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Original article

Impact of cardiac amyloidosis on outcomes of patients hospitalized with heart failure

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ABSTRACT

Background: Amyloidosis is a multi-systemic disease potentially leading to failure of affected organs. We aimed to investigate prevalence and prognostic implications of cardiac amyloidosis of any etiology on outcomes of hospitalized patients with heart failure (HF) in Germany.

Methods: We analyzed data of the German nationwide inpatient sample (2005–2018) of patients hospitalized for HF (including myocarditis with HF and heart transplantation with HF). HF patients with amyloidosis (defined as cardiac amyloidosis [CA]) were compared with those HF patients without amyloidosis and impact of CA on outcomes was assessed.

Results: During this fourteen-year observational period 5,478,835 hospitalizations for HF were analyzed. Amyloidosis was coded in 5,407 HF patients (0.1%). CA prevalence was 1.87 hospitalizations per 100,000 German population. CA patients were younger (75.0[IQR 67.0–80.0]vs.79.0[72.0–85.0]years, $p < 0.001$), predominantly male (68.9%) and had a higher prevalence of cancer (14.8% vs. 3.6%, $p < 0.001$). Adverse in-hospital events including necessity of transfusions of blood constituents (7.1% vs. 5.4%, $p < 0.001$) and cardio-pulmonary resuscitation (CPR, 2.7% vs. 1.4%; $p < 0.001$) were more frequent in CA. CA was independently associated with acute kidney failure (OR 1.40 [95%CI 1.28–1.52], $p < 0.001$), CPR (OR 1.58 [95%CI 1.34–1.86], $p < 0.001$), intracerebral bleeding (OR 3.13 [95%CI 1.68–5.83], $p < 0.001$) and in-hospital mortality between the 5 and 8th decade of life, but in-hospital mortality was strongly influenced by cancer.

Conclusions: CA was identified as an independent risk factor for complications and in-hospital mortality in HF patients, whereby it has to be mentioned that amyloidosis subtypes could not differentiated in the present study. Physicians should be aware of this issue concerning treatments and monitoring of CA-patients.

1. Introduction

Amyloidosis is a multi-systemic disease resulting from deposition of misfolded proteins as insoluble fibrils in the interstitium of affected organs, subsequently leading to organ failure. Cardiac involvement in amyloidosis is common [1] and amyloid fibrils can deposit in several cardiac structures, including coronary arteries, ventricles, atria and heart valves [2,3]. Although more than 30 proteins can form amyloid

Abbreviation: AL, Amyloid light chain; ATTR, Amyloid transthyretin; ATTRh, Hereditary amyloid transthyretin; ATTRwt, Wild type amyloid transthyretin; CA, Cardiac amyloidosis; DRG, Diagnosis Related Groups; GM, German Modification; HF, Heart failure; HfpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid-range ejection fraction; HfrEF, Heart failure with reduced ejection fraction; ICD, International Classification of Diseases and Related Health Problems; IQR, Inter-quartile range; OR, Odds ratio; RDC, Research Data Center; AKF, Acute kidney failure; CPR, Cardio-pulmonary resuscitation.

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fibrils, cardiac amyloidosis is typically attributable to misfolded transthyretin (ATTR) or immunoglobulin light chain (AL) aggregation [4]. ATTR amyloidosis can result from the aggregation of either wild type transthyretin (ATTRwt) or by a variety of inherited genetic mutations of TTR (ATTRh), respectively. In patients with ATTRwt, a cardiac phenotype is almost always present, whereas ATTRh is more varied depending on the specific mutation and other parameters [5,6]. In AL amyloidosis the heart is involved in approximately 50 to 75% of cases [7]. Once considered a rare disease, some smaller studies indicate a higher prevalence of cardiac amyloidosis especially in older patients diagnosed with heart failure with preserved ejection fraction (HFpEF). In a small study of the 108 patients (median age 66 years), cardiac amyloidosis was diagnosed in 15 (14%) patients (7 patients with ATTR-wt, 4 patients with hereditary ATTR, 3 patients with light-chain amyloidosis, and 1 patient with AA secondary amyloidosis) [8], while another study indicates a prevalence of 13% for cardiac ATTRwt amyloidosis in a study population of 120 patients with HFpEF aged 60 years or older [9]. Contemporary treatment options have significantly improved survival of patients not only with AL amyloidosis but also with ATTR [10,11]. In this condition "disease modifying" therapies are nowadays available which have been shown to slow down or halt disease progression and even favorably affecting clinical outcome [12]. Therefore, early diagnosis is mandatory in order to provide best treatment efficacy. However, early identification of patients with cardiac amyloidosis is challenging as clinical symptoms are heterogenous and unspecific, frequently misleading by mimicking other more common diseases. Therefore, diagnosis is often significantly delayed for both patients with AL amyloidosis [13] and patients with ATTR amyloidosis [14,15] resulting in worse outcome due to late start of adequate treatment in advanced disease stages at the time of diagnosis [16].

