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Review Article

A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction

Mohamed Magdi[1], Mostafa Reda Mostafa[1], Waiel Abusnina[2], Ahmad Al-abdouh[3], Ramy Doss[4], Sarah Mohamed[5], Chidera Philippa Ekpo[5], Richard Alweis[1], Bipul Baibhav[6]

[1]Department of Internal Medicine, Rochester Regional Health, NY, USA; [2]Department of Cardiology, Creighton University School of Medicine, NE, USA; [3]Department of Medicine, University of Kentucky, KY, USA; [4]Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas; [5]Department of Ophthalmology, Cairo University, Cairo, Egypt; [6]Department of Cardiology, Rochester General Hospital, NY, USA

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Abstract: Background: Heart failure with preserved ejection fraction is a complex clinical syndrome marked by different phenotypes and related comorbidities. Transthyretin amyloidosis is an underestimated phenotype. We aim to evaluate the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. Methods: This meta-analysis was conducted according to PRISMA guidelines. A search strategy was designed to utilize PubMed/Medline, EMBASE, and Google scholar to locate studies whose primary objective was to analyze the prevalence of transthyretin amyloidosis in heart failure preserved ejection fraction. Results: Of 271 studies initially identified, 5 studies comprising 670 patients were included in the final analysis. The prevalence of transthyretin amyloidosis was 11%. Patients with transthyretin amyloid cardiomyopathy were more likely to be males (RR 1.38; 95% CI 1.09 to 1.75; P<0.01; I^2=37%), and more likely to have low voltage criteria on ECG (RR 2.98; 95% CI 1.03 to 8.58; P=0.04; I^2=75%) compared with transthyretin negative group. They also have higher SMD of age (SMD 0.73; 95% CI 0.48 to 0.97; P<0.01; I^2=0%), and NT-proBNP (SMD 0.48; 95% CI 0.02 to 0.93; P=0.04; I^2=36%) compared with transthyretin negative group. On reported echocardiogram, they have higher SMD of mass index (SMD 0.77; 95% CI 0.27 to 1.27; P<0.01; I^2=65%), posterior wall thickness (SMD 0.92; 95% CI 0.62 to 1.21; P<0.01; I^2=0%), and septal wall thickness (SMD 1.49; 95% CI 0.65 to 2.32; P<0.01; I^2=87%) compared with transthyretin negative group. Conclusion: Transthyretin amyloidosis affects 11% of HFpEF patients. Therefore, screening HFpEF patients at risk of cardiac amyloidosis is warranted.

Keywords: Transthyretin amyloidosis, cardiac amyloidosis, wild-type transthyretin amyloidosis, heart failure, heart failure with preserved ejection fraction, diastolic heart failure

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of the heart failure cases [1]. With the growing population age, obesity, hypertension, and diabetes, the prevalence is predicted to rise. Several trials over the last decade have failed to identify a medical therapy to improve mortality and enhance the quality of life in patients with HFpEF. The most compelling reason is the disease's heterogeneity, with various associated etiologies and pathophysiological phenotypes. There is no universally accepted classification for HFpEF-related phenotypes, though some attempts have been made [2, 3]. The goal of HFpEF treatment was to maintain the associated co-morbidities under tight control. Ultimately, the future of management will be phenotype-specific treatment [4].

Cardiac amyloidosis is one of the underestimated phenotypes. The clinical condition is caused by the deposition of amyloid fibrils in the heart, which leads to myocardial dysfunction [5]. Light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) account for nearly all cases of cardiac amyloidosis [6, 7]. Light chain cardiac amy-

loidosis (AL-CM) is a plasma cell dyscrasia leading to the deposition of excess misfolded light chains [8, 9]. However, transthyretin amyloidosis is caused by the deposition of misfolded unstable monomers, which is either secondary to a genetic mutation in the hereditary form (hATTR-CM) or age-related protein instability in the wild type (wtATTR-CM) [10, 11]. Transthyretin amyloidosis is an infiltrative disease that causes left ventricular hypertrophy and as a result it leads to heart failure with preserved ejection fraction (diastolic heart failure).

Tafamidis, approved by the FDA in 2019, is the first medication for treating ATTR-CM [12]. The drug stabilizes the transthyretin (TTR) tetramer and slows the dissociation to unstable monomer, thus reducing the deposition in the tissues, including the heart [13, 14]. The ATTR-ACT trial enrolled patients with ATTR-CM and NYHA classes I to III. It demonstrated that tafamidis is associated with reducing mortality and related cardiac hospitalization and decreasing the decline in functional capacity and quality of life [15]. In light of this finding, we sought to determine the prevalence of ATTR-CM in patients with a prior diagnosis of HFpEF using a meta-analysis of multiple studies.

