Cardiol Ther
https://doi.org/10.1007/s40119-025-00439-z

ORIGINAL RESEARCH

Functionally Limiting Symptoms and Inability to Independently Complete Daily Activities Increase the Burden Felt by Caregivers to Patients with ATTR-CM

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Received: August 20, 2025 / Accepted: October 28, 2025

ABSTRACT

***Introduction*:** The Burden of Disease survey characterized the humanistic burden of transthyretin amyloid cardiomyopathy (ATTR-CM) in 208 international patients not receiving disease-modifying therapy and their primary caregivers.

***Methods*:** Post hoc univariate analyses evaluated the relationships between patients' current symptoms and ability to complete activities of daily living (ADLs) with their caregivers' Zarit Burden Interview (ZBI), Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue, and Hospital Anxiety and Depression Survey Anxiety (HADS-A) and Depression (HADS-D) subscale scores.

***Results*:** Most patients had wild-type ATTR-CM (91%; $n=141/155$) and a New York Heart Association functional classification of I/II (78%; $n=156/199$). Caregivers ($n=208$) were a median age of 68 years, 85% were female, and 66% lived with the patient. Current patient symptoms of paralysis, heart failure, weakness (especially in the legs), leg pain, leg and ankle swelling, loss of sensation in the legs/arms, fatigue, insomnia, and weight loss were associated with a significantly ($P<0.05$) higher caregiver ZBI score. Many

Previous Presentation: Parts of this work were presented as a poster at the Heart Failure Association (HFA) of the European Society of Cardiology Annual Conference, 17–20 May 2025, Belgrade, Serbia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40119-025-00439-z.

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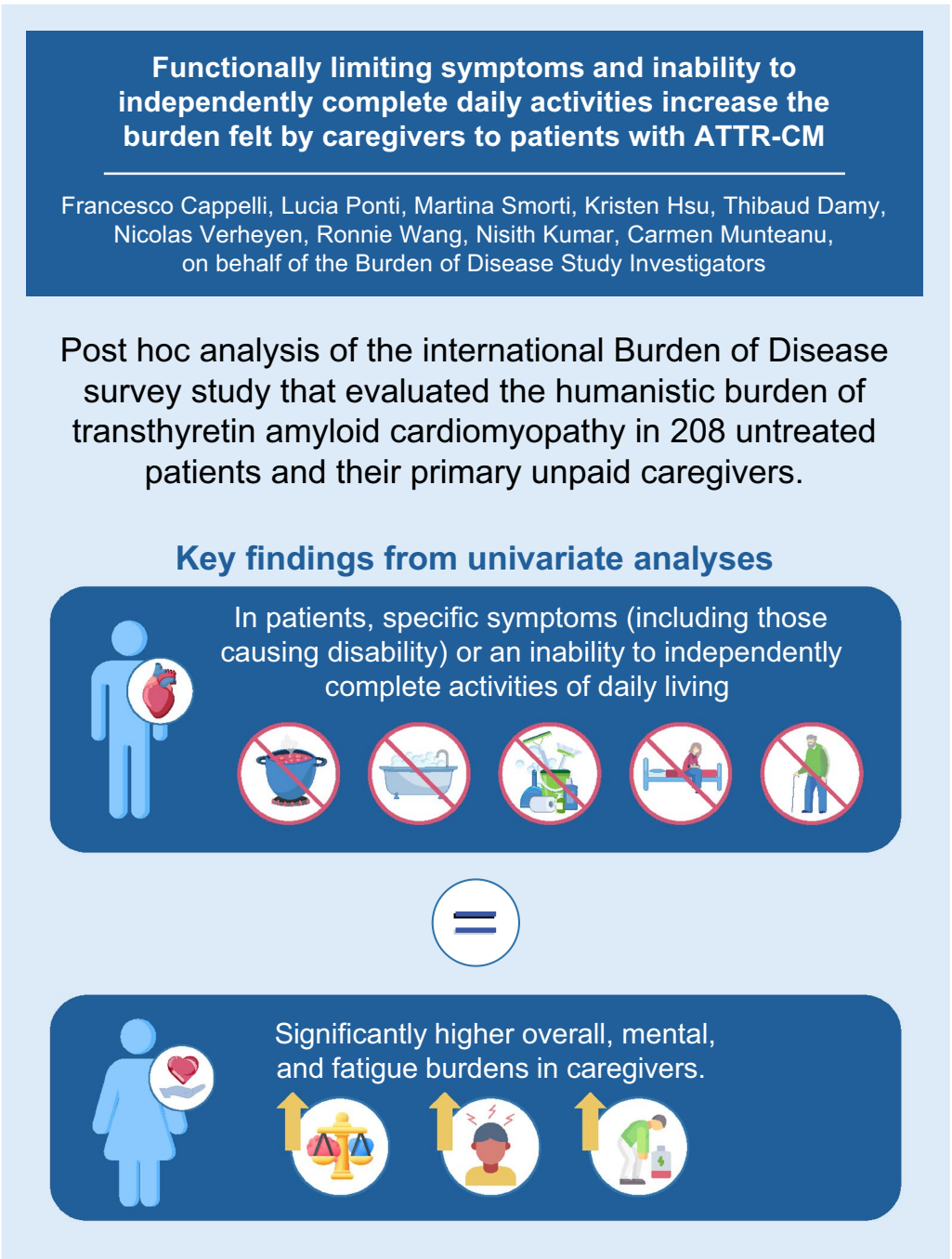
Published online: 18 December 2025

of these symptoms were also associated with significantly ($P<0.05$) higher PROMIS Fatigue and HADS-A scores; heart failure and weakness (especially in the legs) were associated with a significantly ($P<0.05$) higher HADS-D score. Inability of patients to independently clean, bathe, cook, get in/out of bed, or walk were associated with significantly ($P<0.05$) higher caregiver ZBI and HADS-D scores. Inability to independently clean and walk were associated with significantly ($P<0.05$) higher PROMIS Fatigue and HADS-A scores.