Information on the prevalence and clinical implications of amyloidosis in heart failure among hospitalized patients with HF is sparse. Recently, Gilstrap et al. reported for the first time on incidence and prevalence of CA in hospitalized Medicare beneficiaries in the United States of America (US) [17], but data for Europe are missing [11]. In addition, intercontinental differences between North America and Europe regarding CA subtypes have to be assumed and expected [18] and the assessment of epidemiological data for CA in Europe are of outstanding interest. Having access to the administrative data of a large-scale population in Germany consisting of more than 5 million hospitalizations of patients with HF between 2005 and 2018, we aimed with the present study to assess prevalence, temporal trends, hospitalization rates, treatment characteristics and outcomes, of patients with CA in comparison to those with HF of other etiologies.

2. Material and methods

2.1. Data source

The German nationwide inpatient sample (diagnosis related groups [DRG] statistic) was used for the planned analyzes (source: Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2018, and own calculations). In Germany, diagnoses are coded by the hospitals to get their remuneration according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and diagnostical, surgical and interventional procedures with OPS codes (surgery, diagnostic and procedures codes [Operationen- und Prozedurenschlüssel]). Data were collected by the RDC of the German Federal Statistical Office and the Statistical Offices of the federal states.

The German nationwide inpatient sample (2005–2018) was used for this present study. All patients hospitalized for HF (inpatients with a main diagnosis of HF [ICD-code I50]), or myocarditis (ICD-code I40) with a diagnosis of HF as well as patients undergoing heart transplantation (OPS-code 5–375) with diagnosis of HF were included in the analysis. The main diagnosis of a patient is defined as that diagnosis, which was mainly responsible for hospitalization documented by the discharging physician [19]. HF patients were stratified for presence of amyloidosis (ICD-code E85) and the co-prevalence of HF and amyloidosis was defined as cardiac amyloidosis (CA) [17]. Due to coding reasons, we were not able to differentiate between the subtypes of amyloidosis (i.e. ATTRh, ATTRwt and AL). Hospitalizations of HF patients with and without amyloidosis were compared for patient profile, treatments and outcomes %) (flowchart is presented in Fig. S1 in the Supplementary Material).

As an additional investigation, the prevalence of amyloidosis was analyzed in all hospitalized patients in Germany (2005–2018) regardless of the cause of hospitalization (inpatients with and without HF). The prevalence of CA was analyzed regardless of coded as main or secondary diagnosis (Statistisches Bundesamt, DEStatis, source: DRG-Statistik, Sonderauswertung des Statistischen Bundesamtes).

2.2. Study endpoints and in-hospital adverse events

The primary study outcome was death of all-causes during in-hospital stay (in-hospital death). Additionally, we analyzed the occurrence of major adverse cardiovascular disease and cerebrovascular events (MACCE, composite of all-cause in-hospital death, acute myocardial infarction [ICD-code I21], and/or ischemic stroke [ICD-code I63]), pneumonia (ICD-codes J12-J18), acute kidney failure (AKF, ICD-code N17), myocardial infarction (ICD-codes I21 and I22), stroke (ischemic and hemorrhagic stroke, ICD-codes I61-64), cardiopulmonary resuscitation (CPR, OPS code 8-77), shock (ICD-code R57), deep venous thrombosis or thrombophlebitis (DVT, ICD-codes I80-82), pulmonary embolism (ICD-code I26), intracerebral bleeding events (ICB, ICD-code I61), subarachnoid bleeding (ICD-code I60), gastrointestinal bleeding (GIB, ICD-codes K920-K922), and transfusion of blood components (OPS-code 8-800).

