ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 751–760
Published online 9 November 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13606

ORIGINAL ARTICLE

Prognostic significance of unexplained left ventricular hypertrophy in patients undergoing carpal tunnel surgery

Aldostefano Porcari[1], Linda Pagura[1], Francesca Longo[1], Enrico Sfriso[1], Giulia Barbati[2], Luigi Murena[3], Emiliano Longo[3], Vittorio Ramella[4], Zoran Marij Arnež[4], Claudio Rapezzi[5,6], Marco Merlo[1]* and Gianfranco Sinagra[1]

[1]*Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Via P. Valdoni 7, Trieste, 34100, Italy;* [2]*Department of Medical Sciences, Biostatistics Unit, University of Trieste, Trieste, Italy;* [3]*Orthopaedics and Traumatology Unit, Cattinara Hospital- Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy;* [4]*Plastic and Reconstructive Surgery Unit, Cattinara Hospital- Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy;* [5]*Cardiothoracic Department, University of Ferrara, Ferrara, Italy and* [6]*Maria Cecilia Hospital, GVM Care & Research, Cotignola, Ravenna, Italy*

Abstract

Aims Carpal tunnel (CT) syndrome is a recognized red-flag of cardiac amyloidosis (CA) and increased cardiovascular (CV) morbidity. We designed this study to characterize the CV profile of patients with CT syndrome at the time of first surgery and to identify high-risk presentations.

Methods and results We retrospectively reviewed 643 patients who underwent CT surgery between 2007 and 2019. Of them, 130 patients (77 years, 45% male patients, left ventricular ejection fraction 62%) with available CV characterization within ±12 months from CT surgery were included. Abnormal loading conditions causing cardiac left ventricular hypertrophy (LVH) were investigated to distinguish explained LVH (Ex-LVH) from unexplained LVH (Un-LVH). LVH was found in 66 (51%) patients, 33% of them presented Un-LVH. Compared with the others, Un-LVH patients were older (77 and 75 vs. 70 years in Un-LVH, Ex-LVH, and non-LVH, respectively; $P = 0.002$), had higher rates of electrocardiogram-echo discrepancy (70%, 14.3%, and 1.6%, respectively; $P < 0.001$) and of echocardiographic findings of CA (24%, 7%, and 0%, $P < 0.001$). Among Un-LVH patients, 9 (43%) experienced death and 7 (33%) developed heart failure (HF) at 3.8 and 2.4 years from CT surgery, respectively. Compared with the others, death and HF development rates were higher in Un-LVH patients both at unadjusted ($P = 0.01$ and $P = 0.02$, respectively) and adjusted analysis for age, gender, and renal insufficiency ($P = 0.00038$ and $P = 0.050$, respectively).

Conclusions At the time of CT surgery, Un-LVH was found in more than 30% of patients with LVH, and 24% of them showed echocardiographic features suggesting an underdiagnosed CA. Un-LVH was associated with higher all-cause mortality and HF development.

Keywords Carpal tunnel syndrome; Unexplained cardiac hypertrophy; Cardiac amyloidosis; Diagnosis; Prognosis; Epidemiology

Received: 7 April 2021; Revised: 8 June 2021; Accepted: 25 August 2021
**Correspondence to: Marco Merlo, Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Via P. Valdoni 7, 34100 Trieste, Italy. Phone: +39-040-3994477; Fax: +39-040-3994878. Email: marco.merlo79@gmail.com*
[Correction added on 24 November 2021, after first online publication: Second affiliation to Claudio Rapezzi has been added in this version.]

Introduction

Carpal tunnel (CT) syndrome has been recently proposed as an early disease marker for future development of heart failure (HF) and other adverse cardiovascular (CV) outcomes, including cardiac amyloidosis (CA).[1] The strong association between CT syndrome and CA has been extensively reported, particularly in transthyretin amyloidosis (ATTR).[2–7] Therefore, in clinical practice, CT syndrome represents a recognized 'red-flag' orienting towards the suspicion of CA in the

evaluation of patients with left ventricular hypertrophy (LVH) at echocardiography.[3,8] However, only very few studies addressed this issue prospectively, namely, from the diagnosis of CT syndrome or CT surgery.[1,9] Of note, no study investigated the echocardiographic characteristics of patients at the time of CT surgery, profiling those at higher risk of CV events. This information would be of great importance to provide a reference to all medical figures involved in the management of patients with CT syndrome and ensure an adequate multidisciplinary follow-up.

Therefore, we carried out an analysis to investigate specific clinical and echocardiographic phenotypes of patients recently operated for CT syndrome and their possible association with major CV events during the follow-up.

Methods

Study design and study population

This is a retrospective observational study. Data from consecutive patients who underwent CT surgery between 1 January 2007 and 31 March 2019 at University Hospital of Trieste were extracted from an electronical database and retrospectively analysed. Patients with an available cardiologic assessment, defined as the presence of (i) clinical examination, (ii) electrocardiogram (ECG), and (iii) echocardiography performed within ±12 months from the first CT surgery, were included in the study population. Patients with post-traumatic CT syndrome and known amyloidosis at the time of surgery were excluded. Bilateral CT release was defined as right-hand and left-hand surgery performed within 6 months from each other. Patients' baseline was set at the first surgical procedure for CT syndrome. The study was conducted according to the Declaration of Helsinki and received institutional review board approval (identifier 43_2009). Informed consent was obtained under the institutional review board policies of the hospital administration.

