# Association of Wild-Type Transthyretin Amyloidosis (ATTRwt) with Inflammatory Arthritis and Cytomegalovirus Infection

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*Article*

# Association of Wild-Type Transthyretin Amyloidosis (ATTRwt) with Inflammatory Arthritis and Cytomegalovirus Infection

**Short Title: Wild-type Transthyretin Amyloidosis Risk Factors**

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**Abstract**

**Background:** Transthyretin amyloid cardiomyopathy (ATTR-CM), particularly the wild-type form (ATTRwt), is an underdiagnosed cause of heart failure with preserved ejection fraction (HFpEF) in older adults. Despite growing recognition, its risk factors remain incompletely characterized. **Methods:** We analyzed 2016-2020 data from the National Inpatient Sample to identify demographic and clinical factors associated with ATTRwt, using ICD-10 code E85.82. Multivariable logistic regression assessed associations with age, sex, race, comorbidities, and inflammatory or infectious conditions. **Results:** Among 2,515 patients with ATTRwt, the mortality rate was 4.57%, versus 3.05% in those without ATTRwt (p=0.04). After multivariate analysis, ATTRwt was significantly associated with age (OR 1.07, p<0.001), Black race (OR 2.79, p<0.001), cytomegalovirus infection (OR 12.33, p<0.001), psoriatic arthritis (OR 5.61, p=0.003), CKD (OR 3.67, p<0.001), and gout (OR 3.39, p=0.033). **Conclusion:** This nationally representative study identifies several novel clinical associations with ATTRwt, including inflammatory arthritides (gout, psoriatic arthritis) and CMV infection. These findings support the hypothesis that chronic inflammation and immune dysregulation may contribute to TTR destabilization and amyloidogenesis. Future studies should explore these associations

**Keywords:** transthyretin amyloidosis; wild-type transthyretin amyloidosis; gout; psoriatic arthritis; cytomegalovirus

## Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, infiltrative cardiomyopathy caused by extracellular deposition of misfolded transthyretin (TTR) fibrils in the myocardium.[1] TTR, a primarily liver-synthesized tetrameric protein that transports thyroxine and retinol-binding protein, undergoes pathogenic dissociation in two distinct forms: hereditary aka variant aka mutant ATTR (hATTR, ATTRv, ATTRmt) and wild-type aka senile cardiac amyloidosis (ATTRwt).[1] Upon destabilization due to genetic mutation (hATTR) or aging (ATTRwt), TTR dissociates and misfolds into insoluble amyloid fibrils. These fibrils deposit within the myocardial interstitium, causing increased stiffness, impaired diastolic filling, and, in advanced disease, systolic dysfunction.[1]

ATTR-CM is an increasingly recognized diagnosis, accounting for an estimated 20% of patients with heart failure with preserved ejection fraction (HFpEF) and unexplained left ventricular hypertrophy (>14 mm)[2,3]. In the U.S., approximately 5,000-7,000 new cases are diagnosed annually[2,3]. However, ATTRwt appears to be underdiagnosed, as evidenced by multiple studies

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showing a higher prevalence when systematic screening is performed. In patients over 60 with HFpEF, dedicated screening revealed ATTRwt in 6-13% of cases, compared to just 1% without screening.[2,4] Similarly, among patients with aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR), 16% were found to have ATTRwt when actively screened.[5] These findings suggest that ATTRwt is more common than previously recognized and often missed without targeted diagnostic evaluation. ATTRwt also disproportionately affects elderly males—25% of men over 80 show amyloid deposits at autopsy—while hATTR affects both sexes more equally, with significant male predominance at clinical presentation.[3]

