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ORIGINAL ARTICLE

Early diagnosis, disease stage and prognosis in wild-type transthyretin amyloid cardiomyopathy: The DIAMOND study

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Abstract

Aims Disease staging and prognostic scoring in wild-type transthyretin-related cardiac amyloidosis (ATTRwt-CA) can be captured by two systems (NAC and Columbia scores). However, uncertainty remains as epidemiology of the disease is evolving rapidly. We evaluated features associated with staging systems across ATTRwt-CA patients from different diagnostic pathways, and their association with prognosis.

Methods We performed an analysis on DIAMOND patients with available data to evaluate NAC and Columbia score. DIAMOND was a retrospective study from 17 Italian referral centres for CA, enrolling 1281 patients diagnosed between 2016 and 2021, and aimed at describing characteristics of pathways leading to ATTRwt-CA diagnosis. Of the original cohort, 811 patients were included in this analysis. Each patient had NAC and Columbia score calculated. Patients were grouped according to NAC and Columbia scoring classes. We described characteristics of patients according to staging classes and diagnostic pathways at diagnosis. Prevalence of early diagnoses, defined as NAC Ia, NYHA class I, no use of diuretics, no history of heart failure (HF) hospitalizations nor of atrial fibrillation prior to diagnosis, was investigated. Finally, prognostic variables were tested alone and grouped as NAC or Columbia scores in Cox univariate and multivariate regression analyses. Prognosis was investigated as all-cause mortality, in the whole population and dividing patients in HF versus other diagnostic pathways.

Results Only 1% of the study population had an early ATTRwt-CA diagnosis. Distribution of prognostic variables and of NAC and Columbia classes was heterogeneous across diagnostic pathways. The prevalence of NAC III and Columbia III was higher in the HF diagnostic pathway, but all NAC and Columbia classes were present in all pathways. Both NAC and Columbia scores

were associated with all-cause mortality at univariate Cox regression analysis in the whole population, in patients from the HF diagnostic pathway and in those from other pathways. At multivariate analysis, Columbia score remained significantly associated with the outcome, together with age at diagnosis, left ventricular ejection fraction and maximal wall thickness.

Conclusions In this contemporary nationwide cohort, an ATTRwt-CA early diagnosis was very rare. Disease staging with NAC and Columbia scoring systems determined classes of patients with heterogeneous features. Both scores were significantly associated with mortality, but other variables also had prognostic significance.

Keywords Cardiac amyloidosis; Disease stage; NAC score; Prognostic scoring; Wild-type transthyretin cardiac amyloidosis

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[Correction added on 25 October 2024, after first online publication: Lia Crotti's affiliation links have been changed to '19, 22' in this version.]

Introduction

Wild-type transthyretin (TTR)-related cardiac amyloidosis (ATTRwt-CA) is increasingly recognized. Being a progressive disease, earlier diagnosis and, thus, earlier access to disease-modifying therapies is related to a better prognosis. Landmark trials of TTR-stabilizer drugs have shown that the greatest efficacy of treatment is obtained in patients in NYHA functional class I or II.[1,2] However, despite increased awareness, ATTRwt-CA patients still experience a significant diagnostic delay,[3] and in half of cases, the final diagnosis is made in the context of overt heart failure (HF).[4] HF patients, presenting with an already advanced disease, show a worse prognosis as compared with those diagnosed incidentally or in the context of other clinical events.

Disease stage in ATTRwt-CA can be captured by two major staging systems proposed in 2017 by the National Amyloid Centre in the UK (NAC score)[5] and in 2020 by the Columbia University in the USA (Columbia score).[6] These scores define disease severity by assessing natriuretic peptide and glomerular filtration rate (GFR) values (NAC score), and diuretic use and NYHA class on top of the NAC score (Columbia score). Moreover, within the original NAC score, a group of patients treated with low dose of diuretics and showing low values of NT-proBNP at diagnosis (i.e., NAC Ia) was identified as having a survival comparable with age-matched general population.[7] Both the NAC and the Columbia scores proved to adequately predict prognosis.[5,6] However, some uncertainty remains for prognostic scoring in ATTRwt-CA, as epidemiology of the disease is evolving rapidly and differently in different countries.[4,8,9] Moreover, a number of other clinical features have been shown to influence prognosis in ATTRwt-CA,[4,10–12] of which was not accounted for in NAC and Columbia multivariate models.[5,6]

We evaluated features associated with staging scores and their association with prognosis in a large, contemporary, Italian nationwide cohort of ATTRwt-CA.