2.3. Definitions

The investigated diagnostic approaches were coded as follows: Myocardial biopsy (OPS codes 1-497.0, 1-497.1, 1-497.2), cardiac magnet resonance imaging (MRI, OPS code 3-824), myocardial scintigraphy (OPS code 3-721), scintigraphic examination, positron emission tomography (PET, OPS code 3-741), positron emission tomography with computed tomography (PET-CT, OPS code 3–751), renal biopsy (OPS codes 1-460, 1-461, 1-462, 1-463, 1-465.0, 1-560), liver biopsy (OPS codes 1-441, 1-551, 1-497.3), osseous biopsy (OPS codes 1-424; 1-503.5, 1-480.5; 1-481.5), biopsy of the lower gastro-intestinal tract (OPS codes 1-444, 1-557), biopsy of the lungs (OPS codes 1-581.3; 1-431.0; 1-431.1; 1-430.2; 1-430.3). We calculated the Charlson Index score [20] to compare the patient groups regarding comorbidity risk regarding in-hospital mortality.

2.4. Ethical aspects

Since this study did not involve direct access by the investigators to data of individual patients, approval by an ethics committee and informed consent were not required in accordance with German legislation.

2.5. Statistical methods

Descriptive statistics for relevant baseline comparisons of HF patients with and without amyloidosis are provided as median and interquartile range (IQR) or absolute numbers and corresponding percentages. We tested the continuous variables using the Mann-Whitney-U test; categorical variables were analyzed with the Fisher's exact or the chi^2 test, as appropriate.

Total hospitalization rates for both groups, relative mortality rate (case-fatality rate), rate of MACCE and other in-hospital events as well as

treatments were calculated on an annual basis, and linear regressions were used to assess trends over time. The results are presented as beta (β)-estimates with corresponding 95% confidence intervals (CI).

Univariate and multivariate logistic regression models were computed in HF patients to investigate the impact of amyloidosis on the mentioned adverse in-hospital events and outcomes.

Results of the logistic regressions are presented as odds ratio (OR) and 95%CI. The multivariate regression models were adjusted for age, sex, cancer, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, hyperlipidaemia, diabetes mellitus, as well as atrial fibrillation/flutter (AF). We selected this epidemiological adjustment-approach with age, sex and all mentioned comorbidities to be convinced that detected associations were widely independent of these other potential drivers of aggravated in-hospital outcomes, since especially cardiovascular diseases, renal diseases, COPD and cancer are well-known drivers for poor in-hospital outcomes. The software SPSS® (version 20.0; SPSS Inc., Chicago, Illinois) was used for computerised analysis. *P* values of <0.05 (two-sided) were considered to be statistically significant.

3. Results

3.1. Prevalence of amyloidosis in Germany 2005–2018

First, we analyzed the total numbers of hospitalizations with amyloidosis in all German inpatients regardless of coded comorbidities (consecutively also regardless of HF): The calculated prevalence was 8.16 hospitalizations per 100,000 German population (2005–2018) increasing from 5.03 in the year 2005 to 13.02 per 100,000 population in 2018.

3.2. Prevalence of cardiac amyloidosis

The prevalence of CA (for this analysis HF was coded as main or secondary diagnosis) was calculated as 1.87 hospitalizations per 100,000 German population in the observational period (2005–2018) increasing from 0.91 to 3.61 per 100,000 German citizens in the same observational period (Fig. 1A).

3.3. HF patients with and without CA

The present study included 5,478,835 hospitalizations of HF patients (51.7% females; 81.0% aged 70 years or older) in Germany between 2005 and 2018. Among these, 510,424 died (9.3%) during in-hospital stay. Amyloidosis was coded in 5407 patients (0.1%) (Fig. S1 in the Supplementary Material).