***Conclusions*:** Burden is higher in caregivers of patients with ATTR-CM who have specific symptoms (including those causing disability) or an inability to independently complete ADLs.

Graphical Abstract available for this article.

Graphical Abstract:



Adis PEER-REVIEWED FEATURE

Keywords: Anxiety; Caregiver burden; Depression; Fatigue; Heart failure

Key Summary Points

Why carry out this study?

The Burden of Disease study was an international, cross-sectional survey of patients with untreated transthyretin amyloid cardiomyopathy and their primary caregivers.

Published findings describe the multifaceted burden of transthyretin amyloid cardiomyopathy experienced by both groups.

This post hoc analysis specifically evaluated the relationship between the patient's current symptoms and ability to complete activities of daily living with the burden felt by their primary caregiver.

What was learned from the study?

We found caregiver's burden to be significantly higher across several domains when the patients they cared for had specific symptoms (including those with the potential to cause disability) or were unable to independently complete activities of daily living.

Tailored interventions to prevent the loss of functional ability in patients with transthyretin amyloid cardiomyopathy are important to support them and limit the burden felt by their caregivers.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30432334.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive condition leading to restrictive cardiomyopathy and heart failure [1]. There are two forms of ATTR-CM, namely variant and wild-type, which are causatively associated with transthyretin gene variants and aging, respectively [1, 2]. Globally, significant proportions of patients are likely to remain undiagnosed [2, 3]. ATTR-CM is considered a rare disease and the symptoms can be similar to those associated with comorbidities or other types of heart failure [1, 3]. These factors, along with a historical lack of clinical awareness and non-invasive testing, have previously contributed to diagnostic delays [2, 3]. Imaging-based diagnostic testing is now available and, in 2019, tafamidis became the first disease-modifying therapy specifically approved to treat patients with ATTR-CM anywhere in the world [1, 2]. Prior to this, patients commonly received supportive treatment only [1, 2]. In these "untreated" patients, life expectancy was generally less than 5 years from diagnosis [1, 3]. During the advanced stages of disease, patients typically find physical activities challenging and most rely on help from caregivers [4, 5].

Few studies have specifically evaluated the humanistic burden of ATTR-CM on patients and their caregivers [4, 5]. One such study, entitled the Burden of Disease study, surveyed 208 untreated patients with ATTR-CM and their primary caregivers on several aspects of their physical and mental health [5]. Findings showed untreated ATTR-CM was a burden to both patients and caregivers [5]. In both groups, burdens were higher when the patient had more severe heart failure symptoms [5]. Post hoc analyses have shown that having symptomatic heart failure, a current symptom of "weakness, especially in the legs", older age, and female sex are independent predictors of higher patient-reported burden [6]. A poorer health status in the patient was the best predictor of a higher burden in the caregiver [6].

The ability of patients to independently complete activities of daily living (ADLs) is an

important determinant of caregiver burden in the context of many diseases, including those predominantly affecting older adults [7–9]. Advanced age and a high comorbidity burden are often seen among patients with ATTR-CM [1, 3, 10]. More than one in ten patients are considered to show frailty, which is independently associated with higher incidence of falls, poor mobility, inability to complete ADLs, hospitalization, and mortality [11–15]. Additionally, studies have found frailty to be associated with a degradation in the relationship between patients with ATTR-CM and their caregivers, perhaps reflecting the additional responsibilities and emotional burden experienced by the caregiver [11].

To optimize the support provided to both patients and caregivers, it is of interest to further evaluate the burden caused by ATTR-CM. This analysis assessed the influence of caregiver demographics and selected patient characteristics on caregiver-reported burden. In particular, the impact of specific ATTR-CM symptoms and patients' ability to independently complete key ADLs on aspects of caregiver burden were evaluated.

METHODS

The methods applied in the international, multicenter, real-world Burden of Disease study have been published [5]. Surveys were completed by 208 pairs of patients with ATTR-CM and their primary unpaid caregivers between July 2021 and August 2022. Patients could have been receiving symptomatic but not disease-modifying therapy. The recruiting investigator provided each patient's age, sex, transthyretin genotype, time from diagnosis, New York Heart Association (NYHA) functional classification, and current symptoms (independent of NYHA class). They also provided each caregiver's age and sex. Other data were directly reported by the patient or caregiver. The ability of the patient to complete ADLs was reported by the caregiver.

Patients and caregivers provided informed consent to participate in the study. The study was approved by the institutional review board or independent ethics committee at each site. The study was conducted in accordance with the Declaration of Helsinki.

This post hoc analysis used unadjusted univariate analyses to evaluate individual relationships between selected patient and caregiver variables and single measures of caregiver burden. Acknowledging that variables may have a synergistic impact with others, univariate analyses were chosen to inclusively identify variables that had an association with burden. Variables were selected by the authors on the basis of their experience in the disease area and included (1) demographic characteristics of the caregiver: age, sex, if they lived with the patient, their relationship to the patient, the number of hours spent each week with the patient, and how long they had provided care to the patient; (2) if the patient had each of the pre-specified current symptoms: weakness (especially in the legs), leg and ankle swelling, leg pain, loss of sensation in the legs or arms, pain, numbness, and tingling in the hand and arm, paresthesia, paralysis, speech dysfunction, erectile dysfunction, fatigue, insomnia, heart failure, chest pain, heart palpitations/irregular/rapid heartbeat not due to atrial fibrillation, atrial fibrillation, weight loss, and gastrointestinal or urinary problems, as reported by the recruiting investigator; (3) if the patient needed no help, could only do with help, or was completely unable to do specific ADLs: bathing, cooking, cleaning, getting on/off the toilet, getting in/out of bed, walking, as reported by the caregiver; and (4) measures of patient-reported burden: Hospital Anxiety and Depression Scale Anxiety (HADS-A) and Depression (HADS-D) subscale scores [16, 17], 12-Item Short Form Health Survey Physical Component Summary (SF-12 PCS) score (range 0–100; population median 39 [interquartile range (IQR) 29–48] for people aged ≥ 75 years) [18–21], and Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue T score [range 0–83; population norm 50 (SD 10)] [22, 23]. The effect of each variable was individually assessed on the caregivers' continuous Zarit Burden Interview (ZBI) score (range 0–88, where higher score indicates a higher degree of burden) [24, 25],