Methods

We performed an analysis on DIAMOND patients with available data to evaluate NAC and Columbia score (GRF, natriuretic peptide values, NYHA functional class and diuretic dose at diagnosis). Briefly, DIAMOND (*DIagnostic pathways to transthyretin AMyloid cardiomyOpathy: a multicentre Network stuDy*) was a retrospective study from 17 Italian referral centres for CA, enrolling 1281 patients diagnosed between January 2016 and December 2021, and aimed at describing characteristics of pathways leading to ATTRwt-CA diagnosis.[4] Patients were categorized into four diagnostic pathways: re-evaluation in the context of a previous diagnosis of hypertrophic cardiomyopathy (*HCM pathway*), evaluation for HF (*HF pathway*), incidental imaging findings (*incidental imaging pathway*), evaluation for a medical reason other than HCM or HF (*incidental clinical pathway*). From March to September 2023, all centres were asked to add to the original dataset information about creatinine and natriuretic peptide values, left ventricular ejection fraction (LVEF), maximal wall thickness (at the time of ATTRwt-CA diagnosis) and therapies; moreover, follow-up was updated. Tafamidis therapy was considered as effectively received if patients were treated for at least 18 months.

There were 811 (63% of the original cohort) patients with available data to calculate NAC and Columbia scores. There were no significant differences between patients included and excluded from the present study, apart from use of tafamidis (*Table* S1).

For all patients with available data, GFR was calculated by standard Modification of Diet in Renal Disease study equation. NAC score was calculated as previously described, based on GFR and NT-proBNP values.[5] NAC I was defined as NT-proBNP $\leq$ 3000 ng/L and GFR $\geq$ 45 mL/min, NAC III was defined as NT-proBNP $>$ 3000 ng/L and GFR $<$ 45 mL/min, with the remainders defined as NAC II. NAC I patients were further divided into Ia, defined as a diuretic dose $<$0.75 mg/kg and

an NT-proBNP ≤ 500 ng/L (or ≤1000 ng/L in the presence of atrial fibrillation), and Ib, comprising all remaining NAC I patients.[7] Columbia score was calculated as previously described, based on NAC score, diuretic dose and NYHA functional class at diagnosis.[6] Diuretic dose was categorized into dosages of 0, >0 to 0.5, >0.5 to 1, and >1 mg/kg. For the purpose of the scoring system, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg, 2 points for >0.5 to 1 mg/kg, and 3 points for >1 mg/kg. One point was assigned per NYHA functional class. The final score was obtained by adding diuretic dose and NYHA functional class points to each patients' NAC score. Patients were grouped in three classes, defined as Columbia I (score 1–3), Columbia II (score 4–6) and Columbia III (score 7–9). Diuretic dose was given by furosemide equivalents normalized by body weight (in kg), with standard conversion factors of bumetanide 1 mg = torsemide 20 mg = furosemide 40 mg.[6] For patients with only BNP values available, NT-proBNP was calculated by multiplying BNP values by a factor of 6.25.[6,13]

We defined ATTRwt early diagnosis as a NAC score Ia and a Columbia score of 1 (i.e., NAC Ia, NYHA class I and no use of diuretics at the time of diagnosis), in the absence of a history of HF hospitalizations (HFH) or of atrial fibrillation prior to diagnosis.

Prognosis was investigated with all-cause mortality as endpoint and evaluated in the whole study population, and dividing patients in those diagnosed in the HF pathway and those diagnosed in pathways other than HF. Diagnostic pathways other than HF were grouped together based on the similar prognosis previously described in our original cohort.[4] A comparison of patients from HCM, incidental imaging and incidental clinical pathways is presented in Table S2.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or as median with interquartile range (IQR). The distribution of continuous variables across NAC and Columbia classes was compared with the ANOVA test; the comparison of continuous variables between outliers was performed with Student's *t*-test. The standard chi-square test was used to compare proportions. A *P*-value ≤ 0.05 was considered statistically significant for these tests. Cohen's kappa was used to assess agreement between NAC and Columbia classes distribution. Survival analyses were conducted with the Kaplan–Meier method, and univariate and multivariate Cox regression analysis. Performance of NAC and Columbia scores was assessed by the area under the curve (AUC) with receiver-operating characteristic curves method. In the whole cohort, in the HF diagnostic pathway subgroup and in the other diagnostic pathways subgroup, we first tested NT-proBNP values (NT-proBNP >3000 pg/mL), GFR (GFR < 45 mL/min), NYHA functional class (NYHA functional class III-IV) and diuretic dose (0 mg/kg; >0 to 0.5 mg/kg; >0.5 to 1 mg/kg; >1 mg/kg) at univariate Cox regression analysis. Once they all showed significant association with all-cause mortality, we tested NAC and Columbia score at univariate Cox regression analysis. We then evaluated at univariate Cox regression analysis other variables selected among those significantly differing when comparing characteristics of dead versus alive patients. Finally, we performed a multivariate Cox regression analysis where we included Columbia score (rather than NAC due to AUC results) and variables from the second pool, which resulted significantly associated with all-cause mortality in the univariate analysis (*P*-value ≤ 0.20). Variables included in multivariate Cox regression analyses were tested for multicollinearity, which was defined as a variable inflation factor (VIF) > 2[14]; all variables in the final multivariate Cox regression analyses showed no multicollinearity (all had VIF < 2).