Total numbers of patients with CA increased significantly from 142 (0.05% of all HF patients) in the year 2005 to 858 (0.19%) in 2018 (β 1.72 [95%CI 1.61 to 1.83], $p < 0.001$) (Fig. 1B). The frequency of CA was highest in HF patients in-between the 4th to 7th decades of life; statistically, the frequency of CA decreased with growing age (β −0.45 [95%CI −0.48 to −0.42], $p < 0.001$) (Fig. 1C). In contrast, highest proportion of CA hospitalizations related to all HF patients of the different age decades was detected in the 6th decade of life (Fig. S2 in the Supplementary Material). Remarkably, the in-hospital mortality rate of CA patients decreased substantially in the observational period from 20.5% in the year 2005 to 8.2% in 2018 (β −1.06 [95%CI −1.39 to −0.73], $P < 0.001$) (Fig. 1B). No trend over time was observed with respect to the performance of interventional treatment options such as cardiac catheterizations and implantation of cardioverter defibrillators and pacemakers (Fig. S3 in the Supplementary Material).

3.4. Patients' characteristics, treatment and outcome stratified for presence of amyloidosis

HF patients in whom amyloidosis was coded were in median 4 years younger at the time of hospitalization compared to those without amyloidosis, had a higher prevalence of cancer (14.8% vs. 3.6%, $P < 0.001$), especially multiple myeloma (10.6% vs. 0.2%, $P < 0.001$) and were predominantly male. The highest proportions of cancer and multiple myeloma were found in the 5th to 7th decade of life (Fig. S4 in the Supplementary Material).

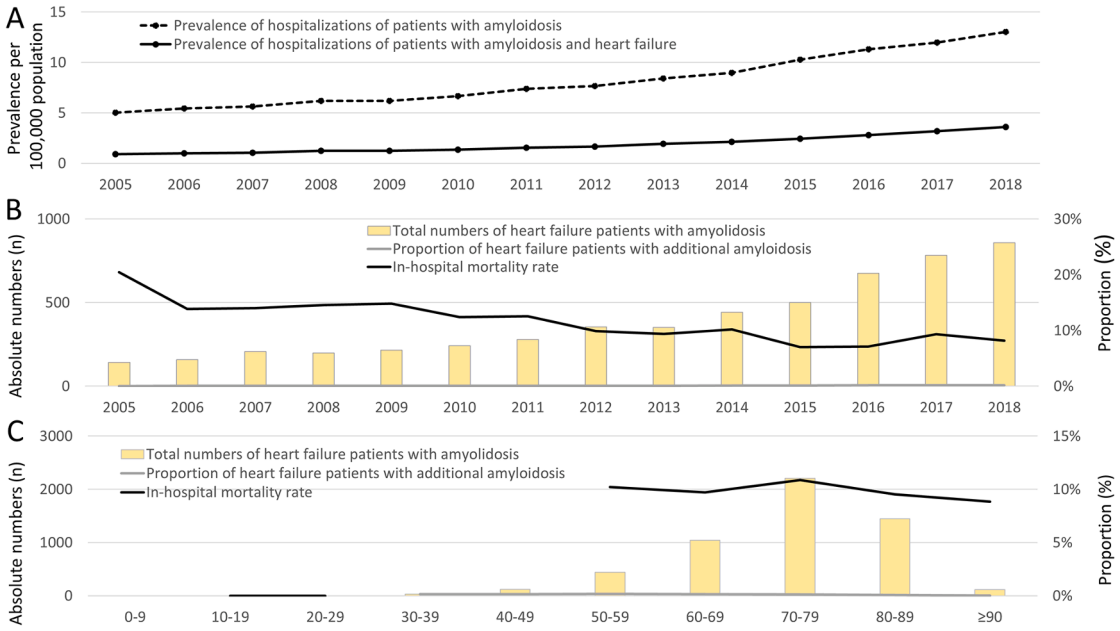

Fig. 1. Temporal trends on prevalence, total numbers and mortality Panel A: Temporal trends in prevalence of hospitalizations with amyloidosis in Germany (dashed black line) and prevalence of hospitalizations of heart failure patients with amyloidosis stratified by years (solid black line). Panel B: Temporal trends in absolute numbers of heart failure patients with amyloidosis (yellow bars), mortality rate (black line) and proportion of heart failure patients with amyloidosis related to all heart failure patients (gray line) stratified by years. Panel C: Temporal trends in absolute numbers of heart failure patients with amyloidosis (yellow bars), mortality rate (black line) and proportion of heart failure patients with amyloidosis related to all heart failure patients (gray line) stratified by years (A) and age decades.