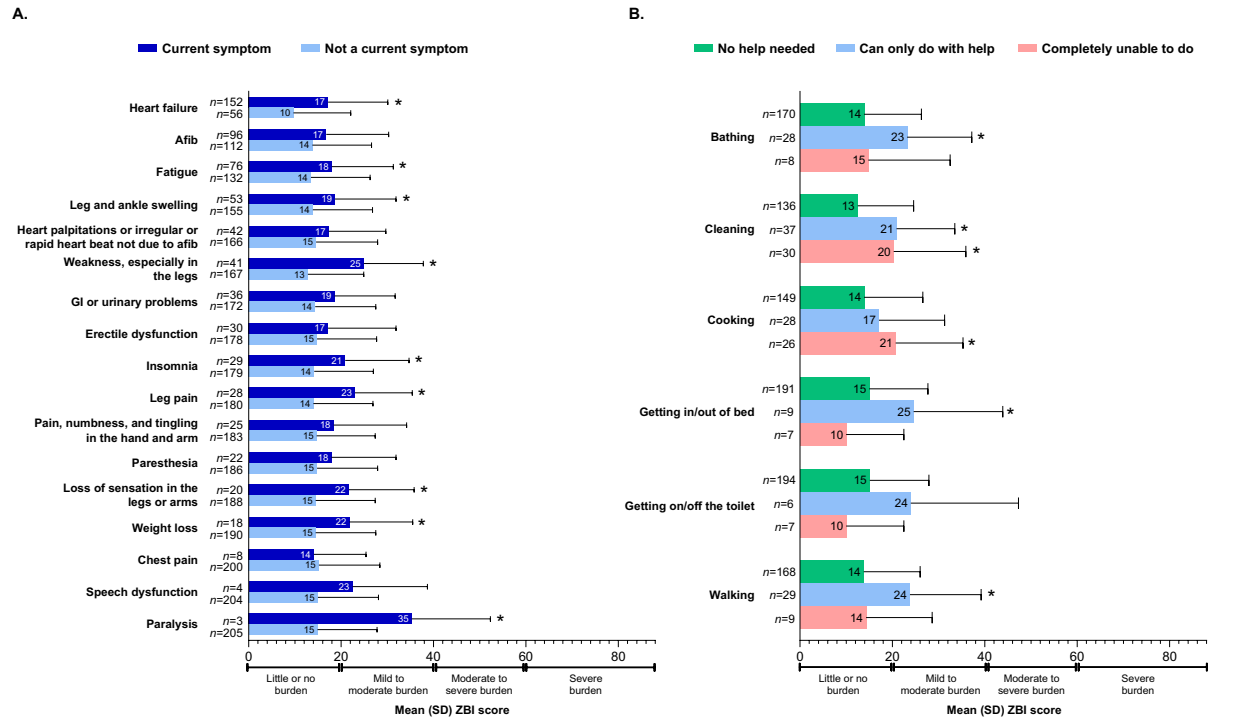


Fig. 1 The effect of **A** patients' current symptoms and **B** patients' ability to do tasks of daily life on their caregivers' ZBI. Numbers in each bar show the mean score. *$P < 0.05$ in a *t* test vs **A** not a current symptom in and **B** no help needed. *Afib* atrial fibrillation, *GI* gastrointestinal, *SD* standard deviation, *ZBI* Zarit Burden Interview

PROMIS Fatigue score, and HADS-A and HADS-D subscale scores. Significant relationships were defined as those with a $P<0.05$ by *t* test between categorical groups or linear regression for continuous variables.

Additional descriptive analyses explored differences in the impact of patients' ability to complete ADLs by the caregivers' sex (female or male), or where the patient and caregiver lived (Southern Europe, Northern Europe, or other regions).

RESULTS

Of the 208 pairs of patients and caregivers who participated in the Burden of Disease study, 126 were from Southern Europe ($n=95$ from Italy, $n=31$ from Spain), 49 were from Northern Europe ($n=34$ France, $n=15$ from Austria), and 33 were from other regions ($n=17$ from Australia, $n=10$ from Canada, $n=6$ from Russia) [5].

Patient and Caregiver Populations

Demographics and clinical characteristics for the patient and caregiver groups were published with the primary Burden of Disease study analysis [5]. The variables of relevance to this post hoc analysis are presented in Supplementary Tables S1 and S2.

Patients had a median age of 81 (range 46–90) years, 86% were male, and 91% of the 155 patients with genetic testing had wild-type ATTR-CM (Supplementary Table S1). Most patients (60% of the 199 with data) were NYHA class II. The median Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score among patients was 68 (IQR 46.4–84.8; $n=183$). The most common current symptoms were heart failure (73%), atrial fibrillation (46%), and fatigue (37%; Fig. 1). Reporting of patients' current symptoms was independent of the PROMIS Fatigue score obtained as part of the survey. The mean PROMIS score

