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# Exploring the association between quality of life and survival in patients with transthyretin amyloidosis

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**EXPLORING THE ASSOCIATION BETWEEN QUALITY OF LIFE AND  
SURVIVAL IN PATIENTS WITH TRANSTHYRETIN AMYLOIDOSIS**

by

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Sc.B., Brown University, 2007

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2016

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## **DEDICATION**

I would like to dedicate this body of work to the patients of the Boston University (BU) Amyloidosis Center and all those dedicated to the treatment of rare diseases, specifically TTR Amyloidosis. It has been a privilege to be a part of the BU Amyloidosis Community, and I am forever grateful for the experiences and friendships gained. It is my hope that the knowledge derived from this research will offer clinically meaningful insights that will contribute to the continued advancement of disease understanding. Additionally, I hope that the results of this study will be of use in the development of novel therapies and improved treatment outcomes for patients with amyloidosis.

## ACKNOWLEDGMENTS

There are many individuals who were instrumental in the preparation of this thesis.

Specifically, I would like to recognize:

My thesis readers, Stacey Hess Pino, M.S., Dr. John Berk, M.D. and Dr. Howard Cabral, Ph.D. for their patience, as well as their thoughtful and thorough review of this body of work. In particular, I would like to thank Stacey for her mentorship throughout the MSCI program, Dr. Berk for his subject matter insights, and Dr. Cabral for his statistical expertise.

My friends, both old and new who served as a support system throughout my MSCI degree program. I am thankful for all their insights and reassurance, especially while developing and writing this thesis.

My family for their unwavering support and belief in my abilities, even when I have doubted myself the most. They continue to be my source of strength and motivate me to pursue my goals, no matter the obstacles presented. Every day I strive to make them proud.

**EXPLORING THE ASSOCIATION BETWEEN QUALITY OF LIFE AND  
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**VICTORIA J. LATTANZI**

**ABSTRACT**

*Background:* Studies in various chronic diseases have correlated health-related quality of life (HRQOL) with disease state and treatment outcomes. Limited data exists on the association between HRQOL, survival, and clinical biomarkers of disease in wild-type and familial TTR amyloidosis (ATTRwt & ATTRm) patient populations.

*Objectives:* To assess the association between HRQOL and survival, as well as HRQOL and clinical biomarkers of disease in transthyretin-mediated amyloidosis (ATTR) patient populations.

*Methods:* Using a retrospective cohort study design, HRQOL was assessed via SF-36 health surveys collected from patients with ATTRwt and ATTRm presenting for their initial evaluation at the BU Amyloidosis Center between 1985 and 2015. Kaplan-Meier curves and hazard ratios (HRs) calculated using Cox proportional hazards regression analysis were used to examine the association between physical (PCS) and mental (MCS) component scores derived from the SF-36 health surveys and survival follow-up. All analyses were adjusted for potential confounders such as age at presentation, gender, and co-morbidities including diabetes mellitus, hypertension and hyperlipidemia. Spearman's rank correlations were calculated to assess the association between PCS, MCS and

clinical biomarkers of disease (mBMI, troponin I and BNP) also collected at time of initial evaluation visit. Statistical significance was set at a two-sided  $\alpha=0.05$ .

*Results:* In the ATTRwt cohort, 133 white males, aged  $74.6 \pm 6.0$  years (mean  $\pm$  SD) presented with mean MCS ( $45.7 \pm 12.3$ ) and PCS ( $36.7 \pm 10.8$ ) that were respectively, 0.5 and 1.5 SD below 50. Patients with PCS or MCS scores  $< 35$  had a significantly higher risk of death during follow-up than those with scores  $\geq 35$  for PCS (HR=2.45;  $p=0.002$ ) and for MCS (HR=3.38,  $p<0.0001$ ). BNP and troponin I associated with MCS ( $r= - 0.24$ ;  $p=0.01$  and  $p=0.02$ , respectively) and PCS ( $r= - 0.29$ ;  $p=0.002$  and  $r= - 0.25$ ;  $p=0.012$ , respectively). In the ATTRm cohort, 331 white (82%) males (67%), aged  $57.5 \pm 13.9$  years presented with mean MCS ( $45.2 \pm 11.7$ ) and PCS ( $37.2 \pm 13.3$ ). Patients with PCS scores  $< 35$  had a significantly higher risk of death during follow-up than those with scores  $\geq 35$  (HR=2.76;  $p= <0.0001$ ). In contrast, MCS scores  $< 35$  did not correlate with increased risk of death during follow-up (HR=1.38,  $p=0.13$ ). BNP and troponin I most strongly associated with PCS ( $r= - 0.50$ ;  $p<0.0001$  and  $r= - 0.41$ ;  $p<0.0001$ , respectively) and less with MCS ( $r= - 0.16$ ;  $p=0.03$  and  $r= - 0.24$ ;  $p=0.007$ , respectively). mBMI did not associate with MCS or PCS in the ATTRwt and ATTRm cohorts.

*Conclusions:* ATTR disease significantly decreased an individual's physical and mental HRQOL. PCS and MCS were shown to be independent predictors of mortality but their ability to predict survival varied by cohort. Assessment of HRQOL may provide valuable prognostic information that could be of use in the management of ATTR disease.



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## LIST OF ABBREVIATIONS

AA.....	Amyloid A
AL.....	Amyloid Light Chain Amyloidosis
ATTR.....	Transthyretin Amyloidosis
ATTRm.....	Mutant Transthyretin Amyloidosis
ATTRwt.....	Wild-Type Transthyretin Amyloidosis
BNP.....	B-type Natriuretic Peptide
BP.....	Bodily Pain
BU.....	Boston University
GH.....	General Health
HR.....	Hazard Ratio
HRQOL.....	Health-Related Quality of Life
mBMI.....	Modified Body Mass Index
MCS.....	Mental Component Summary
MH.....	Mental Health
MOS.....	Medical Outcomes Study
NIH.....	National Institute of Health
PCS.....	Physical Component Score
PF.....	Physical Functioning
QOL.....	Quality of Life
RE.....	Role Limiting Emotional Problems
RP.....	Role Limiting Physical Problems

SF .....	Social Functioning
SF-36.....	36 Question Short Form Health Survey
SAA.....	Serum Amyloid A
SSA .....	Senile Systemic Amyloidosis
TTR.....	Transthyretin
VT .....	Vitality

## SECTION 1. INTRODUCTION

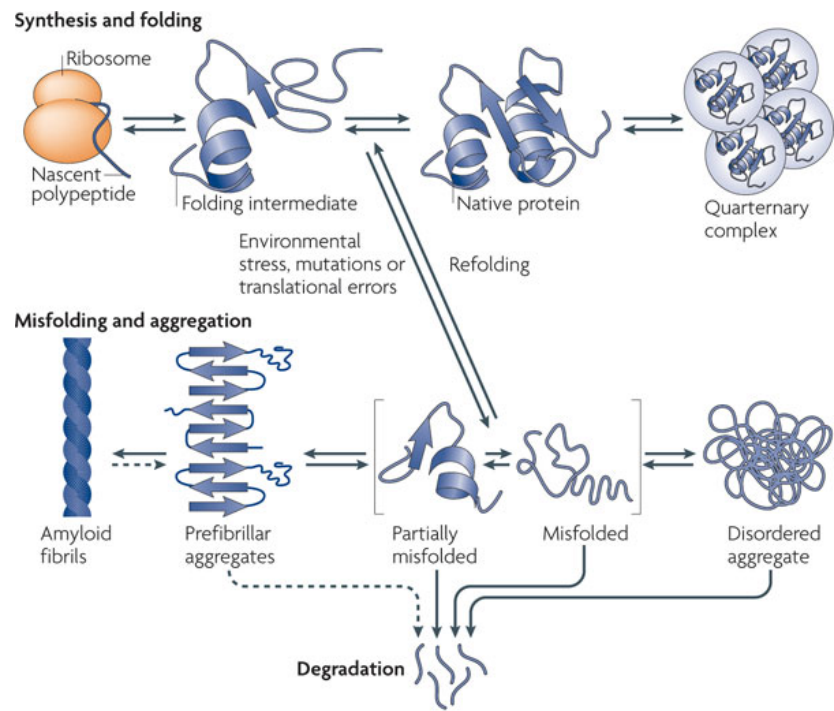
### 1.1 Amyloidosis

Amyloidosis represents a group of disease states caused by the misfolding and accumulation of proteins. The folded structure of a protein, known as its native state dictates its function. When a protein is misfolded it is unable to carry out its highly specialized biological role and must be cleared from the body (**Figure 1**).<sup>1</sup> Typically, misfolded protein removal is achieved through proteasomal degradative pathways as part of normal cellular processes.<sup>2</sup> However, failure to remove aberrantly folded proteins triggers a multi-step self-assembly pathway where build-up of misfolded protein results in the development of large molecular aggregates.<sup>3-4</sup> These aggregates continue to accumulate into insoluble amyloid fibrils that can deposit into various organs and tissue types, causing progressive disruption of normal organ and tissue function.<sup>5-6</sup>



## Figure 1. Protein Folding, Misfolding and Aggregation

When a protein is unable to maintain its native state, misfolded proteins are degraded and cleared from the body. However, if degradation does not occur, misfolded proteins accumulate, aggregate and deposit as amyloid fibrils in organs and tissue.



Nature Reviews | Molecular Cell Biology

Source: Tyedmers J, Mogk A and Bukau B. Cellular strategies for controlling protein aggregation. *Nature Reviews Molecular Cell Biology*. 2010;11:777-788. Reproduced with permission from Nature Publishing Group.

To date, approximately 30 proteins have been shown to have misfolding capabilities that result in specific amyloidotic disease states.<sup>7</sup> The clinical manifestations of amyloid disease are dependent on the protein type involved and the target organ or tissue. Alzheimer's disease (AD) and Parkinson's disease (PD) are examples of well-known amyloidotic diseases hallmarked by progressive neurodegeneration in the brain.<sup>8</sup> Both are considered forms of localized amyloidoses as they involve amyloid fibril deposition exclusively in one organ. There are also 4 major systemic amyloidoses that involve the deposition of specific proteins and affect multiple organs. Amyloid light-chain (AL) amyloidosis is the most common type, caused by the accumulation of misfolded immunoglobulin light chain proteins. Approximately 4,000 new cases are diagnosed annually in the US, most frequently affecting the kidney and the heart.<sup>9-10</sup> Amyloid A (AA) amyloidosis results from the deposition of serum amyloid A (SAA) protein aggregates and is secondarily associated with inflammatory diseases such as rheumatoid arthritis and chronic infection.<sup>11-12</sup> The remaining 2 major forms of systemic amyloidosis involve deposition of normal and genetically mutated transthyretin (TTR) protein in various organs and tissues.<sup>13-14</sup>

Regardless of etiology or pathology, amyloidoses are rare diseases affecting populations worldwide.<sup>13</sup> In the United States, they are estimated to affect less than 200,000 people total and have been granted orphan disease designation by the National Institute of Health (NIH).<sup>15-17</sup> However, it is possible that amyloidoses are not truly rare, but rarely diagnosed due to a lack of disease awareness.<sup>18</sup> In addition to the advancing disease

treatment options, current research initiatives aim to better educate the general and medical communities on disease risk factors and common disease symptoms. It is hoped that increased awareness will lead to early diagnosis, more effective management of disease, and ultimately, improved disease prognosis. As part of this disease awareness initiative, attention should also be directed toward better understanding how patient perception of health can serve as a measure of disease extent. Determining this association is of particular interest in patient populations with TTR-mediated amyloidosis, as they have limited effective treatment options available.