We performed a sensitivity analysis evaluating only patients for whom NAC score was calculated from NT-proBNP values (*n* = 706) and a further one excluding patient treated with tafamidis (*n* = 72), showing consistency of results (data not shown).

Results

Distribution of patients across staging categories

Characteristics of study populations are reported in *Table* 1. Of the 811 patients included in the analysis, 335 (41%) were in NAC I, 326 (40%) in NAC II and 150 (19%) in NAC III; whereas 167 (21%) were in Columbia I, 449 (55%) in Columbia II and 195 (24%) in Columbia III. Concordance between NAC and Columbia classes was 0.41 by Cohen's kappa, indicating fair-moderate agreement.

Of those in NAC I, 37 (11%) were grouped in NAC Ia and 298 (89%) in NAC Ib. Patients in NAC Ia were 5% of the overall cohort. Of these, 14 had a Columbia score of 1 (38%, 2% of overall cohort). Furthermore, five had known atrial fibrillation at the time of diagnosis or had an HFH prior to diagnosis. Accordingly, nine (24% of NAC Ia, 1% of overall cohort, *Figure* 1) patients had an ATTRwt early diagnosis. Seven of these patients were diagnosed in the incidental imaging pathway (six after an echocardiogram as part of a routine check-up and one after a bone scintigraphy due to oncologic reasons) and two in the incidental clinical pathway (referral to cardiological evaluation after carpal tunnel syndrome surgery). These nine patients had a median age of 65 [min–max 58–85] years, a median LVEF of 60% [min–max 35%–67%] and a median maximal wall thickness of 15 [min–max 11–18] mm. All the nine patients were alive at the time of analysis; one had an HFH during follow-up.

