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REVIEW

Estimating the Gender Distribution of Patients with Wild-Type Transthyretin Amyloid Cardiomyopathy: A Systematic Review and Meta-Analysis

Florint Kroi · Nils Fischer · Ana Gezin · Mahmoud Hashim · Mark Hermannes Rozenbaum

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ABSTRACT

Introduction: This study investigates the gender distribution in patients diagnosed with wild-type transthyretin amyloidosis cardiomyopathy (ATTRwt).
Methods: A systematic review and meta-analysis of the male proportion in diagnosed ATTRwt patients were conducted. To avoid overlapping population, pooled estimates in the primary analysis were based on all unique studies. In secondary analyses, we considered predefined subsets of studies based on study sample size, recruitment years, geography, study design, age at diagnosis, and method of diagnosis. Additional meta-regression analyses were tested for potential determinants of gender distribution.

Results: Twenty-eight unique studies (2542 patients) were included in the meta-analysis. Male proportion in patients with ATTRwt was 86.9% (95% confidence interval 81.5–91.6%). Studies, including patients older than 80 years at diagnosis, had a 29.1% (p value < 0.001) lower male proportion compared to studies, including younger patients. After adjusting for age, studies using autopsy as a method of diagnosis had a 21.1% (p value 0.002) lower male proportion compared to other studies.
Conclusions: Studies conducted to date suggest ATTRwt disproportionally affects males. The proportion of males was significantly impacted by the age at diagnosis and method diagnosis, which may suggest important gender-based differences in the clinical manifestation and diagnostic challenges of ATTRwt in females that warrant future research.

Keywords: Meta-analysis; Systematic review; Wild-type transthyretin amyloidosis cardiomyopathy

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F. Kroi · A. Gezin · M. Hashim
Ingress-Health, Rotterdam, The Netherlands

N. Fischer
Pfizer, NewYork, USA
e-mail: nils.fischer@pfizer.com

M. H. Rozenbaum (✉)
Pfizer, Rotterdam, The Netherlands
e-mail: mark.rozenbaum@pfizer.com

Key Summary Points

This is the first meta-analysis of male proportion in patients with ATTRwt.

Studies conducted to date suggest that ATTRwt disproportionately affects male patients.

In the primary analysis, the male proportion was 86.9% (95% CI: 81.5–91.6%).

The mean age at diagnosis is a determinant of the gender distribution.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. You can access the digital features on the article's associated Figshare page. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13214594.

INTRODUCTION

Transthyretin amyloidosis cardiomyopathy (ATTR-CM) is a rare, progressively debilitating, fatal disease [1]. ATTR-CM is caused by instability of the transthyretin tetramer, leading to the formation of amyloid deposited in the heart, which, subsequently, impairs its function [1]. Two different subtypes of ATTR-CM are clinically identified, hereditary ATTR-CM (hATTR) and wild-type ATTR-CM (ATTRwt). HATTR is caused by a mutation in the transthyretin (TTR) gene and is transmitted from parents to offspring in an autosomal dominant pattern [2]. As a result, hereditary ATTR-CM generally affects men and women equally, although, depending on the mutation, men usually have an earlier onset and more aggressive course of disease [3]. On the other hand, in ATTRwt, the TTR protein forming the amyloid is not mutated; instead, the disease is caused by age-related changes in the wild-type TTR [4, 5]. Therefore, it is typically seen in patients older than 65 years of age, while hATTR can affect patients as young as 30 years of age [2, 6–11].

ATTRwt's epidemiology is poorly characterized; an estimation of ATTRwt prevalence ranges from 2.8 to 3.9 cases per 10,000 in the European Union [12]. Patients with ATTRwt experience progression in heart failure (HF) symptoms (e.g., dyspnea, fatigue, and edema), leading to increasing impairment and death, primarily caused by HF [10, 13–15]. Untreated, ATTRwt is associated with a median survival of approximately 3.5 years, post-diagnosis [16, 17]. Delays in diagnosis are common in the current treatment landscape, which further shortens the survival time in some patients [18–21]. Thus, there is a need to characterize these patients better and subsequently provide optimal care.