Left ventricular hypertrophy: echocardiographic characterization

Echocardiographic images stored on our electronic database were systematically reviewed offline for this specific study by three authors (A.P., M.M., and L.P.), blinded to the outcome of patients. All parameters were collected according to standard international definitions.[10] A gender-tailored cut off was adopted to define LVH: ≥1.2 cm in women and ≥1.3 cm in men.[11] Among LVH group, abnormal secondary conditions known to cause cardiac hypertrophy were investigated (i.e. arterial hypertension and aortic valve stenosis [AS]) in order to distinguish between explained (Ex-LVH) and unexplained LVH (Un-LVH). No patient received a detailed diagnosis of hypertrophic cardiomyopathy or other phenocopies at the time of baseline echocardiography. In detail, arterial hypertension at the time of CT surgery was defined as a blood pressure > 140/90 mmHg certified in multiple measurements in the absence of specific therapy or the need of ≥2 antihypertensive drugs for a minimum of 2 years. Mild and moderate AS were considered as a cause of Ex-LVH in presence of left ventricular (LV) wall thickness of 1.3–1.5 cm, while severe AS was considered as a cause of Ex-LVH in presence of LV wall thickness ≥ 1.6 cm. Un-LVH was defined as either LVH without coexisting known causes of hypertrophy or LVH disproportioned to the degree of arterial hypertension or AS (LV wall thickness ≥ 1.6 cm).[12,13]

Echocardiography was considered suggestive of CA in presence of: (i) LVH with normal LV end-diastolic volume and LV ejection fraction ≥ 50% and (ii) at least one additional criterion including grade 2 or worse LV diastolic dysfunction, granular sparkling appearance of the myocardial wall, pericardial effusion of any entity, atrioventricular valve, or interatrial septal thickening (>0.5 cm).[14,15] Although official indications are lacking, there is a general consensus that these echocardiographic findings can suggest the presence of CA in hypertrophic hearts.

The presence of QRS voltages on ECG not consistent with LV thickness at echocardiography was systematically assessed.[16,17] The indexed LV mass–ECG voltage ratio was defined as LV mass measured by the Devereux formula indexed to body surface area divided by the ECG voltage measured as the sum in millivolt of the S-wave in V1 + the tallest R-wave in V5 or V6.[16] Of note, this parameter was not measured in patients with ventricular pacemaker (PM) and left or right complete bundle branch block.

Outcomes

The primary outcome of the study was all-cause mortality. The secondary outcome measures were the occurrence of (i) new-onset HF or worsening HF requiring hospitalization (HHF) or (ii) PM implantation. New-onset HF was defined as the development of HF signs and symptoms requiring an unplanned cardiologic examination or hospitalization. The end of follow-up was set at 31 December 2019. The events were collected from the dedicated CV software of our hospital and, if needed, from patients' general practitioners and/or telephone contacts with patients and their relatives. CV events were independently assessed by three cardiologists (A.P., M.M., and L.P.).

Statistical analysis

Descriptive statistics between the study groups were calculated. Continuous variables were expressed as median

with interquartile range (IQR) [25°; 75°] as data were not normally distributed according to the results of Kolmogorov–Smirnov test; categorical variables were expressed as absolute numbers and percentages. Differences between groups were evaluated using Mann–Whitney test and Kruskal–Wallis test (when comparing more than two groups simultaneously) for continuous variables, while χ^2 or Fisher's exact test was used for dichotomous variables.

The Kaplan–Meier method was used to estimate the global survival and the composite endpoint curve, and the log rank test was used to compare the curves. In case of secondary endpoints, since the presence of competing risks, cumulative incidence curves were estimated and compared using the appropriate methods.[18] Furthermore, Un-LVH patients were matched for age, gender, and renal insufficiency in a 1:3 ratio with Ex-LVH and non-LVH patients. For each Un-LVH patient, three controls from the Ex-LVH and non-LVH group were matched, creating 126 distinct pairs (63 patients for each group). Note that the same patient from the Ex-LVH and non-LVH group could be matched to different Un-LVH patients. The matching algorithm used is based on a propensity score estimated using logistic regression with covariates age, gender, and renal insufficiency.[19] For matched data, differences between cumulative incidence curves were appropriately evaluated considering matched pairs as a cluster factor.[20] We defined a two-sided P value < 0.05 as statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24.0 package (New York, NY) statistical software version 20, Prism 7 and R (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/), packages 'Matching', 'cmprsk', and 'crrSC'.

Results

Study populations: baseline characteristics and echocardiographic findings

Among the 643 CT release procedures performed in the study period, 130 subjects having a scheduled cardiological evaluation including reviewable ECG and echocardiography were included and represented the study population. Cardiological data were collected at a median time of 3 months (IQR −2, 7) from CT surgery, as shown in *Figure 1*, Phase 1. Baseline characteristics of the study population are summarized in *Table 1*. Median age at CT surgery was 73 years (IQR 67–80). Most procedures were unilateral (n = 122, 94%) and 29 patients (22%) underwent at least two procedures by the end of the study. Arterial hypertension, chronic HF, and previous myocardial infarction were found in 80%, 30%, and 13% of patients, respectively.

At echocardiographic evaluation, half of the population (n = 66, 49%) had LVH, one-third of them presented Un-LVH (n = 21, 33%; 16% of the study population). Compared with the others, Un-LVH patients were older (77 and 75 vs. 70 years in Un-LVH, Ex-LVH, and non-LVH, respectively; global P = 0.002) and had higher rates of estimated glomerular filtration rate $<$ 60 mL/min (52% and 39% vs. 18% in Un-LVH, Ex-LVH, and non-LVH, respectively; global P = 0.003), as shown in *Table 1*. Of note, Un-LVH patients had lower systolic values compared both with Ex-LVH and non-LVH patients (125 vs. 142 and 134 mmHg, in Un-LVH, Ex-LVH, and non-LVH respectively; global P = 0.015), thicker LV walls (16 vs. 13 and 10 mm, in Un-LVH, Ex-LVH, and non-LVH, respectively; global $P <$ 0,001), higher rates of ECG-echo discrepancy (70% vs.

Figure 1 Flow-chart of the study population: inclusion criteria (Phase 1) and in-depth analysis in the echocardiographic phenotype (Phase 2). CMP, cardiomyopathies; LVH, left ventricular hypertrophy.