Methods

The present meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane handbook® [16]. Studies were identified using a search strategy utilizing MEDLINE/PubMed, EMBASE and Google scholar until November 30, 2021. Two of the authors (M.M. and M.R.M.) developed a search strategy. The search included the following key terms; ("Heart failure preserved ejection fraction" or "diastolic heart failure") and ("transthyretin amyloidosis" or "Cardiac amyloidosis" or "wild type transthyretin amyloidosis") and ("Prevalence").

We hand-reviewed the reference list of articles included in this review to include other relevant studies.

Study selection

We included retrospective or prospective cohort studies with the following eligibility criteria 1) studies evaluating the prevalence of transthyretin amyloidosis in HFpEF with EF>40%; 2) studies were written in the English language.

Articles were rejected if they were: 1) published in review or abstract form only; 2) studies looking for the prevalence of light-chain cardiac amyloidosis.

Screening and data extraction

Initial title and abstract screening were conducted by two reviewers (M.M. and M.R.M.). Potentially eligible articles were imported for full-text review and assessed for inclusion. Data were extracted using Excel (Microsoft Corporation, Redmond, Washington, USA). The collected data included first author name, study design, study country, sample size, baseline characteristics (median age, male%, hypertension%, diabetes myelitis%, CAD%), NT pro-BNP, mean LV EF%, LV mass index, septal wall thickness, posterior wall thickness and Low voltage ECG.

The subgroup analysis sorted data into ATTR positive or negative groups.

Data synthesis and analysis

We calculated the standardized mean difference (SMD) from the means and standard deviations. When unavailable in the selected studies, means and standard deviations were calculated as described by Wan et al. [17]. We analyzed the outcome variables using the random-effects model (inverse variance) to calculate the pooled standardized mean difference of the outcomes with a statistical significance of probability value $P<0.05$. The overall effect of the outcomes was reported as z value corroborating the 95% confidence interval's inference. We used The Mantel-Haenszel method to estimate $\tau 2$. The I^2 was used to measure heterogeneity over the included studies (<25% considered low heterogeneity, and >50% considered significant heterogeneity) [18]. Analyses were performed using R Studio Version 3.6.3.

Study quality and risk of bias assessment

The quality of the included studies was assessed using the Newcastle Ottawa scale for prevalence studies [19] as shown in

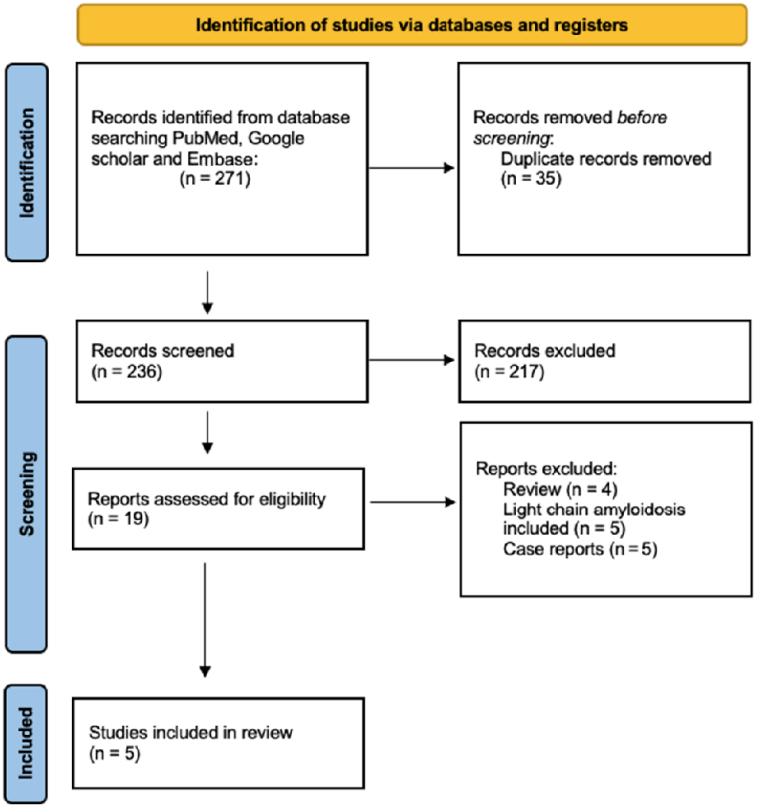


Figure 1. Flow diagram.