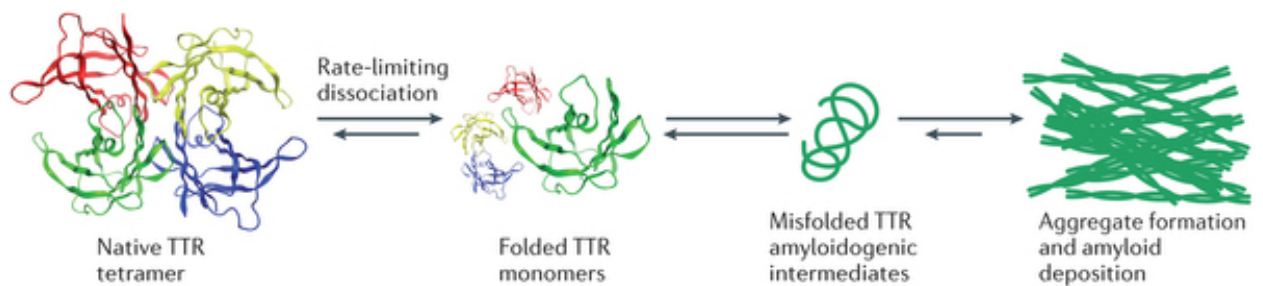
## 1.2 Transthyretin-mediated Amyloidosis

Transthyretin-mediated amyloidosis (ATTR) is a progressively debilitating disease at both the organ and functional level resulting in death due to the systemic aggregation of misfolded transthyretin (TTR) protein.<sup>6,19,48</sup> Biologically, TTR protein is produced predominantly by the liver and transports vitamin A and thyroid hormone throughout the body.<sup>14</sup> TTR circulates as a tetramer comprised of 4 monomeric subunits. If destabilization of the tetramer occurs, the monomeric subunits dissociate, misfold and aggregate as amyloid fibril deposits (**Figure 2**).<sup>20</sup> There are two major categories of ATTR: wild-type TTR (ATTRwt) and familial ATTR (ATTRm). ATTRwt results from the destabilization, misfolding and deposition of normal TTR.<sup>21-23</sup> Conversely, ATTRm results from specific point mutations in the TTR gene conferring one amino acid

substitution that destabilizes the tetramer, promoting misfolding and misaggregation of the monomeric subunits.<sup>20,24-26</sup>

## Figure 2. Overview of TTR Amyloidogenesis

Dissociation of the functional TTR tetramer results in misfolding of monomeric subunits. Subsequent accumulation and aggregation of misfolded monomers result in the deposition of TTR amyloid deposits throughout the body.



Nature Reviews | Drug Discovery

Source: Eisele YS, Monteiro C, Fearn C, et al. Targeting protein aggregation for the treatment of degenerative diseases. *Nature Reviews Drug Discovery*. 2015;14(11):759-780. Reproduced with permission from Nature Publishing Group.

### 1.3 Clinical Presentation of Wild-type Transthyretin-mediated Amyloidosis

Wild-type Transthyretin-mediated Amyloidosis (ATTRwt) predominantly targets the heart. It is a sporadically acquired disease, typically affecting elderly males and is often

referred to as age-related or senile systemic amyloidosis (SSA).<sup>27</sup> Although extensive prevalence studies have not been conducted, ATTRwt is considered the most common systemic form of amyloidosis based on autopsy studies.<sup>28</sup> Disease onset is reported to occur after 60 years of age, but predominately affects those in their eighth and ninth decade of life.<sup>14,29</sup> The diagnosis is often overlooked due to the older patient population often experiencing multiple age-related system declines.<sup>10,30</sup> The most commonly reported clinical symptoms include cardiomyopathy, heart failure, atrial fibrillation, and conduction disturbances.<sup>26,28</sup>

#### 1.4 Clinical Presentation of Familial Transthyretin-mediated Amyloidosis

Familial Transthyretin-mediated Amyloidosis (ATTRm) is the most common heritable form of amyloidosis. It is caused by autosomal dominant inheritance of specific TTR genetic mutations.<sup>31</sup> To date, there are over 120 TTR mutations reported, most of which result in symptomatic amyloid disease, predominantly in males.<sup>32</sup> It is estimated that ATTRm affects 1 in 100,000 individuals in the United States.<sup>10</sup> On average, ATTRm patients will experience symptomatic onset at approximately 50 to 60 years of age. However, ATTRm has been reported as early as age 20 for aggressive mutations and as late as 90 years of age for those with milder, later onset mutations.<sup>33-35</sup> Overall, the specific underlying TTR mutation and environmental influences will dictate disease age of onset and clinical manifestations.

TTR Val30Met is one of the most common mutations worldwide. It is largely associated with neuropathy due to progressive dysfunction of the peripheral and autonomic nervous systems.<sup>36</sup> Cardiac disease activity is also seen in those with late stage disease. While first described in Portugal, other endemic foci of the TTR Val30Met mutation have been found throughout Sweden, Brazil, Europe, Japan and the United States.<sup>14,37</sup> Interestingly, age of disease onset will vary based the specific geographic origin of the Val30Met mutation. For example, symptomatic age of onset for TTR Val30Met mutation endemic to Portugal and Japan is 30-40 years of age in contrast to 50-60 years of age for Val30Met mutations endemic to Sweden.<sup>14,25,38</sup> The reason for such variation in age of onset is unknown, but serves to highlight the complexities that must be considered when diagnosing and treating ATTRm disease.

Other commonly reported TTR mutations include, Val122Ile, Ile68Leu, Thr60Ala and Leu111Met. These mutations largely affect the heart, but not exclusively. The TTR Val122Ile is of particular interest as it is almost exclusively found in African American populations. More specifically, it is found in 3.9% of the African American male population, in contrast to Caucasian and Hispanic populations where it affects 0.44% and 0%, respectively.<sup>39</sup> TTR Thr60Ala, Ile68Leu and Leu111Met are all associated with late onset disease hallmarked by cardiac involvement endemic to different geographic regions. Thr60Ala is most commonly seen in populations of Irish descent, whereas Ile68Leu and Leu111Met largely affect Danish and Northern Italian populations, respectively.<sup>26,40-41</sup>

## 1.5 Prognosis & Diagnosis of ATTR

All ATTR-mediated organ damage caused by protein deposition is irreversible and no specific therapy exists to eliminate existing deposits. Consequently, early disease detection and management is needed to achieve the best possible clinical outcomes. Unfortunately, it is not uncommon for patients to have active disease long before the clinical diagnosis of amyloidosis is made.<sup>6</sup> In the ATTRm population, the average time from symptom onset to diagnosis of amyloid cardiomyopathy is 22 months, and 30 months for those with peripheral neuropathy.<sup>42</sup> Diagnoses made in late stages of both ATTRm and ATTRwt disease often correlate with poor outcomes as treatment is ineffective or impossible due to extensive organ involvement and damage. On average, ATTRm survival is 10 years from time of symptomatic onset of peripheral nerve dysfunction.<sup>14,19</sup> However, survival prognosis can vary by organ involvement and mutation type where those with more aggressive mutations or more extensive organ involvement experience earlier death. Due to this variability, without intervention, ATTRm survival can range from 5 to 15 years from time of symptomatic onset.<sup>6, 35, 43</sup> In patients presenting with significant heart involvement, survival from time of diagnosis is as low as 2 years in the ATTRm population and ranges from 2 to 6 years in the ATTRwt population.<sup>44-45, 89-90</sup>

ATTR diagnosis requires pathologic evidence of amyloid deposits in any tissue. Tissue collected from any source is stained with Congo red, which displays apple green

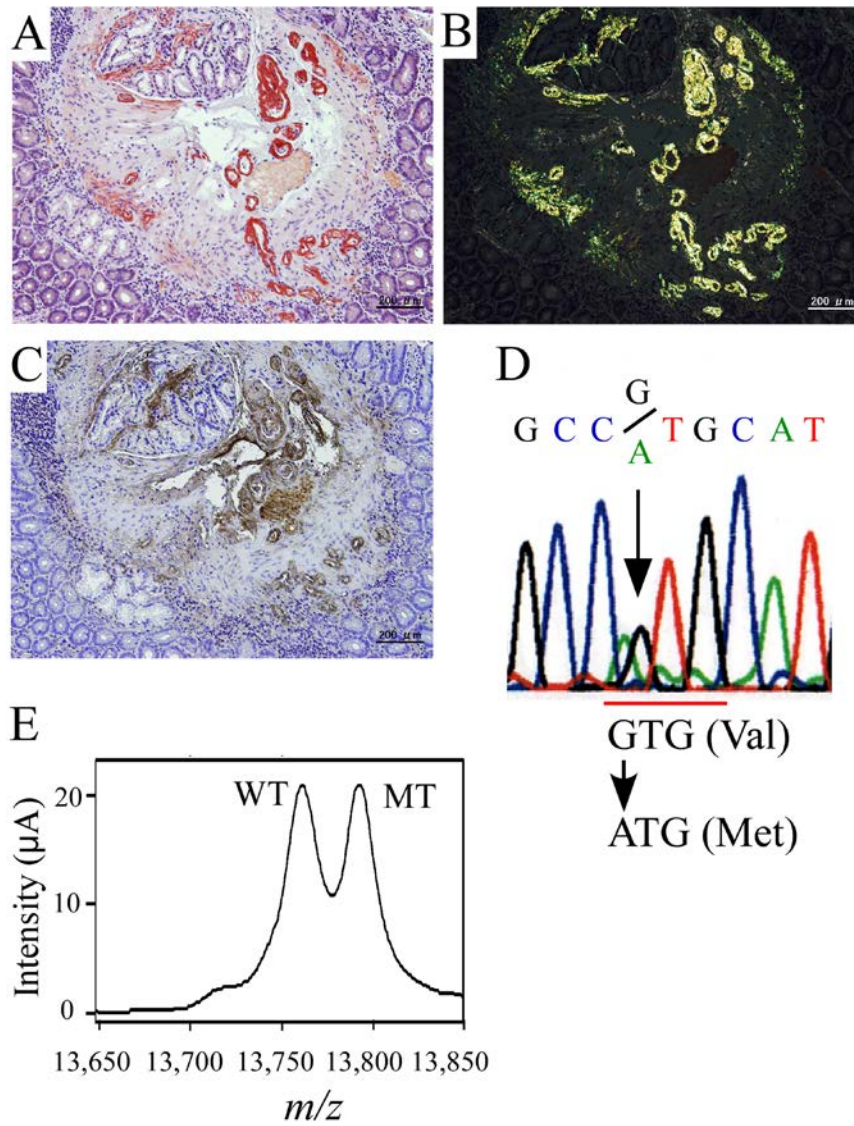
birefringence in the presence of amyloid deposits under polarized light.<sup>6,19</sup>