Based on the available evidence from large cohort studies, it is generally believed that ATTRwt is more common in male patients [22, 23]. This may hinder the identification of female patients in need of optimal care. Nevertheless, the gender distribution of patients diagnosed with ATTRwt cardiomyopathy was never formally established in the literature. Hence, this study aimed to conduct the first meta-analysis of gender distribution in ATTRwt patients and identify potential effect modifiers.

METHODS

Systematic Literature Review

A systematic literature review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [24]. The search was performed on February 19, 2020 with no restriction on publication date. The bibliographic databases of PubMed, Embase, and Cochrane Collaboration Central Register of Clinical Trials were used to identify published studies on ATTRwt populations specifically. The only criterion for the inclusion of the studies for analysis was reporting the male or female proportion of patients with ATTRwt. Reports

published in the English language were considered irrespective of study design, intervention, or study outcomes. Studies reporting the male proportion in a conference abstract or a subgroup population were also considered. Supplementary material Table 1 presents the search syntax and the hits per database.

A rigorous approach was followed in the study selection stage. Two independent reviewers performed the screening, and disputes relating to eligibility were resolved through discussion between reviewers until consensus, or through consultation with a third reviewer. First, all duplicate studies were excluded. Second, for each identified publication, the title and the abstract were assessed against the eligibility criteria. Finally, for those relevant records, or for which the relevance was still unclear based on the title or abstract, full-text reports were obtained and screened for relevance. If any systematic reviews and meta-analyses were identified, they were excluded at the title/abstract screening stage. However, the full texts of the reports were acquired and hand-searched to find any additional relevant primary studies not identified through the database searches. Data extraction was carried out in a prespecified Excel grid. Data extraction items included information on study characteristics (authors, recruitment years, country and city, clinical center, sample size, study design and method of diagnosis), patient population characteristics (gender distribution, mean age at diagnosis, and presence of comorbidities like atrial fibrillation or carpal tunnel syndrome). Additionally, reported differences in baseline characteristics by gender were extracted.

Since ATTRwt is a rare disease, many specialized amyloidosis centers tend to use the patient data collected by them to answer different research questions. Subsequently, patients included in these different studies are overlapping. A set of unique studies was identified systematically to avoid double-counting of the same patient population. First, all the identified studies from the qualitative analysis were grouped based on the study center. Second, the unique studies were selected based on the following factors: authors, recruitment years, and sample size. If more than one study reported data from the same database, the study with the largest sample size was included, and the other studies were excluded from the quantitative analysis. Finally, the list with the studies that did not include overlapping population was used in the quantitative analysis to estimate the gender proportion for ATTRwt patients. The methodological quality of these unique studies was accessed using the Downs and Black checklist [25]. The methodological quality assessment did not impact subsequent decisions to include or exclude studies in the quantitative analyses. The bias across studies was assessed using a Funnel plot [26–28].

Meta-Analysis

Meta-analysis is a statistical examination that combines the results from individual studies to derive meaningful conclusions about an outcome of interest [29]. The estimations and findings from meta-analyses may be more accurate compared to those derived from individual studies [29]. In this study, pooled male proportion estimates were calculated using the DerSimonian–Laird random-effects model with Freeman–Tukey double arcsine transformation [30, 31]. When meta-analyzing proportions, it is usually advantageous to first transform the proportions into a measure that has better statistical properties (i.e., a sampling distribution that is closer to a normal distribution and whose sampling variance can be better approximated). A transformation that works particularly well for normalizing and variance-stabilizing the sampling distribution of proportions is the Freeman–Tukey (double arcsine) transformation [32]. The corresponding back-transformation equation was derived by Miller [33]. This approach does not require making any adjustments to the observed data, even when proportions are equal to 1 or 0.