Table 1 Comparison of patients grouped according to NAC and Columbia score

	Overall study cohort	NAC I	NAC II	NAC III	*P* value	Columbia I	Columbia II	Columbia III	*P* value
n	811	335	326	150		167	449	195	
Age (years)	78 ± 7	76 ± 7	79 ± 7	82 ± 5	<**0.0001**	75 ± 8	78 ± 6	81 ± 6	<**0.0001**
Gender					0.43				**0.01**
Males	731 (90)	303 (90)	297 (91)	131 (87)		155 (93)	411 (92)	165 (85)	
Females	80 (10)	32 (10)	29 (9)	20 (13)		12 (7)	38 (8)	30 (15)	
Diagnostic pathways					<**0.0001**				<**0.0001**
HCM	59 (7)	29 (9)	22 (7)	8 (5)		15 (9)	35 (8)	9 (5)	
HF	409 (50)	125 (37)	191 (59)	93 (62)		28 (17)	241 (54)	140 (72)	
With HFH	*246 (60)*	*57 (46)*	*121 (63)*	*68 (73)*		*10 (36)*	*139 (58)*	*102 (73)*	
Incidental imaging	183 (23)	96 (29)	66 (20)	21 (14)		71 (42)	92 (20)	20 (10)	
Incidental clinical	160 (20)	85 (25)	47 (14)	28 (19)		53 (32)	81 (18)	26 (13)	
NYHA					<**0.0001**				<**0.0001**
I/II	575 (71)	275 (82)	217 (67)	83 (55)		167 (100)	334 (74)	74 (38)	
III/IV	236 (29)	60 (18)	109 (33)	67 (45)		0	115 (26)	121 (62)	
Arterial hypertension	592 (73)	232 (69)	238 (73)	122 (81)	**0.02**	114 (68)	332 (74)	146 (75)	0.29
Diabetes mellitus	136 (17)	53 (16)	53 (16)	30 (20)	0.50	16 (10)	83 (19)	37 (19)	**0.02**
CAD	165 (20)	60 (18)	60 (18)	45 (30)	**0.01**	29 (17)	88 (20)	48 (24)	0.20
GFR < 45 mL/min	215 (27)	0	65 (20)	150 (100)	<**0.0001**	5 (3)	88 (20)	122 (63)	<**0.0001**
COPD	115 (14)	35 (10)	55 (17)	25 (17)	**0.04**	13 (8)	65 (15)	39 (19)	**0.01**
Cancer					0.57				0.68
Previous	115 (14)	48 (14)	42 (13)	25 (17)		25 (15)	63 (14)	27 (14)	
Active	37 (5)	19 (6)	13 (4)	5 (3)		11 (7)	19 (4)	7 (4)	
BMI (kg/mq)	26 ± 4	27 ± 4	26 ± 3	26 ± 4	**0.01**	26 ± 4	26 ± 3	26 ± 4	0.58
Atrial fibrillation	502 (62)	182 (54)	218 (67)	102 (68)	**0.001**	73 (44)	297 (66)	132 (68)	<**0.0001**
LVEF (%)	51 ± 10	54 ± 9	50 ± 10	49 ± 11	<**0.0001**	56 ± 9	50 ± 10	48 ± 11	<**0.0001**
Maximal wall thickness (mm)	18 ± 3	18 ± 3	18 ± 3	18 ± 3	0.47	17 ± 3	18 ± 3	18 ± 3	0.28
Diuretic dose					<**0.0001**				<**0.0001**
0 mg/kg	219 (28)	153 (46)	54 (17)	12 (8)		151 (90)	68 (15)	0	
>0 to 0.5 mg/kg	285 (37)	119 (36)	124 (38)	42 (28)		16 (10)	255 (57)	14 (7)	
>0.5 to 1 mg/kg	181 (23)	45 (13)	93 (28)	43 (29)		0	113 (25)	68 (35)	
>1 mg/kg	96 (12)	18 (5)	55 (17)	53 (35)		0	13 (3)	113 (58)	
Tafamidis therapy	72 (9)	42 (13)	28 (9)	2 (1)	<**0.0001**	19 (11)	51 (11)	2 (1)	**0.001**
GFR (mL/min)	59 ± 20	71 ± 16	59 ± 17	35 ± 8	<**0.0001**	73 ± 17	61 ± 18	45 ± 16	<**0.0001**
NT-proBNP (pg/mL) [median, IQR]	3168 [1681–5603]	1505 [768–2244]	4485 [3289–6948]	6463 [4465–10 717]	<**0.0001**	1024 [563–1995]	3256 [1850–5227]	5627 [4008–9682]	<**0.0001**
BNP (pg/mL) [median, IQR]	433 [230–669]	110 [174–329]	592 [460–728]	775 [608–1033]	<**0.0001**	227 [155–303]	441 [272–672]	591 [489–954]	**0.001**

Note: Bolded values indicate significant *p*-values.

Figure 1 Proportion of early ATTRwt-CA diagnoses in the DIAMOND cohort. An 'early diagnosis' was defined as a NAC score Ia and a Columbia score of 1, in the absence of a history of HF hospitalizations or of atrial fibrillation prior to diagnosis. Early diagnoses accounted for only 1% of the population. Notably, NAC Ia accounted for 5% of the population.

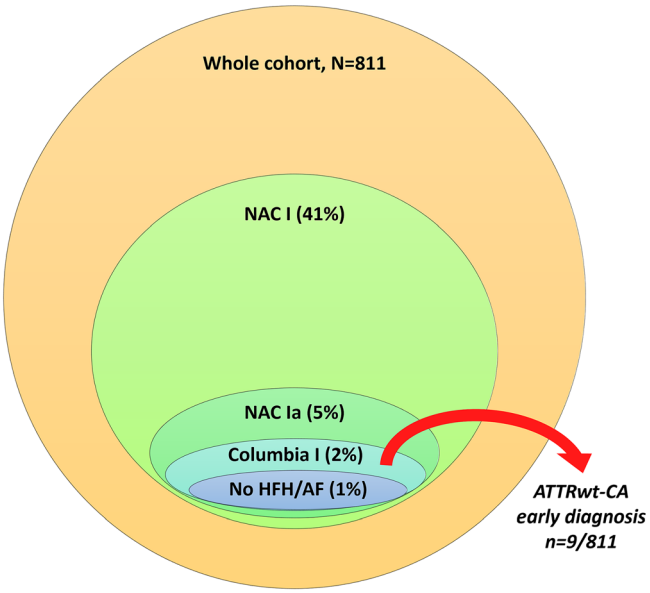


Table 2 Distribution of NYHA class, diuretic dose class and NAC and Columbia score classes across ATTRwt diagnostic pathways