HF patients without CA had more frequently at least one heart failure predisposing disease (including coronary artery disease, cardiomyopathy, aortic or mitral valve disease, sleep apnea, myocardial infarction in medical history, diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease).

3.5. Diagnostic approach for CA in HF patients

As shown in Table 1, myocardial biopsy (9.4% vs. 0.3%, $P < 0.001$), cardiac magnetic resonance imaging (MRI) (7.6% vs. 0.9%, $P < 0.001$), and bone scintigraphy (1.0% vs. 0.2%, $P < 0.001$) were more often performed in HF patients with CA than in those without. Right heart catheter examination was also more often conducted in CA (9.8% vs. 2.8%, $P < 0.001$). The most frequent biopsy sites in CA patients were myocardial biopsy and biopsy of the lower gastrointestinal tract (Fig. S5 in the Supplementary Material).

The use of the diagnostic approaches of myocardial biopsy (β 0.03 (95%CI −0.31 to 0.37); $P = 0.869$), scintigraphic examination (β 0.28 (95%CI −0.23 to 0.81); $P = 0.278$) and cardiac MRI (β 0.17 (95%CI −0.21 to 0.55); $P = 0.870$) did not change over the observational period (2005–2018), whereas biopsies of the lower gastrointestinal tract (β −1.52 (95%CI −1.93 to −1.12); $P<0.001$) and bone biopsies (β −0.17 (95%CI −0.32 to −0.02); $P = 0.028$) decreased over time (Fig. S6 in the Supplementary Material). The use of all of these investigated diagnostic approaches was highest in the 4th to 6st decade of life in CA patients (Fig. S6 in the Supplementary Material).

3.6. Patients' treatment and outcome stratified for presence of amyloidosis

Although patients without amyloidosis had an unfavorable cardiovascular risk profile with higher prevalence of arterial hypertension, diabetes mellitus, obesity and coronary artery disease, adverse in-hospital events during hospitalization were more often documented in patients with CA (Table 1). In this context, patients with CA were more often coded with AKF, shock, emergency requiring cardiopulmonary resuscitation (CPR), myocarditis, sepsis and bleeding complications with a necessity of transfusion of blood constituents. Additionally, we observed a trend towards a higher in-hospital mortality in patients with CA. With respect to treatments, patients with CA more often required pacemaker implantations, cardiac resynchronization therapy and underwent more frequently heart transplantation. The Charlson score was slightly higher in HF with CA than in those without amyloidosis (mean ± standard deviation: 6.29 ± 2.13 vs. 6.17 ± 2.14, $p < 0.001$). As expected, a higher Charlson index score in patients with CA was associated with an increased mortality (univariate: OR 1.18 [95%CI 1.13–1.22], $p < 0.001$) (Table 1).

3.7. Impact of amyloidosis on outcome of patients with heart failure

In the multivariate logistic regression analyzes, CA was identified as an independent risk factor for AKF (OR 1.40 [95%CI 1.28–1.52], $p < 0.001$), shock (OR 1.65 [95%CI 1.42–1.92], $p < 0.001$), CPR (OR 1.58 [95%CI 1.34–1.86], $p < 0.001$) and ICB (OR 3.13 [95%CI 1.68–5.83], $p < 0.001$) in HF patients during hospitalization (Table 2).