The statistical heterogeneity among the studies was assessed by the Cochran's Q test and the I^2 statistic [34]. Given the diverse nature of studies and the likely heterogeneity, we applied random-effects models to carry out meta-analysis by the Der-Simonian Laird method [30]. Generally, a p value ≤ 0.10 for the Cochran's

Q test or an $I^2 \geq 50\%$ was suggestive of significance among-study heterogeneity [34].

Primary Analysis

For the primary analysis, the pooled male proportion estimate was calculated based on all identified unique studies. Effect modifier is a variable that differentially (positively and negatively) modifies the observed meta-analysis outcome: male proportion in this study. Effect modifiers can distort estimate measures and mislead interpretations [35]. The exploration of effect modification in meta-analysis is essential since the presence of unaccounted covariate interactions can cause confounding and bias. There is no objective test to decide whether a variable is an effect modifier or not. However, subset analysis or meta-regression can provide more insights into the impact of identified effect modifiers. Therefore, in secondary analyses, we attempted to identify potential effect modifiers of gender distribution.

Secondary Analyses

First, analyses were repeated in subsets of studies based on different available covariates, including sample size, recruitment years, geography, study design, mean age at diagnosis, and method of diagnosis. Median cut-off values were used to create subsets based on the sample size and mean age at diagnosis. Due to changes in diagnostic criteria and greater awareness of treatment availability, analysis in subsets based on recruitment years (before 2010 vs. after 2010) was performed. A subset analysis based on specific detailed demographic characteristics, including race, was not feasible due to underreporting. Still, a subset analysis based on the study location, Asian studies versus non-Asian studies, was feasible due to the availability of several Asian studies. In the study design subset, the male proportion in prospective studies was compared to the same in retrospective studies. Typically, retrospective studies might be of lower quality compared to prospective studies [36]. Finally, studies with at least one patient identified through an autopsy were compared to other studies assuming that autopsies may be more objective and less subjective to physician bias.

Second, additional meta-regression analyses were performed. Thus, the effect of different variables in the male proportion estimate could be interpreted when controlling for likely effect modifiers.

Third, whenever reported, differences in baseline characteristics by gender in any of the retrieved studies were extracted and summarized.

The meta-analysis and the meta-regression analysis were conducted using the "metafor" R package and the JASP software, respectively [37–39].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Included Studies

Supplementary material Fig. 1 shows the flow of the study selection process. After duplicate removal, of the 3201 potentially relevant hits, 198 hits qualified for full-text screening. Subsequently, 104 reports fulfilled the eligibility criteria. The list of the total records included in this review is presented in Supplementary material Table 2.

Twenty-eight reports qualified as unique studies for further quantitative analysis [19, 20, 22, 40–64]. Table 1 presents an overview of the characteristics of these studies. In total, 2542 patients were included in these studies. Significantly more studies were conducted in non-Asian countries ($n = 23$) compared to Asian countries ($n = 5$). The mean age at diagnosis ranged from 74.0 to 93.8 years. Few studies used autopsies ($n = 5$) to identify eligible patients [20, 46, 61, 62, 64]. Seventeen studies used endomyocardial biopsy to diagnose at least one patient [19, 20, 22, 42, 43, 46, 47, 50–53, 55, 56, 60–62, 64], nine studies used either extracardiac biopsy or other diagnostic methods (e.g., scintigraphy) [41, 44, 45, 48, 54,