Supplementary Table 1. For this adapted Newcastle-Ottawa Scale, each asterisk counts as one point. The maximum points are five for selection, two for comparability and three for the outcome. A score of less than five is considered low quality, five to six is satisfactory quality, seven to eight is good quality, and nine to ten is very good quality. All the included studies scored five or more in quality assessment. Publication bias was not assessed since the number of the included studies was less than 10 [20].

Results

Summary of studies

A comprehensive electronic database literature search revealed a total of 271 publications. Five studies were identified for the meta-analysis after applying our inclusion and exclusion criteria [21-25]. The search process is detailed in (**Figure 1**). The included studies in the meta-analysis are illustrated in **Tables 1-3**. A total of 670 patients were included in this study: 74 patients in the transthyretin amyloid cardiomyopathy group and 596 patients in the transthyretin negative group.

Outcomes

In our pooled analysis, the prevalence of ATTR in patients with HFpEF is 11%. When compared with the transthyretin negative group, patients with transthyretin amyloid cardiomyopathy were more likely to be males (RR 1.38; 95% CI 1.09 to 1.75; P<0.01; I^2=37%), have higher SMD of age (SMD 0.73; 95% CI 0.48 to 0.97; P<0.01; I^2=0%), and less likely to have diabetes mellitus (RR 0.63; 95% CI 0.42 to 0.93; P=0.0.02; I^2=0%) compared with transthyretin negative group (**Figure 2A-C**). Patients with transthyretin amyloid cardiomyopathy were more likely to have low voltage criteria on electrocardiogram (RR 2.98; 95% CI 1.03 to 8.58; P=0.04; I^2=75%), higher SMD of NT pro B-natriuretic peptide (NT pro-BNP) (SMD 0.48; 95% CI 0.02 to 0.93; P=0.04; I^2=36%), higher SMD of mass index (SMD 0.77; 95% CI 0.27 to 1.27; P<0.01; I^2=65%), higher SMD of posterior wall thickness (SMD 0.92; 95% CI 0.62 to 1.21; P<0.01; I^2=0%), and higher SMD of septal wall thickness (SMD 1.49; 95% CI 0.65 to 2.32; P<0.01; I^2=87%) when compared with transthyretin negative group (**Figure 2F-J**). There were no significant differences between transthyretin amyloid cardiomyopathy and transthyretin negative groups in terms of incidence of hypertension (RR 0.96; 95% CI 0.84 to 1.08; P=0.48; I^2=12%), coronary artery disease (RR 0.92; 95% CI 0.71 to 1.20; P=0.55; I^2=0%), or SMD of left ventricular ejection fraction (SMD -0.15; 95% CI -0.43 to 0.12; P=0.27; I^2=18%) (**Figure 2D**, **2E**, **2K**).

Discussion

To our knowledge, this is the first meta-analysis to look at the prevalence of transthyretin amyloidosis in heart failure patients with a pre-

Table 1. Summary of the included studies

Study	Year	Sample size	Design	Age mean or median (males' percentage %)	Hypertension %	DM%	CAD	Diagnosis of amyloidosis	Prevalence of ATTR
Esther Gonzalez-Lopez/Spain	2015	120	Prospective analysis	82 (males 41%)	84%	37%	9%	99m Tc-DPD scan. Followed by TTR gene test if scan is positive	16 patients (13.3%)
Omar F. AbouEzzeddine/USA	2021	286	Prospective analysis	78 (males 52%)	96%	50%	65%	99m Tc-pyrophosphate scintigraphy	18 patients (6.3%)
Ana Devesa/Spain	2021	58	Prospective analysis	79 (males 54%)	83%	36%	14%	99m Tc-DPD scan then TTR gene testing if scan is positive	3 patients (5%)
Saberio Lo Presti/USA	2019	100	Retrospective analysis	76 (males 64%)	85%	32%	34%	99mTc-PYP	19 patients (19%)
Selma F. Mohammed/USA	2013	106	Retrospective analysis	74 (males 43%)	78%	42%	62%	Autopsy and histological analysis	18 patients (17%)

