IJC Heart & Vasculature 55 (2024) 101551

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

# Myocardial work assessment to improve baseline risk stratification in patients with transthyretin amyloidosis

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ARTICLE INFO

*Keywords:*
Myocardial Work
Cardiac Transthyretin amyloidosis
Tafamidis
Non-invasive imaging
Strain
NT-proBNP

ABSTRACT

*Background:* Cardiac transthyretin (ATTR) amyloidosis is an often underdiagnosed and potentially fatal disorder associated with poor survival. The National Amyloidosis Centre (NAC) staging system, based on NT-proBNP level and eGFR value, discriminates patients according to survival rates. However, NAC stage II involves a heterogenous group of patients with variable prognosis. This retrospective single-center study was set up to explore the potential role of myocardial work (MW) analysis to enhance risk stratification of ATTR patients prior to therapy.
*Methods and Results:* 37 patients diagnosed with ATTR between March 2021 and August 2023 were included. Baseline NT-proBNP and eGFR values were collected and LVEF, GLS and MW parameters were obtained from stored echocardiographic images. Patients were categorized per NAC stage (16 NAC I, 13 NAC II and 8 NAC III). Whereas the survival rate in NAC II and NAC III was significantly worse than in NAC I ($p = 0.031$ and $p = 0.045$ respectively), no significant difference was found between NAC II and III. In the ROC analysis, GCW proved to be the best survival predictor (AUC: 0.7) with optimal cut-off value 1294 mmHg%. Patients from NAC stage II were re-stratified according to GCW cut-off into HIGH RISK together with patients from NAC III or LOW RISK together with patients from NAC I. Patients in the HIGH RISK group exhibited a significantly worse prognosis with only 40 % survival at 2 years follow-up.
*Conclusion:* Our results demonstrate the advantages of incorporating MW analysis, particularly the use of a GCW cut-off, in the baseline risk stratification of ATTR patients.

## 1. Introduction

Cardiac transthyretin amyloidosis (ATTR) is a fatal disorder characterized by the progressive deposition of misfolded transthyretin amyloid fibrils in the myocardium resulting in biventricular hypertrophy and subsequent impairment of systolic and diastolic function [1]. This disease manifests in two distinct forms, hereditary and wild-type with the latter being more prevalent among elderly males. The prognosis when untreated is poor, with median survival estimates ranging from 2 to 6 years following diagnosis [2]. To date, no curative treatment exists for the wild-type of ATTR. However, the treatment with Tafamidis has shown to slow disease progression by stabilizing transthyretin with an acceptable safety profile [3,4].

Despite the increasing awareness of the disease, which has certainly improved the diagnosis rates, the early detection of ATTR remains challenging due to its heterogenic presentation [5]. As determining the stage of the disease at the time of diagnosis plays a critical role in prognosis and patient risk stratification, Gillmore and colleagues [6] developed a prognostic staging system called the National Amyloidosis Centre (NAC) stages, applicable to both, the wild-type and the hereditary form of ATTR. This system relies in the assessment of cardiac biomarkers' levels, particularly N-terminal pro B-type natriuretic peptide (NT-proBNP), and renal function, as reflected by the estimated glomerular filtration rate (eGFR). Stage I is defined as NT-proBNP $<$ 3000 ng/L and eGFR $>$ 45 ml/min, stage III is defined as NT-proBNP $>$ 3000 ng/L and eGFR $<$ 45 ml/min, and the remaining patients are

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https://doi.org/10.1016/j.ijcha.2024.101551
Received 26 August 2024; Received in revised form 15 October 2024; Accepted 3 November 2024
Available online 8 November 2024

classified as stage II. This staging system proves to be effective in differentiating between patients with different survival rates [7]. NAC stage I, II and III are associated with an estimated survival of 62, 47, 24 months respectively.

However, it should be noted that stage II represents a rather heterogenic group of patients with either predominantly cardiac or renal dysfunction. Therefore, additional characterization of patients in this subgroup may be beneficial.

In the surveillance of patients with ATTR, echocardiography plays a crucial role in evaluating the progression of the disease by characterizing the functional and morphological impact of amyloid depositions in the myocardium. Recent studies demonstrated that 40 % of patients had impaired ventricular function at the time of ATTR diagnosis [9]. However, standard echocardiographic parameters alone are insufficient for determining the prognosis accurately at the time of diagnosis. As the left ventricular ejection fraction (LVEF) is significantly impaired mainly in advanced stages of the disease, this parameter lacks the necessary sensitivity in the early stages [8]. Additionally, the strain pattern referred to as 'apical sparing' characterized by reduced strain values in the basal segments and preserved strain values in the apical region, is not specific to ATTR and may only be modestly present [2,10].

Non-invasive myocardial work (MW) has emerged as a potential alternative method for assessing LV function through echocardiography by incorporating both myocardial deformation and afterload in its analysis [11]. Several recent studies have investigated the diagnostic and predictive value of MW indices in different pathological conditions [12–14], however, the potential role of MW analysis in risk stratification of ATTR patients has not yet been explored.

This retrospective single-center study was set up to examine whether MW analysis can be utilized to enhance risk stratification and prognosis estimation of ATTR patients prior to therapy.