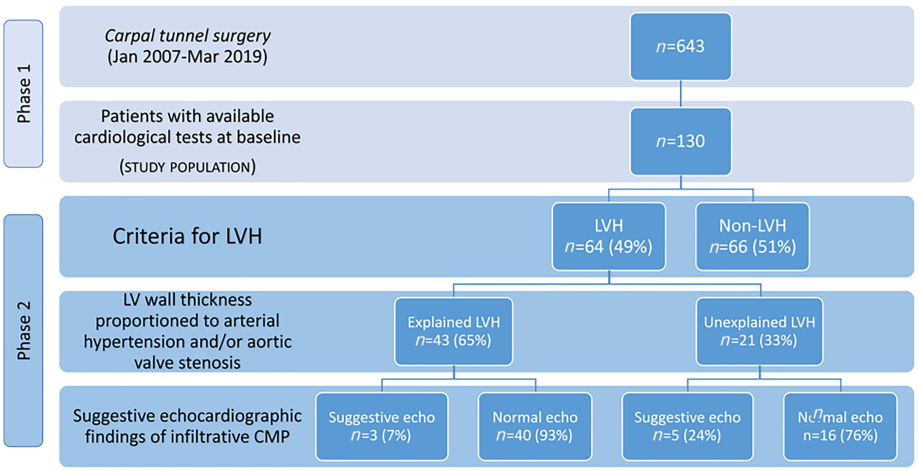

Table 1 Baseline characteristics of the study population

	All (n = 130)	Non-LVH (n = 66)	Explained LVH (n = 43)	Unexplained LVH (n = 21)	P value
Age	73 (67–80)	70 (62–80)*°	75 (72–80)	77 (71–83)	**0.002**
Sex (M)	59 (45.4%)	31 (47.0%)	17 (37.8%)	11 (52.3%)	0.605
BMI	27 (24–30)	27 ± 6	28 ± 4	26 ± 3	0.251
Bilateral CTS at first procedure	8 (6.2%)	4 (6.3%)	1 (2.3%)	3 (16.7%)	0.152
SBP (mmHg)	140 (120–150)	134 ± 20	142 ± 23	125 ± 21 ^	**0.015**
Arterial hypertension	104 (80%)	48 (72.7%)*°	42 (97.7%)	14 (66.7%) ^	<**0.001**
Need for downtitration/discontinuation of antihypertensive drugs	10 (7.8%)	2 (3.2%)*	5 (11.6%)	3 (16.7%)	0.077
Diabetes mellitus	40 (30.8%)	21 (31.8%)	12 (27.9%)	7 (33.3%)	0.902
CKD (eGFR < 60 mL/min)	38 (30.4%)	11 (17.5%)*°	16 (39.0%)	11 (52.4%)	**0.003**
Chronic heart failure	22 (16.9%)	7 (10.6%)	10 (23.3%)	5 (23.8%)	0.132
Atrial fibrillation	31 (23.8%)	11 (16.7%)	13 (30.2%)	7 (33.3%)	0.135
Ischaemic heart disease	38 (29.2%)	17 (25.8%)	13 (30.2%)	8 (38.1%)	0.494
Myeloproliferative disorders (MGUS included)	5 (3.8%)	0 (0.0%)*°	3 (7.0%)	2 (9.5%)	**0.028**
Therapy (n = 128)					
Beta blocker	60 (46.8%)	28 (43.1%)	22 (52.4%)	10 (47.6%)	0.641
RAASi	76 (59.4%)	37 (56.9%)	28 (66.7%)	11 (52.4%)	0.496
Calcium channel blocker	23 (18%)	15 (23.1%)	6 (14.3%)	2 (9.5%)	0.313
Diuretic agents	20 (15.7%)	8 (12.3%)	11 (26.8%)	1 (4.8%) ^	0.052
ECG					
Sinus rhythm	113 (87.6%)	61 (92.4%)	35 (81.4%)	17 (85%)	0.230
1st degree AV block	12 (9.8%)	8 (12.7%)	3 (7.5%)	1 (5.3%)	0.646
Low voltage QRS	14 (10.9%)	9 (13.6%)	4 (9.3%)	1 (5.0%)	0.591
ECG vs echo discrepancy for LVH	21 (16%)	1 (1.6%)*°	6 (14.3%)	14 (70.0%) ^	<**0.001**
Indexed LV mass– ECG voltage ratio	55 (40–70)	50 (34–61)	54 (42–72)	69 (62–110) ^	**0.001**
QRS > 120 ms	23 (17.8%)	9 (13.6%)	8 (18.6%)	6 (30.0%)	0.239
Q waves	8 (6.4%)	3 (4.5%)	2 (4.8%)	3 (17.6%)	0.127
Negative T waves	22 (17.1%)	9 (13.6%)	8 (18.6%)	5 (25.0%)	0.431
QTc > 440 ms	18 (13.8%)	6 (9.2%)*	6 (15.8%)	6 (33.3%)	**0.040**
Echocardiogram					
IVS (mm)	12 (10–14)	10 (9–11)*°	13 (13–14)	16 (14–17)	<**0.001**
PW (mm)	10 (9–11)	10 (9–11)*°	11 (9–12)	11 (10–14) ^	**0.002**
LVEDV (mL)	82 (65–107)	86 (69–111)°	74 (57–93)	95 (75–111) ^	0.064
LVESV (mL)	31 (22–42)	31 (25–39)	25 (19–40)	34 (28–48) ^	**0.050**
LVEF (%)	62 (57–68)	62 (56–66)	62 (56–72)	60 (51–65)	0.342
Restrictive diastolic pattern	5 (4%)	1 (1.6%)	3 (7.3%)	1 (5.3%)	0.295
E/E'	11 (8–14)	10 (8–13)	12 (9–14)	13 (9–21)	0.080
RVH	5 (4%)	0 (0.0%)*	2 (6.3%)	3 (17.6%)	**0.007**
RV dysfunction	5 (4%)	2 (3.1%)	1 (2.4%)	2 (10.0%)	0.361
LAESA (cm^2)	22 (18–27)	21 (17–25)	23 (19–28)	27 (19–30)	0.287
Pulmonary hypertension (estimated at echo)	20 (15%)	8 (17.8%)*	4 (18.2%)	8 (47.1%)	0.055
Valvular thickening	16 (12%)	3 (5.7%)*°	7 (20.0%)	6 (30.0%)	**0.013**
Mitral regurgitation ≥ moderate	5 (4%)	2 (3.0%)	2 (4.7%)	1 (4.8%)	0.711
Aortic stenosis ≥ moderate	8 (6%)	2 (3.0%)	4 (9.3%)	2 (9.5%)	0.277
Granular sparkling	2 (1.5%)	0 (0.0%)	1 (3.6%)	1 (7.1%)	0.272
Pericardial effusion	5 (4%)	1 (1.6%)*	1 (2.4%)	3 (15.8%) ^	**0.047**
IA septum thickening	11 (8%)	4 (10.8%)	4 (16.7%)	3 (23.1%)	0.461
Suggestive echo for amyloidosis	8 (6%)	0 (0.0%)*°	3 (7.0%)	5 (24.0%) ^	<**0.001**