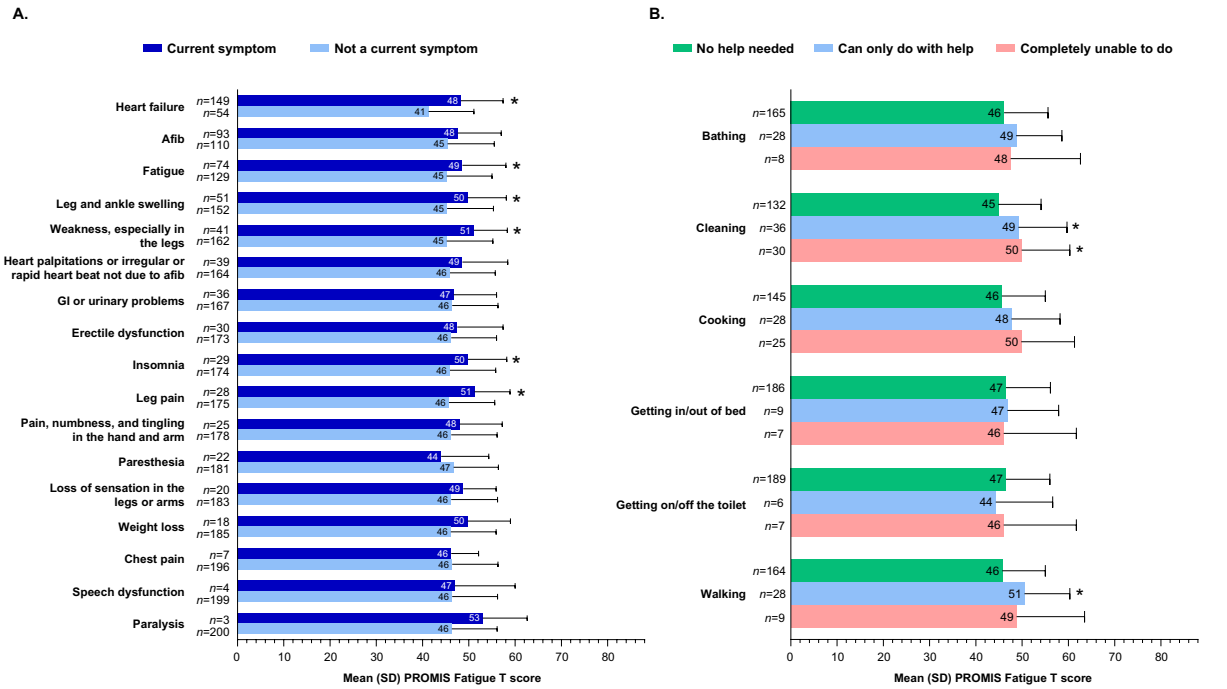


Fig. 2 The effect of **A** patients' current symptoms and **B** patients' ability to do tasks of daily life on their caregivers' PROMIS Fatigue score. Numbers in each bar show the mean score. *$P < 0.05$ in a *t* test vs **A** not a current symptom in and **B** no help needed. *Afib* atrial fibrillation, *GI* gastrointestinal, *PROMIS* Patient-Reported Outcomes Measurement Information System, *SD* standard deviation

was 51 (SD 9.4; $n = 203$). On entering the study, 11% of patients had diagnosed depression and 8% had diagnosed anxiety [5]. This was irrespective of the HADS scoring obtained as part of the survey. The median (IQR) HADS-A and HADS-D scores were 5 (3.0–8.0; $n = 205$) and 6 (3.0–10.0; $n = 204$), respectively; 26% ($n = 54$) of patients had a HADS-A score ≥ 8 and 40% ($n = 82$) had a HADS-D score ≥ 8 [5]. In the 206 patients who completed the SF-12 survey, median (IQR) PCS was 36 (27.5–43.5) and Mental Component Summary was 47 (39.4–54.5). Among patients with responses to each question, 62% ($n = 127/206$) reported being unable to walk normally, 29% ($n = 59/204$) an inability to participate in social or leisure activities in the past 3 months, and 27% ($n = 55/203$) an inability to do household chores in the past 3 months [5]. The majority of patients were able to independently (i.e., without any help needed) bathe (83%; $n = 170/206$), cook (73%; $n = 149/203$), clean (67%; $n = 136/203$), get on or off the toilet (94%; $n = 194/207$), get in or out of bed (92%; $n = 191/207$), or walk (82%; $n = 168/206$; Fig. 2).

Caregivers had a median age of 68 (range 32–88) years, 85% were female, and 59% were the spouse of the patient (Supplementary Table S2). Two-thirds (66%) of caregivers lived with the patient they cared for. The average duration of caregiving was 1.5 years. Median ZBI score among all caregivers was 13, with most caregivers indicating they felt little or no caregiving burden (64% scored 0–20) [24, 25]. Another third (30%) of caregivers reported a mild to moderate overall burden (scored 21–40). Median HADS-A and HADS-D scores were 6 and 3, respectively; 34% ($n = 70$) had a HADS-A score ≥ 8 and 25% ($n = 52$) had a HADS-D score ≥ 8 [5]. The mean PROMIS Fatigue score among caregivers was 46. Overall, 10% of caregivers ($n = 21/204$ respondents) reported at least 1 day in the past 3 months where they were unable to complete typical household chores as a result of caregiving responsibilities [5].

Table 1 The effect of demographic and clinical characteristics on caregivers' ZBI, HADS subscales, and PROMIS Fatigue scores