	HCM	HF	Incidental imaging	Incidental clinical	*P* value
n	59	409	183	160	
NT-proBNP >3000 pg/mL	24 (41)	248 (61)	75 (41)	64 (40)	<**0.0001**
GFR < 45 mL/min	13 (22)	130 (32)	34 (19)	38 (24)	**0.01**
NYHA class					<**0.0001**
I	7 (12)	15 (4)	61 (33)	31 (19)	
II	42 (71)	215 (53)	101 (55)	103 (64)	
III	10 (17)	170 (41)	21 (12)	26 (16)	
IV	0	9 (2)	0	0	
Diuretic dose					<**0.0001**
0 mg/kg	18 (31)	62 (15)	77 (42)	62 (39)	
>0 to 0.5 mg/kg	22 (37)	142 (35)	65 (36)	56 (35)	
>0.5 to 1 mg/kg	13 (22)	115 (28)	24 (13)	29 (18)	
>1 mg/kg	6 (10)	90 (22)	17 (9)	13 (8)	
NAC score					<**0.0001**
I	29 (49)	125 (30)	96 (52)	85 (53)	
Ia	*5 (17)*	*9 (7)*	*15 (16)*	*8 (9)*	
II	22 (37)	191 (47)	66 (36)	47 (29)	
III	8 (14)	93 (23)	21 (12)	28 (18)	
Columbia score					<**0.0001**
I	15 (26)	28 (7)	71 (39)	53 (33)	
II	35 (59)	241 (59)	92 (50)	81 (51)	
III	9 (15)	140 (34)	20 (11)	25 (16)	

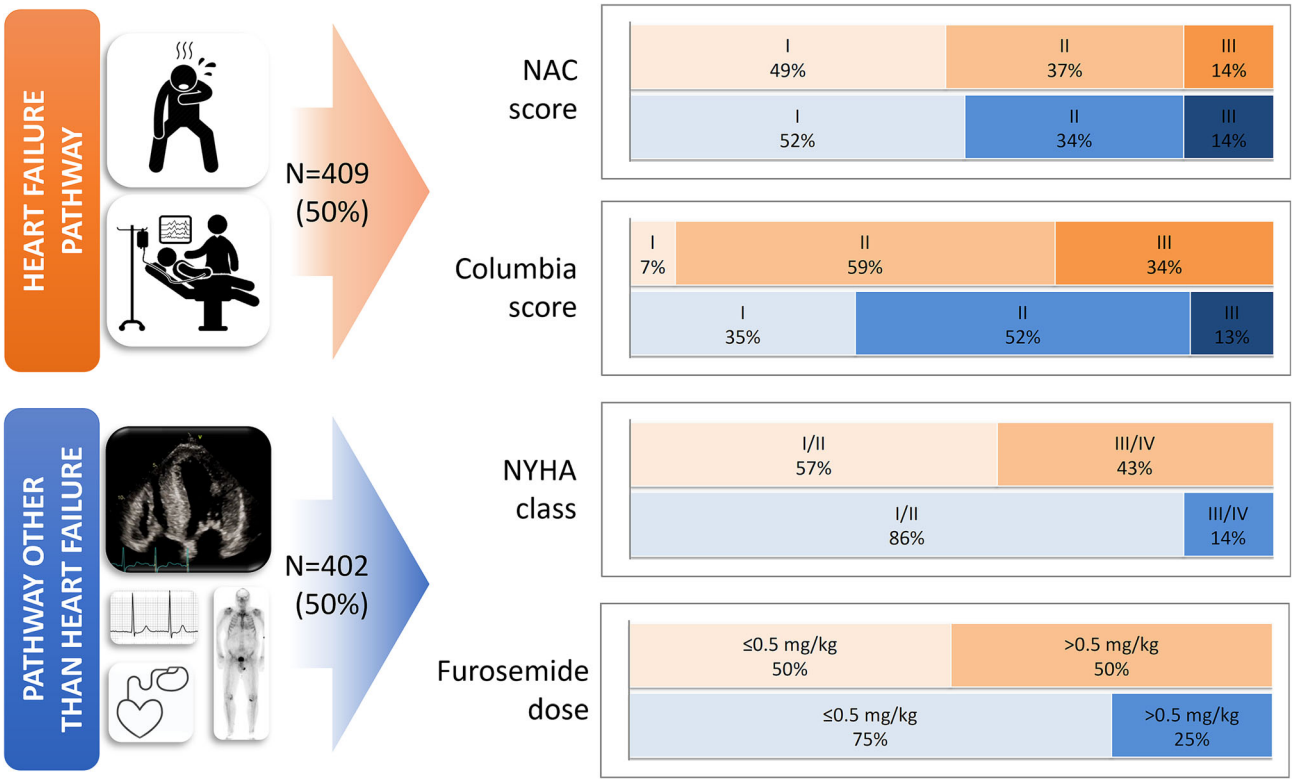
Note: Bolded values indicate significant *p*-values.