## 2. Methods

### 2.1. Patient screening and data collection

All patients, diagnosed with ATTR and referred for Tafamidis treatment between March 2021 and August 2023 were retrospectively screened for inclusion. Patients lacking laboratory data or echocardiographic images prior to therapy or with images of suboptimal quality were excluded as well as patients who were missing blood pressure measurements for MW calculation at the time of examination (Fig. 1). Clinical data, patients' risk factors, comorbidities and medical therapy were collected at the time of inclusion. Baseline serum levels of creatinine, troponins and NT-proBNP as well as baseline eGFR values were collected and the NAC stage was calculated for each patient [6]. The extent of cardiac amyloid deposition was estimated using Technetium scintigraphy and graded with Perugini [15]. Echocardiographic measurements for LV structure and function were obtained from two-dimensional (2D) images, color Doppler, pulsed-wave and continuous-wave Doppler images of parasternal and apical views, adhering to current echocardiographic guidelines [16].

### 2.2. Myocardial work calculation

The 2-, 3- and 4-chamber apical view images of the LV, digitally stored in cine-loop format at high frame rates (55–75 frames per second) were used for offline calculation of LVEF, global longitudinal strain

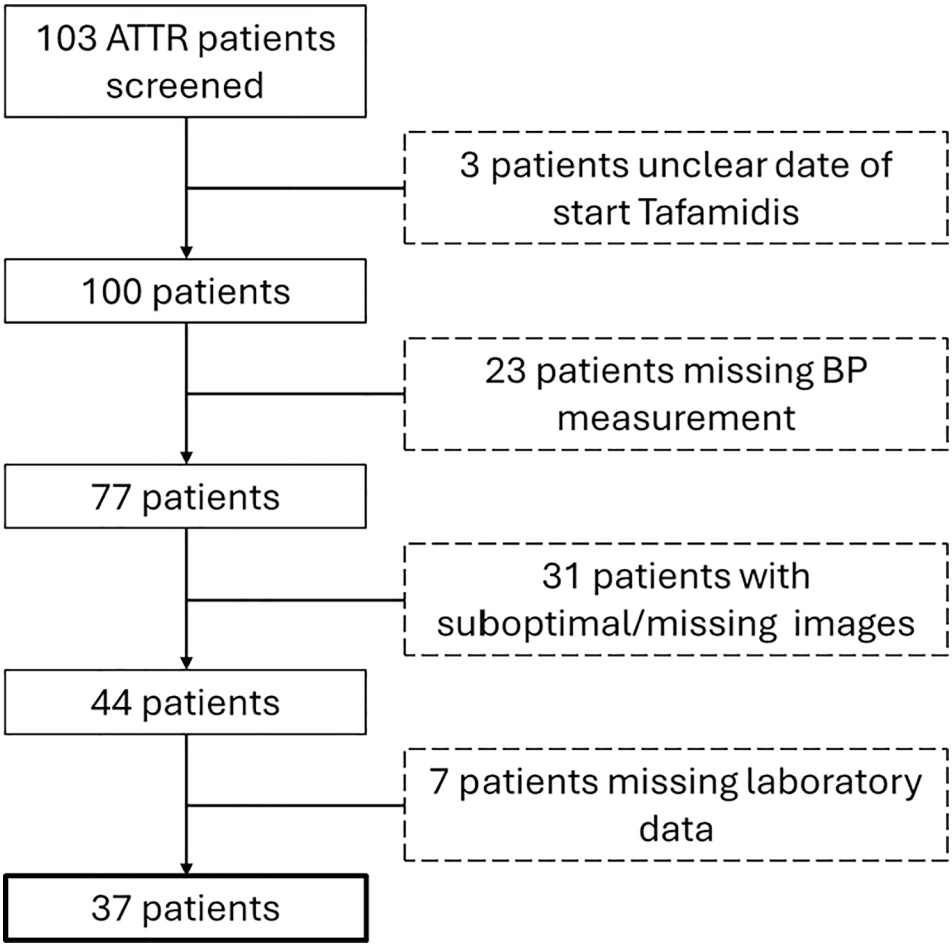


**Fig. 1.** Patient's screening and inclusion.

(GLS) and MW parameters using dedicated software (EchoPac, GE Vingmed Ultrasound, Horten, Norway). In the 2- and 4-apical views, LVEF was calculated using the Simpson's biplane method of discs. Semi-automated 2D speckle tracking was employed to analyze the three apical views to obtain the LV bull's-eye with the segmental strain values and calculate GLS. If necessary, the myocardium contour and the width of the region of interest were manually adjusted by the operator based on the patient's anatomy. Simultaneous measurement of aortic systolic pressure obtained from a cuff measurement was used as surrogate for LV peak systolic pressure. For the MW analysis, blood pressure measurements were input into the program following the strain analysis derived from the three apical views. The timing of aortic and mitral valve events was visually determined on the apical 3-chamber view. Ultimately, the LV strain values, estimated LV systolic pressure and valve events were integrated through a specialized software tool to construct non-invasive pressure-strain loops of the LV. The software computed global work index (GWI) and efficiency (GWE) as well as global constructive (GCW) and wasted work (GWW) using previously described methods [17].

