptomatic HF, and evaluated longitudinal determinants of circulating TTR using linear mixed-effects modeling.

METHODS

STUDY POPULATION. This was a prospective single center study of consecutive 134 ATTR amyloidosis patients between September 2018 and November 2025, who attending Miyazaki University Hospital, Japan. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miyazaki (Protocol number: O-0651). Informed consent was obtained from all participants.

Patients recruit criteria: "*Isolated CTS*" refers to patients if the TTR amyloid was positive in the carpal ligament tissue, but negative for 99m-technetium pyrophosphate uptake in the myocardium (n = 24). ATTR cardiomyopathy was diagnosed when either by a positive endomyocardial biopsy or myocardial uptake of 99m-technetium pyrophosphate >2 on computed tomography/single photon emission computed tomography imaging in the absence of a plasma cell dyscrasia.[15] They were divided into 2 groups: "asymptomatic cardiac involvement" (n = 25), and "symptomatic HF (n = 85)". Severe hepatic disease (eg, liver cirrhosis and acute hepatitis) was excluded. The presence or absence of *TTR* gene mutation was confirmed by amplifying and sequencing exons 1 to 4 of the *TTR* gene using DNA extracted from whole blood through a polymerase chain reaction assay.[16]

ECHOCARDIOGRAPHIC ASSESSMENT. Echocardiographic parameters were assessed on the same day as blood sampling for serum TTR measurement, and the detailed echocardiographic assessments are described elsewhere.[16]

SERUM TTR MEASUREMENTS

Serum TTR concentrations were determined using an immunoturbidimetric assay based on antigen-antibody reactions (N-Assay TIA Prealbumin; Nittobo Medical Co.) with an automated analyzer, which reflects circulating TTR without specifically restricting detection to tetramers. Of 134 patients with ATTR amyloidosis, serum TTR concentrations were measured at the initial visit in 91 patients, and at 347 multiple, irregular time points during routine follow-up (the median number of measurements per patient was 3 (IQR: 1-4) (**Figure 1**).

OTHER BIOCHEMICAL ANALYSES. Serum albumin concentrations were determined by a bromocresol purple colorimetric method (L-Type Wako ALB-BCP), whereas C-reactive protein (CRP) concentrations were measured using a latex-enhanced immunoturbidimetric assay (CRP-Latex X2). Brain natriuretic peptide (BNP), as a marker of cardiac stress, was measured using an automated immunoassay system (Abbott), whereas high-sensitive troponin T, reflecting myocardial injury, was measured using the Roche Diagnostics assay. Estimated glomerular filtration rate (eGFR) was calculated using the standard Modification of Diet in Renal Disease study equation: $\text{eGFR (mL/min/1.73 m}^2) = 194 \times (\text{serum Cr})^{-1.094} \times (\text{age})^{-0.287}$ ($\times 0.739$, when female).[17]

STATISTICAL ANALYSES. The normality of continuous variables was assessed using the Shapiro-Wilk test. For both linear regression and mixed-effects models, homoscedasticity was evaluated using scatterplots of residuals vs fitted values, and normality of residuals was assessed using Q-Q plots. Continuous data are presented as mean ± SD for normally distributed variables or as median (IQR) for

non-normally distributed variables, whereas categorical variables are expressed as absolute numbers.

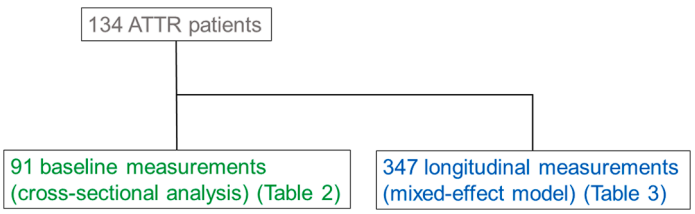
Categorical variables among 3 groups were compared using Pearson chi-square test. For comparisons of continuous variables across 3 independent groups, one-way analysis of variance with Tukey post hoc test was used for normally distributed variables, whereas the Kruskal-Wallis test followed by Tukey-type post hoc comparisons was applied for non-normally distributed variables. Given the non-normal distribution of serum TTR levels, associations between TTR and echocardiographic parameters were evaluated using Spearman rank correlation coefficients. Associations of baseline TTR and BNP levels with HF hospitalization were evaluated using Cox proportional hazards models. Kaplan-Meier curves were constructed according to TTR groups and compared using the log-rank test.