AV, atrioventricular; BMI, body mass index; CKD, chronic kidney disease; CTS, carpal tunnel surgery; ECG, electrocardiogram; IA, inter atrial; IVS, interventricular septum; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH; LV hypertrophy; MGUS, monoclonal gammopathy of uncertain significance; PW, posterior wall; RAASi, renin–angiotensin–aldosterone system inhibitors; RVH, RV hypertrophy; RV, right ventricular; SBP, systolic blood pressure.
Values are expressed as medians and first to third quartile, or counts and percentages, as appropriate.
*$P < 0.05$ between non-LVH and Un-LVH.
°$P < 0.05$ between non-LVH and Ex-LVH.
^$P < 0.05$ between Un-LVH and Ex-LVH.

14.3% and 1.6%, in Un-LVH, Ex-LVH, and non-LVH, respectively; $P < 0.001$), and higher indexed LV mass–ECG voltage ratio (50 vs. 54 and 69 g/m^2/mV, in Un-LVH, Ex-LVH, and non-LVH, respectively; P = 0.001). Interestingly, the prevalence of echocardiographic findings suggestive of CA was higher in presence of Un-LVH than Ex-LVH and non-LVH (24% vs. 7% vs. 0%, in Un-LVH, Ex-LVH, and non-LVH, respectively; global $P < 0.001$) (*Figure 1*, Phase 2).

Unexplained left ventricular hypertrophy: outcomes

During a median follow-up of 63 months (IQR 30–95), patients with Un-LVH experienced higher all-cause mortality rates compared with Ex-LVH and non-LVH patients (n = 10, 48% vs. n = 7, 23% vs. n = 10, 15% in Un-LVH, Ex-LVH, and non-LVH, respectively; P = 0.01). Moreover, Un-LVH was associated with higher risk of developing new-onset HF/HHF (n = 7, 33% vs. n = 9, 20.8% vs. n = 6, 9% in Un-LVH, Ex-LVH, and non-LVH, respectively; P = 0.02). After matching for age, gender, and renal insufficiency (*Table 2*), the presence of Un-LVH remained significantly associated with increased all-cause mortality (P = 0.00038) and with an increased cumulative incidence of new-onset HF/HHF (P = 0.050). Notably, the separation of the adjusted curves occurred after 36 months from first CT surgery for both the outcome measures (*Figure 2*).

Table 3 shows the incidence of considered events in the three subgroups (i.e. non-LVH, Ex-LVH, and Un-LVH). Of note, Un-LVH at the time of CT surgery was associated to an incidence of overall mortality and development of new onset HF/HHF of 8.15/100 and 6.35/100 persons/years, respectively. Death and new-onset HF/HHF occurred at a mean time of 45 and 29 months from CT surgery, respectively.

Three patients received a new diagnosis of CA at a median time of 46 months (IQR 31–66) from the first CT surgery, with a cumulative incidence of 0.44 cases/100 patients/year by the whole follow-up. Importantly, not all Un-LVH patients were tested for CA, resulting in underestimation of the real CA prevalence among CT syndromes. Only one patient had history of chronic HF at the time of CT surgery, while the other two developed new-onset HF after 3 to 4 years from CT surgery. At baseline, two patients had Un-LVH with suggestive echocardiography of CA, and one patient had Ex-LVH. CA accounted for 11% (1/9 events) of all deaths, for 29% (2/7 events) of new-onset HF/HHF and for 100% (1/1 event) of PM implantations observed in Un-LVH group. Of note, no other diagnosis clarifying the cause underlying Un-LVH has been made during follow-up.

Discussion

Cardiologists and other physicians have long ignored the role of CT syndrome in CV disease. Recent advances in knowledge[1,7,9] strongly support the hypothesis that most cases of 'idiopathic' CT syndromes are attributable to early signs of amyloidosis and recognize in the progressive cardiac