Immunohistochemical staining of tissue with antibodies specific to known amyloidogenic proteins or mass spectrometry are used to identify the type the amyloid present.<sup>26</sup> In addition to identifying the specific amyloid proteins present, genetic sequencing is also performed to determine the specific mutation present if ATTRm or to confirm the presence of wild-type sequence, if ATTRwt. **Figure 3** displays examples of these routinely used diagnostic assays.<sup>19</sup>

### **Figure 3. Diagnostic Assays Used to Classify the Type of TTR Amyloid Present**

(A-C) Light microscopy images of duodenum biopsy tissue from a patient with Val30Met TTR histochemically prepared with: (A) Congo red staining, where presence of red stain indicates amyloid deposit, (B) Congo red staining under polarized light, demonstrating signature amyloid protein apple green birefringence and (C) immunohistochemistry staining with an anti-TTR antibody. The scale bar represents 200  $\mu\text{m}$ . (D-E) Genetic and proteomic based assays show (D) Genetic sequencing analysis of the TTR gene, revealing the Val30Met TTR mutation and (E) Mass spectrometry analysis of serum from a patient with Val30Met TTR. Presence of Val30Met TTR mutation is evidenced by a peak shift reflective of a difference in the molecular weight detected. (Note: the molecular weight of Val30Met TTR is known to be 32 m/z higher than the molecular weight of WT TTR).<sup>19</sup>





Source: Ueda M, Ando Y. Recent Advances in transthyretin amyloidosis therapy.

*Translational Neurodegeneration*.2014;3:19.

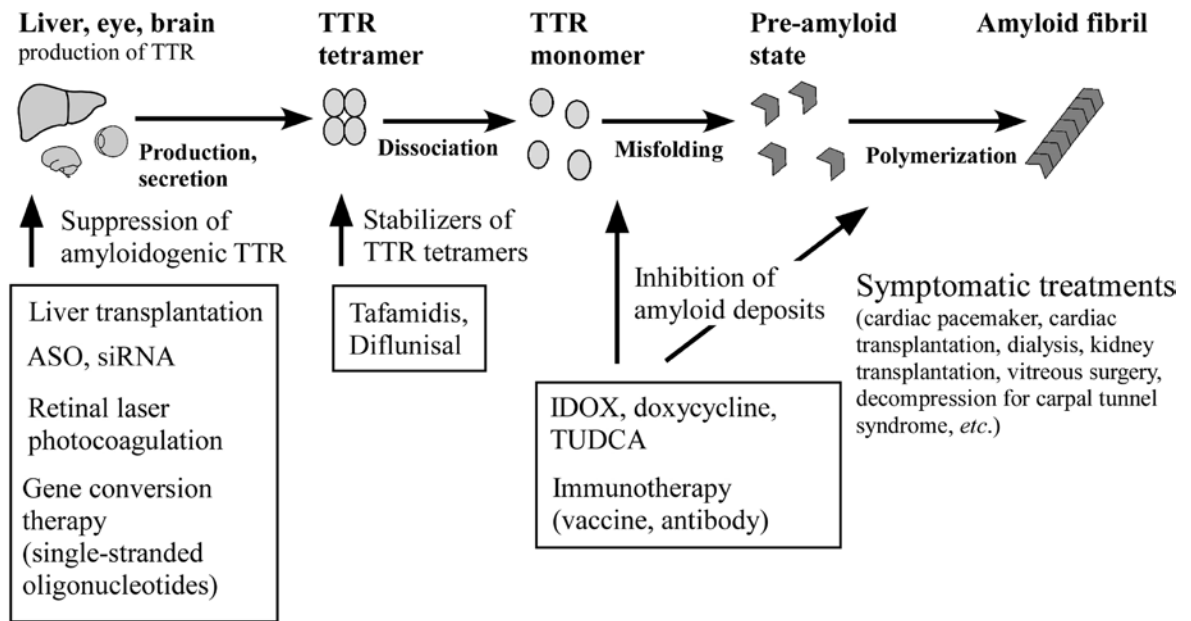
## 1.6 Clinical Management of ATTR

Current clinical management of ATTR involves symptomatic treatment of end-organ disease as well as various interventions aimed to stabilize and/or eliminate TTR. In the ATTRm population, early liver transplantation has been shown to successfully eliminate the production of amyloidotic TTR precursors preventing further amyloid formation.<sup>35</sup> Heart transplantation is also a plausible treatment option, but only for those with severe cardiac disease as it carries significant risk of complication.<sup>6</sup> Other treatments include diflunisal, a non-steroidal, anti-inflammatory TTR tetramer stabilizing agent, as well as gene-silencing drug therapies currently in clinical trials, which inhibit TTR production at the RNA level.<sup>47-48</sup> While the interventions mentioned above have shown to demonstrate the most promise in halting disease progression, **Figure 4** provides an overview of the current treatment landscape, including all conventional and investigational treatment options along with their therapeutic targets.<sup>19</sup> Overall, the most appropriate disease management plan varies based on organ involvement at time of presentation. The ability to quantify disease-mediated organ involvement typically involves the assessment of well-characterized clinical biomarkers of disease.

## Figure 4. Conventional and Investigational Treatment Options for TTR

### Amyloidosis

This schematic shows the various TTR amyloidosis treatment options and their therapeutic targets. The aim is to slow disease progression by altering various stages of the TTR production pathway.



Source: Ueda M, Ando Y. *Recent Advances in transthyretin amyloidosis therapy.*

*Translational Neurodegeneration.* 2014;3:19.

## 1.7 ATTR Biomarkers of Disease

Cardiac biomarkers such as troponin I and B-type natriuretic peptide (BNP) are routinely measured to assess the level of heart muscle injury and ventricle pressure overload, respectively.<sup>49-50</sup> These diagnostic measures of ATTR cardiac involvement have been shown to predict survival in ATTRwt patients.<sup>21-22</sup> Other clinical biomarkers of ATTR disease include modified body mass index (mBMI), a measure of nutritional status. Interestingly, in the ATTRm population, mBMI has been shown to correlate with survival in the context of mortality post liver transplantation. ATTRm patients with higher mBMI experience better survival outcomes.<sup>51-52</sup> Since these cardiac and nutritional biomarkers offer insights into overall organ dysfunction and survival, they are often the primary measures used to define health status and direct disease management decisions. As organ involvement progresses, ATTRwt and ATTRm patients will experience significant disease-related impact on their daily functioning, both physically and mentally. Understanding how progressive functional debilitation impacts health-related quality of life (HRQOL) is an area of study that warrants further investigation, as it is possible that patient-reported health status could impact disease outcome in ways not previously considered in the ATTR patient population.

## 1.8 Quality of Life in Other Disease Areas

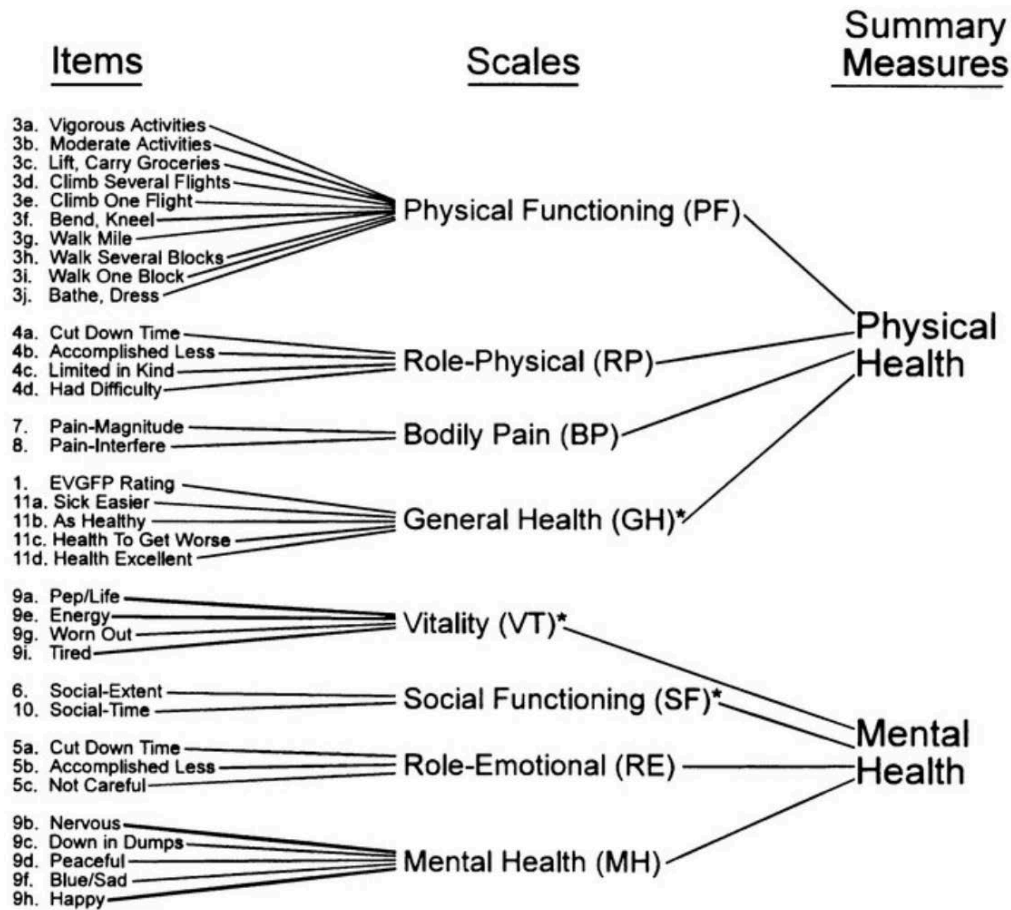
Patient-reported HRQOL has become a powerful prognostic measure of disease outcome in many diseases. One of the most widely used measures of HRQOL is a validated, self-administered health status questionnaire called the 36 question short form (SF-36) health survey instrument. The SF-36 health survey was one of several health survey instruments developed to assess self-perceived health status as part of the Medical Outcomes Study (MOS), a longitudinal, observational study examining the effects of variable physician care models on patient outcomes.<sup>53</sup> This study emphasized the clinical importance of gaining patient perspectives on general health, suggesting that a HRQOL health survey could be just as valuable as biological markers of disease when assessing survival and treatment efficacy.<sup>54</sup>

The SF-36 health survey is a short-form which means that it is able to assess functional health status with fewer questions compared to its long-form counterparts. This distinction reduces the burden placed on the individual completing the questionnaire, thereby making it more accessible to a diverse patient population. While one might think that fewer questions would reduce the precision of a health survey, when evaluated in adequate sample sizes, the SF-36 health survey has been validated to reliably capture HRQOL differences between groups.<sup>53</sup> It is comprised of 36 specific questions designed to provide a comprehensive assessment of overall HRQOL as categorized by 8 scales defining important health domains that affect aspects of everyday living. These 8 scales

include physical functioning (PF), role limiting physical problems (RP), bodily pain (BP), general health (GH), social functioning (SF), mental health (MH), role limiting emotional problems (RE), and vitality (VT). These scales further aggregate into summary measures that describe physical and mental health status, expressed as a physical component summary (PCS) and mental component summary (MCS) scores, respectively. Scales contributing to PCS include PF, RP, BP, and GH whereas SF, MH, RE, and VT contribute to the MCS.<sup>54-55</sup> **Figure 5** provides an overview of how each of the 36 health survey questions contributes to the overall PCS and MCS.<sup>56</sup>

**Figure 5. Description of SF-36 Health Survey Measurement Model**

This schematic provides an overview of how each SF-36 health survey question (item) contributes to the overall PCS and MCS (summary measures).