	Caregiver burden measure			
	ZBI score	**PROMIS Fatigue**	**HADS-A score**	**HADS-D score**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Categorical caregiver characteristics				
Relationship with patient				
Spouse	14.2 (12.8) [*n* = 122]	47.1 (9.4) [*n* = 117]	6.4 (4.4) [*n* = 119]	4.8 (4.5) [*n* = 120]
Other	16.3 (13.7) [*n* = 83]	45.3 (10.4) [*n* = 83]	5.8 (4.1) [*n* = 83]	4.4 (4.1) [*n* = 83]
Sex				
Female	15.7 (13.1) [*n* = 176]	47.2 (9.5) [*n* = 172]	6.5 (4.3) [*n* = 173]	4.9 (4.4) [*n* = 174]
Male	12.3 (13.4) [*n* = 32]	**42.0 (10.4)*** [*n* = 31]	**4.5 (3.4)*** [*n* = 32]	**3.3 (3.2)*** [*n* = 32]
Caregiver lives with the patient				
Yes	14.4 (13.0) [*n* = 138]	47.1 (9.9) [*n* = 133]	6.3 (4.5) [*n* = 135]	4.9 (4.6) [*n* = 136]
No	16.6 (13.4) [*n* = 70]	45.2 (9.5) [*n* = 70]	5.9 (3.8) [*n* = 70]	4.2 (3.7) [*n* = 70]
Continuous caregiver characteristics[a]				
	RC	RC	RC	RC
Age	− 0.078	0.042	− 0.012	0.002
Hours/week spent with the patient	− 0.006	0.018	0.004	0.005
Years providing care	− 0.003	− 0.008	0.069	0.018
Patients' clinical characteristics				
HADS-A score	**1.167***	**0.722***	**0.288***	**0.348***
HADS-D score	**0.923***	**0.405***	**0.200***	**0.327***
SF-12 PCS score	**− 0.393***	**− 0.218***	**− 0.108***	**− 0.109***
PROMIS Fatigue score	**0.634***	**0.474***	**0.157***	**0.153***

RC is for a one-unit increase in the characteristic

HADS-A Hospital Anxiety and Depression Scale Anxiety, *HADS-D* Hospital Anxiety and Depression Scale Depression, *PROMIS* Patient-Reported Outcomes Measurement Information System, *RC* regression coefficient, *SD* standard deviation, *SF-12* 12-item Short Form Health Survey, *ZBI* Zarit Burden Interview

[a]Analyses of continuous variables did not require paired data and include all patients and caregivers with responses for each characteristic and measure of burden (*n* = 166 to 208)

*$P < 0.05$ in a *t* test between subgroups or for the linear regression

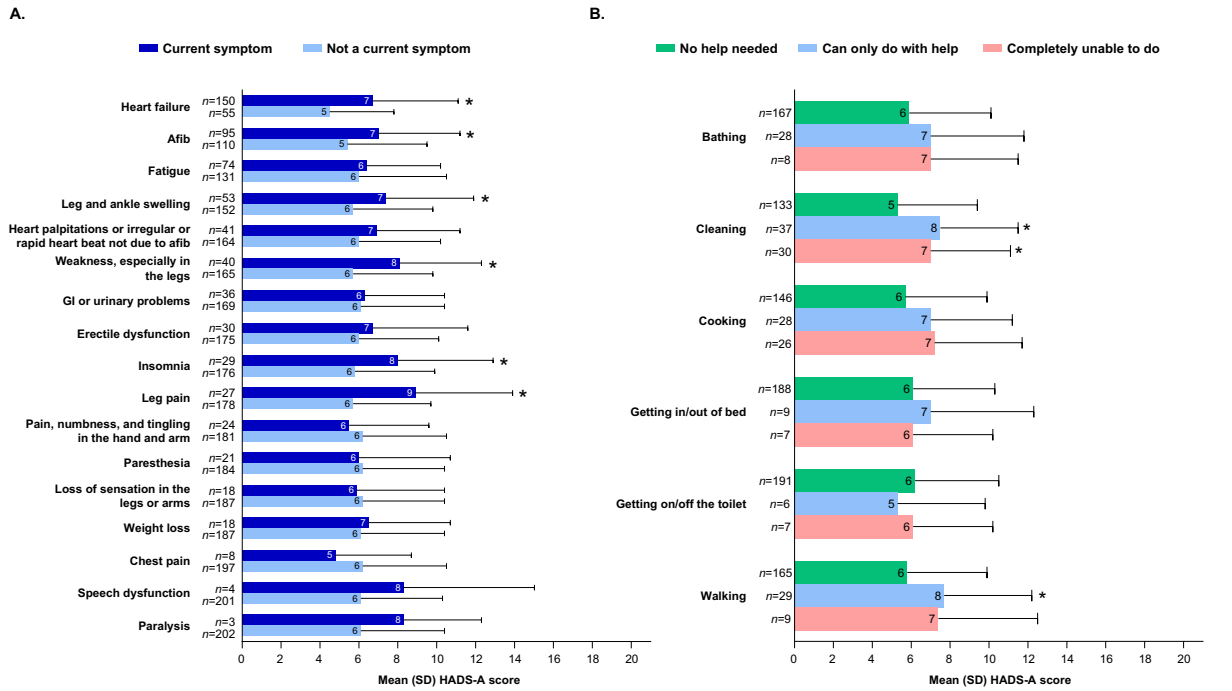


Fig. 3 The effect of **A** patients' current symptoms and **B** patients' ability to do tasks of daily life on their caregivers' HADS-A score. Numbers in each bar show the mean score. *$P < 0.05$ in a *t* test vs **A** not a current symptom in and **B** no help needed. *Afib* atrial fibrillation, *GI* gastrointestinal, *HADS-A* Hospital Anxiety and Depression Scale Anxiety, *SD* standard deviation

Variables Related to Caregivers' Overall Burden

Adding to previously published findings from the Burden of Disease study, poorer physical and mental health in patients was associated with a significantly higher ZBI score in caregivers (i.e., lower SF-12 PCS; higher HADS-A, HADS-D, and PROMIS Fatigue scores; and presence of specific ATTR-CM symptoms or inability to independently complete several ADLs; Table 1, Fig. 1) [5, 6]. No significant relationships were seen between caregiver demographics and their ZBI score (Table 1). Current symptoms of paralysis, heart failure, weakness (especially in the legs), leg pain, leg and ankle swelling, loss of sensation in the legs or arms, fatigue, insomnia, and weight loss in patients were each associated with a significantly higher ZBI score in caregivers (Fig. 1). Non-significant trends for higher ZBI score were observed with the presence of most other current symptoms.