Table 2 Characteristics of the matched population: Un-LVH vs. other patients

	Unexplained LVH (n = 63)	Non-LVH + Explained LVH (n = 63)	P value
Age	77 (72–82)	75 (70–82)	0.425
Sex (M)	33 (52.4%)	30 (47.6%)	0.593
BMI	26 ± 3	28 ± 5	0.110
Bilateral CTS at first procedure	9 (14.3%)	3 (4.8%)	0.056
Arterial hypertension	42 (66.7%)	59 (93.7%)	<**0.001**
Need for downtitration/discontinuation of antihypertensive drugs	9 (14.3%)	8 (12.7%)	0.568
Diabetes mellitus	21 (33.3%)	28 (44.%)	0.201
CKD (eGFR < 60 mL/min)	33 (52.4%)	33 (52.4%)	0.97
Chronic heart failure	15 (23.8%)	19 (19%)	0.515
Atrial fibrillation	21 (33.3%)	17 (27%)	0.437
Ischaemic heart disease	24 (38.1%)	23 (36.5%)	0.854
Myeloproliferative disorders (MGUS included)	6 (9.5%)	4 (6.3%)	0.510
Therapy			
Beta blocker	30 (47.6%)	37 (58.7%)	0.211
RAASi	33 (52.4%)	37 (58.7%)	0.473
Calcium channel blocker	6 (9.5%)	13 (20.6%)	0.081
ECG			
Sinus rhythm	51 (81%)	54 (85.7%)	0.911
QRS > 120 ms	18 (28.6%)	12 (19%)	0.157
Echocardiogram			
LVEF (%)	60 (56–65)	60 (52–67)	0.868
Restrictive diastolic pattern	3 (4.8%)	7 (11.1%)	0.226
RV dysfunction	6 (9.7%)	4(6.3%)	0.459
Mitral regurgitation ≥ moderate	3 (4.8%)	3 (4.8%)	1.000
Aortic stenosis ≥ moderate	6 (9.5%)	7 (11.1%)	0.770

AV, atrioventricular; BMI, body mass index; CKD, chronic kidney disease; CTS, carpal tunnel surgery; ECG, electrocardiogram; IA, inter atrial; IVS, interventricular septum; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH; LV hypertrophy; MGUS, monoclonal gammopathy of uncertain significance; PW, posterior wall; RAASi, renin–angiotensin–aldosterone system inhibitors; RVH, RV hypertrophy; RV, right ventricular; SBP, systolic blood pressure.
Values are expressed as medians and first to third quartile, or counts and percentages, as appropriate.

Figure 2 Overall survival (A) and cumulative incidence of new onset HF and HHF (B) among patients with Un-LVH, Ex-LVH, and non-LVH (unmatched population); overall survival (C) and cumulative incidence of new onset HF and HHF (D) in Un-LVH vs. other patients after matching for age, gender, and renal insufficiency. CKD, chronic kidney disease; Ex, explained; HF, heart failure; HHF, hospitalization for HF; Un, unexplained; LVH, left ventricular hypertrophy. Un-LVH patients were matched in a 1:3 ratio with Ex-LVH and non-LVH patients using a matching algorithm based on a propensity score estimated using logistic regression with covariates age, gender, and renal insufficiency.

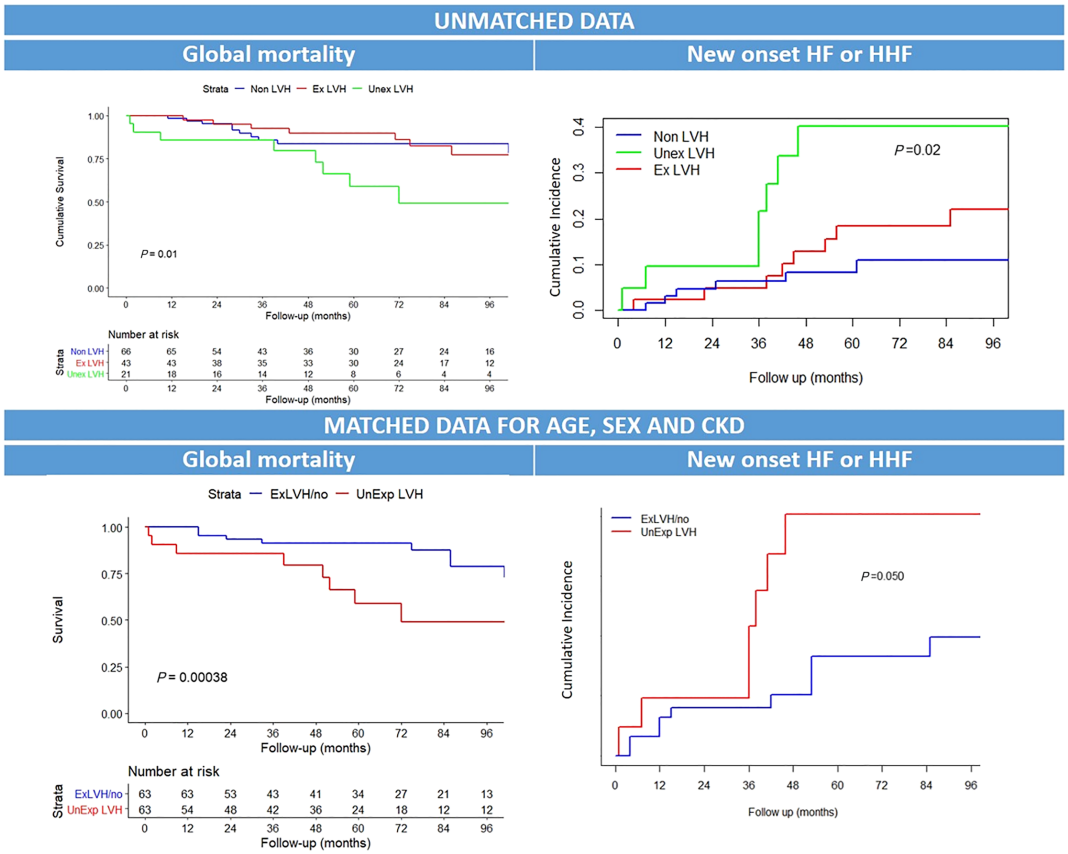

Table 3 Cumulative incidence of primary and secondary outcomes in Un-LVH vs. Ex-LVH and non-LVH

	Un-LVH (n = 21)		Ex-LVH + non-LVH (n = 109)	
	Events	IR (100 p/yrs)	Events	IR (100 p/yrs)
All-cause mortality	9 (43%)	8.15	17 (16%)	3.00
New onset HF/HHF	7 (33%)	6.35	15 (14%)	2.60
PM implantation	1 (5%)	0.90	5 (5%)	0.87

Ex, Explained; HF, heart failure; HHF, hospitalization for heart failure, IR, incidence rate; LVH, left ventricular hypertrophy; PM, pacemaker; p/yrs, patients/years; Un, unexplained.
IR was measured as [(no. of events/no. of patients)*100]/median follow-up (years).

accumulation of amyloid the biological link with the increased CV morbidity. Nevertheless, a detailed cardiological characterization of patients at the time of CT surgery has never been reported so far.