Table 2. Baseline characteristics between the ATTR positive and negative groups

Study	Men		Age		Hypertension		DM		CAD		Low voltage ECG%		NT-proBNP	
	ATTR+	ATTR-	ATTR+	ATTR-	ATTR+	ATTR-	ATTR+	ATTR-	ATTR+	ATTR-	ATTR+	ATTR-	ATTR+	ATTR-
Esther Gonzalez-Lopez	50%	39%	86±6	81±8	88%	84%	25%	39%	13%	9%	42	26	6467 (2818-13146)	3173 (1363-7139)
Omar F. AbouEzzeddine	83%	50%	84 (79-89)	78 (71-83)	78%	97%	28%	51%	56%	66%	31	9	2093 (1638-4126)	1337 (552-3050)
Ana Devesa	54%	67%	84	79 (75-85)	33%	86%	33%	36%	0%	15%	N.A	N.A	1230	1830 (1110-3800)
Saberio Lo Presti	84%	59%	82±7	75±13	84%	85%	16%	36%	32%	35%	N.A	N.A	N.A	N.A
Selma F. Mohammed	43%	43%	86±7	72±13	78%	78%	33%	34%	61%	62%	8	3	N.A	N.A

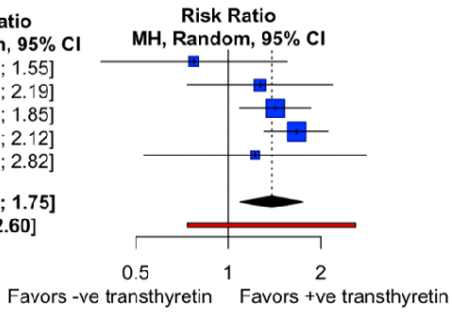
Table 3. Echocardiographic findings in both ATTR positive and negative groups

ECHO / Study	LVEF			Mean LV mass index (g/m^2)			Septal wall thickness, mm			Posterior wall thickness, mm		
	ATTR+	ATTR-	P	ATTR+	ATTR-	P	ATTR+	ATTR-	P	ATTR+	ATTR-	P
Esther Gonzalez-Lopez	60±7	61±8	0.5	161±43	115±34	0.001	18 (15.7-21)	14 (13-16)	0.001	12.5 (11-17)	11.5 (10-13)	0.028
Omar F. AbouEzzeddine	57 (50-63)	60 (55-64)	0.2	125 (113-140)	114 (97-133)	0.06	14 (13-17)	12 (12-13)	<0.001	13 (12-15)	12 (10-13)	<0.001
Ana Devesa	60	60 (55-60)	0.2	N.A	N.A		11	10.5 (9.5-11)		N.A	N.A	
Saberio Lo Presti	59±9	61±7	0.38	160±50	131±44	0.01	16 (14-20)	14 (13-16)	0.002	16 (15-18)	14 (12-15)	<0.001
Selma F. Mohammed	59±9	59±9	1	N.A	N.A		N.A	N.A		N.A	N.A	

A

Study	+ve Events	+ve Total	-ve Events	-ve Total	Weight	Risk Ratio MH, Random, 95% CI
Mohammed et al. 2014	6	18	38	88	9.5%	0.77 [0.38; 1.55]
Gonzalez-Lopez et al. 2015	8	16	41	104	14.1%	1.27 [0.74; 2.19]
Presti et al. 2019	16	19	48	81	33.2%	1.42 [1.09; 1.85]
AbouEzzeddine et al. 2021	15	18	134	268	36.2%	1.67 [1.31; 2.12]
Devesa et al. 2021	2	3	30	55	7.0%	1.22 [0.53; 2.82]
Total (95% CI)		**74**		**596**	**100.0%**	**1.38 [1.09; 1.75]**
Prediction interval						**[0.74; 2.60]**

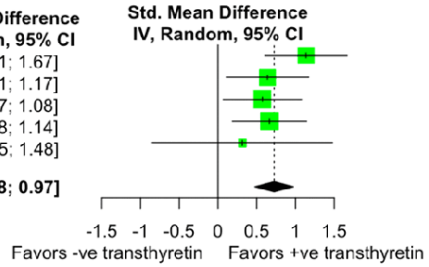
Heterogeneity: $Tau^2 = 0.0249$; $Chi^2 = 6.39$, df = 4 (P = 0.17); $I^2 = 37\%$
Test for overall effect: Z = 2.70 (P < 0.01)