Of the study population, 91 patients who were not receiving TTR tetramer stabilizers or siRNA-based therapies at the time of evaluation were included in cross-sectional regression analyses. Serum TTR concentration was analyzed as a continuous dependent variable. Univariate and multivariable linear regression analyses were performed to identify factors associated with serum TTR concentration. CRP, BNP, and troponin T showed right-skewed distributions and were therefore $\log_{10}$-transformed before analysis; CRP values were transformed using $\log_{10}(\text{CRP} + 0.1)$. TTR genotype was included as a binary variable (wild-type vs variant). Multivariable linear regression analyses were conducted using the forced-entry method, including all prespecified covariates based on clinical relevance. Results are presented as unstandardized β coefficients with 95% CIs. Multicollinearity was assessed using variance inflation factors.

To evaluate longitudinal associations with serum TTR concentration, all available serum TTR measurements (n = 347) obtained during follow-up were incorporated into linear mixed-effects models, accounting for within-subject correlation across repeated measurements. This longitudinal data set included patients receiving DMTs, including stabilizers (tafamidis [n = 69], acoramidis [n = 2]) and siRNA (vutrisiran [n = 2]).

Fixed effects included $\log_{10}(\text{CRP} + 0.1)$, $\log_{10}$BNP, $\log_{10}$troponin-T, serum albumin concentration, age, eGFR, TTR genotype (wild-type vs variant), use of TTR tetramer stabilizers, and use of siRNA therapy. Dummy variables were coded such that the reference categories were variant ATTR for genotype, no TTR stabilizer use for stabilizer therapy, and no siRNA use for RNA interference therapy. A random intercept for each patient was included to account for within-subject correlations across repeated measurements. Model parameters were estimated using restricted maximum likelihood.

FIGURE 1 Study Design and Data Structure



Gray box indicates the overall patient cohort, green box indicates the baseline cohort for cross-sectional analysis in treatment-naive patients, and blue box indicates the longitudinal data set used for mixed-effects modeling. ATTR = transthyretin amyloidosis.

To visualize the longitudinal changes in serum TTR concentrations, follow-up time was categorized into clinically meaningful intervals relative to treatment initiation: >30 days before initiation, −30 to 0 days, 1 to 180 days, 181 to 365 days, 366 to 730 days, and >731 days after treatment initiation. When multiple TTR concentration measurements were present within the same time bin, their mean value was calculated.

A 2-sided P value <0.05 was considered statistically significant.

All statistical analyses and graphing were performed using SPSS Statistics (version 29; IBM Corporation) and GraphPad Prism 8.0.

RESULTS

BASELINE CHARACTERISTICS AND TTR CONCENTRATIONS ACROSS CLINICAL STAGES IN TREATMENT-NAIVE PATIENTS. As shown in Table 1, patients with isolated CTS were younger than those with symptomatic HF. They had higher serum albumin and eGFR levels, and lower BNP and troponin-T levels compared with patients with asymptomatic or symptomatic cardiac involvement. Accordingly, isolated CTS patients exhibited higher left ventricular ejection fraction (LVEF) and more preserved (more negative) global longitudinal strain (GLS) compared with patients with asymptomatic or symptomatic cardiac involvement. CRP levels did not differ significantly among 3 groups.

Circulating TTR levels differed across clinical stages. Patients with isolated CTS had the highest TTR levels (median 27 mg/dL; IQR: 23–30), whereas those with symptomatic HF had the lowest levels

TABLE 1 Study Baseline Characteristics

	Overall (N = 91)	Isolated CTS (n = 20)	Asymptomatic Cardiac Involvement (n = 21)	Symptomatic Heart Failure (n = 50)	*P* Value
Age (y)	76 ± 6	72 ± 7	75 ± 6	79 ± 6[a]	<0.001
Sex (M/F)	72/19	13/7	16/5	43/7	0.138
BMI (kg/m^2)	24 ± 4	26 ± 3	23 ± 3	24 ± 5	0.103
ATTR subtype (wt/v)	85/6	18/2	19/2	48/2	0.545
LVEF (%)	55 [46, 60]	61 [57, 65]	55 [49, 61][b]	50 [43, 57][a,c]	<0.001
GLS	−14 ± 4	−18 ± 3	−14 ± 3[b]	−12 ± 3[a,c]	<0.001
Albumin (g/dL)	4.04 ± 0.34	4.28 ± 0.21	4.02 ± 0.28[b]	3.95 ± 0.36[a]	<0.001
eGFR (mL/min/1.73 m^2)	58 ± 15	67 ± 14	60 ± 14	53 ± 17[d]	0.002
BNP (pg/mL)	114 [45, 246]	18 [6, 42] (n = 19)	101 [38, 170][d]	223 [94, 411][a,e]	<0.001
Troponin-T (ng/mL)	0.034 [0.019, 0.052]	0.012 [0.008, 0.019]	0.033 [0.018, 0.050][d]	0.045 [0.034, 0.062][a,c]	<0.001
CRP (mg/dL)	0.08 [0.04, 0.175] (n = 85)	0.07 [0.04, 0.14] (n = 18)	0.06 [0.035, 0.100]	0.115 [0.04, 0.3225] (n = 46)	0.248
TTR (mg/dL)	23 [18, 27]	27 [23, 30]	24 [21, 29]	20 [18, 24][a,c]	<0.001