While amyloidosis was not independently associated with in-hospital mortality when analyzed for all ages (OR 1.08 [95%CI 0.99–1.18], $P = 0.102$) (Table 2), the univariate logistic regression (Fig. 2B) as well as the multivariate logistic regression model adjusted for age and sex as well as the multivariate logistic regression model adjusted for age, sex and the cardiovascular risk factors diabetes mellitus, hyperlipidaemia, arterial hypertension and obesity (Fig. S7 in the Supplementary Material) revealed an association of CA with increased in-hospital mortality for the 5th, 6st, 7th and 8th age-decade of life. In contrast, the fully adjusted multivariate logistic regression model (adjusted for age, sex, cancer, coronary artery disease, chronic obstructive pulmonary disease,

Table 1
Baseline characteristics, clinical presentation, treatment and outcomes of the 5478,835 heart failure patients stratified for presence of amyloidosis.

Parameters	HF with amyloidosis ($n = 5407$; 0.1%)	HF without amyloidosis ($n = 5473,428$; 99.9%)	P-value
Age (years)	75.0 (67.0–80.0)	79.0 (72.0–85.0)	**<0.001**
Age ≥70 years	3768 (69.7%)	4431,761 (81.0%)	**<0.001**
Female sex*	1683 (31.1%)	2831,716 (51.7%)	**<0.001**
Length of in-hospital stay (days)	10.0 (6.0–16.0)	9.0 (6.0–14.0)	**<0.001**
Obesity	207 (3.8%)	602,416 (11.0%)	**<0.001**
NYHA functional class			
NYHA I/II	330 (6.1%)	370,450 (6.8%)	**<0.001**
NYHA III/IV	4218 (78.0%)	4144,906 (75.7%)	
Not classified according NYHA classification	859 (15.9%)	958,072 (17.5%)	
Comorbidities			
Cancer	799 (14.8%)	199,679 (3.6%)	**<0.001**
Metastatic cancer	21 (0.4%)	48,782 (0.9%)	**<0.001**
Multiple myeloma	573 (10.6%)	8781 (0.2%)	**<0.001**
Monoclonal gammopathy of undetermined significance (MGUS)	282 (5.2%)	9651 (0.2%)	**<0.001**
Lymphoma	28 (0.5%)	12,828 (0.2%)	**<0.001**
Coronary artery disease	1867 (34.5%)	2215,736 (40.5%)	**<0.001**
Myocardial infarction in medical history	241 (4.4%)	433,974 (7.9%)	**<0.001**
Cardiomyopathy	879 (16.2%)	479,420 (8.7%)	**<0.001**
Mitral valve disease	587 (10.8%)	543,315 (9.9%)	**0.025**
Aortic valve disease	304 (5.6%)	425,325 (7.8%)	**<0.001**
Atrial fibrillation/flutter	2766 (51.2%)	2783,739 (50.9%)	0.663
Chronic obstructive pulmonary disease	507 (9.4%)	937,564 (17.1%)	**<0.001**
Essential arterial hypertension	1927 (35.6%)	2485,174 (45.4%)	**<0.001**
Hyperlipidaemia	1130 (20.9%)	1245,182 (22.7%)	**0.001**
Diabetes mellitus	999 (18.5%)	2129,693 (38.9%)	**<0.001**
Sleep apnea	132 (2.4%)	154,003 (2.8%)	0.094
Acute and chronic kidney disease	3409 (63.0%)	2541,210 (46.4%)	**<0.001**
Nephrotic syndrome	131 (2.4%)	3595 (0.1%)	**<0.001**
Pleural effusion	381 (7.0%)	196,834 (3.6%)	**<0.001**
At least one heart failure predisposing diseases (including coronary artery disease, cardiomyopathy, aortic or mitral valve disease, sleep apnea, myocardial infarction in medical history, diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease)	4624 (85.2%)	5059,782 (92.2%)	**<0.001**
Myocarditis	27 (0.5%)	18,701 (0.3%)	**0.048**
Sepsis	125 (2.3%)	70,846 (1.3%)	**<0.001**
Viral hepatitis	20 (0.4%)	10,914 (0.2%)	**0.009**
Mycosis	108 (2.0%)	122,437 (2.2%)	0.227
Chalson comorbidity index	6.0 (5.0–8.0)	6.0 (5.0–8.0)	**<0.001**
Adverse events during hospitalization			
In-hospital mortality	545 (10.1%)	509,879 (9.3%)	0.053
MACCE	636 (11.8%)	618,537 (11.3%)	0.284
Pneumonia	566 (10.5%)	698,095 (12.8%)	**<0.001**
Acute kidney failure	691 (12.8%)	342,564 (6.3%)	**<0.001**
Shock	176 (3.3%)	72,623 (1.3%)	**<0.001**
Deep venous thrombosis or thrombophlebitis	77 (1.4%)	48,224 (0.9%)	**<0.001**