This information would be of utmost importance to identify specific profiles of patients at higher risk of CV events at time of CT surgery, deserving tailored diagnostic and follow-up strategies.

To the best of our knowledge, this is the first study to provide this information. The main findings here reported are (i) Un-LVH was found in 16% of patients with CT syndrome and available cardiologic evaluation at the time of surgery and in 33% of those presenting with LVH; (ii) 24% of Un-LVH patients presented findings compatible with CA already at the time of CT surgery; and (iii) Un-LVH was associated with a mid-term (i.e. 2 to 5 years, on average) increased risk of

all-cause death and greater incidence of new-onset HF/HHF compared with Ex-LVH and non-LVH. Of note, CA was subsequently diagnosed in 10% of Un-LVH patients and accounted for 11% of all deaths and for 29% of new-onset HF/HHF in this specific population. None of Un-LVH patients received other diagnosis than CA explaining the cause of LVH during follow-up, a finding in line with the known under-diagnosis of CA in current clinical practice.

These observations support the role of CT syndrome as CV risk factor and strengthen the relevance of performing dedicated tests to diagnose Un-LVH in patients with CT syndrome. Of note, important efforts are required to reach an aetiological diagnosis of Un-LVH, even after ruling out CA, as this condition is associated with an unfavourable prognosis. So far as known, these data deserve attention, especially because disease-modifying treatments for ATTR-CA have recently become available.[21,22]

Echocardiographic phenotypes at carpal tunnel surgery: an aetiological classification for prognosis

Carpal tunnel surgery is considered a low-risk procedure in most cases, not requiring general anaesthesia and with a modest incidence of significant complications (frequently local).[23] Therefore, patients scheduled for this surgery currently do not undergo pre-procedural cardiologic evaluation on a regular basis, making difficult to define systematically the CV profile. In detail, echocardiography is not included in the pre-procedural work-up of patients with planned CT surgery. However, this approach might be reconsidered as half of the subjects included in this study exhibited findings consistent with structural heart disease (i.e. LVH) at the time of planned surgery. Among them, about one patient out of three had Un-LVH, which was often disregarded.

Diagnosing Un-LVH, even by a routine pre-operative echocardiography, emerges as a major finding that should prompt further evaluations including careful anamnestic collection (i.e. family history of sudden death or diagnosed cardiomyopathies, syncope, orthostatic hypotension, and erectile dysfunction), ECG, and accurate review of echocardiographic images.[24] Identification of abnormal loading conditions or secondary causes of cardiac hypertrophy allows starting appropriate treatments (i.e. antihypertensive drugs). This is the most likely explanation for the similar observed all-cause mortality between LVH and non-LVH patients (P = 0.88). Conversely, Un-LVH was associated with a higher frequency of CV events because some mechanisms of cardiac hypertrophy not related to arterial hypertension and/or AS, such as CA, have been missed. In fact, Un-LVH patients experienced significantly lower global survival and higher incidence of HF compared with Ex-LVH and non-LVH patients, even after adjustment for age, gender, and renal insufficiency (*Figure 2*). Furthermore, Un-LVH was associated to HF development and death at 2–3 and 3–5 years following CT surgery, respectively. When encountering Un-LVH, a cardiomyopathy-oriented evaluation is essential to rule out primary myocardial diseases.[15] Of note, the identification of the specific cause of cardiac hypertrophy in our Un-LVH cohort was not possible based on exams performed at the time of CT surgery and was beyond the scope of the present study. Nevertheless, unrecognized hypertension, severe AS, and hypertrophic cardiomyopathy are unlikely among Un-LVH patients of this study. Hypertensive heart disease leading to severe cardiac hypertrophy [interventricular septum 16 mm (IQR 14–17) in Un-LVH patients] is extremely rare, especially if blood pressure values are well controlled (systolic blood pressure 125 ± 21 mmHg in Un-LVH patients) (*Table 1*). Although possible, an unrecognized hypertrophic cardiomyopathy is a very unlikely diagnosis considering the median age of Un-LVH patients (i.e. 77 years). Finally, mild-to-moderate AS was found in 9.5% of Un-LVH patients and the anatomy and normal opening of the aortic valve were visually assessed in each case, thus ruling out severe valve diseases.

Based on these observations, CA is a possibly missed cardiomyopathy in our Un-LVH group considering the advanced median age (>75 years) and the presence of CT syndrome. Further elements supporting this possibility are as follows: (i) greater discrepancy between LV thickness and QRS voltages in Un-LVH than Ex-LVH (70% vs. 14.3%, respectively), further confirmed by higher indexed LV mass–ECG voltage ratio in Un-LVH than Ex-LVH and non-LVH; (ii) increased frequency of right ventricular hypertrophy (17.6% vs. 6.3%) and pericardial effusion (15.8% vs. 2.4%) in Un-LVH compared with Ex-LVH; and (iii) a global higher percentage of suspected echocardiographic findings of CA in Un-LVH compared with Ex-LVH.

Although our findings support the speculation that patients with Un-LVH might have harboured amyloid in their hearts at the time of surgery, this was beyond the scope of the study, which focused on the echocardiographic characterization of patients undergoing CT surgery.