B

Study	+ve transthyretin Mean	SD	Total	-ve transthyretin Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammed et al. 2014	86.00	7.00	18	72.00	13.00	88	22.1%	1.14 [0.61; 1.67]
Gonzalez-Lopez et al. 2015	86.00	6.00	16	81.00	8.00	104	22.0%	0.64 [0.11; 1.17]
Presti et al. 2019	82.00	7.00	19	75.00	13.00	81	24.3%	0.57 [0.07; 1.08]
AbouEzzeddine et al. 2021	84.00	8.00	18	77.60	9.70	268	27.0%	0.66 [0.18; 1.14]
Devesa et al. 2021	82.10	5.60	3	79.70	7.60	55	4.6%	0.31 [-0.85; 1.48]
Total (95% CI)			**74**			**596**	**100.0%**	**0.73 [0.48; 0.97]**

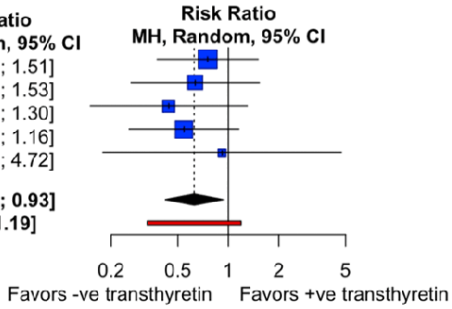
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.31$, df = 4 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 5.69 (P < 0.01)



C

Study	+ve Events	+ve Total	-ve Events	-ve Total	Weight	Risk Ratio MH, Random, 95% CI
Mohammed et al. 2014	6	18	39	88	32.7%	0.75 [0.38; 1.51]
Gonzalez-Lopez et al. 2015	4	16	41	104	20.3%	0.63 [0.26; 1.53]
Presti et al. 2019	3	19	29	81	13.5%	0.44 [0.15; 1.30]
AbouEzzeddine et al. 2021	5	18	137	268	27.7%	0.54 [0.26; 1.16]
Devesa et al. 2021	1	3	20	55	5.9%	0.92 [0.18; 4.72]
Total (95% CI)		**74**		**596**	**100.0%**	**0.63 [0.42; 0.93]**
Prediction interval						**[0.33; 1.19]**

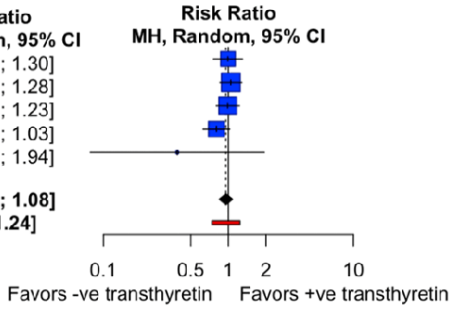
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.04$, df = 4 (P = 0.90); $I^2 = 0\%$
Test for overall effect: Z = -2.32 (P = 0.02)



D

Study	+ve Events	+ve Total	-ve Events	-ve Total	Weight	Risk Ratio MH, Random, 95% CI
Mohammed et al. 2014	14	18	69	88	18.9%	0.99 [0.76; 1.30]
Gonzalez-Lopez et al. 2015	14	16	87	104	30.5%	1.05 [0.85; 1.28]
Presti et al. 2019	16	19	69	81	28.0%	0.99 [0.80; 1.23]
AbouEzzeddine et al. 2021	14	18	260	268	22.0%	0.80 [0.63; 1.03]
Devesa et al. 2021	1	3	47	55	0.6%	0.39 [0.08; 1.94]
Total (95% CI)		**74**		**596**	**100.0%**	**0.96 [0.84; 1.08]**
Prediction interval						**[0.74; 1.24]**

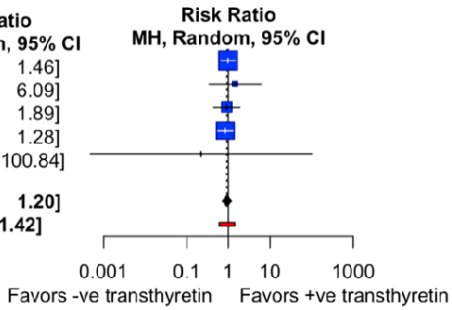
Heterogeneity: $Tau^2 = 0.0025$; $Chi^2 = 4.55$, df = 4 (P = 0.34); $I^2 = 12\%$
Test for overall effect: Z = -0.71 (P = 0.48)