Symptoms of ATTR-CM may impact patients' ability to complete ADLs. Inability of patients to independently (i.e., no help needed) clean, bathe, cook, get in/out of bed, or walk were associated with a significantly higher ZBI score in caregivers (Fig. 1). Interestingly, for bathing, getting in/out of bed, and walking, the significantly higher caregiver burden (vs no help needed) was only found when patients required help to complete the activity, and not when they were completely unable to do the activity. A similar, non-significant relationship was seen with the ability to get on/off the toilet. For cleaning, caregiver burden was significantly higher both when patients required help and were completely unable to do, as compared with when no help was needed. For cooking, caregiver burden increased stepwise as patients' ability decreased but was only significantly higher versus when no help was needed, when patients were completely unable to do.

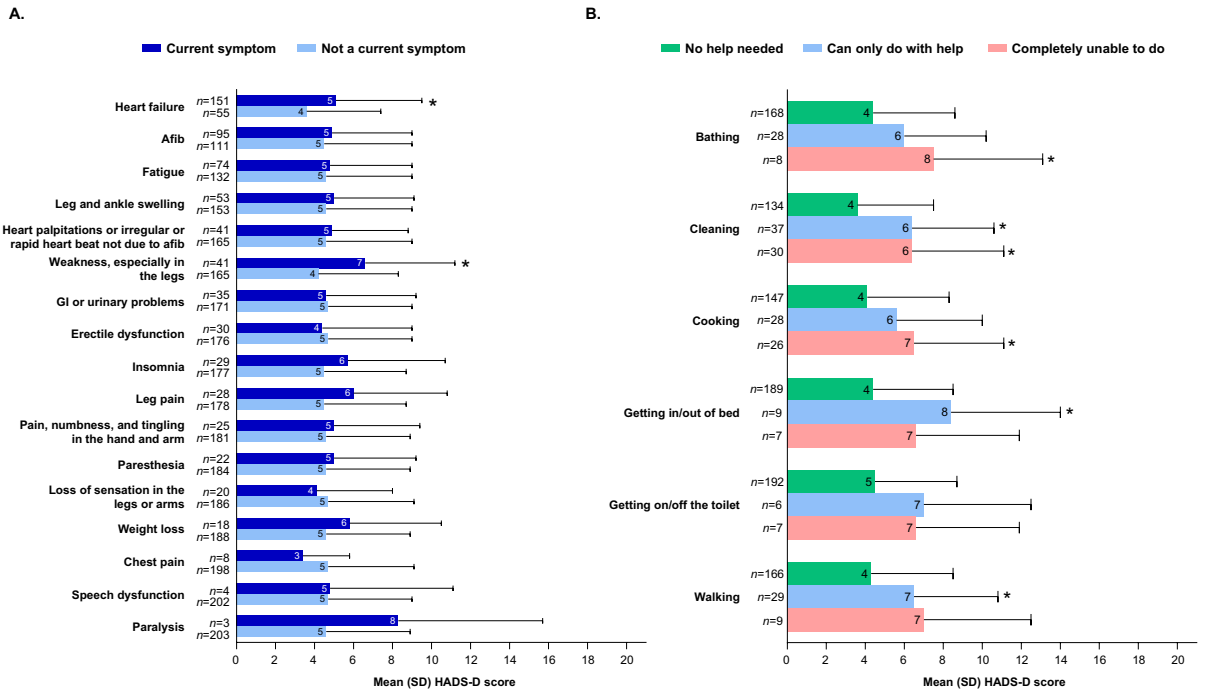


Fig. 4 The effect of **A** patients' current symptoms and **B** patients' ability to do tasks of daily life on their caregivers' HADS-D score. Numbers in each bar show the mean score. *$P < 0.05$ in a *t* test vs **A** not a current symptom and **B** no help needed. *Afib* atrial fibrillation, *GI* gastrointestinal, *HADS-D* Hospital Anxiety and Depression Scale Depression, *SD* standard deviation

Variables Related to Caregivers' Fatigue Burden

A patient's experience of fatigue can have both mental and physical aspects [26]. Though neither patient nor caregiver cohorts had mean PROMIS Fatigue scores outside of the normal range of the general population, the recruiting investigator reported 76 (37%) patients had fatigue (Fig. 1) [22]. Female caregivers had a significantly higher PROMIS fatigue score than male caregivers (Table 1).

Poorer physical and mental health in patients (i.e., lower SF-12 PCS; higher HADS-A, HADS-D, and PROMIS Fatigue scores; and presence of specific ATTR-CM symptoms or inability to independently complete several ADLs) was associated with a significantly higher PROMIS Fatigue score in caregivers (Table 1, Fig. 2). Symptoms of heart failure, weakness (especially in the legs), leg pain, leg and ankle swelling, fatigue, and insomnia in patients were associated with a significantly higher PROMIS Fatigue score in caregivers (Fig. 2). Inability of patients to independently clean (requiring help or being completely unable to do) and requiring help to walk were each associated with a significantly higher PROMIS Fatigue score in caregivers than when patients did not require help (Fig. 2). The impact of individual symptoms and inability to independently complete specific ADLs was of small magnitude and unlikely to individually result in a clinically relevant increase in fatigue burden.

Variables Related to Caregivers' Mental Health Burden

Poorer physical and mental health (i.e., lower SF-12 PCS; higher HADS-A, HADS-D, and PROMIS Fatigue scores; and presence of specific ATTR-CM symptoms or inability to independently complete several ADLs) in patients was

associated with significantly higher HADS-A and HADS-D scores in caregivers (Table 1, Figs. 3 and 4). Additionally, female caregivers had significantly higher HADS-A and HADS-D scores than male caregivers.