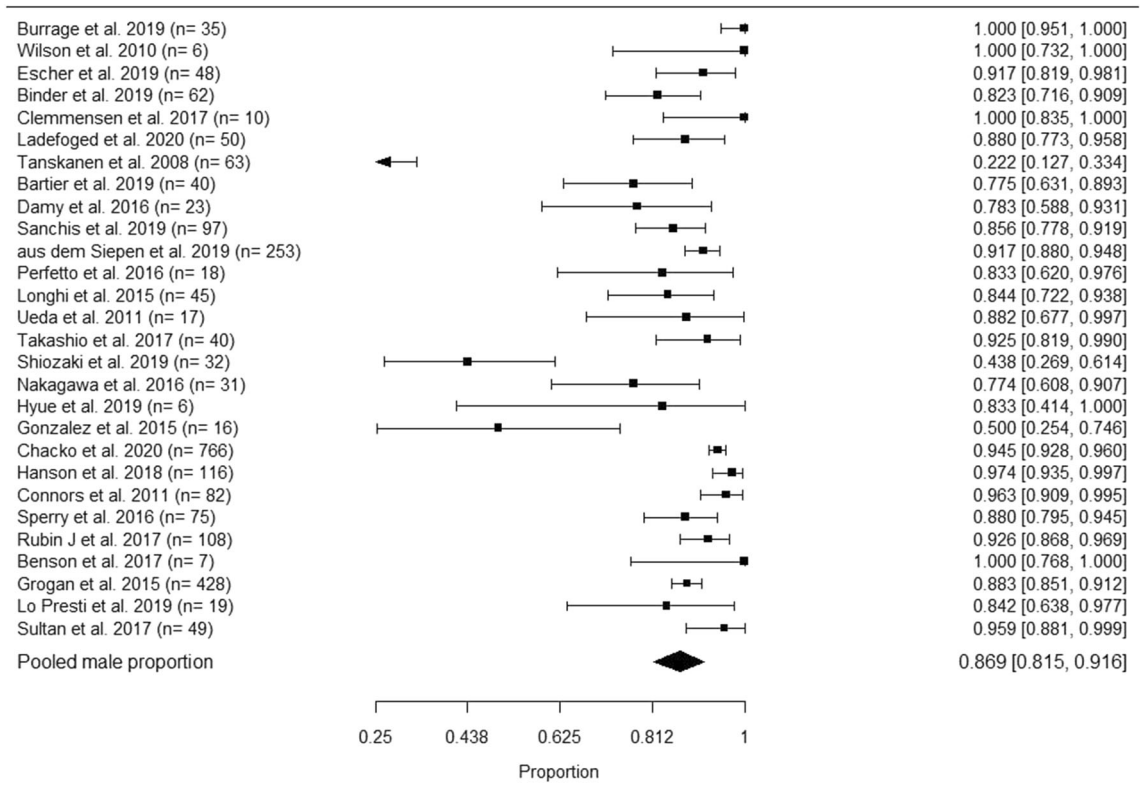

Fig. 1 Male proportion estimate in the primary analysis—Forest plot

57–59, 63] and two studies did not report any diagnostic methods [40, 49]. Further detailed information on the characteristic of these studies and the quality of individual studies are presented in Supplementary material Table 3 and Supplementary material Table 4, respectively. The checklist used for the quality assessment of the individual studies is presented in Supplementary material Table 5.

A visual examination of the funnel plot (see Supplementary material Fig. 2) shows that the risk of publication bias is unlikely. Three studies reported the proportion of male patients of 50% or less: Tanskanen et al., Shiozaki et al., and Gonzalez et al. [20, 62, 63]. On the other hand, four studies included only male patients: Clemmensen et al., Burrage et al., Benson et al. and Wilson et al. [40, 49, 55, 56].

Primary Analysis Results

Figure 1 displays the male proportion (per unique study and pooled) along with a 95% confidence interval (CI). The pooled estimate of male proportion is 86.9% (95% CI 81.5–91.6%).

Secondary Analyses Results

Subset Analyses

Table 2 summarizes pooled male proportion estimates in the predefined subset of studies. Only the subset analysis based on mean age at diagnosis showed meaningful differences: 95% CIs are not overlapping in defined subsets. Studies, including older ATTRwt patients ($\geq$ 80 years) at baseline [19, 20, 41, 48, 53, 54, 58, 62, 63], reported lower male proportion compared with studies including younger ATTRwt patients (< 80 years) at baseline [22, 40, 42–44, 46, 47, 49, 50, 56, 57, 59, 61, 64]: 69.5% (95% CI 49.3–86.7%) vs. 92.7% (95% CI 89.8–95.2%), respectively. The results of the individual studies and the pooled estimates are also shown in Fig. 2. Non-significant differences were observed in studies that had recruited patients before 2010 vs. those which had