Ten patients were randomly selected for intra- and inter-observer variability analysis of de MW parameters. Intra-observer variability was performed by the sonographer repeating measurements on off-line data with a time interval of at least three months. Interobserver variability was performed by repeating measurements from the same images by 2 independent expert sonographers blinded to the patient's clinical data and each other's results. Intra- and interobserver variability were calculated by intraclass coefficient (ICC) and the standard error of measurements. The results of the intra- and inter-observer variability are presented in Supplemental Table 1.

### 2.3. Statistical analysis

Categorical data are presented as n (%). Descriptive data are reported as the mean ± SD for normally distributed continuous variables. Normality testing was performed by graphical analysis with histograms and QQ-plots. Differences between NAC stages were analyzed using the one-way ANOVA test for continuous variables and the Chi-square test for categorical variables. The Receiver Operating Characteristic (ROC) method was applied to assess the survival predictive value of MW parameters and determine the optimal cut-off with the highest sensitivity and specificity. Patients from NAC stage II were reclassified according to GCW value either to HIGH RISK (GCW < 1294 mmHg%) together with NAC stage III patients or to LOW RISK (GCW ≥ 1294 mmHg%) together with patients from NAC stage I. Survival rates were calculated by the Kaplan-Meier method using the long rank (mantel-cox) test for inter-group difference. For all tests, a p-value below 0.05 was considered statistically significant. All statistical analysis were performed using SPSS for Windows Version 25 (SPSS, IBM headquarters, Armonk, NY, USA).

## 3. Results

A total of 37 patients were included in the analysis before starting Tafamidis treatment for ATTR. Among them, sixteen patients were classified in NAC stage I, 13 in NAC stage II, 8 in NAC stage III. Table 1 displays the baseline characteristics of the patients according to their NAC stage. Throughout a mean follow-up of 572 [321, 752] days, eight patients died, and seven patients were hospitalized at least once with symptomatic heart failure.

Patients in NAC stage III were older and had significantly higher levels of serum troponins and creatinine along with worse right ventricle function compared to NAC stage I and II patients (Table 1). Higher NAC stage was associated with worse LVEF, GLS, GWI and GCW although the differences between stages did not reach statistical significance. The only parameter that showed a significant difference between NAC stage III and NAC stage I was GCW. Additionally, GCW exhibited a negative correlation with NT-proBNP level (R = -0.477, p < 0.05) and a positive

**Table 1**
Patients' baseline characteristics, laboratory and echocardiographic data per NAC stage. Categorical variables are presented as n (%) and continuous variables as mean ± sd.