E

Study	+ve Events	+ve Total	-ve Events	-ve Total	Weight	Risk Ratio MH, Random, 95% CI
Mohammed et al. 2014	11	18	55	88	43.5%	0.98 [0.65; 1.46]
Gonzalez-Lopez et al. 2015	2	16	9	104	3.4%	1.44 [0.34; 6.09]
Presti et al. 2019	6	19	28	81	13.3%	0.91 [0.44; 1.89]
AbouEzzeddine et al. 2021	10	18	177	268	39.6%	0.84 [0.55; 1.28]
Devesa et al. 2021	0	3	8	55	0.2%	0.22 [0.00; 100.84]
Total (95% CI)		**74**		**596**	**100.0%**	**0.92 [0.71; 1.20]**
Prediction interval						**[0.60; 1.42]**

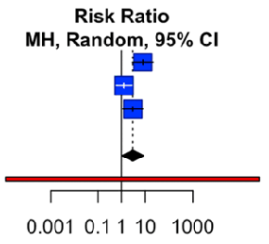
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.85$, df = 4 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = -0.60 (P = 0.55)



F

Study	+ve Events	+ve Total	-ve Events	-ve Total	Weight	Risk Ratio MH, Random, 95% CI
Mohammed et al. 2014	8	18	5	88	31.9%	7.82 [2.89; 21.17]
Gonzalez-Lopez et al. 2015	5	16	26	104	35.5%	1.25 [0.56; 2.78]
AbouEzzeddine et al. 2021	4	18	20	268	32.6%	2.98 [1.14; 7.79]
Total (95% CI)		**52**		**460**	**100.0%**	**2.98 [1.03; 8.58]**
Prediction interval						**[0.00; 687593.72]**

Heterogeneity: $Tau^2 = 0.6535$; $Chi^2 = 7.99$, df = 2 (P = 0.02); $I^2 = 75\%$
Test for overall effect: Z = 2.02 (P = 0.04)