Characteristics of patients according to staging classes and diagnostic pathways

Age at diagnosis and prevalence of chronic obstructive pulmonary disease (COPD) and atrial fibrillation increased with greater NAC and Columbia classes, whereas LVEF significantly decreased (*Table* 1). A diagnosis in the HF pathway (in particular, during an HFH), NYHA class III/IV and higher diuretic dose were more common with greater NAC and Columbia classes. However, NYHA class III/IV was present in 18% of NAC I, 33% of NAC II and 45% of NAC III patients; all diuretic dose categories were found in all NAC classes.

Distribution of prognostic variables and of NAC and Columbia score classes was heterogeneous across diagnostic pathways (*Table* 2). The prevalence of NAC III and Columbia III was higher in the HF pathway, but all NAC and Columbia clas-

Figure 2 Distribution of prognostic variables in patients diagnosed in the heart failure pathway versus in patients diagnosed in other pathways.



ses were present in all diagnostic pathways. In all pathways, most patients were in NYHA class II, were treated with a diuretic dose up to 0.5 mg/kg and were in Columbia class II (*Figure* 2). In diagnostic pathways other than HF, 40% to 41% of patients had a NT-proBNP value >3000 pg/mL and 19% to 24% had a GFR < 45 mL/min (vs. 61% and 32%, respectively, in the HF pathway). Moreover, 12% to 17% of patients in diagnostic pathways other than HF had a NYHA III/IV at diagnosis, 12% to 18% had a NAC III and 11% to 16% a Columbia III.

All-cause mortality

At a median follow-up of 2.3 [1.4–3.7] years, 321 (40%) patients died. At univariate Cox regression analysis, NT-proBNP > 3000 pg/mL, GFR < 45 mL/min, NYHA functional class III–IV and diuretic dose, and both NAC and Columbia scores were significantly associated with all-cause mortality. NAC score yielded an AUC of 0.67, whereas Columbia score an AUC of 0.71 ($P = 0.16$). At multivariate Cox regression analysis, Columbia score remained significantly associated with all-cause mortality (Columbia II vs. I: HR 2.5 [1.5–4.4]; Columbia III vs. I: HR 3.8 [2.0–7.2], $P < 0.0001$), together with age at diagnosis, LVEF and maximal wall thickness (*Table* 3).

Univariate Cox regression analysis results remained valid when analysing patients from the HF pathway alone (197 deaths) and those from diagnostic pathways other than HF (124 deaths). NAC score yielded an AUC of 0.64 and Columbia score of 0.68 in the HF pathway; while NAC score yielded an AUC of 0.66 and Columbia score of 0.71 in pathways other than HF. At multivariate Cox regression analysis, Columbia score and age at diagnosis were significantly associated with all-cause mortality in the HF pathway; Columbia score, age at diagnosis and LVEF in pathways other than HF (Tables S3 and S4).

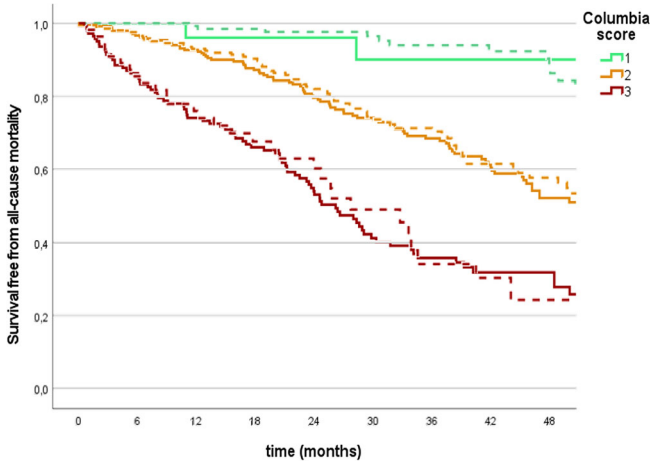
At Kaplan–Meier analysis, survival across the three Columbia classes was similar in patients in the HF pathway as compared with patients in pathways other than HF (HF pathway vs. other pathways in Columbia I, $P_{log} = 0.88$; HF pathway vs. other pathways in Columbia II, $P_{log} = 0.29$; HF pathway vs. other pathways in Columbia III, $P_{log} = 0.88$; *Figure* 3). When repeating the same analysis for the three NAC classes, survival was similar in HF pathway as compared with patients in pathways other than HF in NAC II and III (NAC II, $P_{log} = 0.32$, NAC III, $P_{log} = 0.19$), but not in NAC I, where HF pathway patients had the worst survival ($P_{log} = 0.001$).