(*continued on next page*)

Table 1 (*continued*)

Pulmonary embolism	21 (0.4%)	22,601 (0.4%)	0.779
Cardio-pulmonary resuscitation	147 (2.7%)	74,556 (1.4%)	**<0.001**
Myocardial infarction	98 (1.8%)	113,577 (2.1%)	0.176
ST-elevation myocardial infarction	6 (0.1%)	12,721 (0.2%)	0.065
Stroke (ischemic or hemorrhagic)	41 (0.8%)	36,447 (0.7%)	0.404
Intracerebral bleeding	10 (0.18%)	2488 (0.05%)	**<0.001**
Gastro-intestinal bleeding	50 (0.9%)	42,653 (0.8%)	**0.224**
Transfusion of blood constituents	383 (7.1%)	293,651 (5.4%)	**<0.001**
Specific cardiac amyloidosis diagnostics			
Cardiac MRI	410 (7.6%)	49,049 (0.9%)	**<0.001**
Bone scintigraphy	54 (1.0%)	9808 (0.2%)	**<0.001**
Myocardial biopsy	512 (9.4%)	14,408 (0.3%)	**<0.001**
Further diagnostic approaches			
Myocardial scintigraphy	19 (0.4%)	19,349 (0.4%)	0.973
All scintigraphic examination	208 (3.8%)	187,082 (3.4%)	0.087
Cardiac positron emission tomography (PET)	4 (0.074%)	403 (0.007%)	**0.001**
Cardiac positron emission tomography with computed tomography (PET-CT)	0 (0%)	570 (0.01%)	1.000
Right heart catheter examination	533 (9.8%)	155,122 (2.8%)	**<0.001**
Medicated treatment			
Cytostatics	516 (9.5%)	98,386 (1.8%)	**<0.001**
Bortezomib	92 (1.7%)	245 (0.004%)	**<0.001**
Invasive and surgical Treatment			
Pacemaker	46 (0.9%)	34,043 (0.6%)	**0.032**
Cardiac resynchronization therapy (CRT)	16 (0.3%)	4942 (0.1%)	**<0.001**
Implantable cardioverter-defibrillator	68 (1.3%)	70,301 (1.3%)	0.861
Catheter ablation for the treatment of cardiac arrhythmias	5 (0.1%)	10,441 (0.2%)	0.116
Left heart catheterization	772 (14.3%)	682,873 (12.5%)	**<0.001**
Percutaneous coronary interventions (PCI)	109 (2.0%)	138,265 (2.5%)	**0.017**
Drug eluting stent (DES)	72 (1.3%)	82,333 (1.5%)	0.297
Bare metal stent (BMS)	22 (0.4%)	39,994 (0.7%)	**0.005**
Heart valve surgery	4 (0.1%)	4329 (0.1%)	1.000
Transcatheter aortic valve replacement (TAVR)	3 (0.06%)	2508 (0.05%)	0.742
Ventricular assist device (VAD)	12 (0.2%)	4258 (0.1%)	**<0.001**
Heart transplantation	65 (1.2%)	3935 (0.1%)	**<0.001**

Abbreviations: NYHA, New York Heart Association; MACCE, major adverse cardio-cerebral-vascular events.
* data available for 5478,599 hospitalizations.