Baseline characteristics were summarized for transthyretin amyloidosis (ATTR) patients in whom serum transthyretin (TTR) concentration was measured at the initial visit (n = 91), which constituted the cohort for cross-sectional group comparisons. [a]$P < 0.001$ vs isolated carpal tunnel syndrome (CTS). [b]$P < 0.05$. [c]$P < 0.05$. [d]$P < 0.01$. [e]$P < 0.01$ vs asymptomatic cardiac involvement.

BMI = body mass index; BNP = brain natriuretic peptide; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; F = female; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; M = male; v = variant; wt = wild-type.

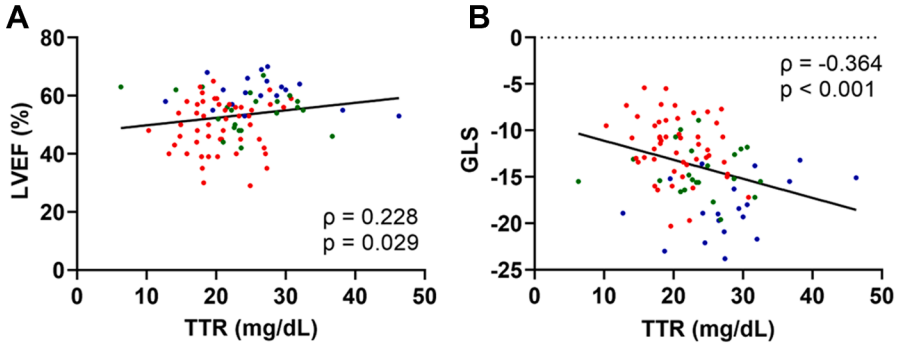
(20 mg/dL; IQR: 18-24). Patients with asymptomatic cardiac involvement showed intermediate TTR concentrations (24 mg/dL; IQR: 21-29).

Serum TTR levels showed a modest positive correlation with LVEF (Figure 2A) ($\rho = 0.228$; $P = 0.029$), whereas a stronger inverse association was observed with GLS (Figure 2B) ($\rho = -0.364$; $P < 0.001$).

During a median follow-up of 367 days (Q1-Q3: 98-523 days), 8 patients were hospitalized for worsening HF. In univariate Cox analysis, baseline TTR levels were not significantly associated with HF hospitalization (HR per 1 mg/dL increase, 0.937; $P = 0.299$), whereas BNP levels were significantly associated with increased risk (HR per 100 pg/mL: 2.009; $P = 0.002$). Consistent with these findings, Kaplan-Meier analysis according to baseline TTR levels (dichotomized at the median, 23 mg/dL) did not demonstrate a significant difference in HF hospitalization between groups (log-rank $P = 0.545$) (Figure 3).

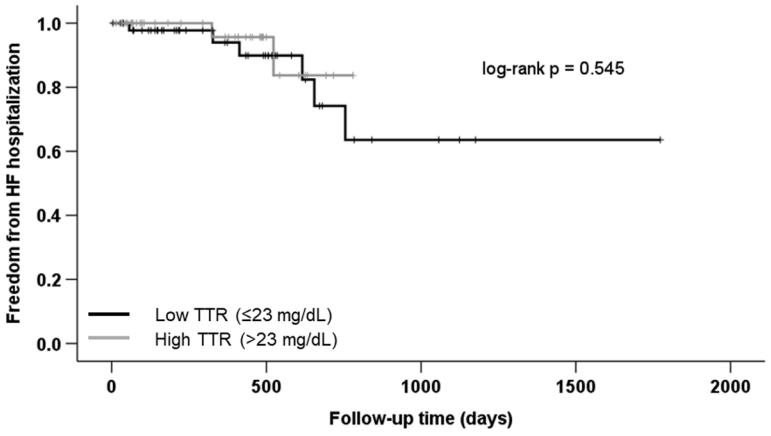
DETERMINANTS OF SERUM TTR CONCENTRATION AT BASELINE. In cross-sectional multivariable linear regression analyses of patients not receiving DMTs at baseline, wild-type TTR genotype, higher serum albumin levels, and lower $\log_{10}$BNP levels were

FIGURE 2 Association Between Serum Transthyretin Levels and Cardiac Function



Scatter plots show the association between serum transthyretin (TTR) levels and (A) left ventricular ejection fraction (LVEF) and (B) global longitudinal strain (GLS). Correlations were assessed using Spearman rank coefficients. Points are color-coded according to clinical stage: blue represents isolated carpal tunnel syndrome, green represents asymptomatic cardiac involvement, and red represents symptomatic heart failure.