Cardiac amyloidosis: the dark side of carpal tunnel syndrome

The incidence of diagnosed CA in our population was 0.44 cases/100 patients/year of those who underwent cardiologic evaluations among patients undergoing CT surgery. In particular, the incidence of diagnosed CA was greater in Un-LVH patients achieving 2.2 cases/100 patients/year (2/21 patients). However, the real prevalence of disease is reasonably higher considering that (i) of the 643 patients, only the subgroup with CV disease was started on regular follow-up and underwent regular ECG and echocardiography allowing to identify features of CA; (ii) the awareness of CA in the

medical class has been low in the past; (iii) these patients were not considered at higher CV risk and were not scheduled on cardiological follow-up on a regular basis; and (iv) the diagnosis of CA requires a high level of suspicion and dedicated testing as cardiac scintigraphy with bone tracers and haematological investigations to evaluate the presence of monoclonal components.

Our study adds an important piece of knowledge to some valuable recently published evidences on the association between CT syndrome and amyloidosis. In the study by Sperry *et al*.,[7] no cardiological characterization of patients was undertaken, excluding a small subgroup of patients (10/98) with amyloid fibrils in the tendon synovial sheath tissue. In our study, we included only patients with comprehensive cardiological evaluations (clinical examination, ECG, and echocardiography) and demonstrated the prognostic value of cardiological profiling at the time of CT surgery. The diagnosis of CT syndrome has itself prognostic implications as demonstrated by the prospective, control-matched study from the Danish National Registry.[1] In that study, if considered in absolute terms, the risk of future diagnosis of amyloidosis was actually extremely low compared with control subjects (47 vs. 3 events by 10 years, respectively).[1] This probably resulted from the lack of cardiological evaluations in the population that could have raised the suspicion of disease. Combining CT syndrome with a detailed CV characterization would certainly increase the diagnostic yield for CA and magnify the relationship between CT syndrome and CA. This association may take years from CT surgery to become evident as reported by a recent study,[9] reporting an overall CA frequency similar to that of the present study. Of note, the observation point of this study[9] is poles apart from ours because patients were enrolled at a median time from the onset of CT syndrome symptoms and from CT surgery of 11 (IQR 8–16) and 6 years (IQR 3.2–9.7), respectively.

According our results, patients undergoing CT surgery should be carefully assessed, because those with Un-LVH are at increased risk of CV events and deserve a dedicated evaluation, including second and third-level exams to rule out specific causes (i.e. cardiac magnetic resonance and cardiac scintigraphy with bone tracers). A thoughtful clinical work-up should combine patients' history, the discrepancy between QRS voltage and the magnitude of LVH, the trends of the pressure profile and the need to discontinue antihypertensive drugs, and the presence of valvular diseases and suggestive echocardiographic findings of infiltrative disease to identify profiles at high global and CV risk. Finally, Orthopaedic and Hand Surgeons should be aware of the possible presence of structural heart disease in patients scheduled for CT surgery and collect information about findings consistent with unrecognized CA and increased CV risk such as bilateral CT syndrome or need of multiple release procedures, previous syncope, or orthostatic hypotension. Biopsy of tendon synovial sheath tissue with subsequent dedicated staining procedures to detect amyloid infiltration and referral for cardiological evaluation might be considered in these patients, especially in men ≥65 years and women ≥70 years, as recently suggested.[7,15]

Limitations

This is a retrospective, single-centre study including subjects who performed cardiologic tests because of different causes (i.e. arterial hypertension, heart valve disease, and chronic HF). The study population was 20% (130/643 patients) of all patients surgically treated as it includes only those with available and reviewable cardiological data at the time of surgery. This condition resulted from the low awareness of the association between CT syndrome and CV risk in the past. Only patients with known CV risk factors or HF underwent cardiologic examinations and tests. Patients were not scheduled on regular follow-up visits, and it was not possible to estimate the number of patients developing AF over time and to determine the specific cause of death in most cases. It is hard to establish the magnitude of cardiac hypertrophy caused by AS and arterial hypertension rather than CA. The time of surgery is an inaccurate parameter as the clinically relevant event is the onset of symptomatic CT syndrome. Thus, some patients might have waited various time, up to years, before undergoing CT surgery. Patients with suggestive echocardiographic findings of CA were a small group (n = 8) and did not allow to perform robust statistical analysis. Echocardiographic images were not acquired for the purpose of speckle-tracking analysis, and their quality was deemed not suitable for accurate measurements. However, this was expected considering the retrospective nature of the study. Finally, it has not been possible to consider CV death among outcome measures due to the difficult attribution of causes of death in a retrospective analysis. Prospective studies are required to confirm these results and assess the role of CT syndrome as additional risk factor for CV events, with Un-LVH conferring the highest risk.

Nevertheless, to the best of our knowledge, this is the first cardiologically well-characterized cohort of patients at the time CT surgery in literature. Therefore, this represents a unique opportunity to deepen cardiologic characteristics of this population.

Conclusions

At the time of CT surgery, more than 30% among patients with available cardiologic evaluation and evidence of cardiac hypertrophy presented Un-LVH. Compared with non-LVH and Ex-LVH, the presence of Un-LVH was associated with higher all-cause mortality and new-onset HF/HHF at 45 and

29 months, respectively, even after adjustment for age, gender, and renal insufficiency. It emerges the need to reconsider the current approach to patients undergoing CT syndrome and to identify the causes of Un-LVH with additional specific exams.

Acknowledgements

We would like to thank Fondazione CRTrieste, Fondazione CariGO, Fincantieri, and all the healthcare professionals for the continuous support to the clinical management of patients affected by cardiomyopathies, followed in Heart Failure Outpatient Clinic of Trieste, and their families.