Current symptoms of heart failure, weakness (especially in the legs), leg pain, leg and ankle swelling, insomnia, and atrial fibrillation in patients were associated with a significantly higher HADS-A score in caregivers (Fig. 3). The differences in scores between caregivers to patients with and without each symptom were often of a magnitude > 2, and several symptoms were associated with a mean caregiver HADS-A score ≥ 8 (leg pain, paralysis, speech dysfunction, weakness [especially in the legs], and insomnia), i.e., crossing the threshold indicating clinically relevant anxiety [16, 17]. Most patient symptoms had a relatively small individual impact on the caregivers' HADS-D score (< 2-point change; Fig. 4). Current symptoms of heart failure and weakness (especially in the legs) were associated with a significantly higher HADS-D score in caregivers. Though only three caregivers looked after patients with paralysis, together they had a mean HADS-D score of 8. No other groups had a mean ≥ 8, which is a threshold indicating clinically relevant depression [16, 17].

Patients' inability to independently clean (requiring help or being completely unable to do) and needing help with walking were each associated with a significantly higher HADS-A score in caregivers, as compared with when patients required no help (Fig. 3). Differences in HADS-A scores across caregivers to patients with different capacities to complete ADLs were a maximum of approximately 2. Caregivers to patients who can clean or walk only with help had a mean HADS-A score of approximately 8. Though not statistically significant in all comparisons, trends for bathing, cleaning, cooking, and walking suggested a similar additional anxiety burden to caregivers when patients required help and were completely unable to do the ADL. Patients' inability to independently clean (requiring help or being completely unable to do), needing help to get in/out of bed or walk, and being completely unable to bathe or cook were each associated with a significantly higher HADS-D score in caregivers as compared with patients who required no help (Fig. 4). For many ADLs, differences in HADS-D between caregivers to patients requiring no help and at least some help (help or completely unable to do) were > 2, and caregivers to patients who required help to bathe and get in/out of bed had a mean HADS-D score of approximtely 8.

Exploratory Analyses by Caregiver Sex and Geographic Region

Exploratory analyses looked at the impact of patients' ability to complete ADLs on caregivers' ZBI score by the sex of the caregiver, and by the region in which the pair lived. These were conducted to get an indication of the cultural differences in caregiving expectations and associated burden (Supplementary Figs. S1 and S2). Though the analyses were descriptive and included limited numbers of caregivers in each subgroup, we noted slightly lower levels of overall burden in male versus female caregivers and, further, the impact of patients being unable to complete ADLs appeared generally less pronounced in male caregivers than in female caregivers. Exploratory regional analyses suggested caregiver burden was generally less in those who resided in Southern Europe as compared with Northern Europe or other regions (namely Australia, Canada, and Russia).

DISCUSSION

This post hoc analysis of an international, multicenter, cross-sectional, real-world survey study provides valuable insights into the factors influencing disease burden in unpaid primary caregivers to patients with untreated ATTR-CM, predominantly of the wild-type form. Findings confirm that symptoms affecting patients' physicality and their ability to complete ADLs are frequently associated with higher burdens in their caregivers. The findings also suggest female caregivers experience a higher mental and fatigue burden than male caregivers.

ATTR-CM is associated with cardiac, extracardiac, and mental symptoms, potentially

contributing to a wide range of disabilities [1, 2]. A mental health burden is also common in families dealing with ATTR-CM, both as a result of caregiving responsibilities and the emotional impact of having a loved one with a progressive disease [4, 5]. The primary analysis from the Burden of Disease study showed caregiver burden increased alongside the severity of heart failure symptoms in patients with ATTR-CM [5]. Post hoc analyses found that, among selected variables, patients' KCCQ-OS score was the strongest predictor of burden in caregivers, where a poorer health status predicted a higher caregiver burden [6]. As the KCCQ-OS score encompasses multiple aspects of health status, we further investigated the impact of individual symptoms and patients' ability to complete common ADLs on different facets of caregiver burden. Findings showed symptoms of ATTR-CM that contribute towards an inability to independently complete ADLs (i.e., heart failure, fatigue, symptoms associated with the limbs, and insomnia) significantly contributed to caregivers' overall burden. Many symptoms also contributed to the mental aspects of burden, where the presence of heart failure, symptoms associated with the limbs, and insomnia in patients increased the caregivers' anxiety burden. Similar variables contributed to caregiver fatigue. Our findings are in agreement with those from a qualitative study where patients reported intolerance to activity, inability to exercise, insomnia, and fatigue to be among the most challenging aspects of ATTR-CM [27].

The Burden of Disease study asked caregivers about the ability of the patient to complete ADLs. Our analyses showed that, for nearly all ADLs evaluated, an inability of patients to independently complete the activities was associated with a higher overall burden in their caregiver. For some ADLs, the difference in overall caregiver burden when patients required help or was completely unable to do the activity was similar (i.e., cleaning and cooking), whereas for others, the largest burdens were reported where the patient required help but could still complete some of the activity (i.e., bathing, getting in/out of bed, on/off the toilet, or walking). These findings suggest that additional coping mechanisms or equipment might be utilized for some ADLs when patients are completely unable to do the activity, limiting the additional burden on caregivers. We additionally hypothesize there may be emotional and physical strain placed on caregivers during the transition between independence and dependence; for example, when a patient requires help to walk there may be anxieties around the potential for accidents and negative external perceptions, whilst also requiring more physical support from the caregiver. When the patient progresses to being unable to walk these anxieties may be lessened. Interventions such as health education, home visits, calls, counseling, and support groups have been evaluated as ways to reduce burden in caregivers to patients with heart failure [28]. Identification of specific interventions to support caregivers to patients with ATTR-CM would be clinically valuable.

Though statistical significance was not seen on all outcomes, there are notable trends for increased HADS-A and HADS-D scores for caregivers both when patients required help with ADLs and when they are completely unable to do the activity. The impact of inability of patients to complete ADLs was seen to impact on caregivers' depression symptoms more strongly than their anxiety symptoms. Similar relationships were also seen with caregivers' fatigue, although the magnitude of differences across the spectrum of disability was small. Together, findings suggest the initial loss of independence is a time when the caregiving burden increases and is a time when caregivers may be at increased risk of anxiety, depression, and fatigue.