Table 1 Overview of the characteristics of included studies in the quantitative analysis

Variable	Number of studies	Percentage of studies (%)
All studies	28	100
Country		
Australia	2	7.1
Austria	2	7.1
Denmark	2	7.1
Finland	1	3.6
France	3	10.7
Germany	1	3.6
Italy	2	7.1
Japan	4	14.3
South Korea	1	3.6
Spain	1	3.6
UK	1	3.6
USA	8	28.6
Sample size		
50 patients and over	11	39.3
Less than 50 patients	17	60.7
Data collection[a]		
Before 2010	4	14.3
After 2010	7	25.0
Region		
Asia	5	17.9
No-Asia	23	82.1
Study type		
Prospective	9	32.1
Retrospective	19	67.9
Method of diagnosis include autopsy		
Yes	5	17.9
No	23	82.1
Mean age at diagnosis[b]		
80 and over	9	32.1
Less than 80	14	50.0

[a] The time of data collection for 17/28 studies (60.7%) extended across the 'before 2010' and 'after 2010' periods; these studies were not included

[b] Mean age at diagnosis was not reported in 5/28 studies (17.9%); these studies were not included

recruited patients after 2010, Asian studies vs. non-Asian studies, and autopsy studies vs. other studies (see Table 2 for more details). In contrast, male proportions were similar to the primary analysis for studies with > 50 patients vs. studies with ≤ 50 patients and in prospective vs. retrospective studies.

Meta-Regressions

For the meta-regression, we considered three analyses controlling for mean age at diagnosis only or geography (Asian studies vs. non-Asian studies), method of diagnosis (autopsy studies vs. other studies), or both.

Table 3 presents results from performed meta-regressions. When controlled the meta-analysis for age, studies including older ATTRwt patients (≥ 80 years at diagnosis) had a 29.1% (p value < 0.001) lower male proportion compared to studies including younger ATTRwt patients (< 80 years at diagnosis). This difference remained significant even after adjusting for geography or method of diagnosis. Also, studies using autopsy as a method of diagnosis had a 21.1% (p value 0.002) or 20.6% (p value 0.003) lower male proportion compared to other studies after adjusting for age only or both age and geography, respectively. On the other hand, after adjusting for age at diagnosis or method of diagnosis, the male proportion did not differ in Asian vs. non-Asian studies.

Table 2 Pooled male proportion estimates in the predefined subset of studies

Subgroup	Sample size per subgroup	Male proportion (%)	Lower CI (%)	Upper CI (%)
Study sample size				
> 50 patients	2100	86.9	79.3	93.1
≤ 50 patients	442	86.7	78.4	93.5
Data selection[a]				
Before 2010	200	84.1	36.3	100
After 2010	200	91.9	83.1	98.1
Region				
Asian studies	126	78.3	56.5	94.5
Non-Asia studies	2416	88.3	82.9	93.0
Method of diagnosis				
Autopsy studies	588	69.3	36.9	93.9
Other studies	1954	90.8	87.3	93.9
Study design				
Prospective	1081	88.8	80.9	95.0
Retrospective	1461	86.1	78.4	92.5
Mean age at diagnosis[b]				
≥ 80 years	341	69.5	49.3	86.7
< 80 years	1911	92.7	89.8	95.2

[a] The time of data collection for 17/28 studies (60.7%) extended across the 'before 2010' and 'after 2010' periods; these studies were not included

[b] Mean age at diagnosis was not reported in 5/28 studies (17.9%); these studies were not included

Reported Differences in Baseline Characteristics by Gender in Individual Studies

Out of the total of 104 studies, seven reports detailed differences in the baseline characteristics by gender in ATTRwt patients [11, 19, 20, 43, 46, 62, 65]. See Supplementary Material Table 6.