| | All patients (37) | NAC stage I (16) | NAC stage II (13) | NAC stage III (8) | p-value # |
|---|---|---|---|---|---|
| *Male* | 33 (89) | 14 (87) | 11 (85) | 8 (100) | 0.522 |
| *Dead* | 8 (22) | 1 (6) | 4 (31) | 3 (38) | 0.131 |
| *Perugini 1* | 2 (5) | 1 (6) | 0 | 1 (13) | 0.175 |
| *Perugini 2* | 24 (65) | 12 (75) | 10 (77) | 2 (25) | |
| *Perugini 3* | 10 (27) | 3 (20) | 3 (23) | 4 (50) | |
| *NYHA class 1* | 25 (68) | 11 (69) | 10 (76) | 4 (50) | 0.262 |
| *NYHA class ≥ 2* | 11 (30) | 4 (25) | 3 (23) | 4 (50) | |
| ***Comorbidities*** | | | | | |
| *Myocardial infarction* | 3 (7) | 1 (6) | 0 | 2 (25) | 0.117 |
| *Cardiac device* | 7 (16) | 0 | 3 (23) | 4 (50) | 0.012 |
| *Arterial hypertension* | 22 (50) | 7 (44) | 6 (46) | 5 (63) | 0.670 |
| *Atrial fibrillation* | 22 (50) | 6 (38) | 6 (46) | 6 (75) | 0.217 |
| *Coronary artery disease* | 15 (34) | 4 (25) | 5 (39) | 5 (63) | 0.203 |
| *Diabetes* | 11 (25) | 5 (31) | 2 (15) | 1 (13) | 0.457 |
| ***Medical therapy*** | | | | | |
| *ACEi/ARB/ ARNI* | 21 (48) | 9 (56) | 7 (54) | 2 (25) | 0.316 |
| *BB* | 25 (58) | 7 (44) | 8 (62) | 5 (63) | 0.405 |
| *MRA* | 26 (59) | 10 (63) | 8 (62) | 7 (88) | 0.396 |
| *SGLT2i* | 7 (16) | 4 (25) | 0 | 2 (25) | 0.144 |
| ***Clinical data*** | | | | | |
| Age (years) | 81 ± 7 | *78 ± 8** | *81 ± 5* | *86 ± 5* | *0.030* |
| BSA ($m^2$) | 1.89 ± 0.16 | 1.93 ± 0.17 | 1.94 ± 0.12 | 1.82 ± 0.17 | 0.210 |
| SBP (mmHg) | 125 ± 18 | 131 ± 18 | 120 ± 18 | 121 ± 20 | 0.623 |
| DBP (mmHg) | 72 ± 9 | 74 ± 7 | 72 ± 12 | 70 ± 7 | 0.724 |
| ***Laboratory data*** | | | | | |
| Creatinine (mg/dL) | 1.28 ± 0.63 | *1.01 ± 0.21** | *1.29 ± 0.36** | *2.05 ± 1.04* | *<0.001* |
| Troponin (ng/L) | 67.6 ± 51.1 | *46.9 ± 39.6** | *68.0 ± 29.1* | *102.2 ± 78.2* | *0.054* |
| NT-proBNP (ng/L) | 401 ± 3506 | *1278 ± 980** | *5380 ± 3330°* | *7251 ± 3100* | *<0.001* |
| eGFR (mL/min/1.73 $m^2$) | 58 ± 19 | *70 ± 13** | *53 ± 15*°* | *34 ± 10* | *<0.001* |
| ***Echocardiographic data*** | | | | | |
| LVEDD (mm) | 46 ± 6 | 47 ± 6 | 45 ± 8 | 47 ± 7 | 0.724 |
| LVESD (mm) | 35 ± 7 | 35 ± 8 | 34 ± 5 | 38 ± 10 | 0.420 |
| IVS (mm) | 14 ± 4 | 15 ± 3 | 14 ± 3 | 14 ± 2 | 0.816 |
| PW (mm) | 14 ± 4 | 15 ± 4 | 15 ± 3 | 14 ± 4 | 0.927 |
| LV mass (g) | 268 ± 70 | 313 ± 80 | 259 ± 66 | 263 ± 29 | 0.106 |
| LV mass index ($g/m^2$) | 141 ± 36 | 161 ± 39 | 134 ± 39 | 145 ± 18 | 0.180 |
| E peak velocity (m/s) | 79 ± 24 | 79 ± 22 | 69 ± 32 | 88 ± 16 | 0.271 |
| e' lateral (m/s) | 6.8 ± 2.3 | 6.6 ± 2.6 | 6.3 ± 1.9 | 7.8 ± 2.0 | 0.459 |
| e' septal (m/s) | 4.7 ± 1.8 | 4.4 ± 1.4 | 5.0 ± 2.1 | 4.6 ± 2.9 | 0.727 |
| E/e' lateral | 12 ± 5 | 13 ± 4 | 12 ± 8 | 12 ± 4 | 0.838 |
| E/e' septal | 20 ± 11 | 20 ± 6 | 18 ± 15 | 25 ± 14 | 0.436 |
| E/e' average | 15 ± 7 | 16 ± 5 | 15 ± 11 | 15 ± 5 | 0.876 |
| TAPSE (mm) | 18 ± 5 | *20 ± 4** | *18 ± 4** | *14 ± 4* | *0.005* |
| ***Left Ventricular Function*** | | | | | |
| LVEF (%) | 45 ± 10 | 47 ± 10 | 43 ± 11 | 40 ± 9 | 0.282 |
| GLS** (%) | 13.3 ± 4.3 | 14.2 ± 4.1 | 12.5 ± 5.0 | 10.9 ± 2.7 | 0.200 |
| GWI (mmHg%) | 1281 ± 527 | 1404 ± 563 | 1081 ± 410 | 1021 ± 411 | 0.110 |
| GCW (mmHg %) | 1498 ± 569 | *1657 ± 617** | *1297 ± 406* | *1149 ± 459* | *0.057* |
| GWW (mmHg %) | 79 ± 49 | 87 ± 57 | 82 ± 58 | 69 ± 36 | 0.742 |
| GWE (%) | 94 ± 4 | 93 ± 5 | 93 ± 5 | 94 ± 2 | 0.945 |

# intergroup difference with all groups together (one-way ANOVA test) *p < 0.05 vs NAC stage III (T-test), °p < 0.05 vs NAC stage I (T-test), **absolute value. ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor/neprilysin inhibitor, BB: beta blocker,

MRA: mineralocorticoid receptor antagonist, BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, IVS: inter-ventricular septum, LV: left ventricle, LVEDD: left ventricle end diastolic diameter, LVEF: left ventricle ejection fraction, LVESD: left ventricle end systolic diameter, NAC: National Amyloidosis Centre, NT-proBNP: N-terminal pro b-type natriuretic peptide, NYHA: New York Heart Association, PW: posterior wall, SBP: systolic blood pressure, SGLT2i: sodium-glucose co-transporter-2 inhibitors TAPSE: tricuspid annulus plane systolic excursion.

correlation with eGFR ($R = 0.405$, $p < 0.05$). Therefore, among all MW parameters, GCW emerged as the most appropriate for patient risk stratification. Furthermore, in the ROC analysis, we determined the optimal GCW cut-off value for predicting survival according to the Youden index (area under the curve = 0.7). A GCW of 1294 mmHg%, corresponded to the highest specificity (0.63) and sensitivity (0.58) values.