ATTR-CM is most commonly diagnosed in older adults who may have comorbidities and symptoms associated with aging [1, 3, 10]. Frailty is reported in between one in ten and one in two patients with ATTR-CM, with the wide prevalence range likely reflecting differences in the populations and measures used [11–13]. Frailty is independently associated with limitations in the ability to complete ADLs and could directly contribute to caregivers' physical and mental burden [11, 12, 14, 15]. Although not directly assessed, frailty may have been a contributing factor to our findings, as the median patient age was 81 years and median caregiver age was 68 years. Frailty also has potential to

influence caregivers' ability to provide physical assistance; however, caregivers' age was not found to be significantly associated with any aspect of their burden.

Evidence suggests that caregiving for elderly family members is most commonly done by women [29]. Though inconclusive, there is evidence to suggest that female caregivers often experience a larger burden than male caregivers [29–31]. Sex differences in overall caregiver burden were not identified in this study; however, our analyses found female caregivers had a significantly higher mental (HADS-A and HADS-D subscores) and fatigue burden than male caregivers. In further exploratory analyses, it appeared that male caregivers were less impacted by a patients' inability to complete ADLs than female caregivers. In combination with our findings suggesting regional differences in caregiver burden, we propose that these likely reflect cultural variations in the approach to caregiving. For example, female caregiving (in particular to children and spouses) is a part of many traditional cultures worldwide. In addition, the familial and public health support networks around caregivers may vary by region. In keeping with our findings, Stewart et al. found a lower ZBI score was reported by caregivers of patients with untreated ATTR-CM in Spain versus the USA [4]. This may explain our findings of lower burden related to ADLs in caregivers residing in Southern Europe as compared with Northern Europe and other international regions.

Limitations

Our results should be interpreted within the populations analyzed, namely unpaid primary caregivers to patients with reasonably newly diagnosed and untreated ATTR-CM, mostly of the wild-type form. The majority of patients and caregiver pairs were of a male/female spousal relationship and resided in Europe. Another limitation is that some responses were provided by low numbers of caregivers or patients, reducing the ability to identify statistical significance. For this reason, numerical trends within the data have also been considered when interpreting the findings. Additionally, the Burden of Disease study was not specifically designed with this post hoc analysis in mind. Questionnaires used were not optimized for the analysis. Additionally, the enrolled patients and caregivers reflected the real-world population and the range of disease severity, mental, and physical burdens was not optimized for this analysis. Further evaluation of patient and caregiver pairs affected by more advanced ATTR-CM would help contextualize our findings.

CONCLUSIONS

In this post hoc analysis of an international survey study among patients with untreated ATTR-CM and their primary unpaid caregivers, the physical and mental health of patients was shown to contribute to the burden felt by their caregivers. Caring for patients with specific ATTR-CM symptoms (including those that may contribute to disability) or an inability to complete ADLs was associated with higher burdens in caregivers. Further, our findings suggest there are cultural factors that influence caregiver-reported burden, including a higher mental and fatigue burden in female versus male caregivers. Overall findings suggest that interventions to prevent the loss of functional ability in patients is important to support them, but also to limit the burden felt by their caregivers. Additionally, approaches to assist caregivers in the care of patients with ATTR-CM are valuable in reducing the burden they feel.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the non-author investigators who contributed to the study and their teams: Scott McKenzie, The Prince Charles Hospital, Australia; Eduardo Villacorta Argüelles, Complejo Asistencial Universitario de Salamanca—H. Clinico, Spain; Johannes Kastner, Medical University of Vienna, Austria; Dariusz Korczyk, Princess Alexandra Hospital, Australia; Ryan Davey, London Health Sciences

Centre, Canada; Michele Emdin, Fondazione Toscana Gabriele Monasterio, Italy; Miguel Angel Aibar, Hospital Clinico Universitario Lozano Blesa, Spain; Igor Zhirov, Russian Cardiology Research and Production Center, Russian Federation; Albert Galyavich, Kazan State Medical University, Russian Federation; and James Gunton, Flinders Medical Centre, Australia.

Medical Writing/Editorial Assistance. Medical writing support was provided by Jennifer Bodkin of Engage Scientific Solutions and was funded by Pfizer.

Author Contributions. Francesco Cappelli, Lucia Ponti, Martina Smorti, Kristen Hsu, Thibaud Damy, Nicolas Verheyen contributed to conceptualization, investigation, methodology, and writing—review and editing. Nisith Kumar and Carmen Munteanu contributed to conceptualization, funding acquisition, methodology, and writing—review and editing. Ronnie Wang contributed to conceptualization, formal analysis, methodology, and writing—review and editing. All authors read and approved the final version of the manuscript.

Funding. This study was sponsored by Pfizer. The journal's Rapid Service Fee was funded by Pfizer.

Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Conflict of Interest. Francesco Cappelli reports honoraria for advisory board participation from Alnylam, Astra Zeneca, Bayer, BridgeBio, Novo Nordisk, and Pfizer; his institution has received an unconditional research grant from Pfizer. Martina Smorti reports speaker fees from Pfizer. Lucia Ponti and Kristen Hsu have no disclosures. Thibaud Damy has received consulting fees from Alnylam, GlaxoSmithKline, Pfizer, and Prothena; honoraria from Alnylam, Pfizer, and Prothena; research grants from GlaxoSmithKline and Pfizer; and clinical trial support from Alnylam, Ionis, and Pfizer. Nicolas Verheyen has received research grant, honoraria for advisory board participation, and speaker's fees from Pfizer. Ronnie Wang, Nisith Kumar, and Carmen Munteanu are employees of Pfizer and hold stock/stock options.

Ethical Approval. Patients and caregivers provided informed consent to participate in the study. The study was approved by the institutional review board or independent ethics committee at each site. The study was conducted in accordance with the Declaration of Helsinki.

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