FIGURE 3 Kaplan-Meier Curves for HF Hospitalization According to Transthyretin Levels



No. at Risk					
Low TTR	49	18	3	0	0
High TTR	42	8	0	0	0

Kaplan-Meier curves for heart failure (HF) hospitalization according to transthyretin levels dichotomized at the median (23 mg/dL). No significant difference was observed between groups (log-rank $P = 0.545$). Numbers at risk are shown below the x-axis. TTR = transthyretin.

independently associated with higher serum TTR concentrations, whereas age, body mass index, $\log_{10}$(CRP + 0.1), and $\log_{10}$troponin T were not independently associated after adjustment for other covariates. Although eGFR was not associated with serum TTR in univariable analyses, it became independently associated with lower TTR levels after multivariable adjustment. This likely reflects confounding by age, cardiac stress, and nutritional status rather than collinearity, as all variance inflation factor values were <3 (Table 2).

LONGITUDINAL DETERMINANTS OF SERUM TTR CONCENTRATION. As shown in Table 3, a multivariate longitudinal linear mixed-effects model demonstrated that increasing age correlated with lower TTR concentrations (β = −0.310; 95% CI: −0.446 to −0.174; $P < 0.001$), whereas wild-type ATTR genotype was associated with higher TTR compared with variant ATTR (β = 6.766; 95% CI: 1.781-11.751; $P < 0.001$). In addition, systemic inflammation, assessed by $\log_{10}$(CRP+0.1), was strongly and inversely associated with serum TTR concentration

TABLE 2 Linear Regression Analysis of Factors Associated With Serum Transthyretin Concentrations

	Univariate Analysis				Multivariate Analysis			
	β	95% CI Lower	95% CI Upper	*P* Value	β	95% CI Lower	95% CI Upper	*P* Value
Age (y)	−0.263	−0.455	−0.071	0.008	−0.184	−0.372	0.004	0.055
BMI (kg/m^2)	0.355	0.064	0.646	0.017	0.196	−0.085	0.360	0.223
Wild-type (vs variant)	9.007	4.084	13.930	<0.001	7.333	3.304	11.362	<0.001
Albumin (g/dL)	8.927	5.564	12.291	<0.001	3.558	0.156	6.959	0.041
$\log_{10}$(CRP+0.1)	−5.028	−8.929	−1.128	0.012	−1.470	−4.585	1.646	0.350
eGFR (mL/min/1.73 m^2)	0.005	−0.081	0.091	0.909	−0.126	−0.202	−0.049	0.002
$\log_{10}$BNP	−5.696	−7.817	−3.575	<0.001	−5.219	−8.113	−2.324	<0.001
$\log_{10}$troponin-T	−8.747	−12.582	−4.911	<0.001	−1.773	−6.969	3.422	0.498

Univariate and multivariate linear regression analyses were performed to identify factors associated with serum transthyretin (TTR) concentration in 91 patients who were not receiving TTR tetramer stabilizers or siRNA-based therapies at the time of evaluation. Serum TTR concentration was analyzed as a continuous dependent variable. Age, body mass index (BMI) and estimated glomerular filtration rate (eGFR) were included as continuous variables. TTR genotype was included as a binary variable (wild-type vs variant). C-reactive protein (CRP), B-type natriuretic peptide (BNP), and troponin T were $\log_{10}$-transformed prior to analysis; CRP values were transformed using $\log_{10}$(CRP + 0.1). Multivariate analyses were conducted using the forced-entry method, including all prespecified covariates based on clinical relevance. Results are presented as unstandardized β coefficients with 95% CIs. Regression coefficients (β) are expressed as changes in circulating TTR concentration (mg/dL) per 1-unit increase in each variable. For log10-transformed variables, coefficients correspond to the change associated with a 10-fold increase in the respective biomarker.