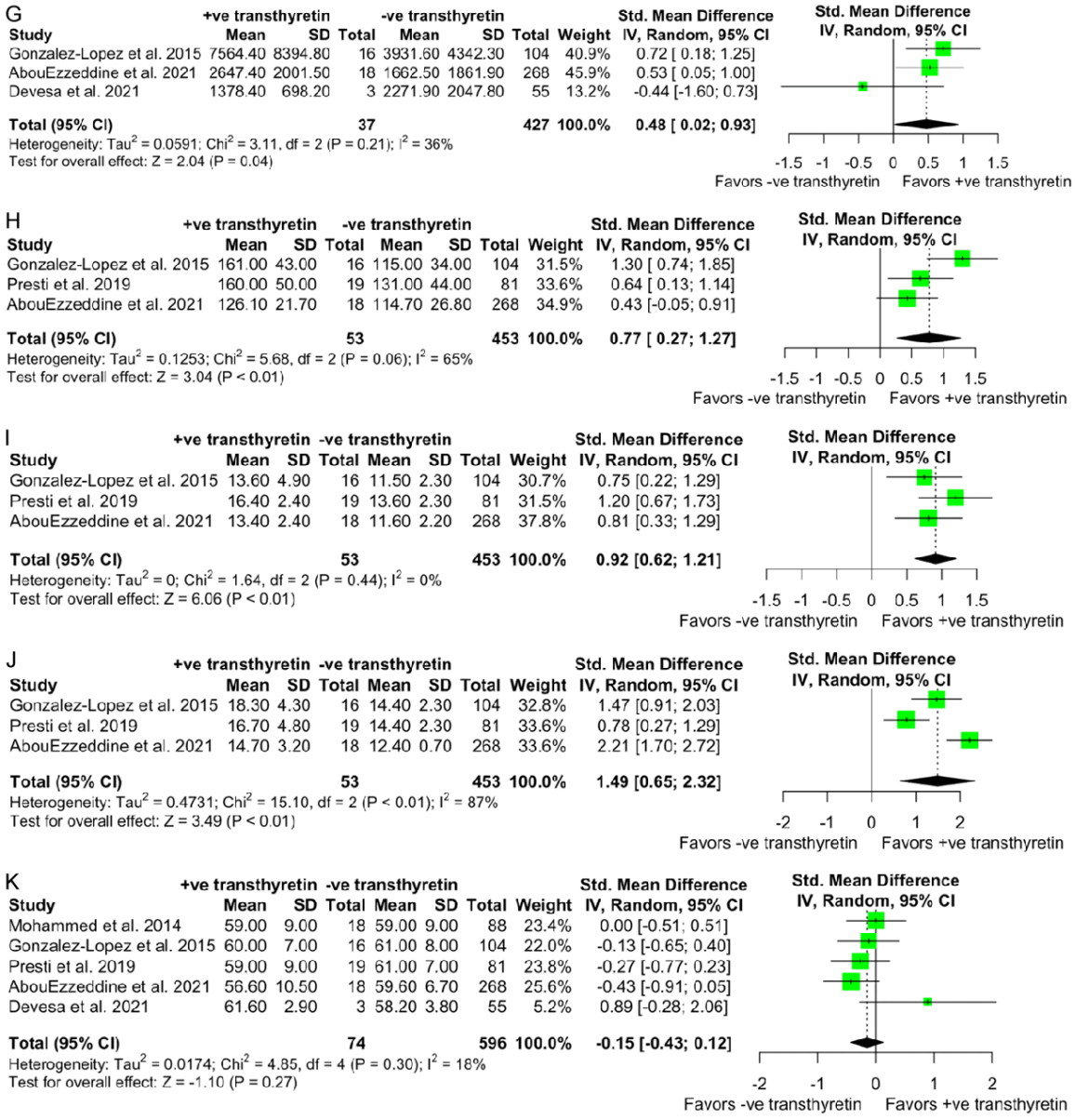


Figure 2. A: Forest plot of being male. B: Forest plot of age. C: Forest plot of diabetes mellitus. D: Forest plot of hypertension. E: Forest plot of coronary artery disease. F: Forest plot of low voltage criteria. G: Forest plot of NT pro-BNP. H: Forest plot of mass index. I: Forest plot of posterior wall thickness. J: Forest plot of septal thickness. K: Forest plot of left ventricular ejection fraction.

served ejection fraction (HFpEF). In our analysis, the prevalence of ATTR in patients with HFpEF is 11%. Previous prevalence data exist in particular patient populations and report widely disparate results. Several autopsy studies have looked into the prevalence of cardiac amyloidosis in the elderly. In a Finnish autopsy investigation of adults over 85, wild-type transthyretin amyloids were found in 25% of patients, regardless of heart failure [26]. A Japanese autopsy study reported ATTR amyloidosis in 8.8% of people over 80 in randomly selected post-mortem cases [27].

Hahn et al. enrolled 108 patients with HFpEF who underwent a right heart catheter and endomyocardial biopsy. Cardiac amyloidosis was prevalent in 14% of cases, with transthyretin amyloidosis accounting for 10% [28]. In a large cohort study in Sweden, patients who

have heart failure and myocardial hypertrophy (interventricular septum thickness >14 mm) underwent a diphosphono-1,2-propanodicarboxylic acid (DPD) scan, with the prevalence of cardiac amyloidosis placed at approximately 20% [29]. Another study of Afro-Caribbean individuals with heart failure in the United Kingdom found that 11% had cardiac amyloidosis [30].

The clinical characteristics of patients with ATTR-CM in our study were comparable to those seen in the literature. The majority of the patients were men older than 80 years, consistent with other studies showing that more than 88% of ATTR-CM patients are men, with an average age of 74 years [31, 32]. Although the clinical presentation is similar to other cardiomyopathies, specific indications justify further investigation for cardiac amyloidosis. Heart failure patients with intolerance to ACE-I and beta-blockers may have cardiac amyloidosis (CA). Furthermore, spontaneous resolution of hypertension is highly predictive of CA [32]. This phenomenon is observed in elderly patients when blood pressure begins to stabilize and blood pressure drugs are gradually withdrawn. Other disorders associated with amyloid accumulation outside the heart raise suspicion of cardiac amyloidosis. Bilateral Carpal tunnel syndrome is a common association and presents in around 40-50% of cases [33, 34]. Another link is lumbar spinal stenosis secondary to the amyloid deposition resulting in ligamentum flavum thickening and spinal canal stenosis [35]. Spontaneous rupture of the distal Biceps tendon presents in 33% of wild-type ATTR-CM [36].

The diagnosis of transthyretin amyloidosis is challenging. Although an ECG is rarely diagnostic for ATTR-CM, it can reveal some clues. Low voltage QRS in limb leads and pseudo infarction patterns are the most prevalent findings, but both have a sensitivity of roughly 28% [37]. Our analysis showed that low voltage criteria are more familiar with ATTR (RR 2.98; 95% CI 1.03 to 8.58; P=0.04). Moreover, our findings revealed that NT-pro BNP tends to be higher in patients with ATTR. Several reports found that the level of NT-pro BNP is higher in patients with cardiac amyloidosis and has a prognostic value [38-41].