\* indicates significant correlation with other summary measure. Reproduced with permission from Ware JE, Jr. SF-36® Health Survey Update; <http://www.sf-36.org/tools/sf36.shtml>.

*Source: Derraik JGB, deBock M, Hofman PL, Cutfield WS. Increasing BMI is associated with progressive reduction in physical quality of life among overweight middle-aged. Scientific Reports.2014;4:3677.*

The ability to distinguish between physical and mental health status afforded by the SF-36 health survey is useful when examining health outcomes within a population. This is particularly relevant in the context of disease as it is possible for physical and mental health effects to vary in a disease-dependent manner. Overall, given its ease of administration and ability to gather meaningful health status data, the SF-36 health survey continues to be used as a clinical supplement to assess disease burden and patient prognosis in populations with chronic disease.

In various chronic diseases, SF-36 health survey data have been utilized to assess survival outcomes. In an observational study examining HRQOL and survival in patients with head and neck cancer, mean PCS ( $42.3 \pm 10.9$ ) and MCS ( $44.7 \pm 12.2$ ) were reported to be approximately 0.5 to 1 SD below the US population norm of 50. PCS significantly associated with survival (HR=0.86; 95% CI 0.80 to 0.93) in such a manner that every 5-unit increase in PCS associated with an 0.14 times lower risk of death. Comparable deficits in MCS did not significantly associate with mortality.<sup>58</sup> Similar findings have been reported in patients with chronic liver disease where only low PCS significantly associated with increased risk of death ( $p < 0.0001$ ).<sup>59</sup>

A prospective population-based cohort study examining HRQOL changes following lung cancer surgery showed that both MCS and PCS significantly associated with survival over time. Baseline mean MCS and PCS were reported as  $39 \pm 13$  and  $47 \pm 11$ , respectively. At baseline, only PCS significantly associated with survival (HR=0.958;



p=0.003). However, at 6-month follow-up, a 10% decrease in MCS (HR=0.82; p=0.033) and PCS (HR=0.87; p=0.014) associated with an 18% and 13% higher risk of death, respectively.<sup>91</sup>

In patients with chronic kidney disease undergoing hemodialysis, both mental and physical HRQOL deficits were independently associated with increased mortality. As part of 1-year survival analysis, patients with scores less than 30 for both MCS (HR=1.48; 95% CI 1.32 to 1.64) and PCS (HR= 1.62; 95% CI 1.36 to 1.92), experienced the greatest risk of death when compared to US population norm of 50 or more.<sup>60</sup>

Another study evaluating HRQOL in patients with chronic kidney disease also showed that lower PCS and MCS scores associated with significantly poorer survival. As such, each 10-unit decrease in PCS (HR=1.12; p<0.001) and MCS (HR=1.08; p<0.001) associated with a greater risk of death. Interestingly, within the African-American subset of the overall population, only MCS deficits were able to predict survival (HR=1.10, p<0.001). In addition to examining the relationship between HRQOL and mortality, this study also showed that lower HRQOL as reported by the SF-36 health survey associates with protein energy wasting status by serum albumin and creatinine levels, both disease-specific clinical biomarkers of disease.<sup>61</sup>

While disease pathology may differ, these studies demonstrate an intriguing relationship between HRQOL, survival and clinical biomarkers of disease that could be of clinical value. This relationship suggests that HRQOL is an important metric of functional health

status that should be considered when evaluating the overall health of patients with chronic disease. The variability shown by these studies in how HRQOL associates with survival in different diseases, suggests that generalizations should not be made and applied across chronic disease states. Accordingly, HRQOL and survival assessments should be conducted in a disease-specific manner in order to gain a better understanding of how physical and/or mental deficits affect overall health outcomes within a population of interest. The information gained from such disease-specific study could guide more effective disease management decisions and lead to improved patient outcomes.

### 1.9 Quality of Life in Amyloidosis

No data to date examine the specific relationship between HRQOL and survival in the ATTR patient population. The current data suggest that ATTR patients with the greatest disease burden report the poorest quality of life as measured by the SF-36 health survey.<sup>62</sup> However, it is unclear how the self-perceived assessment of physical and mental functioning, represented as PCS and MCS, relates to disease prognosis in this patient population. While studies in ATTRm and light-chain amyloidosis (AL) have shown correlations between HRQOL, disease progression, and treatment outcomes, respectively, they do not examine HRQOL and survival in a context representative of the greater ATTR patient population.<sup>47,63</sup>

For patients with ATTR, the lack of curative treatments coupled with the irreversible functional decline due to disease-related organ damage make timely and thorough disease management planning imperative. Understanding how HRQOL, specifically physical and mental health status, relates to survival and clinical biomarkers of disease could have clinical value in that it might potentially help predict disease outcomes more effectively for this specific population. The ability to better predict disease outcomes may have clinical significance as it could help guide individualized disease management plans that may ultimately lead to improved survival.

#### 1.10 Boston University Amyloidosis Center

As TTR amyloidoses are complex diseases involving multiple organ systems, clinical management requires a multidisciplinary approach. Specialized treatment and research centers exist worldwide to provide diagnostic evaluation and disease-specific treatment options. Boston University (BU) Amyloidosis Center is an internationally recognized leader in amyloidosis research and patient care. The Center follows hundreds of ATTRwt and ATTRm patients from all over the world. At initial presentation to the Center, patients undergo an extensive evaluation process, often involving full neurological, cardiac and genetic workups to assess disease state. Also, as part of this process, patients complete a SF-36 health survey to determine their self-perceived assessment of mental and physical status. SF-36 health surveys are also collected at annual follow-up visits.

Clinical information collected at all visits is stored in a patient database and, with patient consent, can be used for research purposes. Specific information captured in this database include patient diagnosis, biopsy status, clinical involvement, SF-36 health survey, as well as clinical biomarkers of disease. The extensive clinical information collected in this database on such a large patient population, makes it an ideal source of data to examine the relationship between HRQOL and survival in the TTR population.

### 1.11 Study Rationale

Upon review of HRQOL studies in other disease areas it is clear that patient-reported health status has meaningful implications on patient outcomes. Given the progressively debilitating disease course and limited treatment options for patients with ATTR, understanding how HRQOL relates to overall health outcomes, particularly survival warrants investigation. To date there has been no formal evaluation of this relationship in the TTR amyloidosis community. As a world renowned amyloid center of excellence following a large cohort of both ATTRm and ATTRwt patients, the BU Amyloidosis Center systematically collects SF-36 health surveys as part of Center's clinical evaluation process. It is possible that HRQOL is an important metric of functional health that could help predict disease outcomes. It is also possible that functional health varies by TTR disease type. For this reason, studying how disease status relates to functional health in both ATTRm and ATTRwt patients could be of clinical significance in that it could guide

individualized disease management plans that may ultimately lead to improved survival in the overall ATTR patient population.

#### 1.12 Purpose

The purpose of this research is to determine the association between HRQOL, clinical biomarkers of disease, and survival in the ATTR patient population followed by the BU Amyloidosis Center.

#### 1.13 Study Questions

1. Primary Study Question: Is HRQOL status predictive of survival in the ATTR patient population at presentation to the BU Amyloidosis Center?
2. Secondary Study Question: Do clinical biomarkers of disease (troponin I, BNP, mBMI) correlate with HRQOL status in the ATTR population at presentation to the BU Amyloidosis Center?

#### 1.14 Study Objectives

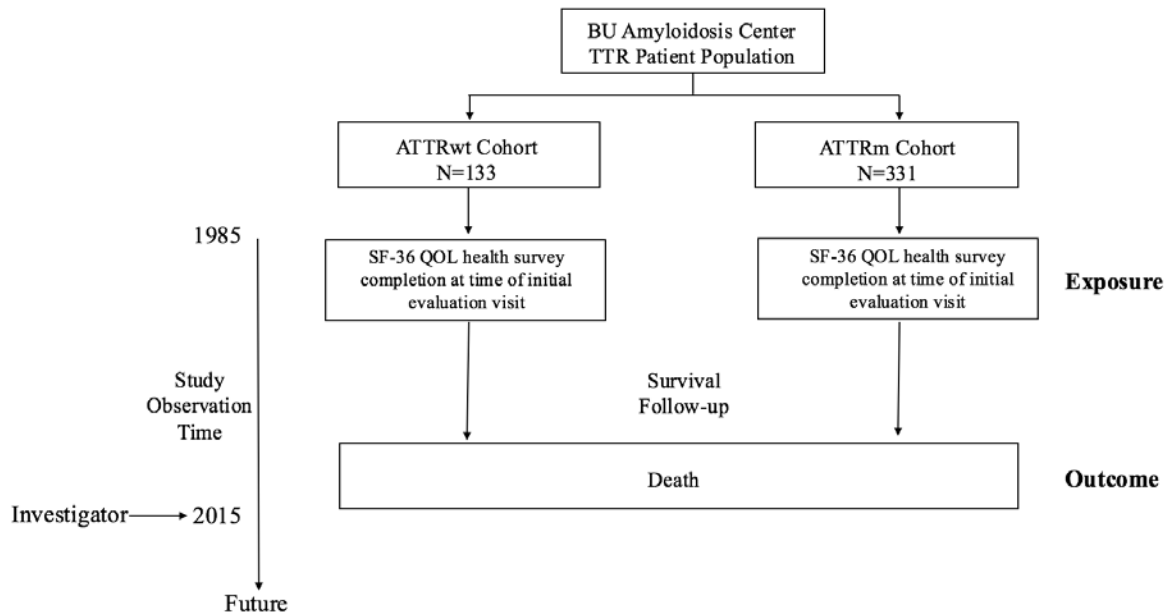
1. Primary Objective: Determine the association between SF-36 health survey scores and relative risk of death for patients upon presentation to the BU Amyloidosis Center.
2. Secondary Objective: Evaluate the relationship between clinical biomarkers of disease (troponin I, BNP, mBMI) and SF-36 health survey scores for patients upon presentation to the BU Amyloidosis Center.