TABLE 3 Determinants of Serum Transthyretin Concentration in ATTR Amyloidosis

	Univariate Analysis				Multivariate Analysis			
	β	95% CI Lower	95% CI Upper	*P* Value	β	95% CI Lower	95% CI Upper	*P* Value
Age (y)	−0.260	−0.438	−0.083	0.004	−0.310	−0.446	−0.174	<0.001
Wild-type (vs variant)	15.884	10.694	21.074	<0.001	6.766	1.781	11.751	<0.001
Albumin (g/dL)	8.586	6.631	10.541	<0.001	3.041	1.518	4.563	<0.001
eGFR (mL/min/1.73 m^2)	−0.120	−0.183	−0.057	<0.001	−0.041	−0.085	0.002	0.061
log_{10}(CRP+0.1)	−7.901	−9.508	−6.294	<0.001	−6.011	−7.200	−4.822	<0.001
log_{10}BNP	−4.068	−5.986	−2.151	<0.001	−1.460	−2.803	−0.117	0.033
Log_{10}troponin-T	−3.049	−6.760	0.662	0.107				
TTR stabilizer use (vs no use)	8.047	6.856	9.238	<0.001	8.095	7.235	8.956	<0.001
Vutrisiran use (vs no use)	−18.635	−24.861	−12.410	<0.001	−13.456	−17.067	−9.845	<0.001

Univariate and multivariate linear mixed-effects model analyses were performed to identify determinants of serum transthyretin (TTR) concentration using all available longitudinal measurements. All serum TTR measurements obtained during follow-up were included, regardless of treatment status. Fixed effects included age, serum albumin concentration, TTR genotype (wild-type vs variant), log_{10}(CRP + 0.1), log_{10}BNP, log_{10}troponin-T, use of TTR tetramer stabilizers, and use of the siRNA agent vutrisiran. Model parameters were estimated using restricted maximum likelihood (REML). Results are presented as unstandardized estimates with 95% CIs. Statistical significance was defined as a 2-sided *P* value < 0.05. Regression coefficients (β) are expressed as changes in circulating TTR concentration (mg/dL) per 1-unit increase in each variable. For log10-transformed variables, coefficients correspond to the change associated with a 10-fold increase in the respective biomarker.

Abbreviations as in Table 1.

(β = −6.011; 95% CI: −7.200 to −4.822; $P < 0.001$). Similarly, HF severity, assessed by log_{10}BNP, showed an independent negative association with TTR (β = −1.460; 95% CI: −2.803 to −0.117; $P = 0.033$). Nutritional status, reflected by serum albumin levels, was positively associated with TTR (β = 3.041; 95% CI: 1.518-4.563; $P < 0.001$). DMTs demonstrated directionally distinct associations with circulating TTR. The use of TTR tetramer stabilizers was associated with higher TTR levels (β = 8.095; 95% CI: 7.235-8.956; $P < 0.001$), whereas treatment with vutrisiran was strongly associated with reduced TTR (β = −13.456; 95% CI: −17.067 to −9.845; $P < 0.001$).

TABLE 4 Sensitivity Analysis Excluding Patients Treated With Vutrisiran

	Multivariate Analysis			
	β	95% CI Lower	95% CI Upper	*P* Value
Age (y)	−0.326	−0.463	−0.189	<0.001
Wild-type (vs variant)	7.986	7.040	8.933	<0.001
Albumin (g/dL)	3.473	1.825	5.121	<0.001
eGFR (mL/min/1.73 m^2)	−0.053	−0.099	−0.007	0.023
log_{10}(CRP+0.1)	−5.821	−7.132	−4.511	<0.001
log_{10}BNP	−1.556	−3.001	−0.111	0.035
TTR stabilizer use (vs no use)	7.986	7.040	8.933	<0.001

This linear mixed-effects model excludes patients receiving vutrisiran and was constructed to assess the robustness of fixed-effect estimates. Reference categories were defined as follows: variant ATTR for "wild-type (vs variant)" and no TTR stabilizer use for "TTR stabilizer use (vs no use)". The model was estimated using restricted maximum likelihood (REML). The outcome variable was serum transthyretin (TTR) concentration (mg/dL). Statistical significance was defined as a 2-sided *P* value < 0.05. Regression coefficients (β) are expressed as changes in circulating TTR concentration (mg/dL) per 1-unit increase in each variable. For log 10-transformed variables, coefficients correspond to the change associated with a 10-fold increase in the respective biomarker.

Abbreviations as in Table 1.