ATTR-CM typically manifests with heart failure symptoms—dyspnea, fatigue, and peripheral edema—along with arrhythmias, conduction disease (e.g., AV block, bundle branch block), and extracardiac signs like carpal tunnel syndrome, particularly in ATTRwt.[6] Clinical onset typically occurs after age 60 in hATTR, although onset is variable depending on mutation; ATTRwt onset is usually later—often beyond age 70.[6] Noninvasive diagnosis relies on echocardiography, cardiovascular magnetic resonance imaging (MRI) with contrast and late gadolinium enhancement (LGE), and bone tracer cardiac scintigraphy. A key echocardiogram finding is reduced global longitudinal strain with apical sparing of longitudinal strain. Other findings may include biventricular wall thickening mimicking hypertrophy, nondilated ventricles, biatrial enlargement, or valvular and interatrial septal thickening.[7,8] Cardiac MRI with LGE shows different patterns of subendocardial and transmural amyloid burden, with an overall pooled sensitivity and specificity of 85% and 92%, respectively.[7–9] Lastly, bone tracer cardiac scintigraphy can compare cardiac uptake versus bone uptake of 99m technetium [Tc]-labeled pyrophosphate (99mTc-PYP).[8,10] A meta-analysis found that when cardiac uptake increased and even surpassed bone uptake (Grade 1-3) cardiac scintigraphy had a pooled sensitivity of 82% and specificity of 99%.[7] While endomyocardial biopsy remains the gold standard—confirming amyloid via Congo red staining and mass spectrometry—diagnosis can safely be made noninvasively when scintigraphy is positive and AL amyloidosis has been excluded via monoclonal protein testing.[7,10] Many of these tests have limited to no reliability in distinguishing hATTR from ATTRwt, and thus genetic testing is essential.[7,10]

Prognostic models, such as the Mayo staging system, utilize biomarkers including N-terminal pro B-type Natriuretic Peptide (NT-proBNP) and cardiac troponin T[11]; later updates also incorporate estimated glomerular filtration rate (eGFR)[12]. Untreated median survival is poor: 2.5 years for hATTR and 3.6 years for ATTRwt[11,13], though staging using the above system has a marked prognostic advantage as median survival in ATTRwt was 5.8 years in Stage 1 patients, 3.9 years in Stage 2 patients, and 2.0 years in Stage 3 patients[12].

Disease-modifying therapies have also transformed the management landscape. TTR-stabilizers such as tafamidis and acoramidis prevent tetramer dissociation.[14,15] Notably, acoramidis (Attruby) received U.S. FDA approval in November 2024 after showing a significant reduction in cardiovascular hospitalizations and mortality in a phase III trial.[16] Patients with ATTR-CM may also benefit from gene-silencing therapies (vutrisiran, patisiran, inotersen).[15] Supportive therapy—diuretics for congestion, rhythm control, and device therapy—remains essential.[15]

Our study aimed to identify the risk factors associated with ATTRwt. Specifically, we correlated rates of ATTRwt with age, gender, race, viral infections, inflammatory disease, and traditional cardiovascular risk factors.

## Materials and Methods

This study utilized data from the National Inpatient Sample (NIS), a nationwide database derived from discharge records provided by state-level data organizations and hospital associations. The NIS includes information from more than 4,500 hospitals across the United States, representing roughly 20% of all inpatient admissions annually. It focuses on community hospitals and excludes federal hospitals, long-term care, psychiatric, and rehabilitation facilities. The dataset is weighted to produce nationally representative estimates of hospital utilization, clinical outcomes, and healthcare costs. The NIS provides de-identified, patient-level data for each inpatient stay, including

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demographic details, primary and secondary diagnoses, procedures, length of hospitalization, total charges, and outcomes such as in-hospital mortality and discharge status. It encompasses all types of payers, including Medicare, Medicaid, private insurers, and uninsured.

For this analysis, we used data spanning the years 2016 to 2020. Diagnoses were identified using ICD-10 codes, including E85.82 for wild-type transthyretin amyloidosis (ATTRwt), along with codes for cardiovascular risk factors, inflammatory conditions, and viral infections.

Patient demographics, clinical variables, and hospital characteristics were summarized using means and standard deviations for continuous data and proportions with 95% confidence intervals for categorical variables. Two-sample t-tests were employed to assess differences in continuous variables, while categorical variables were compared using Chi-square or Fisher's exact tests, as appropriate. Logistic regression was used to estimate the odds of binary outcomes in relation to patient and hospital factors. Multivariable logistic regression models were constructed to determine adjusted odds ratios (ORs) with 95% confidence intervals. All analyses incorporated the appropriate discharge weights to account for the complex sampling design of the NIS. Statistical significance was defined as a two-tailed p-value < 0.05. Data analyses were conducted using STATA version 17 (StataCorp, College Station, TX).