Echocardiography is often the first test used to assess people with heart failure. The most typical finding is a thickening of the LV wall. Increased interventricular septal thickness was shown to be one of the clues to suspect ATTR amyloidosis in a study by Thibaud Damy [42]. Although LV wall thickening is a suggestive finding for CA. However, it is not specific, and other more common diseases are attributed to the same findings as hypertension, aortic stenosis and HCM. Diastolic dysfunction is another common early sign of amyloidosis, and later in the disease, other signs could be seen like restrictive pattern, bi-atrial enlargement and pericardial effusion [43]. In our study, patients with ATTR-CM have a bigger LV mass, thicker posterior wall and thicker septal wall.

Although endomyocardial biopsy is the gold standard for diagnosis, cardiac scintigraphy is now an excellent non-invasive method for diagnosing CA, with a sensitivity of >99% and specificity of >86% [44]. As a result, the diagnostic algorithm for ATTR-CM consists of a high index of suspicious, suggestive echocardiogram, cardiac scintigraphy, and genetic testing to confirm the diagnosis.

The high prevalence of transthyretin amyloid in HFpEF and the significant advances in the treatment suggest that all patients with HFpEF should be screened for underlying amyloidosis. However, it may not be possible to screen all patients with HFpEF. It is critical to raise clinician awareness of the clinical characteristics of ATTR-CM to identify patients who are at risk. For example, 1) Males in their seventies and eighties. 2) HFpEF patients who are intolerant to ACE-I or beta-blockers. 3) Patients with HFpEF who have spontaneous hypertension resolution. 4) HFpEF is associated with bilateral carpal tunnel syndrome or spinal canal stenosis. 5) HFpEF with low voltage criteria in ECG and persistent elevation of NT-proBNP. 6) HFpEF with LV wall thickness ≥ 12 mm.

Finally, we propose developing a validated scoring system for patients with HFpEF to guide cardiac amyloidosis screening.

There are a few limitations to the current analysis. First, most of the included studies were observational studies which are subject to selection bias and confounding. Second, some endpoints had a considerable degree of heterogeneity, which could be explained by the different characteristics of patients included in the studies.

Conclusion

According to our findings, transthyretin amyloidosis affects 11% of HFpEF patients. After the initial assessment of HFpEF patients, screening those at risk of transthyretin amyloidosis becomes essential. Therefore, a scoring system to identify patients at risk of cardiac amyloidosis is the most appropriate to guide the physicians.

Disclosure of conflict of interest

None.

Abbreviations

HFpEF, Heart failure preserved ejection fraction; HFrEF, Heart failure reduced ejection fraction; TTR, Transthyretin; ATTR, Transthyretin amyloidosis; ATTR-CM, Transthyretin amyloidosis cardiomyopathy; CA, Cardiac amyloidosis; CAD, Coronary artery disease; HTN, Hypertension; CTS, Carpal tunnel syndrome; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; wtATTR-CM, Wild type transthyretin amyloidosis cardiomyopathy; hATTR, Hereditary transthyretin amyloidosis; 99m Tc-PYP scintigraphy, Technetium-99m pyrophosphate scintigraphy; 99m Tc-DPD scintigraphy, Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid.

Address correspondence to: Dr. Mohamed Magdi, Department of Internal Medicine, Rochester Regional Health, 239 Greystone Lane, Apt 17 Rochester, NY 14618, USA. Tel: 585-748-2775; E-mail: drmmm1988@gmail.com

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Supplementary Table 1. Newcastle Ottawa scale quality scores for the included studies

Study	Selection				Comparability	Outcome		Total quality score	Study quality
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	The subjects in different outcome groups are comparable	Assessment of outcome	Statistical test		
Esther Gonzalez-Lopez	1	0	0	1	1	2	1	6	Satisfactory
Omar F. AbouEzzeddine	1	1	1	1	2	2	1	9	Very good
Ana Devesa	0	0	0	1	1	2	1	5	Satisfactory
Saberio Lo Presti	1	0	0	1	1	2	1	6	Satisfactory
Selma F. Mohammed	1	1	1	0	2	1	1	7	Good

The quality of the study; We assigned stars to evaluate study quality, with nine to ten stars indicating “very good” quality, seven to eight stars indicating “good” quality, five to six stars indicating “satisfactory” quality, and zero to four stars indicating “unsatisfactory” quality.