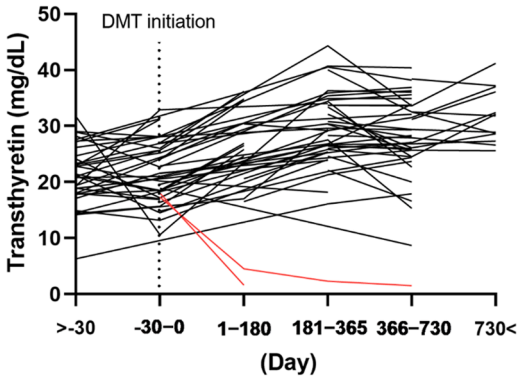
However, this estimate should be interpreted with caution given the limited number of patients treated with vutrisiran (n = 2; 8 post-treatment measurements). In a sensitivity analysis excluding patients treated with vutrisiran, the estimated associations between serum TTR concentration and systemic factors—including age, ATTR subtype, nutritional status, renal function, inflammation, HF severity, and tetramer stabilizer therapy—remained materially unchanged (Table 4).

LONGITUDINAL CHANGES IN SERUM TTR CONCENTRATIONS AFTER DMTs INITIATION. Serum TTR levels were evaluated longitudinally before and after the initiation of DMTs using a spaghetti plot (Figure 4). A time-binned analysis showed a gradual increase in serum TTR concentrations after DMT initiation. The median TTR concentrations were comparable between the pretreatment period (>30 days before initiation, 21.3 mg/dL; n = 34) and at the time of DMT initiation (−30 to 0 days, 21.5 mg/dL; n = 35). The median TTR levels increased during the 1 to 180 days interval after initiation (24.8 mg/dL; n = 16) and further increased during the 181 to 365 days interval (29.1 mg/dL; n = 44). The median TTR levels were similar during the 366 to 730 days interval (27.8 mg/dL; n = 44), with a further increase observed beyond 730 days after initiation (32.2 mg/dL; n = 19).

DISCUSSION

Circulating TTR has traditionally been interpreted as a marker of nutritional status and systemic inflammation in general and cardiovascular

FIGURE 4 Serum Transthyretin Changes Before and After Therapy



Spaghetti plot showing individual serum transthyretin levels over time relative to disease-modifying therapies (DMTs) initiation. The vertical dotted line indicates the time of DMTs initiation. Time periods are categorized as >30 days before initiation, 30-0 days at the time of DMT initiation, 1 to 180 days, 181 to 365 days, 366 to 730 days, and >731 days after initiation. Numbers of patients in each period were 34, 35, 16, 44, 44, and 19, respectively. The number of available measurements differed across time intervals, reflecting routine clinical follow-up. When multiple TTR concentration measurements were present within the same time bin, their mean value was calculated. Red lines indicate 2 patients treated with siRNA therapy (vutrisiran).

populations.[4,5,8,9,18] However, our findings extend this concept specifically to ATTR, a disease in which TTR itself is the pathogenic protein. Importantly, across the clinical spectrum of ATTR, we observed that circulating TTR levels were not primarily determined by disease stage alone, but rather reflected a complex interplay between genotype, cardiac stress, systemic inflammation, nutritional status, aging, and therapeutic interventions (**Central Illustration**). This distinction is critical, as it challenges the intuitive assumption that lower TTR directly reflects more severe amyloid burden. Instead, our data support a conceptual framework in which circulating TTR represents an integrative biomarker strongly influenced by systemic and therapeutic status, rather than a simple surrogate of ATTR disease severity.

In this study, we demonstrated that serum TTR concentrations varied across clinical phenotypes, being lowest in patients with symptomatic HF, intermediate in those with asymptomatic cardiac involvement, and highest in individuals with isolated CTS. These differences likely reflect systemic physiological conditions rather than ATTR disease burden itself, as localized amyloid deposition, such as in CTS, does not substantially influence circulating TTR levels.[19]