### 3.1. Reclassification rate

Based on the GCW cut-off value of 1294 mmHg%, the patients were recategorized into two risk levels: the HIGH RISK group included all patients from NAC stage III, regardless their GCW value, and patients from NAC stage II with GCW value below 1294 mmHg%, the LOW RISK group included all patients from NAC stage I, regardless their GCW value, and patients from NAC stage II with GCW value above or equal to 1294 mmHg%.

For each NAC cohort, the proportion of patients assigned to each risk level according to GCW value is shown in Fig. 2. In details, 8 patients (62 %) from NAC stage II were classified in the HIGH RISK and 5 patients (38 %) in the LOW RISK cohort. Further, 6 patients (38 %) from NAC stage I were categorized as LOW RISK even though presenting GCW < 1294 mmHg% whereas 3 patients (38 %) from NAC stage III were classified as HIGH RISK despite having GCW > 1294 mmHg%.

The adoption of the GCW value on top of the NAC criteria drives a novel system for patient risk stratification based on three cut-offs: eGFR < 45 ml/min, NT-proBNP > 3000 ng/L and GCW < 1294 mmHg%. ATTR patients with two or more positive criteria are labelled as HIGH RISK while patients with one or zero positive criteria are categorized as LOW RISK (Fig. 3A).

### 3.2. HIGH RISK vs LOW RISK

After reclassification, patients labelled as HIGH RISK exhibited not only worse values for creatinine, troponins, NT-proBNP and eGFR, but they also demonstrated more pronounced right and left ventricular dysfunction compared to LOW RISK patients. This was evident from significantly lower values of TAPSE, LVEF, GLS (absolute value), GWI and GCW (Table 2). Nevertheless, when comparing patients from NAC stage II reclassified as HIGH RISK to those reclassified as LOW RISK no significant difference was found in age, comorbidities, biomarkers of echocardiographic parameters (Table 3).

### 3.3. Prognostic value

The Kaplan-Meier curve analysis confirmed that patients within the NAC stage II and III cohort exhibited markedly lower survival rates compared to those within NAC stage I, however, no statistical difference was found between NAC stage II and III (Fig. 3B). By contrast, patients categorized as HIGH RISK had significantly worse survival rates when compared to LOW RISK patients ($p = 0.039$), with only 40 % survival at 2 years follow-up despite medical therapy (Fig. 3C).

## 4. Discussion

In this study, we investigated the added value of MW analysis in combination with the NAC staging system to risk-stratify patients with ATTR, treated by Tafamidis at the time of diagnosis. The three main findings are: i) Among all MW parameters, GCW demonstrated the best predictive value (AUC 0.7) for the survival of patients with ATTR. ii) The NAC stage II cohort consisted of a diverse group of patients with varying levels of risk where the GCW threshold of 1294 mmHg% (specificity 0.63, sensitivity 0.58) permitted to distinguish patients at high risk from those at low risk. iii) The prognostic value of the NAC staging system in estimating outcome of patients with ATTR could be enhanced by incorporating MW assessment, particularly the GCW value. In brief, the results of our study underline the benefit of combining cardiac imaging and laboratory data for a more accurate the risk assessment in patients with ATTR.

### 4.1. ATTR staging: A laboratory data based approach

The NAC staging system presents a simple but powerful method to risk-stratify ATTR patients based on cardiac and renal function as reflected by the NT-proBNP value and the eGFR value [6]. In contrast to previous studies we observed no significant difference in mortality between NAC II and NAC III patients. However, significantly better survival rates were noted in NAC I compared to both NAC II and NAC III, when analyzed separately. These findings indicate, on the one hand, the high sensitivity of the NAC staging system for discriminating patients who are free of risk in the short term while on the other hand highlighting its poor specificity in determining which patients are at the highest risk. Consequently, the incorporation of cardiac imaging parameters may be beneficial in enhancing patient risk stratification based on NAC stages. Furthermore, while patients in NAC stage I and III are associated with a more favorable and a clearly adverse prognosis, respectively, NAC stage II encompasses a rather heterogeneous group of