Differences in the age of male patients vs. female patients were reported in all seven studies [11, 19, 20, 46, 62, 65, 66]. In Ladefoged et al. 2020, the average age of females at baseline was significantly higher than that of males: 86.4 ± 2.6 years vs. 81.1 ± 0.9 years, respectively [19]. Likewise, in Gonzalez-Lopez et al., female patients were significantly older than male patients at the time of symptom onset and diagnosis, 82.3 vs. 76.1, and 83.9 vs. 77.4, respectively [11]. Two studies, Ueda et al. and Shiozaki et al., reported differences between female and male patients at the age of death, 92.5 (± 13.4) vs. 78.5 (± 9.7) and 88.4 (± 6) vs. 85.8 (± 10.5) [46, 62].

Other differences reported between males and females were related to disease severity. Tanskanen et al. reported that the severity of ATTRwt was significantly associated with male gender [20]. Three studies, aus dem Siepen et al., Gonzalez-Lopez et al., and Yamamoto et al. reported that females presented lower values for interventricular septal [11, 66, 67] thickness, posterior wall thickness, and left ventricular

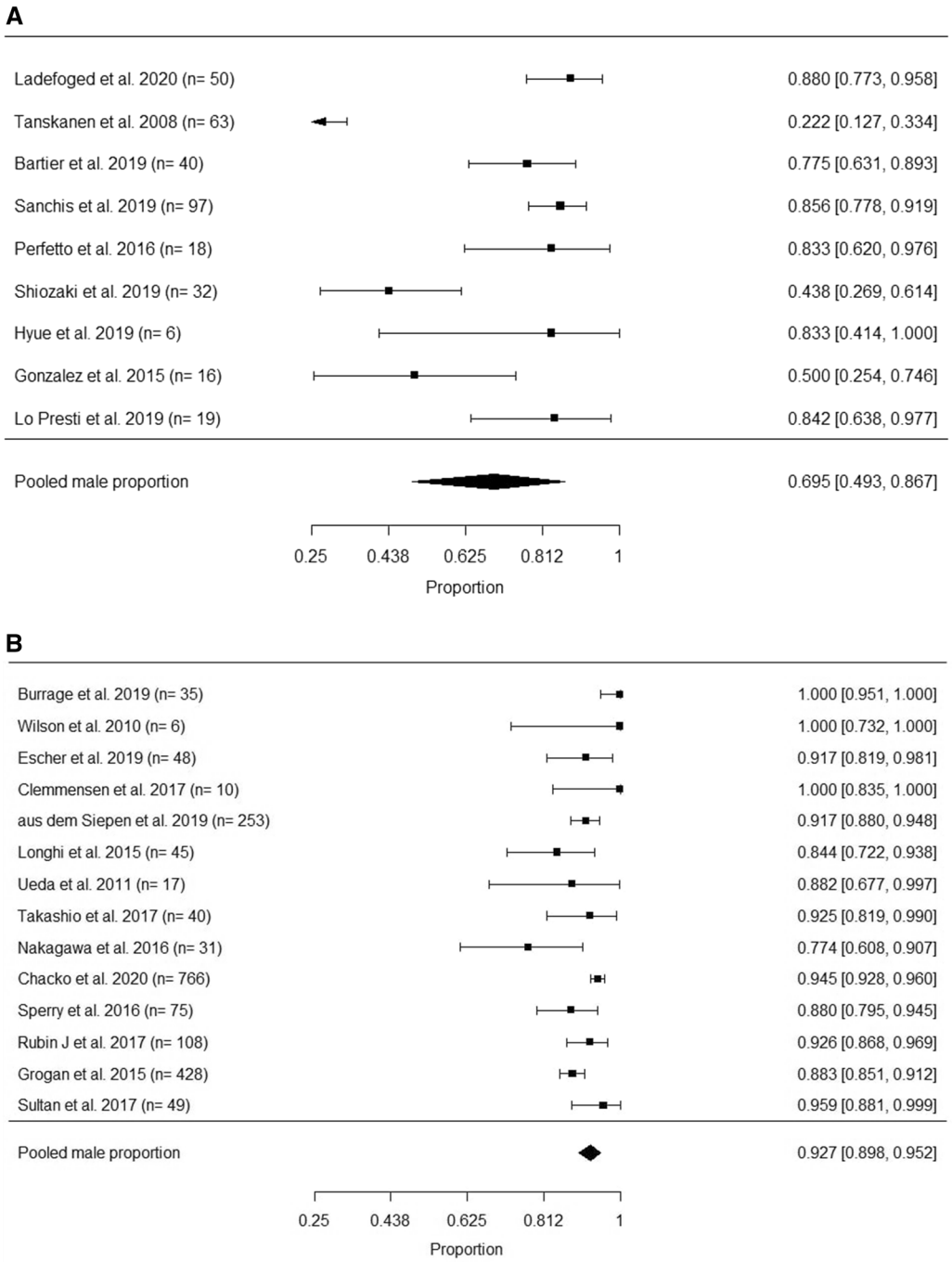

Fig. 2 **a** Male proportion estimate in different studies stratified by baseline mean age at diagnosis: **a** $\geq$ 80 years. **b** Male proportion estimate in different studies stratified by baseline mean age at diagnosis: **b** $<$ 80 years

diastolic diameter compared to males. Additional variations, in particular, include significant differences between females and males in the New York Heart Association (NYHA) classification and glomerular filtration rate scores 3.0 ($\pm$ 0.4) vs. 2.5 ($\pm$ 0.7) and 86.0 ($\pm$ 33.2) vs. 66.7 ($\pm$ 21.4), respectively [66]. Finally, Gonzalez-Lopez et al., reported that females were diagnosed non-invasively more frequently compared to males and presented with better left

Table 3 Results from the different meta-regression analyses

Meta-regression	Male proportion (%)	Standard error	*p* value
Controlling for age at diagnosis			
Intercept	91.0	0.040	< 0.001
Age	− 29.1	0.073	< 0.001
Controlling for age at diagnosis, method of diagnosis, and geography			
Intercept	91.4	0.095	< 0.001
Asian	3.8	0.094	0.683
Autopsy	− 20.6	0.070	0.003
Age	− 26.6	0.066	< 0.001
Controlling for age at diagnosis and method of diagnosis			
Intercept	95.1	0.036	< 0.001
Autopsy	− 21.1	0.065	0.002
Age	− 27.0	0.068	< 0.001
Controlling for age at diagnosis and geography			
Intercept	83.1	0.097	< 0.001
Asian	9.0	0.102	0.375
Age	− 28.5	0.074	< 0.001

ventricular ejection fraction 75% vs. 29% and 59 vs. 51, respectively [11].

DISCUSSION