## Results

2,515 patients were diagnosed with ATTRwt (Table 1). The mortality rate was 4.57%, versus 3.05% in those without ATTRwt (p=0.04). Compared to patients without ATTRwt, patients with ATTRwt were more likely to be older (77.4 vs. 67.1 years, p<0.001), male (79.72% vs. 48.57%, p<0.001, OR 4.16 [3.26-5.32]), Black (26.32% vs 14.16%, p<0.001, OR 2.03 [1.61-2.55]), have cytomegalovirus infection (CMV, 0.60% vs. 0.06%, p<0.001, OR 10.38 [3.33-32.35), gout (0.60% vs. 0.09%, p=0.001, OR 6.73 [2.21-20.47]), chronic kidney disease (CKD, 60.84% vs. 22.50%, p<0.001, OR 5.35 [4.43-6.47]), psoriatic arthritis (0.60% vs. 0.18%, p=0.04, OR 3.38 [1.09-10.43]), coronary artery disease (CAD, 40.56% vs. 26.91%, p<0.001, OR 1.85 [1.56-2.20]), hypertension (81.71% vs. 70.76%, p<0.001, OR 1.85 [1.47-2.32]), and hyperlipidemia (51.46% vs. 43.06%, p<0.001, OR 1.40 [1.17-1.68]).

**Table 1.** Association of demographics and comorbidities with wild-type transthyretin amyloidosis.

| | Total | Wild ATTR | Other | *P-value* | Odds Ratio (C.I) |
|---|---|---|---|---|---|
| | 112,982,565 | 2,515 | 112,980,050 | | |
| Mortality | 3.05% | 4.57% | 3.05% | 0.04 | 1.52(1.02-2.28) |
| Age | | | | <0.001 | |
| (Mean±SD) | 67.11±13.55 | 77.42±9.32 | 67.1±13.55 | | |
| Median(IQR) | 67(57-78) | 79(72-84) | 67(57-78) | | |
| Gender | | | | | |
| Male | 48.57% | 79.72% | 48.57% | <0.001 | 4.16(3.26-5.32) |
| Female | 51.43% | 20.28% | 51.53% | <0.001 | 0.24(0.19-0.31) |
| Race | | | | | |
| White | 71.29% | 65.38% | 71.29% | | REF |
| Black | 14.16% | 26.32% | 14.16% | <0.001 | 2.03(1.61-2.55) |