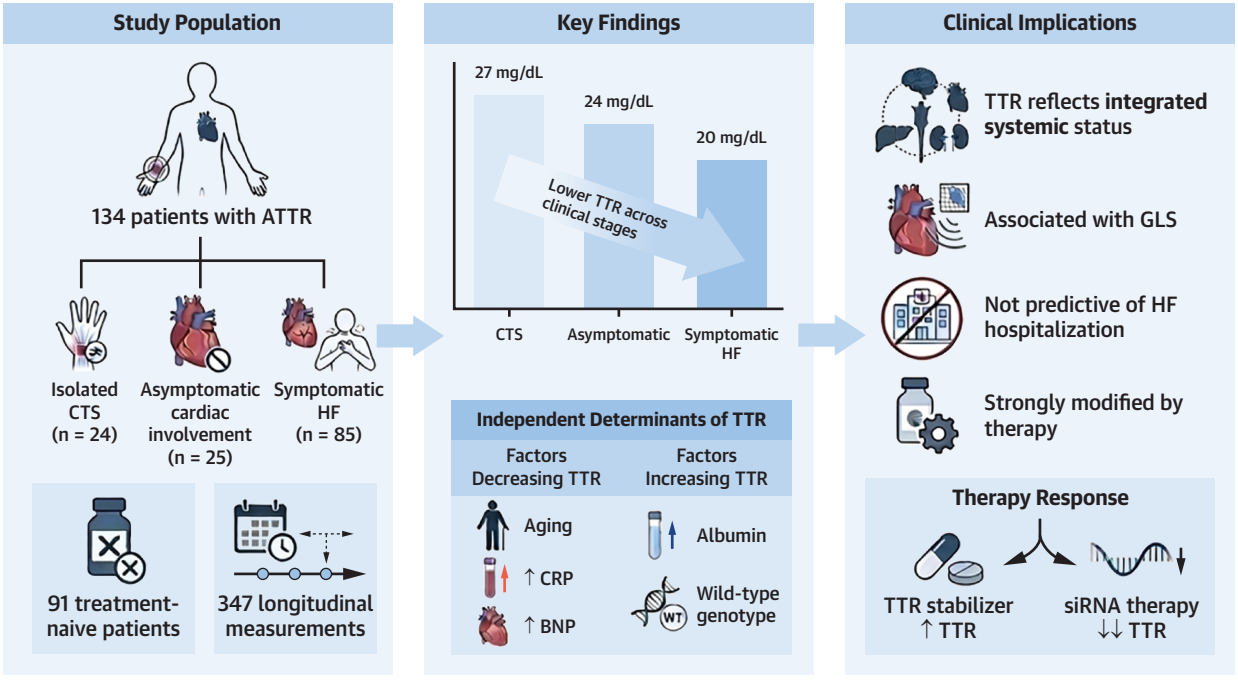
The association between TTR and GLS was stronger than that with LVEF, suggesting that TTR may be more closely related to subclinical myocardial dysfunction than to global systolic function. However, the modest strength of these correlations indicates that TTR is not determined by left ventricular function alone. In contrast, no significant association was observed between TTR and HF hospitalization in this cohort, whereas BNP was significantly predictive of this outcome. Given the limited number of events, these findings should be interpreted with caution, but they are consistent with the concept that TTR primarily reflects systemic status rather than serving as a simple surrogate of ATTR disease severity.

The reduction in TTR concentrations observed in symptomatic HF likely reflects a combination of inflammation and impaired hepatic synthesis. Proinflammatory cytokines, particularly interleukin-6, suppress hepatic TTR production, and their activation increases with HF severity.[20,21] In addition, HF is frequently accompanied by malnutrition and hepatic congestion, both of which further impair protein synthesis and contribute to reduced circulating TTR levels.[22-24] The kidney also plays an important role in TTR catabolism.[3] Consequently, changes in renal function may influence circulating TTR concentrations, although this relationship is likely modified by concurrent systemic conditions.

The discrepancy between cross-sectional and longitudinal associations with eGFR or CRP may be explained by differences in the effects captured by each model. Cross-sectional analyses primarily reflect their interindividual variability, whereas mixed-effects models capture within-individual temporal changes.

Our data further highlight the distinct effects of DMTs on circulating TTR concentrations. Treatment with TTR tetramer stabilizers, predominantly tafamidis in this cohort, was associated with higher serum TTR levels, consistent with stabilization of the tetrameric structure and reduced clearance.[12,13] By contrast, treatment with vutrisiran was associated with a marked reduction in circulating TTR, reflecting effective suppression of hepatic TTR synthesis through siRNA.[14] Although only 2 patients received vutrisiran, the marked and consistent suppression of serum TTR observed across repeated post-treatment measurements underscores the profound pharmacological impact of gene-silencing therapy on circulating TTR levels. Notably, during later observation periods (>730 days), longitudinal trends in serum TTR were primarily driven by tetramer

CENTRAL ILLUSTRATION **Determinants and Clinical Interpretation of Circulating Transthyretin Across the ATTR Spectrum**



Tsuruda T, et al. JACC Adv. 2026;■(■):103047.