Conflict of interest

G.S. reports personal fees for educational activities (Biotronik, Boston Scientific, Astra Zeneca, Novartis, Dompé, Menarini, and Vifor Pharma) outside the submitted work. C.R. reports institutional grants (Pfizer), speaker fees, and advisory board fees (Pfizer, Alnylam, and Sanofi) outside the submitted work. M.M. reports unrestricted research grant (Pfizer) and congress fees (Pfizer, Novartis, and Vifor Pharma) outside the submitted work. B.G. reports research grant (Novartis). The other authors declare that there is no conflict of interest.

Funding

This work was not supported.

References

1. Fosbøl EL, Rørth R, Leicht BP, Schou M, Maurer MS, Kristensen SL, Kober L, Gustafsson F. Association of Carpal Tunnel Syndrome with Amyloidosis, heart failure, and adverse cardiovascular outcomes. *J Am Coll Cardiol* 2019; **74**: 15–23.
2. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, Judge DP, Lenihan DJ, Gottlieb SS, Shah SJ, Steidley DE, Ventura H, Murali S, Silver MA, Jacoby D, Fedson S, Hummel SL, Kristen AV, Damy T, Plante-Bordeneuve V, Coelho T, Mundayat R, Suhr OB, Waddington Cruz M, Rapezzi C. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol United States* 2016; **68**: 161–172.
3. Milandri A, Farioli A, Gagliardi C, Longhi S, Salvi F, Curti S, Foffi S, Caponetti AG, Lorenzini M, Ferlini A, Rimessi P, Mattioli S, Violante FS, Rapezzi C. Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. *Eur J Heart Fail* 2020; **22**: 507–515.
4. Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, Koyama J, Yanagisawa S, Ikeda S-I. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid* 2016; **23**: 58–63.
5. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RMT, Bacchi-Reggiani L, Sangiorgi D, Ferlini A, Cavo M, Zamagni E, Fonte ML, Palladini G, Salinaro F, Musca F, Obici L, Branzi A, Perlini S. Systemic cardiac amyloidoses. *Circulation* 2009; **120**: 1203–1212.
6. aus dem S F, Hein S, Prestel S, Baumgärtner C, Schönland S, Hegenbart U, Röcken C, Katus HA, Kristen AV. Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy? *Clin Res Cardiol* 2019; **108**: 1324–1330.
7. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA, Shapiro D, Evans PJ, Maschke S, Kilpatrick SE, Tan CD, Rodriguez ER, Monteiro C, Tang WHW, Kelly JW, Seitz WH, Hanna M. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol* 2018; **72**: 2040–2050.
8. González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017; **38**: 1895–1904.
9. Zegri-Reiriz I, de Haro-Del Moral FJ, Dominguez F, Salas C, de la Cuadra P, Plaza A, Krsnik I, Gonzalez-Lopez E, Garcia-Pavia P. Prevalence of cardiac amyloidosis in patients with carpal tunnel syndrome. *J Cardiovasc Transl Res* 2019; **12**: 507–513.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the european Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39. e14.
11. Di BG, Minutoli F, Piaggi P, Casale M, Mazzeo A, Zito C, Oreto G, Baldari S, Vita G, Pingitore A, Khandheria BK, Carerj S. Usefulness of combining electrocardiographic and echocardiographic findings and brain natriuretic peptide in early detection of cardiac amyloidosis in subjects with transthyretin gene mutation. *Am J Cardiol* 2015; **116**: 1122–1127.
12. Damy T, Costes B, Hagège AA, Donal E, Eicher J-C, Slama M, Guellich A, Rappeneau S, Gueffet J-P, Logeart D, Planté-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Randé J-L, Goossens M, Canoui-Poitrine F, Buxbaum JN. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 2016; **37**: 1826–1834.
13. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. European society of cardiology guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J* 2014; **35**: 2733–2779.
14. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, Hanna MA, Hazenberg BPC, Kristen AV, Kwong RY, Maurer MS, Merlini G, Miller EJ, Moon JC, Murthy VL, Quarta CC, Rapezzi C, Ruberg FL, Shah SJ, Slart RHJA, Verberne HJ, Bourque JM. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for

multimodality imaging in cardiac amyloidosis: part 1 of 2—Evidence base and standardized methods of imaging. *J Card Fail* 2019; **25**: e1–e39.
15. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, Gospodinova M, Obici L, Rapezzi C, Garcia-Pavia P. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Hear Fail* 2019; **7**: 709–716.
16. Carroll JD, Gaasch WH, McAdam KPWJ. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. *Am J Cardiol* 1982; **49**: 9–13.
17. Quarta CC, Perlini S, Longhi S, Berardini A, Musca F, Salinaro F, Obici L, Milandri A, Gallo P, Gagliardi C, Biagini E, Mingardi F, Pazzi C, Merlini G, Rapezzi C. A simple voltage/mass index improves diagnosis of cardiac amyloidosis: an electrocardiographic and echocardiographic study of 570 patients with left ventricular hypertrophy. *J Am Coll Cardiol* 2012; **59**: E1586.
18. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**: 1141–1154.
19. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. *J Stat Softw* 2011; **42**.
20. Austin PC, Fine JP. Propensity-score matching with competing risks in survival analysis. *Stat Med* 2019; **38**: 751–777.
21. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; **379**: 1007–1016.
22. Emdin M, Aimo A, Rapezzi C, Fontana M, Perfetto F, Seferovic PM, Barison A, Castiglione V, Vergaro G, Giannoni A, Passino C, Merlini G. Treatment of cardiac transthyretin amyloidosis: an update. *Eur Heart J* 2019; **40**: 3699–3706.
23. Van M, Jose R, Power D. Failed carpal tunnel surgery: a guide to management. *J Musculoskelet Surg Res* 2019; **3**: 30.
24. Porcari A, Merlo M, Rapezzi C, Sinagra G. Transthyretin amyloid cardiomyopathy: an uncharted territory awaiting discovery. *Eur J Intern Med* 2020; **82**: 7–15.