Table 3 Cox regression analysis for all-cause mortality in the whole cohort

	Univariate		Multivariate	
Variable	HR	*P* value	HR	*P* value
NT-proBNP > 3000 pg/mL	2.7 [2.2–3.5]	<0.0001	-	-
GFR < 45 mL/min	2.9 [2.1–3.5]	<0.0001	-	-
NYHA functional class III–IV	2.4 [1.9–3.0]	<0.0001	-	-
Diuretic dose		<0.0001	-	-
0 mg/kg	-			
>0 to 0.5 mg/kg	2.2 [1.6–3.2]			
>0.5 to 1 mg/kg	2.8 [1.9–4.0]			
>1 mg/kg	4.8 [3.3–6.9]			
NAC score		<0.0001	-	-
II vs. I	2.5 [1.9–3.2]			
III vs. I	5.0 [3.7–6.7]			
Columbia score		<0.0001		**<0.0001**
II vs. I	4.1 [2.6–6.6]		2.5 [1.5–4.4]	
III vs. I	10.1 [6.2–16.5]		3.8 [2.0–7.2]	
Age at diagnosis, per 1 year	1.1 [1.0–1.1]	<0.0001	1.1 [1.0–1.1]	**<0.0001**
BMI, per 1 kg/mq	1.0 [0.9–1.0]	0.62	-	-
HF pathway, vs. others	1.8 [1.4–2.3]	<0.0001	0.9 [0.8–1.2]	0.76
Arterial hypertension	1.3 [1.0–1.6]	0.08	1.2 [0.9–1.5]	0.24
Diabetes mellitus	1.3 [1.0–1.7]	0.05	1.2 [0.9–1.6]	0.32
Coronary artery disease	1.3 [1.0–1.7]	0.03	1.1 [0.8–1.5]	0.45
COPD	1.5 [1.1–1.9]	0.01	1.3 [0.9–1.8]	0.10
Atrial fibrillation	1.2 [0.9–1.5]	0.22	-	-
LVEF, per 1%	1.0 [0.9–1.0]	<0.0001	1.0 [0.9–1.0]	**0.03**
Maximal wall thickness, per 1 mm	1.0 [1.0–1.1]	0.19	1.0 [1.0–1.1]	**0.05**

Note. Bolded values indicate significant *p*-values.

Figure 3 Kaplan–Meier curves for survival free from all-cause mortality according to Columbia classes in patients diagnosed in the heart failure pathway and in those diagnosed in other pathways. Solid lines represent heart failure pathway; dashed lines represent pathways other than heart failure. No statistical difference was observed between diagnostic pathways in each Columbia class: P_{log} for Columbia I: 0.88, II: 0.29, III: 0.88.



Discussion

The main findings of our study are (i) the distribution of NAC and Columbia prognostic scores is puzzled among ATTRwt-CA patients diagnosed through different pathways, and these scores determine classes of patients with heterogeneous characteristics; (ii) an ATTRwt-CA early diagnosis is very rare; (iii) prognostic variables are reliable independently from the diagnostic pathway, but outcome remains significantly influenced by other clinical features, and primarily by age at diagnosis.

In this analysis from the DIAMOND cohort, both NAC and Columbia scores captured ATTRwt-CA disease stage in an ad-

equate, but still rough, way. Within NAC score classes, there was an evident heterogeneity in terms of NYHA class. In NAC I, 18% of patients was in NYHA III/IV and 18% was treated with >0.5 mg/kg of diuretic dose. Vice versa, in NAC III, 55% was in NYHA I/II. This heterogeneity is in line with the population from which the original NAC score was drawn: 15% of the original cohort patients with NAC I had a NYHA III/IV, even those in NAC Ia.[7] Heterogeneity was less marked when using Columbia score, mainly and simply because it incorporates extra variables on top of NAC score. However, some heterogeneity was still present: in Columbia III, 38% of patients were in NYHA I/II. A significant overlap of NT-proBNP values with NYHA I to III is known to exist in HF patients,[15] meaning that both objective and subjective measures need to be evaluated to comprehensively capture disease severity, in ATTRwt-CA as in other HF aetiologies.

As described in the original DIAMOND study, diagnostic pathways also offer useful information to describe ATTRwt-CA disease severity. Patients diagnosed in the HF pathway had indeed a more advance disease, as all adverse prognostic features were more common in this pathway (*Table* 2, *Figure* 2). However, we report a significant heterogeneity also in this context. In diagnostic pathways other than HF, which also included patients diagnosed 'incidentally', about one fifth of patients was in NYHA III/IV and one fourth was treated with >0.5 mg/kg of diuretic dose, resulting in 13% of patients being in Columbia III.