This study is the first meta-analysis to estimate the gender distribution in patients with ATTRwt. We discovered three key findings. First, among all unique studies, the male proportion in patients with ATTRwt was 86.9% (95% CI 81.5–91.6%), indicating a male to female ratio of approximately 7:1. Second, ATTRwt patients of older age were significantly more likely to be female. Third, patients diagnosed by autopsy were significantly more likely to be female, a result that remained consistent even after adjusting for age.

While still understudied in ATTRwt patients, the observed gender imbalance could involve a combination of sex-specific biological factors and diagnostic challenges in female patients. In cardiovascular disease, certain female sex hormones, particularly estrogen, could be cardioprotective [68]. However, similar guidelines for the identification of ATTR-CM for both sexes (LV wall thickness > 12 mm) but larger cardiac anatomy in males compared to females may result in disease underdiagnosis of the latter as they are less likely to meet this threshold [69]. Other studies suggest ATTRwt may manifest differently in female patients resulting in more atypical symptoms compared to men [70, 71] which may pose additional diagnostic challenges. Individual studies in our review reported that the severity of ATTRwt was overall lower in females vs. males with favorable measures related to NYHA class, left ventricular ejection fraction interventricular septal thickness, posterior wall thickness, and left ventricular diastolic diameter [11, 20, 66]. In line with our findings, earlier onset and more severe disease are more common in male patients with hATTR [4, 5]. Therefore, both the older age of presentation and milder symptoms in female patients would contribute jointly to lower diagnosis rates. Literature suggests that gender imbalances are common in ATTR-CM [69]. Increasing the awareness of these factors among clinicians, in particular, implementing non-invasive techniques such as nuclear scintigraphy, could potentially increase the diagnosis among women if currently underdiagnosed [72]. Besides, the diagnosis of associated features, including carpal tunnel syndrome and lumbar spinal stenosis, raise suspicion, and may afford a means for early diagnosis [44, 73]. Nevertheless, more clinical data on how ATTRwt morbidity and mortality are different in female compared to male patients are needed. In a previous study that examined gender-based differences in over 200 ATTRwt patients, Kristen et al., found a longer delay in the initiation of symptoms and diagnosis of ATTRwt in females compared to male patients [74]. A milder or more atypical disease progression in females could result in diagnosis at an older age, a trend observed in a variety of studies [11, 19, 20, 43, 46, 62, 65].