## SECTION 2. MATERIALS & METHODS

### 2.1 Study Design

To determine the association between HRQOL and survival in the BU Amyloidosis ATTR patient population, a retrospective cohort study was conducted (**Figure 7**). The two study cohorts were comprised of individuals diagnosed with ATTRwt or ATTRm who, as part of their initial evaluation visit occurring between 1985 and 2015, completed a SF-36 health survey and had corresponding clinical biomarkers of disease measures recorded in the BU Amyloidosis Center database. Exposure was defined as completion of a SF-36 health survey at time of initial BU Amyloid Center evaluation visit. SF-36 health survey raw scores for each of the 8 subscales defining health status were further grouped and expressed as physical (PCS) and mental (MCS) summary scores. US healthy population norms, standardized with respect to age and gender were used as controls for evaluating PCS and MCS in both cohorts. In order to determine survival, the study outcome of interest, follow-up data was obtained for individuals in both cohorts. Survival follow-up started at time of SF-36 health survey completion and continued until date of death, or end of study period. Those without a date of death recorded between 1985 and 2015 were considered alive for the purpose of survival analyses.

**Figure 6. Study Design Diagram**



## 2.2 Patient Population

The BU Amyloidosis Center database was queried to identify ATTRwt and ATTRm patients who completed SF-36 health surveys at their initial evaluation visit between 1985 (year when SF-36 health surveys were first introduced to Center) and 2015 (year of data extraction for study analysis). Demographic information collected included sex, gender, and race. To determine survival, date of birth and death were also collected for all those included in the study. Disease-specific data collected included presence of wild-



type versus genetic mutation, date of presentation visit, date of diagnosis, co-morbidities and measures of known clinical biomarkers of disease (mBMI, troponin I and BNP).

#### *Inclusion Criteria*

- Individuals diagnosed with ATTR (ATTRwt or ATTRm) as confirmed by amyloid tissue typing and TTR gene sequencing who presented to the BU Amyloidosis Center between 1985 and 2015 for their initial evaluation visit, and who:
- had completed at least one SF-36 health survey as part of their initial evaluation visit, and
- had corresponding clinical disease measures (co-morbidities, mBMI, troponin I and/or BNP) obtained at time of SF-36 health survey completion recorded in the BU Amyloidosis Center's database.

#### *Exclusion Criteria*

- Individuals without confirmed ATTR diagnosis by amyloid tissue typing and TTR gene sequencing between 1985 and 2015, and/or
- did not complete at least one SF-36 health survey as part of their initial evaluation visit, and/or
- did not have corresponding clinical disease measures (co-morbidities, mBMI, troponin I and/or BNP) obtained at time of SF-36 health survey completion recorded in the BU Amyloidosis Center database.

### 2.3 Institutional Review Board Approval

Prior to the initiation of any study activity, institutional review board (IRB) approval was obtained from the Boston University Medical Campus IRB (BUMC IRB). BUMC IRB approval (H-22838) allowed for de-identified patient data extraction from the BU Amyloidosis Center database. The de-identification process involved generation of unique identification numbers for each patient included in the study analysis.

### 2.4 The 36 Question Short Form (SF-36) Health Survey Instrument

The SF-36 health survey instrument is a validated, self-administered questionnaire that captures both physical and mental health status through 36 questions categorized into 8 subscales: physical functioning (PF), role limiting physical problems (RP), bodily pain (BP), general health (GH), social functioning (SF), mental health (MH), role limiting emotional problems (RE), and vitality (VT). For statistical analyses, these 8 scales were further classified into two health status summaries known as the physical component score (PCS) and mental component score (MCS) according to the SF-36 Health Survey Manual and Interpretation Guide. Scales contributing to PCS included PF, RP, BP, and GH whereas SF, MH, RE, and VT contributed to the MCS.<sup>55</sup> PCS and MCS summary scores were used as measures of HRQOL for all those included in the study.

## 2.5 Statistical Analysis

To obtain PCS and MCS summary scores, the 8 subscale scores were first calculated by adding together subscale-related raw scores recorded for each individual item on the SF-36 health survey. Z-score transformations allowed for conversion of each subscale to a 0 to 100 scoring scale, where 0 is equal to poorest health status and 100 is equal to highest or best possible health status. Subscale scores were aggregated and standardized using physical and mental scoring coefficients, and means and standard deviations from the general US population. The resulting PCS and MCS summary scores were then adjusted for age and gender against US adult population norms, which were used as healthy controls. A PCS or MCS score of 50 indicated an average HRQOL status, while a PCS or MCS score less than 50 will represent a below average HRQOL status. In order to detect the greatest risk possible, PCS and MCS were dichotomized 1.5 standard deviations below the US population mean of 50 for both PCS and MCS summary scores ( $< 35$  vs.  $\geq 35$ ). For missing SF-36 health survey responses, a representative subscale average was determined and imputed to allow each eligible patient to be included in analyses.

In both cohorts, exposure was defined as completion of SF-36 health survey at time of presentation to BU Amyloidosis Center. All individuals underwent survival follow-up until death occurred, the outcome used to assess survival. Survival was defined as the time from presentation to the BU Amyloidosis Center to death by any cause. As part of Cox proportional regression analyses, the relative risk of death associated with PCS and

MCS summary scores was assessed using hazard ratios (HR) by cohort. During the follow-up period examined, death by any cause was considered an event, and those alive at time of last follow-up or at the end of the study period were censored for the purpose of survival analyses. Additionally, all analyses were adjusted for potential confounders such as age at presentation, gender, and co-morbidities including diabetes mellitus, hypertension and hyperlipidemia. The Kaplan-Meier method was used to create survival curves to assess the distribution of death by PCS and MCS < 35 vs.  $\geq$  35 during study follow-up. As part of a secondary analysis, Spearman's rank correlations were also calculated to describe the association between PCS and MCS and clinical biomarkers of disease such as mBMI, troponin I and BNP. For all analyses, statistical significance was set at a two-sided  $\alpha=0.05$ .

Statistical Analysis Software (SAS) was used for all data manipulation and statistical analyses.

### SECTION 3. RESULTS

During the study period, 464 individuals diagnosed with either ATTRwt (n=133) or ATTRm (n=331), were identified as having completed a SF-36 health survey at time of presentation to the BU Amyloidosis Center. Baseline characteristics of both cohorts are presented in **Table 1**.

Overall, at time of SF-36 health survey completion, both cohorts were predominantly comprised of white males in their seventh to eighth decade of life. In the ATTRwt cohort (n=133), the mean age  $\pm$  SD was  $74.6 \pm 6.0$  years; 100% were males, and 100% were white. The ATTRm cohort (n=331) was significantly younger, with a mean age  $\pm$  SD of  $57.5 \pm 13.9$  years, and more diverse with 33% female, and 82% white. The most common genetic mutations in the ATTRm cohort were Thr60Ala (22%, n=74), Val30Met (19%; n=64) and Val122Ile (13%; n=44). The ATTRwt cohort, by definition, had no genetic TTR mutations. These cohorts were representative of the general ATTR population based on previously defined disease demographics.

Of the co-morbidities examined, 40% of the ATTRwt population presented with hyperlipidemia. Although hyperlipidemia was the most prevalent co-morbidity within the ATTRwt cohort, its presentation was not significantly different between the two cohorts (p=0.22). Within the ATTRm cohort, 47% presented with hypertension, which was

significantly greater than in the ATTRwt cohort where only 14% were affected (p<0.0001).

Clinical biomarkers assessed at the time of SF-36 health survey completion include modified BMI, troponin I and BNP for both cohorts. In the ATTRwt cohort, troponin I and BNP mean values (0.17 ng/mL; n=102 and 427.9 pg/mL; n=118, respectively) were significantly higher than those of the ATTRm cohort (0.08 ng/mL; n=130 and 241.9 pg/mL; n=179, respectively) as indicated by the respective p-values of p=0.002 and p<0.0001. Mean modified BMI was also higher in the ATTRwt cohort (1181.6; n=116) when compared to the ATTRm cohort (1114.3; n=149), but not to the same level of significance as troponin I and BNP (p-value=0.02). In both cohorts, not all individuals had complete clinical biomarker data entered in the Center's database. Therefore, the mean values calculated for clinical biomarkers of interest were based on a subset of each cohort population that had data recorded in the database at time of SF-36 health survey completion.

**Table 1.** Comparison of demographic and clinical features for ATTRwt & ATTRm cohorts at time of the SF-36 health survey completion

Feature	ATTRwt (n=133)	ATTRm (n=331)	p-value
Age, y mean (SD)	74.6 (6.0)	57.5 (13.9)	< 0.0001
Age, %			
20-40 years	0%	15%	< 0.0001
41-60 years	1	35	
61-80 years	86	48	
≥ 81 years	13	2	
Sex, %			
Male	100%	67%	--
Female	0	33	
Race, %			
White	100%	82%	--
Black/African American	0	14	
Asian	0	3	
Other <sup>i</sup>	0	1	
Mutation Type (%)			
Thr60Ala (n=74)	--	22%	--
Val30Met (n=64)		19	
Val122Ile (n=44)		13	
Lys58His (n=38)		11	
Ser77Tyr (n=15)		5	
Other (n=91)		27	
Unknown (n=5)		2	
Co-Morbidities, %			
HL	40%	32%	0.12
DM	11	8	0.22
HTN	14	47	< 0.0001
Clinical Assessments, mean (SD, N)			
Modified BMI	1181.6 (188.9; n=116)	1114.3 (264.5; n=149)	0.02
Troponin I (ng/mL)	0.17 (0.25; n=102)	0.08 (0.15; n=130)	0.002
BNP (pg/mL)	427.9 (298.6; n=118)	241.9 (403.31; n=179)	< 0.0001

<sup>i</sup>includes > 1 race, Unknown

**Table 2** presents standardized PCS and MCS values showing that individuals reported lower PCS compared to MCS on average for both cohorts. For the ATTRwt cohort, the mean PCS and MCS scores were  $36.7 \pm 10.8$  and  $45.7 \pm 12.3$ , respectively. Whereas, the mean PCS and MCS scores for the ATTRm cohort were  $37.2 \pm 13.3$  and  $45.2 \pm 11.7$ , respectively. The lowest PCS value reported in the ATTRwt cohort was 12.5 and 7.5 in the ATTRm cohort. For the MCS, the lowest values reported was 16.5 in the ATTRwt and 12.3 in the ATTRm cohort. Conversely, the highest PCS reported was 57.9 in the ATTRwt population and 64.9 in the ATTRm cohort. The highest MCS value reported for the ATTRwt was 72.5 and 71.9 for the ATTRm cohort. Collectively, the range of PCS and MCS observed further demonstrates that individuals experienced lower PCS relative to MCS, which reflects poorer physical health status, even when considering the highest and lowest scores in both cohorts.