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| | | | | | |
|---|---|---|---|---|---|
| Hispanic | 9.03% | 3.64% | 9.03% | 0.002 | 0.44(0.26-0.75) |
| Asian/Pac Isl | 2.33% | 2.23% | 2.33% | 0.91 | 1.04(0.50-2.17) |
| Native American | 0.59% | 0.20% | 0.59% | 0.33 | 0.38(0.05-2.69) |
| Others | 2.60% | 2.23% | 2.60% | 0.82 | 0.93(0.51-1.69) |
| Risk Factors | | | | | |
| Cytomegalovirus infection | 0.06% | 0.60% | 0.06% | <0.001 | 10.38(3.33-32.35) |
| Gout | 0.09% | 0.60% | 0.09% | 0.001 | 6.73(2.21-20.47) |
| CKD | 22.50% | 60.84% | 22.50% | <0.001 | 5.35(4.43-6.47) |
| Psoriatic arthritis | 0.18% | 0.60% | 0.18% | 0.04 | 3.38(1.09-10.43) |
| Coronary Artery Disease | 26.91% | 40.56% | 26.91% | <0.001 | 1.85(1.56-2.20) |
| Hypertension | 70.76% | 81.71% | 70.76% | <0.001 | 1.85(1.47-2.32) |
| Hyperlipidemia | 43.06% | 51.46% | 43.06% | <0.001 | 1.40(1.17-1.68) |
| Protective Factors | | | | | |
| Alcohol use | 6.58% | 1.59% | 6.58% | <0.001 | 0.23(0.11-0.46) |
| Chronic obstructive pulmonary disease | 21.02% | 13.52% | 21.02% | <0.001 | 0.59(0.46-0.76) |
| Type 2 Diabetes Mellitus | 32.76% | 26.04% | 32.76% | 0.004 | 0.72(0.58-0.90) |
| Insignificant Comorbidities | | | | | |
| Antiphospholipid Syndrome | 0.09% | 0.20% | 0.09% | 0.43 | 2.21(0.31-15.77) |
| Bicuspid Valve | 0.10% | 0.20% | 0.10% | 0.49 | 1.99(0.28-14.22) |
| Systemic Connective Tissue Disorders | 0.62% | 1.19% | 0.62% | 0.11 | 1.94(0.86-4.34) |
| Reynaud's Syndrome | 0.22% | 0.40% | 0.22% | 0.42 | 1.77(0.44-7.13) |
| Tobacco use | 26.91% | 30.22% | 26.91% | 0.09 | 1.18(0.98-1.42) |
| Influenza | 0.68% | 0.60% | 0.68% | 0.83 | 0.88(0.28-2.75) |
| Obesity | 9.21% | 7.95% | 9.21% | 0.33 | 0.85(0.62-1.18) |
| Viral infection | 0.27% | 0.20% | 0.27% | 0.76 | 0.73(0.10-5.23) |
| Rheumatoid Arthritis | 2.36% | 1.59% | 2.36% | 0.25 | 0.67(0.34-1.33) |

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| | | | | | |
|---|---|---|---|---|---|
| Lupus | 0.58% | 0.20% | 0.58% | 0.29 | 0.34(0.05-2.46) |
| Scleroderma | 0.13% | 0.00% | 0.13% | NA | 1 |
| Polyarteritis Nodosa | 0.02% | 0.00% | 0.02% | NA | 1 |
| Buerger's Disease | 0.01% | 0.00% | 0.01% | NA | 1 |
| Ankylosing Spondylitis | 0.07% | 0.00% | 0.07% | NA | 1 |
| Herpes simplex virus infection | 0.21% | 0.00% | 0.21% | NA | 1 |
| Infectious mononucleosis | 0.01% | 0.00% | 0.01% | NA | 1 |
| Varicella infection | 0.01% | 0.00% | 0.01% | NA | 1 |

Regarding protective factors, compared to patients with ATTRwt, patients without ATTRwt were more likely to be female (51.53% vs. 20.28%, p<0.001, OR 0.24 [0.19-0.31]), Hispanic (9.03% vs. 3.64%, p=0.002, OR 0.44 [0.26-0.75]), use alcohol (6.58% vs 1.59%, p<0.001, OR 0.23 [0.11-0.46]), have chronic obstructive pulmonary disease (COPD, 21.02% vs 13.52%, p<0.001, OR 0.59 [0.46-0.76]), and Type 2 Diabetes Mellitus (T2DM, 32.76% vs 26.04%, p=0.004, OR 0.72 [0.58-0.90]).

After multivariate analysis (Table 2), age (p<0.001, OR 1.07 [1.06-1.07]), Black race (p<0.001, OR 2.79 [2.2-3.53]), CMV infection (p<0.001, OR 12.33 [3.97-38.25]), psoriatic arthritis (p=0.003, OR 5.61 [1.82-17.28]), CKD (p<0.001, OR 3.67 [2.96-4.55]), and gout (p=0.033, OR 3.39 [1.11-10.37]) remained significant risk factors, while female gender (p<0.001, OR 0.22 [0.17-0.28]), alcohol use (p=0.008, OR 0.51 [0.46-0.56]), COPD (p<0.001, OR 0.50 [0.39-0.65]), and T2DM (p<0.001, OR 0.50 [0.40-0.63]) remained significant protective factors.