This observation was also confirmed in our second finding, as there were 69.5% males (95% CI 49.3–86.7%) vs. 92.7% males (95% CI 89.8–95.2%) in patients over 80 years vs. patients under 80 years of age, respectively. After controlling for geography or method of diagnosis in the meta-regressions, studies including older ATTRwt patients had significantly lower male proportion compared to studies, including younger ATTRwt patients. The older age at diagnosis in females might be influenced by survival bias, i.e., on average, a female person lives longer than a male person. Male proportion did not significantly differ in Asian vs. non-Asian studies after adjusted for age in the meta-regression, implying that the older age partly explains the difference between Asian and non-Asian studies at diagnosis in Asian studies.

Our third finding showed that males were significantly less likely to be diagnosed in autopsies compared to females (coeff. − 21.1, $p = 0.002$) after controlling for age and may support the narrative that ATTRwt is underdiagnosed in women. Other studies have also found that females are more likely to be diagnosed post-mortem vs. premortem [23]. Other gender-specific trends in diagnostic methods cite that females were more likely to be diagnosed non-invasively than invasively [11].

There are sizeable strengths of this review. First, the results reflect a systematic review of all data available for ATTRwt patients, including both Western and Asian populations. Second, the synthesis of the male proportion applied suitable methods for meta-analysis of proportions. Third, we attempted to adjust for confounders employing subset analysis and meta-regression. Our results lay the necessary groundwork for future research on gender differences in diagnosis and disease burden of ATTRwt.

On the other hand, there are a few limitations to this review. First, regarding the subset analysis based on the recruitment years, we acknowledge that due to recent changes in the diagnostic methods (i.e., use of scintigraphy to diagnose ATTR without biopsy), it would have been better to dichotomize the data on studies recruiting patients before and after 2016. However, this analysis was not feasible due to the limited number of studies with patients recruited after 2016. Second, studies with a smaller sample size (frequently conducted at academic medical centers within affluent cities) often have a lower degree of randomness and representation of the general population. Third, while every effort was made to identify unique populations by years of data collection and name of the study center, there remains the possibility of overlapping study populations. Fourth, selection or referral bias within the included studies can be a confounder for the overall analysis, which makes it unclear whether the observed male predominance is due to under-diagnosis of women with ATTRwt or a true male predominance of disease. However, subset analyses based on a higher sample size, i.e., large cohort studies and using autopsy as a method of diagnosis, might be more reflective of the general ATTRwt population. Additional population-based studies are needed to further confirm our findings. Moreover, had we included languages other than English in our search strategy, it is possible that we would have encountered other relevant studies that were not included in this review. Most of our studies were in Western Europe or North America, with no representation from Latin American, Caribbean, Middle Eastern, or African countries. Finally, with only seven studies that stratify by gender, we have limited insight into the differences in clinical and baseline characteristics by gender for ATTRwt patients.

CONCLUSIONS

This is the first meta-analysis to estimate the gender distribution of ATTRwt patients based on existing literature. While we confirm that males are predominantly affected, this analysis also shows that the proportion of males was significantly impacted by the age at diagnosis and method diagnosis. This may suggest important gender-based differences in the clinical manifestation and diagnostic challenges of ATTRwt in females that warrant future research.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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