**Table 2.** Presentation of PCS and MCS scores in ATTRwt & ATTRm cohorts

SF-36 Component Score	Mean	SD	Min	Max
ATTRwt Cohort (n=133)				
PCS	36.7	10.8	12.5	57.9
MCS	45.7	12.3	16.5	72.5
ATTRm Cohort (n=331)				
PCS	37.2	13.3	7.5	64.5
MCS	45.2	11.7	12.3	71.9

Survival characteristics and PCS and MCS scores (< 35 vs.  $\geq 35$ ) by cohort are presented in **Table 3**. During the follow-up period, 54% (n=72) of the ATTRwt and 36% (n=120) of the ATTRm population died. Mean survival time from completion of SF-36 health survey within the ATTRwt was  $3.0 \pm 2.2$  years. This was less than mean survival time



observed for the ATTRm cohort of  $6.4 \pm 5.4$  years. Time-to-death analysis for those who died showed that mean survival was 1 year longer for those in ATTRm cohort ( $4.3 \text{ years} \pm 3.4$ ) when compared to the ATTRwt cohort ( $3.0 \text{ years} \pm 2.0$ ). The disparity in survival and time-to-death for the ATTRm cohort versus the ATTRwt cohort could be influenced by disease extent. As such, it is possible that the ATTRwt cohort represented individuals with more advanced disease, but this distinction was not evaluated in this study. While this could be an area for future investigation, this study focused on the relationship between HRQOL and mortality within each cohort independently.

For both cohorts, there were almost an equal proportion of individuals with PCS scores of  $< 35$  as there were with scores  $\geq 35$ . However, for MCS, a greater proportion of individuals in both cohorts reported MCS  $\geq 35$ . Accordingly, 77% of the ATTRwt and 78% of the ATTRm cohorts had individuals with scores  $\geq 35$ . This implies that while individuals in both cohorts experience low PCS, suggesting significant physical deficits, their mental health status did not appear to be affected to the same extent.

**Table 3.** Presentation of survival characteristics and PCS and MCS QOL scores <35 and  $\geq 35$  in ATTRwt and ATTRm cohorts

Feature	ATTRwt cohort (n=133)	ATTRm cohort (n=331)
Age at completion of QOL, y mean (SD)	74.6 (6.0)	57.5 (13.9)
Age at death, y mean (SD)	78.3 (5.7)	65.0 (11.5)
Number of Deaths, N (%)	72 (54%)	120 (36%)
Survival, y mean (SD)	3.0 (2.2)	6.4 (5.4)
Time-to-death (for those who died), y mean (SD)	3.0 (2.0)	4.3 (3.4)
<b>PCS</b>		
<35, N (%)	65 (49%)	145 (44%)
$\geq 35$ , N (%)	68 (51%)	186 (56%)
<b>MCS</b>		
<35, N (%)	31 (23%)	73 (22%)
$\geq 35$ , N (%)	102 (77%)	258 (78%)

**Table 4** shows results, represented as hazard ratios from Cox proportional regression analysis examining the association between MCS, PCS and survival by cohort. All analyses were adjusted for age at time of SF-36 health survey completion, co-morbidities and sex. Only patients with complete data during the study period were included in the analysis. In the ATTRwt cohort (n=126), 70 deaths occurred and 44% were censored as alive at time of analysis. ATTRwt patients with PCS or MCS less than 35 had a significantly higher risk of death during follow-up than those with scores greater than or equal to 35 (HR=2.45, p=0.002 for PCS; HR 3.38 (p<0.0001) for MCS). In the ATTRm cohort (n=329), 120 deaths occurred and 64% were censored as alive. Within the ATTRm cohort, patients with PCS scores less than 35 also had a significantly higher risk of death during follow up than those with scores greater than 35 (HR=2.76, p<0.0001 for PCS). However, MCS within the same score dichotomization (< 35 vs.  $\geq 35$ ) did not

demonstrate statistically significant increased risk of death during follow up (HR=1.38, p=0.13).

**Table 4.** Cox proportional regression analysis in ATTRwt and ATTRm cohorts<sup>ii</sup>

	<b>Hazard ratio</b>	<b>p-value</b>
ATTRwt (n=126)*		
MCS < 35 vs. ≥ 35	3.38	<0.0001
PCS < 35 vs. ≥ 35	2.45	0.002
ATTRm (n=329)**		
MCS < 35 vs. ≥ 35	1.38	0.13
PCS < 35 vs. ≥ 35	2.76	<0.0001

<sup>ii</sup> adjusted for diabetes mellitus, hypertension, hyperlipidemia, sex, and age at time of SF-36 health survey.

\* (n=126, 70 deaths, 44% censored)

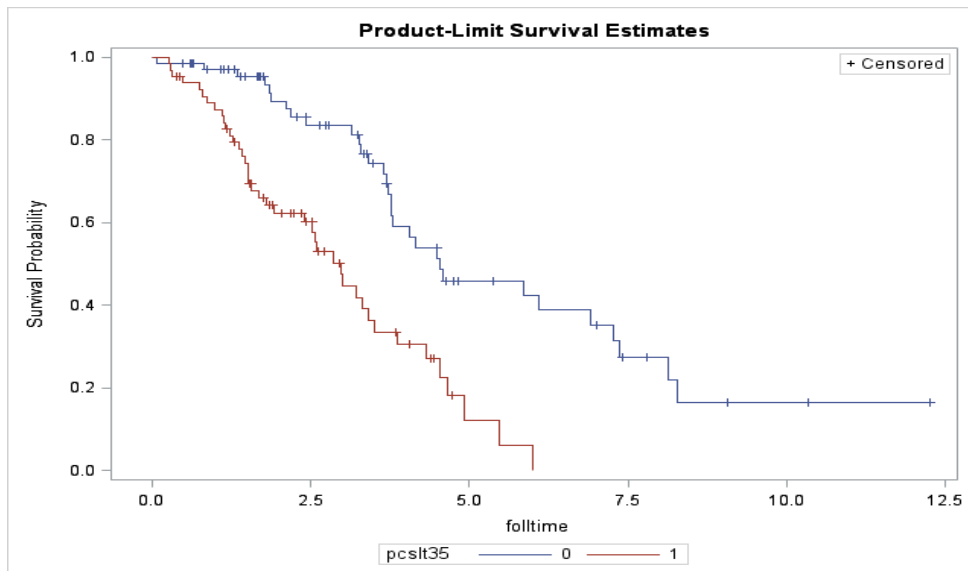
\*\* (n=329, 120 deaths, 64% censored)

**Figures 7 through 10** present the adjusted Kaplan-Meier curves estimating survival based on a dichotomization in PCS and MCS scores (<35 vs. ≥35). Survival curves for PCS and MCS < 35 are shown in red and ≥ 35 in blue. In both cohorts, survival data was collected from time of SF-36 health survey completion to death, the endpoint of interest. Deaths are represented by downward steps in the Kaplan-Meier curves. Individuals alive at time of last follow-up or at the end of the study period examined were censored and represented as tick marks on the Kaplan-Meier curves. Overall, these data describe the survival function for both ATTRwt and ATTRm cohorts.

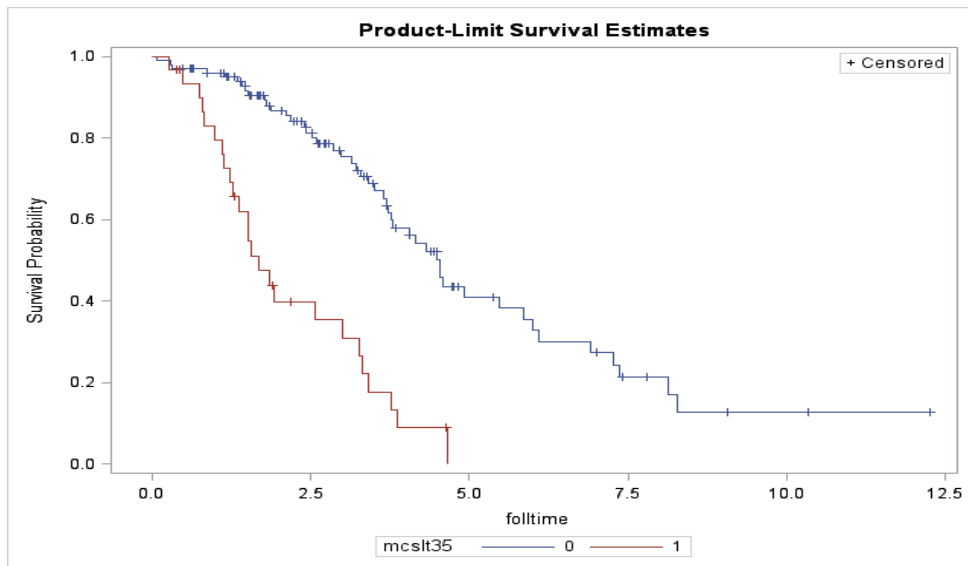
**Figure 7** shows that overall survival was significantly lower for patients with PCS <35 in the ATTRwt cohort when compared to those with PCS ≥ 35 in the ATTRwt cohort (log

rank  $p < 0.0001$ ). **Figure 8** shows similar results for MCS  $< 35$  vs.  $\geq 35$  within the ATTRwt cohort (log rank  $p < 0.0001$ ).