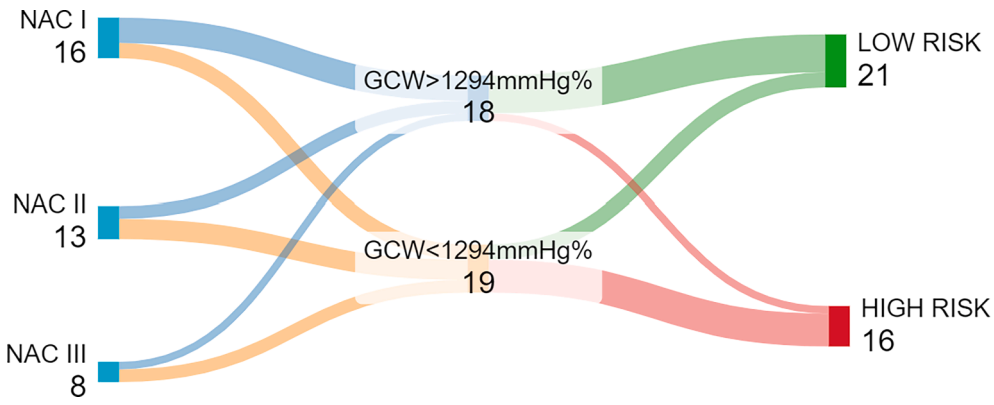


**Fig. 2.** Sankey diagram for patient risk re-stratification by combining NAC stage and MW analysis.

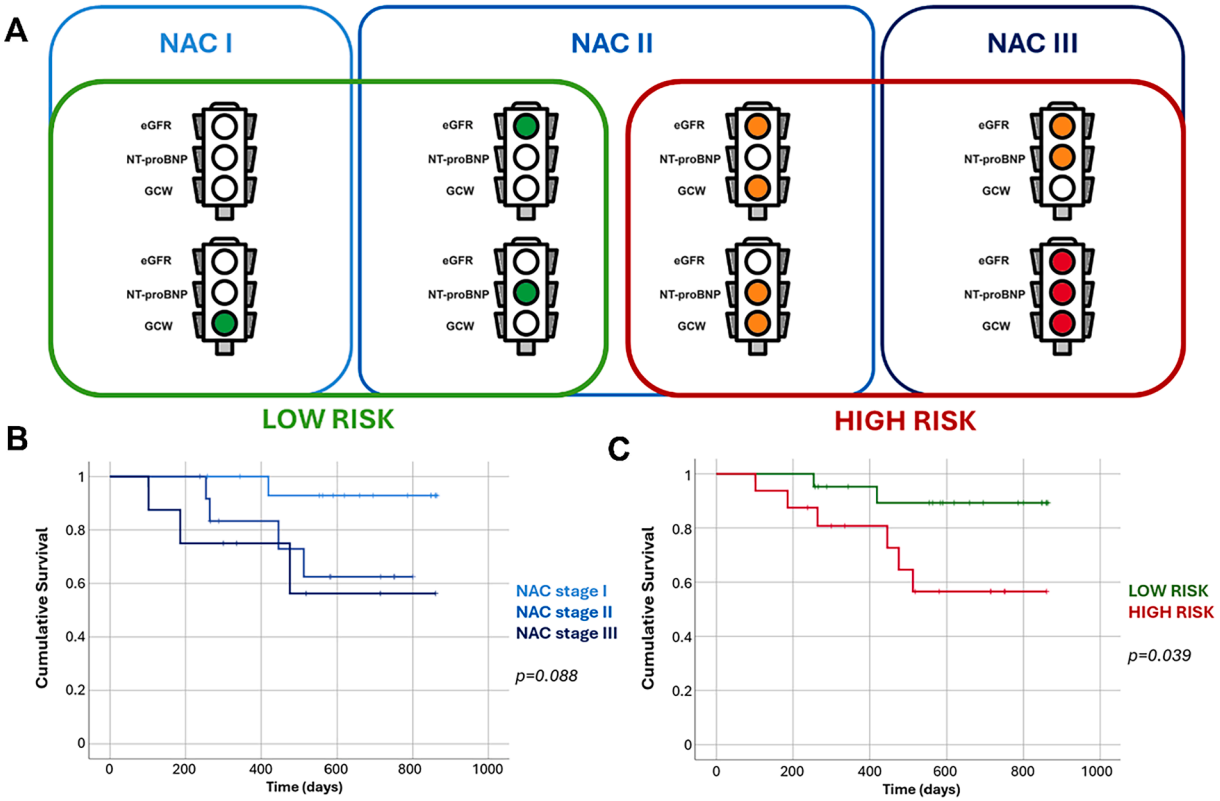


**Fig. 3.** Patient risk assessment combining NAC criteria and MW parameters (cut-offs: eGFR < 45 ml/min, NT-proBNP > 3000 ng/L and GCW < 1294 mmHg%) **A.** Patients with ≤ 1 criteria are classified as LOW RISK and patients with ≥ 2 criteria are classified as HIGH RISK. **B.** Survival analysis per NAC stage. **C.** Survival analysis after re-stratification in HIGH RISK and LOW RISK.

patients exhibiting varying levels of risk. As previously mentioned, all patients with abnormal values for either NT-proBNP or eGFR are classified as NAC stage II. However, apart from cardiac and renal function, other factors such as race, body mass index or the patient's filling state, can significantly influence these parameters, thereby complicating accurate risk estimation. Moreover, the diverse clinical presentation of ATTR and its individual-specific disease progression necessitate the integration of various diagnostic tools into a more comprehensive clinical evaluation.

### 4.2. Myocardial work for patient risk stratification in ATTR

Modern echocardiographic techniques allow for the advanced analysis of myocardial function and morphology. Consequently, advanced echocardiography may prove valuable in evaluating the impact of transthyretin myocardial deposition on the cardiac function and patient survival.

Previous research has already suggested the integration of MW assessment into the clinical evaluation and management of ATTR patients. Roger-Rollé and colleagues demonstrated the correlation between MW indices and well-known prognostic markers [18]. However, in contrast to our study, they exclusively investigated GWI and GWE omitting left GCW and GWW from their analysis. They advocated incorporating MW analysis in the severity assessment of the disease to improve the selection of candidates for therapeutic intervention. Furthermore, Stassen et al. [19] reported the independent diagnostic value of GCW for detecting cardiac amyloidosis, in addition to standard echocardiographic measurements and Ladefoged et al. [20] identified GWI as an independent predictor of survival in patients with wild-type ATTR. The latter finding contrasts with the results of our study which identified GCW as the most effective MW parameter for predicting survival in ATTR patients. While further research is still needed to determine the MW parameter with the highest clinical impact, our results align with previous studies underscoring the benefits of MW analysis in the clinical assessment of ATTR patients.