The study included 134 patients with transthyretin amyloidosis (ATTR), comprising isolated carpal tunnel syndrome (CTS), asymptomatic cardiac involvement, and symptomatic heart failure (HF). Cross-sectional analyses were performed in 91 treatment-naive patients, and longitudinal analyses included 347 serial TTR measurements. Circulating transthyretin (TTR) concentrations progressively declined across clinical stages, from isolated CTS (27 mg/dL) to asymptomatic cardiac involvement (24 mg/dL) and symptomatic HF (20 mg/dL). Independent determinants associated with lower TTR included aging, inflammation (higher C-reactive protein [CRP]), and cardiac stress (higher B-type natriuretic peptide [BNP]), whereas higher albumin levels and wild-type genotype were associated with higher TTR concentrations. Clinically, circulating TTR reflects integrated systemic status and is associated with subclinical myocardial dysfunction, as indicated by global longitudinal strain (GLS). However, TTR is not a simple surrogate of ATTR disease severity and was not predictive of HF hospitalization. Disease-modifying therapies substantially influenced circulating TTR concentrations, with TTR stabilizers increasing and small-interfering RNA (siRNA) therapies markedly reducing TTR levels.

stabilizer therapy rather than siRNA treatment. Exclusion of patients receiving vutrisiran did not materially alter the associations observed in the mixed-effects model, supporting the robustness of our conclusions.

From a mechanistic perspective, our findings support the concept that ATTR pathogenesis is primarily governed by tetramer stability rather than by absolute circulating TTR concentrations.[3] The dynamic regulation and rapid turnover of TTR, together with its sensitivity to systemic conditions, may explain why circulating levels do not directly correspond to clinical disease manifestations.[3,25,26] Although troponin T is a well-established marker of myocardial injury and prognosis in ATTR cardiomyopathy,[27,28] it was not independently associated with circulating TTR levels, supporting that serum TTR reflects systemic physiological status rather than myocardial injury per se. Future advances in assays capable of detecting misfolded or aggregated TTR species may provide more direct insight into amyloid pathology.[29,30]

STUDY STRENGTHS AND LIMITATIONS. Strengths. This study has several notable strengths. First, we analyzed a longitudinal data set comprising repeated serum TTR measurements obtained during routine clinical follow-up, allowing us to capture dynamic changes in circulating TTR levels over time rather than relying on cross-sectional observations alone. Second, the use of a linear mixed-effects model enabled appropriate handling of within-subject correlations arising from repeated measurements, thereby providing robust estimates of independent associations between TTR levels and clinical,

biochemical, and therapeutic factors. Third, our cohort included patients across a broad clinical spectrum of ATTR amyloidosis, ranging from subclinical disease to overt HF, which allowed us to evaluate TTR regulation across distinct disease phenotypes.[31] Finally, the inclusion of patients receiving contemporary DMTs, including TTR tetramer stabilizers and siRNA-based treatment, provides clinically relevant insights into how these interventions influence circulating TTR concentrations in real-world practice.

Limitations. Several limitations should be acknowledged. First, this was a single-center observational study, which may limit the generalizability of our findings to other populations or health care settings. Second, the number of patients treated with vutrisiran was small, precluding detailed subgroup analyses of siRNA therapy and limiting our ability to fully characterize long-term treatment effects. Third, although we adjusted for key clinical and laboratory parameters, unmeasured confounders—such as genetically regulated TTR expression in the liver, cytokine profiles, or body composition—may have influenced circulating TTR levels.[32-34] In addition, the relationship between circulating TTR concentrations and tissue-level amyloid deposition was not quantitatively assessed. Fourth, objective measures of functional capacity, such as the 6-minute walk distance, were not available. Similarly, cardiac magnetic resonance tissue characterization parameters were not included because imaging and blood sampling were not obtained contemporaneously in a standardized manner. Given the temporal variability of circulating TTR, this mismatch in timing may have limited the interpretability of these relationships. Finally, the limited number of events in our cohort may have reduced statistical power to detect associations between TTR and clinical outcomes. In addition, the observational nature of the study precludes causal inference regarding the relationships between TTR levels, disease severity, and therapeutic interventions.

CONCLUSIONS

Circulating TTR levels reflect the combined influences of inflammation, cardiac stress, nutritional status, and DMTs. Accordingly, serum TTR should not be interpreted as a simple surrogate of ATTR disease severity, but rather as an integrative indicator strongly influenced by systemic status and treatment effects.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with transthyretin amyloidosis, circulating TTR levels should be interpreted in the context of systemic inflammation, nutritional status, cardiac stress, and ongoing therapy, rather than as a simple surrogate of disease severity.

TRANSLATIONAL OUTLOOK: Future studies should evaluate whether integrating transthyretin with clinical, imaging, and therapeutic parameters improves risk stratification and monitoring of treatment response in ATTR.

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