**Figure 7.** Kaplan-Meier curve for overall survival by PCS ( $< 35$  (red) vs.  $\geq 35$  (blue)) in ATTRwt cohort (n=133):

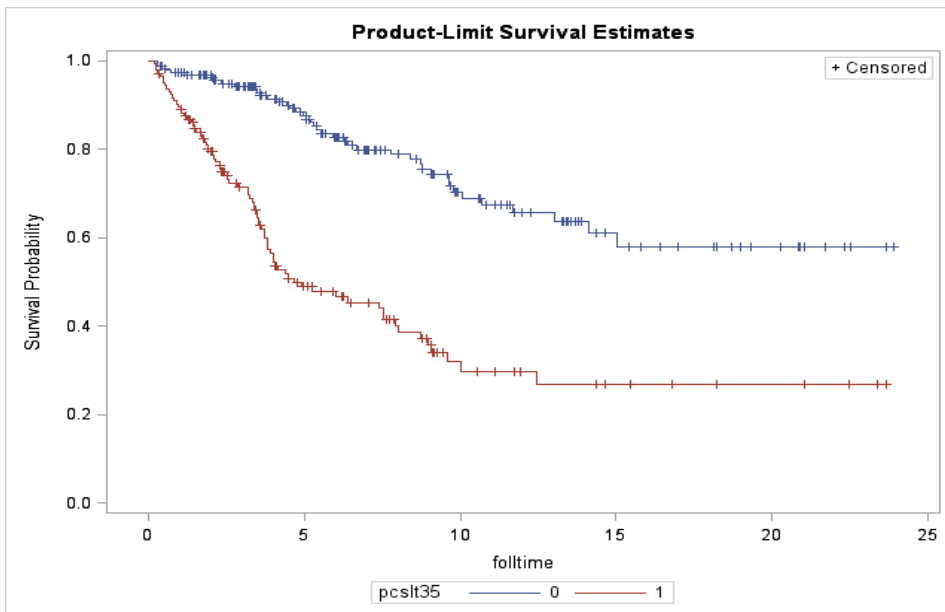


**Figure 8.** Kaplan-Meier curve for overall survival by MCS (< 35 (red) vs.  $\geq$  35 (blue)) in ATTRwt cohort (n=133):

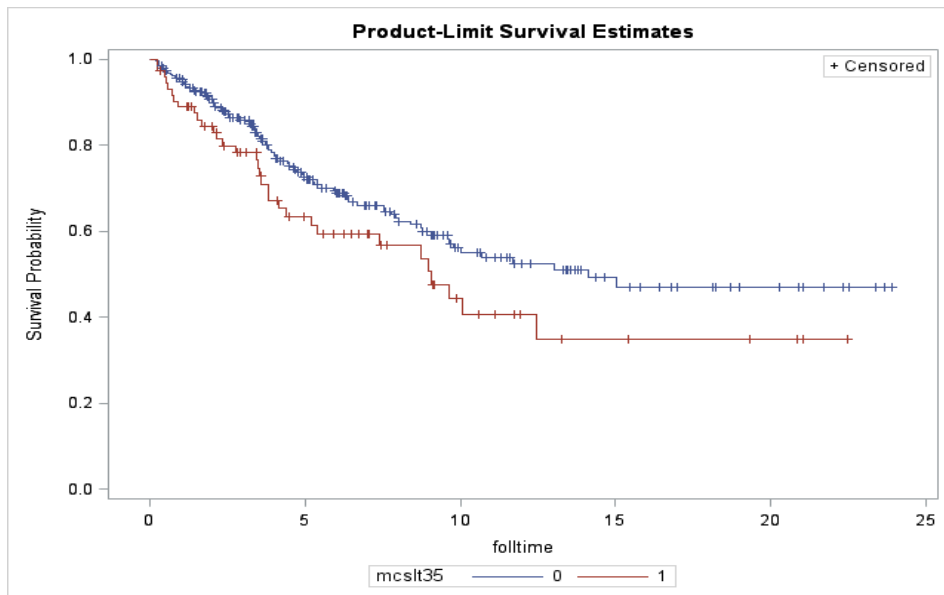


**Figures 9** and **10** present the adjusted Kaplan-Meier survival curves from time of SF-36 health survey completion to death for the ATTRm cohort. Similar to overall survival trend seen in the ATTRwt population, **Figure 9** shows that PCS <35 was significantly associated with lower survival when compared to PCS  $\geq$  35 (log rank  $p < 0.0001$ ). **Figure 10** shows that MCS <35 is also associated with lower survival, but not with the same level of significance (log rank  $p = 0.07$ ).

**Figure 9.** Kaplan Meier Curve for overall survival by PCS scores (< 35 (red) vs.  $\geq$  35 (blue)) in ATTRm cohort (n=331):



**Figure 10.** Kaplan Meier Curve for overall survival by MCS (< 35 (red) vs.  $\geq$  35 (blue)) in ATTRm cohort (n=331):



Secondary analyses examining the relationship between PCS, MCS and clinical biomarkers of disease were also conducted and presented in **Table 5**. Using Spearman's rank correlations, BNP and troponin I were inversely associated with both MCS ( $r = -0.24$ ;  $p=0.01$  and  $p=0.02$ , respectively) and PCS ( $r = -0.29$ ;  $p=0.002$  and  $r = -0.25$ ;  $p=0.012$ , respectively) in the ATTRwt cohort. However, the strength of the association was greatest for PCS. In the ATTRm cohort, BNP and troponin I were also inversely associated with both MCS ( $r = -0.16$ ;  $p=0.03$  and  $r = -0.24$ ;  $p=0.007$ , respectively) and PCS ( $r = -0.50$ ;  $p<0.0001$  and  $r = -0.41$ ;  $p<0.0001$ , respectively). Overall, the association was greatest with PCS as the strength of a negative association measured by Spearman's rank correlation increases as  $r$  approaches  $-1$ . Modified BMI did not appear to

significantly associate with MCS or PCS in the ATTRwt and ATTRm cohorts as evidenced by p-values greater than or equal to 0.05.

**Table 5.** Spearman’s rank correlations between PCS, MCS and clinical biomarkers of disease in ATTRwt and ATTRm cohorts

	MCS	PCS
<b>ATTRwt cohort</b>		
BNP (n=118)	r= - 0.24 (p=0.01)	r= - 0.29 (p=0.002)
Troponin I (n=102)	r= - 0.24 (p=0.02)	r= - 0.25 (p=0.012)
Modified BMI (n=116)	r= - 0.08 (p=0.40)	r= - 0.08 (p=0.40)
<b>ATTRm cohort</b>		
BNP (n=179)	r= - 0.16 (p=0.03)	r= - 0.50 (p<0.0001)
Troponin I (n=130)	r= - 0.24 (p=0.007)	r= - 0.41 (p<0.0001)
Modified BMI (n=149)	r= 0.10 (p=0.40)	r= 0.16 (p=0.05)



## SECTION 4. DISCUSSION

ATTR is a progressive disease with devastating effects on functional health, often resulting in death. While other ATTR studies have shown that those with the greatest disease burden report the poorest HRQOL, no data systematically examined the effects of HRQOL on survival. In other chronic diseases, HRQOL has been shown to be a powerful predictor of survival and is often explored as an important functional health metric with the potential to guide disease management plans. This study appears to be the first study to examine the association between self-perceived physical and mental HRQOL, clinical biomarkers of major end organ function, and survival in the ATTR population.

In this retrospective cohort study, ATTR disease significantly decreased an individual's physical and mental quality of life. Mean PCS and MCS values were respectively 1.5 and 0.5 SD below 50, the age and gender matched US population norm for both cohorts. This suggests that self-perceived physical HRQOL deficits experienced by the ATTRwt and ATTRm populations under study were more pronounced than self-perceived mental HRQOL deficits. Interestingly, overall survival varied by cohort during the follow-up time examined. The ATTRwt cohort exhibited an 18% higher mortality rate and shorter survival from time of SF-36 health survey completion to death when compared to the ATTRm cohort (3.0 years  $\pm$  2.2 and 6.4 years  $\pm$  5.4, respectively). Of those who died during the follow up period, mean survival was approximately 1 year longer in the ATTRm cohort (3.0 years  $\pm$  2.0) than in the ATTRwt (4.3 years  $\pm$  3.4). Despite similar

mean PCS and MCS observed for both cohorts, the higher mortality in the ATTRwt cohort could be explained by differences in disease severity. In support of this explanation, BNP and troponin I, both clinical biomarkers of amyloid cardiomyopathy, were significantly higher in the ATTRwt cohort indicating greater infiltrative heart disease involvement than in the ATTRm cohort. Although examining the association between disease extent and survival was not part of the study design, it is possible that survival differences observed were due to the presence of more individuals with advanced disease in the ATTRwt cohort than in the ATTRm cohort.

Primary study analysis using Cox proportional hazards regression models revealed a significant association between HRQOL and survival. The correlations between PCS and MCS and survival varied significantly between the studied cohorts. In the ATTRwt population, both physical and mental HRQOL deficits predicted a significantly greater risk of death during follow-up. More specifically, PCS <35 associated with a 2.45 times greater risk of death compared to those with PCS  $\geq$  35, and MCS <35 associated with a 3.38 times greater risk of death compared to those with MCS  $\geq$  35. The slightly greater risk of death associated with MCS < 35 when compared to PCS <35 was a finding unique to the ATTRwt cohort and could be reflective of a cohort comprised of individuals with more advanced disease. In the ATTRm cohort, only physical HRQOL deficits as evidenced by PCS <35 associated with a 2.76 times increased risk of death during the follow-up period examined. Similar magnitude mental HRQOL deficits (MCS <35) did not associate with an increased risk of death (HR=1.38, p=0.13).

These findings are further supported by Kaplan-Meier curves showing that MCS and PCS <35 significantly associate with lower survival when compared to MCS and PCS  $\geq 35$  for both cohorts. The Kaplan-Meier curves also demonstrate a cohort-specific difference in follow-up time examined. In the ATTRm cohort, the follow-up time was longer than that of ATTRwt because of the greater number of deaths that were distributed over a longer period of time. Although matching follow-up times would have provided the ability to directly compare the two cohorts in a single survival analysis, it was not possible to do so without sacrificing power to explore the strength of the associations under study. Therefore, in order to capture all deaths observed during the overall 30-year study period, survival analyses were conducted in a cohort-dependent manner. Although, it is not possible to directly compare study results between ATTRwt and ATTRm cohorts, the survival analysis presented by this study show meaningful associations between survival and MCS and PCS in both cohorts that could have clinical value.

The results of the Cox proportional hazards regression analysis and Kaplan-Meier curves presented by this study suggest that HRQOL assessed by the SF-36 health survey could be used as comprehensive predictor of survival in both ATTRwt and ATTRm populations. Overall, PCS and MCS were shown to be independent predictors of mortality. Given the physical deficits that result from progressive organ involvement, it would be expected that PCS was significantly associated with greater risk of death. However, in light of the significant associations between MCS and survival in the ATTRwt, caution should be taken when making inferences from HRQOL data, even

within the same subset of chronic disease. As such, these findings underscore the importance of evaluating HRQOL and survival in a disease-dependent manner in order to account for variations in disease processes that could impact overall health outcomes. In this way, the findings of this study are consistent with the observation across other diseases in that patients with a lower perception of their health status, by either PCS and/or MCS have a higher mortality.

Secondary analyses using Spearman's rank correlations showed significant inverse associations between HRQOL health scores and clinical biomarkers of disease in both cohorts. Both MCS and PCS inversely correlated with BNP and troponin I, however, the strength of the association was greatest for PCS, particularly in the ATTRm cohort. This suggests that HRQOL health status, specifically PCS, could be just as informative as clinical biomarkers of disease when examining disease status and prognosis in the ATTR population. However, this was an exploratory analysis and additional investigation is warranted to determine if HRQOL and clinical biomarkers of disease are interchangeable predictors of death. While preliminary, these findings support the clinical relevance of including HRQOL assessment as part of routine disease evaluation and management process.