### 4.3. ATTR risk stratification: Imaging and laboratory data combined approach

The unspecific risk profile of patients in NAC stage II and the prognostic value of MW indices in ATTR [21], point out the potential complementary role of advanced echocardiography in addition to laboratory data to improve risk assessment in patients with ATTR. Our findings suggest particularly the addition of the GCW cutoff to the well-known NAC criteria. Before cardiac dysfunction becomes evident by a drop in LVEF or the manifestation of heart failure signs and symptoms, impaired GCW may indicate the presence of subclinical myocardial dysfunction. This impairment is characterized by decreased contractile performance and is associated with worse prognosis [12,22]. It is noteworthy that although GCW was identified as the most significant predictor of survival in the ROC analysis, an AUC of 0.7 reflects a moderate level of predictive power. Furthermore, the GCW threshold of 1294 mmHg% was associated with moderate sensitivity and specificity, including both false positive and false negative errors. Nevertheless, our findings suggest that, while patients in NAC stage I or III do not necessitate additional MW assessment, patients in NAC stage II, may still benefit from this approach (Fig. 3).

### 4.4. Clinical implications

The integration of advanced echocardiography and biomarkers profile, allows for a more accurate estimation of patient's prognosis. While suggesting potential benefits, our data lack robust evidence to support the integration of MW assessment in the routine evaluation of

**Table 2**
Clinical, laboratory and echocardiographic data in HIGH RISK patients vs LOW RISK patients.

| | LOW RISK mean ± sd | HIGH RISK mean ± sd | p-value |
|---|---|---|---|
| ***Clinical data*** | | | |
| Age (years) | 80 ± 7 | 83 ± 6 | 0.143 |
| BSA ($m^2$) | 1.93 ± 0.16 | 1.88 ± 1.5 | 0.261 |
| SBP (mmHg) | *130 ± 18* | *117 ± 17* | *0.029* |
| DBP (mmHg) | 74 ± 9 | 70 ± 8 | 0.260 |
| ***Laboratory data*** | | | |
| Creatinine (mg/dL) | *1.1 ± 0.2* | *1.7 ± 0.9* | *0.012* |
| Troponin (ng/L) | *49.0 ± 36.1* | *90.7 ± 59.6* | *0.019* |
| NT-proBNP (ng/L) | *2166 ± 2730* | *6432 ± 2924* | *<0.001* |
| eGFR (mL/min/1.73 $m^2$) | *66 ± 15* | *43 ± 16* | *<0.001* |
| ***Echocardiographic data*** | | | |
| LVEDD (mm) | 47 ± 7 | 46 ± 8 | 0.802 |
| LVESD (mm) | 35 ± 7 | 36 ± 8 | 0.570 |
| IVS (mm) | 14 ± 3 | 14 ± 2 | 0.667 |
| PW (mm) | 14 ± 3 | 15 ± 4 | 0.515 |
| LV mass (g) | 284 ± 83 | 276 ± 51 | 0.747 |
| LV mass index (g/$m^2$) | 146 ± 42 | 148 ± 31 | 0.873 |
| E peak velocity (m/s) | 76 ± 22 | 80 ± 29 | 0.682 |
| e' lateral (m/s) | 6.7 ± 2.4 | 6.7 ± 2.3 | 0.969 |
| e' septal (m/s) | 5.0 ± 1.7 | 4.2 ± 2.3 | 0.271 |
| E/e' lateral | 12 ± 4 | 13 ± 7 | 0.677 |
| E/e' septal | 18 ± 7 | 24 ± 15 | 0.135 |
| E/e' average | 15 ± 5 | 17 ± 10 | 0.443 |
| TAPSE (mm) | *20 ± 4* | *15 ± 5* | *0.003* |
| ***Left Ventricular Function*** | | | |
| LVEF (%) | *47 ± 10* | *40 ± 9* | *0.043* |
| GLS (absolute value, %) | *14,6 ± 4.5* | *10,6 ± 2.8* | *0.002* |
| GWI (mmHg%) | *1419 ± 508* | *931 ± 340* | *0.002* |
| GCW (mmHg%) | *1673 ± 546* | *1089 ± 346* | *0.001* |
| GWW (mmHg%) | 88 ± 54 | 72 ± 51 | 0.388 |
| GWE (%) | 94 ± 5 | 93 ± 5 | 0.828 |

BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, IVS: inter-ventricular septum, LV: left ventricle, LVEDD: left ventricle end diastolic diameter, LVEF: left ventricle ejection fraction, LVESD: left ventricle end systolic diameter, NT-proBNP: N-terminal pro b-type natriuretic peptide, PW: posterior wall, SBP: systolic blood pressure, TAPSE: tricuspid annulus plane systolic excursion.