**Table 2.** Association of demographics and comorbidities with wild-type transthyretin amyloidosis, after multivariate analysis.

| | p-value | OR | 95% C.I.for OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | <0.001 | 1.07 | 1.06 | 1.07 |
| Gender | | | | |
| Male | | REF | | |
| Female | <0.001 | 0.22 | 0.17 | 0.28 |
| Race | | | | |
| White | | REF | | |
| Black | <0.001 | 2.79 | 2.2 | 3.53 |
| Risk Factors | | | | |
| Cytomegalovirus infection | <0.001 | 12.33 | 3.97 | 38.25 |
| Psoriatic arthritis | 0.003 | 5.61 | 1.82 | 17.28 |
| CKD | <0.001 | 3.67 | 2.96 | 4.55 |
| Gout | 0.033 | 3.39 | 1.11 | 10.37 |
| Protective Factors | | | | |
| Alcohol use | 0.008 | 0.39 | 0.2 | 0.79 |
| Chronic obstructive pulmonary disease | <0.001 | 0.5 | 0.39 | 0.65 |
| Type 2 Diabetes Mellitus | <0.001 | 0.5 | 0.4 | 0.63 |

## Discussion

Discovery into ATTRwt risk factors and protective factors has remained stagnant. An association with AS has already been validated: in elderly patients undergoing TAVR for severe AS, 16% screened positive for transthyretin cardiac amyloidosis (ATTR-CM), which was associated with a distinct phenotype of low-flow, low-gradient AS and mildly reduced ejection fraction.[5] An average mitral annular tissue Doppler S' ≤6 cm/s was a highly sensitive predictor of ATTR-CM, suggesting a role for targeted screening in this population.[5]

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ATTRwt is also associated with musculoskeletal disease such as carpal tunnel syndrome, lumbar stenosis, and biceps tendon rupture. In one study, 34% of patients with carpal tunnel syndrome undergoing carpal tunnel release had wild-type transthyretin amyloid deposits in tenosynovial tissue, suggesting that carpal tunnel syndrome may be an early manifestation of ATTRwt, particularly in older men.[17] In another metanalysis of 2,183 patients with orthopedic biopsy during carpal tunnel syndrome repair, lumbar spinal stenosis repair, and hip or knee osteoarthritis repair, 13.7%, 40.8%, and 25.4% had a positive TTR biopsy.[18] Because these surgeries often precede cardiac involvement, identifying amyloid in these settings may allow for earlier diagnosis and treatment of ATTRwt. In a cross-sectional study, 33.3% of patients with ATTRwt had a history of spontaneous distal biceps tendon rupture, compared to only 2.5% of patients with heart failure from other causes.[19] Many cases of distal biceps tendon rupture occurred years before heart failure diagnosis, suggesting distal biceps tendon rupture may be an underrecognized early manifestation of ATTRwt, similar to other musculoskeletal pathologies discussed above.[19]

Our study identified several novel associations and potential risk factors for ATTRwt, including CMV infection and inflammatory arthritic conditions such as gout and psoriatic arthritis. Although no existing studies directly link ATTRwt with gout or psoriatic arthritis, a biologically plausible connection exists via chronic inflammation, metabolic comorbidities, and renal dysfunction. There are persistent pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-$\alpha$) in psoriatic arthritis and gout that may accelerate native TTR destabilization and amyloid formation—similar to mechanisms proposed in RA-associated ATTRwt.[20–22] Monosodium urate (MSU) crystals in gout also activate the NLRP3 inflammasome and IL-1$\beta$ pathways, and a persistently activated innate immune system could contribute to proteostasis imbalance and amyloidogenesis.[23] Lastly, as mentioned earlier, TTR deposits are frequently found in osteoarthritic joints and damaged tendons, and psoriatic and gouty joint inflammation might predispose those tissues to ATTR deposition and eventual cardiac deposition resulting in ATTR-CM.