Demographic and clinical features presented by both study cohorts were consistent with expected differences observed in the general ATTRwt and ATTRm populations. As anticipated, the ATTRwt cohort was comprised of older males (74.6 years of age  $\pm$  6.0)

with significant cardiac involvement as evidenced by elevated troponin I and BNP levels. The ATTRm cohort presented as a younger and more diverse population (57.5 years of age  $\pm$  13.9). The mutation types presented (22% Thr60Ala, 19% Val30Met, 13% Val122Ile) were also consistent with those most commonly reported in the general ATTRm population. The fact that these study cohorts so closely represent anticipated ATTRwt and ATTRm population differences suggest that the associations between HRQOL, clinical biomarkers of disease and survival presented in this study are generalizable and have relevance to the ATTRwt and ATTRm populations worldwide.

Overall, the results of this study have immediate clinical implications suggesting that HRQOL should be integrated into patient evaluations and treatment plans as a routinely collected measure of health status in the ATTR patient population. Whereas most clinicians are reticent to collect data they view as subjective, these results support HRQOL as an objective measurement of disease burden that have clinical relevancy. Reluctance to collect HRQOL data may stem from a lack of training in the interpretation of the results.<sup>64</sup> Despite barriers to acceptance, the predictive value of HRQOL demonstrated in this study should not be overlooked as it could provide meaningful insights on disease prognosis that could help guide more informed disease management decisions.

The ability to effectively manage disease is particularly imperative given the limited treatment options available for ATTR. Every effort must be made to proactively ensure

the best possible health outcomes. The association between HRQOL and survival shown by this study could not only help clinicians select optimal management plans from currently available ATTR treatment options, but could also assist in the development of novel therapies. When developing a drug, demonstrating improved perception of HRQOL is equally as important as treating the underlying disease. It is possible to find a drug that eradicates underlying disease, promotes extended survival, yet is associated with poor HRQOL.<sup>65</sup> This suggests that there is an interplay between disease management, survival and HRQOL that must be considered. For this reason, the ability to quantify the effect of an intervention on HRQOL has become an important measure of treatment efficacy and has been integrated in the clinical trial plans of many drug development efforts.<sup>66</sup>

The results of this study could be useful in the development of novel ATTR therapies as it establishes a relationship between HRQOL and mortality that could be representative of the general ATTR patient population. While the aim of drug development is to discover therapies that extend survival, the association between HRQOL and survival demonstrated by this study suggest that improved HRQOL is equally important and should be considered when assessing overall efficacy of a novel treatment. Researchers can use these results as a baseline measurement of what HRQOL and survival looks like in ATTR population. Overall, these data should be considered during the clinical trial development and evaluation process to ensure that an investigational therapy will not only effectively treat disease but also improve HRQOL.

#### 4.1 Limitations

A potential limitation of this study is the use of a pre-existing database to collect data of interest. Since all data were extracted from the BU Amyloidosis Center database, it was not always possible to cross-reference data reported for consistency and accuracy. Also, there were instances where data of interest were not captured and therefore could not be included in the analysis. Since this study examined HRQOL over a 30-year time interval, another limitation of this study included changes to routinely collected clinical data during the study period examined. For instance, clinical biomarkers of disease such as troponin I and BNP were not routinely collected until 2002. This means that patients presenting for evaluation before 2002 did not have these measures of interest recorded in the database and available for this study. Additionally, not all ATTR patients completed a SF-36 health survey at presentation to the BU Amyloidosis Center.

These limitations reduced the overall sample size that could be included in the analysis, providing less power to determine differences and assess significance of the associations under study. Since significant associations were detected, it is unlikely that sample size affected study findings. However, it is possible that a larger sample size would have demonstrated associations the actual sample size was unable to detect.

An additional study limitation was the inability to determine how long an individual had active disease before completion of the SF-36 health survey. This means that the population under study included individuals at all stages of disease, from those with mild

symptoms to those with severe physical disability. If anything, it would be expected that such a limitation would lead to a bias towards the null. The fact that significant associations were detected despite this limitation suggest that study results may have been even stronger if it had been possible to stratify by disease severity.

#### 4.2 Future Directions

Future directions include conducting a larger, prospective cohort study to examine the association between HRQOL and survival over time. This would involve the collection of multiple SF-36 health surveys as well as clinical measures of disease from an extensive patient population at predefined intervals. By examining HRQOL in such a way it would be possible to more precisely determine how HRQOL varies with respect to disease course. Furthermore, a prospective examination of HRQOL would not be reliant on historical data, thereby overcoming the current study's limited ability to collect all data of interest. In such a way it would be possible to further investigate how the relative associations between clinical biomarkers of disease and HRQOL relate to survival. Additionally, it would also be possible to collect other pertinent data such as current treatment to further explore how HRQOL is affected by various interventions over time. A study of this magnitude would more robustly evaluate HRQOL as a clinically meaningful prognostic measure of survival in the ATTR population. In this way, such a future study would more deeply explore the importance of routinely collecting HRQOL as part of ATTR patient managed care plans, as well as its significance in guiding



individualized disease management plans that may ultimately lead to improved health outcomes

## SECTION 5. CONCLUSION

In conclusion, ATTR disease significantly decreased an individual's physical and mental HRQOL. Low HRQOL, as described by the SF-36 health survey, was associated with an increased risk of death in a disease-specific manner within the ATTR population. PCS and MCS were shown to be independent predictors of mortality by cohort. In the ATTRwt cohort, patients with MCS and PCS <35 had a significantly greater risk of death during follow-up than those with MCS and PCS  $\geq 35$ . In the ATTRm cohort, PCS < 35 also associated with a significantly greater risk of death than those with higher scores. However, similar magnitude deficits of MCS did not associate with increased risk of death. MCS and PCS correlated with BNP and troponin I in both cohorts, however, the strength of the association was greatest for PCS. Additional investigation is warranted to determine if HRQOL and clinical biomarkers of disease are interchangeable predictors of death.

Furthermore, the study findings demonstrate the importance of including HRQOL measures in clinical disease prognostic efforts in order to better inform clinicians about disease extent and predict its overall impact on survival. While not a focus of this study, the associations between HRQOL and survival may also be relevant in the development of novel ATTR therapies and suggest that HRQOL should be included in drug efficacy assessments. Low HRQOL has been shown to correlate with survival in other diseases, but this study appears to be the first observational cohort study to demonstrate the

association in the ATTR population. Future studies confirming this association would further underscore the clinical benefit of systematically collecting HRQOL as part of routine ATTR patient care.

## LIST OF JOURNAL ABBREVIATIONS

Adv Hum Genet	Advances in human genetics
Am Heart J	American Heart Journal
Am J Med	American Journal of Medicine
Ann Med	Annals of Medicine
Ann Neurol	Annals of Neurology
Appl Clin Genet	Application of Clinical Genetics
Arch Intern Med	Archives of Internal Medicine
Arch Neurol	Archives of Neurology
Baillieres Clin Rheumatol	Baillieres Clinical Rheumatology
Biochim Biophys Acta	Biochimica et Biophysica Acta
Br J Cardiol	British Journal of Cardiology
Clin J Am Soc Nephrol	Clinical Journal of American Society of Nephrology
Clin Transplant	Clinical Transplantation
Curr Med Chem	Current Medicinal Chemistry
Curr Pharm Des	Current Pharmaceutical Design
Eur Heart Journal	European Heart Journal
FASEB J	Federation of American Societies for Experimental Biology
Heart Fail Rev	Heart Failure Reviews
Hum Hered	Human Heredity
J Alzheimers Dis	Journal of Alzheimer's Disease

J Am Heart Assoc	Journal of the American Heart Association
JAMA	Journal of the American Medical Association
J Clin Invest	Journal of Clinical Investigation
J Clin Oncol	Journal of Clinical Oncology
J Clin Psychiatry	Journal of Clinical Psychiatry
J Hepatol	Journal of Hepatology
J Intern Med	Journal of Internal Medicine
J Neurol Neurosurg Psychiatry	Journal of Neurology, Neurosurgery, and Psychiatry
J Struct Biol	Journal of Structural Biology
Lancet Neurol	Lancet Neurology
Mayo Clin Proc	Mayo Clinic Proceedings
N Engl J Med	New England Journal of Medicine
Nat Rev Drug Discov	Nature Reviews Drug Discovery
Nat Rev Cardiol	Nature Reviews Cardiology
Neurol Ther	Neurology and Therapy
PNAS	Proceedings of the National Academy of Sciences
Semin Cell Dev Biol	Seminars in Cell and Developmental Biology
Semin Hematol	Seminars in Hematology
Ther Adv Neurol Disord	Therapeutic Advances in Neurological Disorders

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Sc.B. in Biology

### PUBLICATIONS

Paula G. Fraenkel, Yann Gibert, Jason L. Holzheimer, **Victoria J. Lattanzi**, Sara F. Burnett, Kimberly A. Dooley, Rebecca A. Wingert, and Leonard I. Zon. Transferrin- $\alpha$  modulate hepcidin expression in zebrafish embryos. *Blood*, 19 March 2009, Vol. 113, No.12, pp. 2843-2850.

Gibert Y, **Lattanzi VJ**, Zhen AW, Vedder L, Brunet F, et al. (2011) BMP Signaling Modulates Heparin Expression in Zebrafish Embryos Independent of Hemojuvelin. *PLoS ONE* 6(1): e14553.

Steven G. Chaulk, **Victoria J. Lattanzi**, Samantha E. Hiemer, Richard P. Fahlman, and Xaralabos Varelas. The Hippo Pathway Effectors TAZ/YAP Regulate Dicer Expression and MicroRNA Biogenesis through Let-7. *J. Biol. Chem.* 2014 289: 1886-1891.

Chengtien Zhao, Viktoria Andreeva, Yann Gibert, Melissa LaBonty, **Victoria Lattanzi**, Shubhangi Prabhudesai, Yi Zhou, Leonard Zon, Kathleen L. McCann, Susan Baserga, Pamela C. Yelick. (2014) Tissue Specific Roles for the Ribosome Biogenesis Factor Wdr43 in Zebrafish Development. *PLoS Genetics* 10(1): e1004074.  
doi:10.1371/journal.pgen.1004074.

## **PROFESSIONAL EXPERIENCE**

Halloran Consulting Group <i>Consultant I</i>	March 2016 – Present
Boston University Amyloidosis Center <i>Senior Clinical Research Associate</i>	June 2014 – March 2016
Boston Medical Center, Department of Surgery <i>Clinical Research Associate</i>	April 2013 – June 2014
Boston University School of Medicine, Varelas Lab <i>Research Assistant</i>	May 2011 – April 2013
Tufts School of Dental Medicine, Yelick Lab <i>Research Assistant</i>	June 2009 – May 2011
Beth Israel Deaconess Medical Center, Fraenkel Lab <i>Research Assistant</i>	January 2008 – June 2009