ATTR. Nevertheless, these preliminary findings indicate that the integration of MW assessment along with NT-proBNP and eGFR in the diagnostic work-up could potentially enhance the prognosis estimation, particularly in patients with NAC stage II.

## 5. Limitations

This study has some limitations to be acknowledged. Firstly, MW assessment is still a new echocardiographic tool to be underexplored in the context of ATTR. Moreover, this relatively novel approach necessitates the availability of high-quality images which may not always be easily attainable in the routine clinical setting. For optimal image acquisition and analysis, comprehensive operator training is crucial and the lack of knowledge and experience may negatively impact the reproducibility of the measurements. In our study, we chose highly qualified echocardiographers to improve the reproducibility of our results. However, given that all images were acquired and analyzed with GE support, our findings should be interpreted with an awareness of potential vendor dependency. Secondly, the retrospective nature of the study and its single-center design imposed limitations on patient inclusion and availability of data. Therefore, at this stage, our results should be regarded as hypothesis-generating and further studies are warranted to explore the potential role of MW in prognostication of patients with ATTR.

**Table 3**
Reclassified patients from NAC II, LOW RISK (5 patients) vs HIGH RISK (8 patients).

| | LOW RISK mean ± sd | HIGH RISK mean ± sd | p-value |
|---|---|---|---|
| ***Clinical data*** | | | |
| *Age (years)* | *84 ± 5* | *80 ± 5* | 0.19 |
| *BSA ($m^2$)* | *2.0 ± 0.1* | *1.9 ± 0.1* | 0.66 |
| *SBP (mmHg)* | *130 ± 21* | *114 ± 14* | 0.18 |
| *DBP (mmHg)* | *73 ± 15* | *71 ± 10* | 0.71 |
| ***Laboratory data*** | | | |
| *Creatinine (mg/dL)* | 1.3 ± 0.3 | 1.3 ± 0.4 | 0.77 |
| *Troponin (ng/L)* | 55 ± 28 | 77 ± 28 | 0.19 |
| *NT-proBNP (ng/L)* | 5008 ± 4519 | 5612 ± 2679 | 0.79 |
| *eGFR (mL/min/1.73 $m^2$)* | 53 ± 17 | 53 ± 14 | 0.97 |
| ***Echocardiographic data*** | | | |
| *TAPSE (mm)* | 19 ± 2 | 17 ± 4 | 0.26 |
| *LVEF (%)* | 47 ± 10 | 40 ± 11 | 0.27 |
| *GLS (absolute value, %)* | 16 ± 6 | 10 ± 3 | 0.09 |
| *GWI (mmHg%)* | 1466 ± 310 | 841 ± 247 | *0.01* |
| *GCW (mmHg%)* | 1725 ± 237 | 1029 ± 192 | *<0.01* |
| *GWW (mmHg%)* | 92 ± 51 | 76 ± 65 | 0.64 |
| *GWE (%)* | 94 ± 3 | 93 ± 6 | 0.46 |
| ***Patient Characteristics*** | | | |
| *Male (%)* | 80 | 88 | 0.72 |
| *Dead (%)* | 20 | 38 | 0.51 |
| *Perugini 2 (%)* | 80 | 75 | 0.84 |
| *Perugini 3 (%)* | 20 | 25 | 0.84 |
| ***Comorbidities*** | | | |
| *Cardiac device (%)* | 0 | 38 | 0.12 |
| *Arterial hypertension (%)* | 80 | 25 | 0.05 |
| *Atrial fibrillation (%)* | 40 | 50 | 0.73 |
| *Coronary artery disease (%)* | 20 | 50 | 0.28 |
| *Diabetes (%)* | 40 | 0 | 0.05 |
| ***Medical Therapy*** | | | |
| *ACEi/ARB/ARNI (%)* | 40 | 63 | 0.43 |
| *BB (%)* | 40 | 75 | 0.21 |
| *MRA (%)* | 40 | 75 | 0.21 |

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor/neprilysin inhibitor, BB: beta blocker, MRA: mineralocorticoid receptor antagonist, BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, LVEF: left ventricle ejection fraction, NT-proBNP: N-terminal pro b-type natriuretic peptide, SBP: systolic blood pressure, TAPSE: tricuspid annulus plane systolic excursion.

## 6. Conclusion

In conclusion, incorporating MW analysis, particularly GCW, into the baseline evaluation of ATTR patients may potentially improve risk stratification, allowing for more personalized therapeutic decisions. A GCW cut-off might be useful to discriminate patients in NAC stage II who are at higher risk due to impaired myocardial performance. Apart from medical therapy, these patients may benefit from further study to evaluate whether more intensive monitoring is warranted.

## Sources of funding

A.M. reports receiving a research grant from the CardioPaTh Program.

## CRediT authorship contribution statement

**Ana Moya:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Elayne Kelen de Oliveira:** Formal analysis. **Monika Beles:** Investigation, Data curation. **Dimitri Buytaert:** Investigation. **Marc Goethals:** Investigation. **Riet Dierckx:** Investigation, Data curation. **Jeroen Dauw:** Investigation. **Jozef Bartunek:** Investigation. **Ward A. Heggermont:** Investigation. **Marc Vanderheyden:** Investigation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101551.

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