We also identified CKD as a common comorbidity in patients with ATTRwt, consistent with prior studies—though most existing data focus on ATTR-CM more broadly, encompassing both wild-type and hereditary forms. For example, in a study of 134 patients, worsening renal function within the first year after ATTR-CM diagnosis was common, occurring in 41.8% of cases, with a median drop in eGFR of 6%, and even developing de novo in some without prior CKD.[24] In another large retrospective cohort study from the UK National Amyloidosis Center of patients with ATTR-CM, a decline in eGFR >20% over one year occurred in 24% of patients and was independently associated with a significantly increased risk of mortality.[25] This association held across genotypes and disease stages, even after adjusting for cardiac biomarkers and diuretic use. These findings highlight eGFR decline as a prognostic marker of disease progression in ATTR-CM. Although less common, case series have documented biopsy-proven ATTRwt amyloid deposits in renal cortex, vessels, and tubular basement membranes.[26] These findings support impaired renal function due to local amyloid deposition. Overall, the restrictive cardiac physiology in ATTR-CM impairs diastolic filling and cardiac output, which, combined with systemic amyloid deposition including in the kidneys, potentiates renal hypoperfusion and reduced eGFR, ultimately leading to CKD.

Lastly, we found a novel association between CMV infection and ATTRwt, of which there are several mechanisms that may explain this. CMV is known to impair endothelial function by inducing vascular inflammation and increasing permeability, which could enhance cardiac tissue exposure to circulating amyloidogenic proteins.[27] Epidemiologic and immunologic studies have linked CMV seropositivity with increased cardiovascular risk and systemic inflammation.[28] Additionally, CMV has been implicated in direct endothelial injury and myocarditis, while CMV may also provoke autoimmune responses via molecular mimicry, potentially promoting tissue injury and amyloid deposition.[29]

Several limitations in our study related to the NIS dataset should be noted. The cross-sectional design precludes longitudinal follow-up, limiting insight into disease progression, long-term outcomes, and causal inference. Diagnoses rely on ICD-10 codes, which are prone to errors and

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misclassification, potentially affecting prevalence estimates and observed associations. Additionally, the absence of key clinical data—such as lab values, imaging, genetic testing, and biomarkers—restricts diagnostic precision and mechanistic interpretation. The dataset also lacks information on outpatient encounters, which may skew findings toward more severe cases and reduce generalizability.

Overall, our study still led to the discovery of novel associations between ATTRwt and inflammatory arthritis, namely gout and psoriatic arthritis. Future studies should include prospective cohort studies assessing ATTRwt prevalence or progression in patients with these conditions. Mechanistic research exploring cytokine-driven TTR misfolding in chronic inflammatory states is also needed. Lastly, biomarker-driven investigations that examine whether patients with gout or psoriatic arthritis demonstrate early cardiac or soft tissue ATTR deposition would be helpful.

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## Abbreviations

99mTc-PYP: 99m technetium-labeled pyrophosphate
AS: Aortic Stenosis
ATTR: Transthyretin Amyloidosis
ATTR-CM: Transthyretin Amyloidosis Cardiomyopathy
hATTR: Hereditary Transthyretin Amyloidosis
ATTRmt: Mutant Transthyretin Amyloidosis
ATTRv: Variant Transthyretin Amyloidosis
ATTRwt: Wild-Type Transthyretin Amyloidosis
CAD: Coronary Artery Disease
CKD: Chronic Kidney Disease
CMV: Cytomegalovirus
COPD: Chronic Obstructive Pulmonary Disease
eGFR: Estimated Glomerular Filtration Rate
HFpEF: Heart Failure with Preserved Ejection Fraction
ICD-10: International Classification of Diseases, 10th Revision
IL-1: Interleukin-1
IL-6: Interleukin-6
LGE: Late Gadolinium Enhancement
MRI: Magnetic Resonance Imaging
MSU: Monosodium Urate
NIS: National Inpatient Sample
NT-proBNP: N-terminal pro B-type Natriuretic Peptide
OR: Odds Ratio
T2DM: Type 2 Diabetes Mellitus
TAVR: Transcatheter Aortic Valve Replacement
Tc: Technetium
TTR: Transthyretin
TNF-$\alpha$: Tumor Necrosis Factor Alpha

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