Consequently, an ATTRwt-CA early diagnosis was very rare in our cohort. The definition we chose for ATTRwt-CA 'early diagnosis' was on purpose more restrictive than that of NAC Ia, as these patients still exhibit a significant disease progression in the short term.[7] Therefore, we considered as having an early diagnosis those patients not only classified in NAC Ia, but also having NYHA I, not using diuretics, and without previous relevant cardiovascular events. With these criteria, only 1% of the whole cohort had an early diagnosis. Notably, this corresponded to one fourth of NAC Ia patients, again underlining the heterogeneity of clinical features within NAC score classes. Such a very low prevalence of early diagnosis deserves careful consideration, as diverse initiatives are exploring screening strategies for CA, and specifically TTR-related CA, in different scenarios.[16–22] Given the variable yield of these strategies,[23] their cost-effectiveness,[24] and the fact that in a substantial number of cases the unravelled diagnosis is likely not done in an early setting, it may be worth evaluating whether these screening approaches are clinically relevant or effectively represent the best strategies to intercept patients in a therapeutically actionable stage of their disease. Further highlighting discrepancies between increased awareness and timely recognition of the disease, it is worth noting that even in the National Amyloid Centre of London cohort, a NAC II or III class was found in 42% of patients diagnosed in most recent years (i.e., after 2016).[9] Moreover, recent data from the THAOS registry revealed that in recent years diagnostic delay in ATTRwt-CA remained of about 2 years and did not decrease over time.[3]

Finally, we confirmed the prognostic significance in terms of all-cause mortality of the variables identified in NAC and Columbia centres, and, therefore, of the two scoring systems. When first published in 2017, NAC score, drawn from an English cohort of 869 ATTRwt-CA and variant TTR-related CA (ATTRv-CA) patients, was validated in a France cohort of 318 patients.[5] Prognostic value of the NAC score was confirmed in further studies from the London centre.[25,26] Columbia score was proposed in 2020 and drawn from a population of 309 ATTRwt and ATTRv-CA patients and showed to predict all-cause mortality and heart transplantation with a better performance than that of NAC and other scoring systems.[6] Its association with mortality and heart transplantation was recently confirmed in a further analysis from the New York centre including 419 patients.[27] In our Italian nationwide cohort, both scores resulted significantly associated with all-cause mortality, with Columbia score performance appearing slightly better than that of NAC score. The significant association of prognostic variables and of scoring systems with all-cause mortality was further confirmed when analysing patients from the HF pathway and from other pathways separately. In particular, for the same Columbia score class, survival was similar irrespectively of the diagnostic pathway (*Figure* 3). Similarly to what described in the original DIAMOND cohort, it was the clinical status at diagnosis, rather than the scenario where diagnosis was made, that influenced prognosis.[4] Moreover, in the whole cohort, and also when evaluating the two diagnostic pathway subgroups, demographic (age at diagnosis) and echocardiographic (in particular LVEF) features were significantly associated with all-cause mortality, independently from Columbia score. Notably, in the original NAC cohort, age and LVEF appeared significantly associated with mortality, and the score's hazard ratios were adjusted for age,[5] but some additional independent effect of these variables likely remains. In conclusion, our results highlight the importance of a multiparametric evaluation of ATTRwt-CA patients, rather than a prognostication based on a single parameter or a single score.

The present study has limitations that should be acknowledged. This was a secondary analysis of the DIAMOND study; all 17 participating centres were asked to update information of patients included in the first database. As a result, not all patients initially enrolled had available data to calculate NAC and Columbia scores (63% of the original cohort), as it may happen when dealing with real-world populations. Nevertheless, we did not find significant clinical differences between patients included and excluded from the present analysis. Furthermore, as BNP, but not NT-proBNP, was available for all patients, we calculated the latter with a previously reported factor of conversion.[13] Finally, we acknowledge that other variables, not available for this study (i.e., echocardiographic parameters other than LVEF and maximal wall thick-

ness, such as right ventricular function or LV longitudinal strain analysis), may have prognostic value.

Conclusions

In this contemporary nationwide cohort, an ATTRwt-CA early diagnosis was very rare. Disease staging with NAC and Columbia scoring systems determined classes of patients with heterogenous features. As a result, both scores had a significant association with all-cause mortality, but other variables also had prognostic significance.

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Conflict of interest

No conflicts of interest to declare for any author in relation to the submitted work.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of patients with versus without available data to calculate NAC score.
Table S2. Comparison of patients from the HCM, incidental imaging and incidental clinical pathways.
Table S3. Cox regression analysis for all-cause mortality in the HF pathway.
Table S4. Cox regression analysis for all-cause mortality in pathways other than HF.

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