Table 2
Impact of amyloidosis on in-hospital outcomes in patients with acute heart failure (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
In-hospital death	1.09 (1.00–1.19)	0.053	1.08 (0.99–1.18)	0.102
Cardio-pulmonary resuscitation	2.02 (1.72–2.39)	**<0.001**	1.58 (1.34–1.86)	**<0.001**
Pneumonia	0.80 (0.73–0.87)	**<0.001**	0.78 (0.72–0.85)	**<0.001**
Acute kidney failure	2.20 (2.03–2.38)	**<0.001**	1.40 (1.28–1.52)	**<0.001**
Shock	2.50 (2.15–2.91)	**<0.001**	1.65 (1.42–1.92)	**<0.001**
MACCE	1.05 (0.96–1.14)	0.284	1.03 (0.95–1.12)	0.450
Myocardial infarction	0.87 (0.71–1.06)	0.176	0.94 (0.77–1.15)	0.547
ST-elevation myocardial infarction	0.48 (0.21–1.06)	0.069	0.50 (0.23–1.12)	0.091
Myocarditis	1.46 (1.00–2.13)	**0.049**	1.07 (0.73–1.57)	0.731
Stroke (ischemic or hemorrhagic)	1.14 (0.84–1.55)	0.404	1.11 (0.81–1.50)	0.523
Deep venous thrombosis or thrombophlebitis	1.63 (1.30–2.04)	**<0.001**	1.34 (1.07–1.68)	**0.010**
Pulmonary embolism	0.94 (0.61–1.44)	0.779	0.73 (0.47–1.12)	0.146
Sepsis	1.80 (1.51–2.15)	**<0.001**	1.23 (1.03–1.47)	**0.024**
Viral hepatitis	1.86 (1.20–2.88)	**0.006**	1.29 (0.83–2.01)	0.251
Mycosis	0.89 (0.74–1.08)	0.227	0.85 (0.71–1.03)	0.105
Intracerebral bleeding	4.07 (2.19–7.59)	**<0.001**	3.13 (1.68–5.83)	**<0.001**
Subarachnoid bleeding	3.35 (0.84–13.44)	0.088	2.42 (0.60–9.72)	0.214
Gastro-intestinal bleeding	1.19 (0.90–1.57)	0.225	0.99 (0.75–1.31)	0.961
Transfusion of blood constituents	1.35 (1.21–1.49)	**<0.001**	0.97 (0.88–1.08)	0.601

*Adjusted for age, sex, cancer, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, diabetes mellitus, atrial fibrillation/flutter and hyperlipidaemia.

essential arterial hypertension, acute and chronic kidney disease, hyperlipidaemia, diabetes mellitus, as well as AF) showed that amyloidosis was independently associated with in-hospital mortality in HF patients within the 6th (OR 1.40 [95%CI 1.01–1.94], $p = 0.042$) as well as within the 8th decade (OR 1.18 [95%CI 1.03–1.35], $p = 0.02$) of life, but not in the other age-decades (Fig. 2C). Since cancer had its highest prevalence particularly in these age-decades in which the association of CA to in-hospital mortality does not longer exist after additional adjustment for all comorbidities inclusive cancer, we analyzed the impact of cancer on in-hospital mortality and the impact of CA on in-hospital mortality adjusted for age, sex, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, hyperlipidaemia, diabetes mellitus, as well as AF, but without an adjustment for cancer. The analyzes demonstrated an independent association between cancer and increased in-hospital mortality for CA patients in the 7th,8th and 9th age-decades of life (Fig. S8 of the Supplementary Material). As hypothesized, if the multivariate regression model was adjusted for age, sex, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, hyperlipidaemia, diabetes mellitus, as well as AF, but without an adjustment for cancer, the result regarding an association between CA and in-hospital mortality was consistent to the univariate regression and the multivariate regressions adjusted for age and sex as well as age, sex and cardiovascular risk factors, and showed an association of CA with increased in-hospital mortality for the 5th, 6st, 7th and 8th age-decades of life (Fig. S9 in the Supplementary Material).

4. Discussion

Cardiac involvement in amyloidosis is common [1] resulting in severe forms of heart disease with HF [21] and associated with poor life expectancy [22].

In the present study we analyzed nearly 5.5 million hospitalizations of HF patients in Germany, and provided evidence that I) the prevalence of CA was low with 1.87 hospitalizations per 100,000 German population in this fourteen-year observational period. II) While the prevalence of CA increased significantly (4.0-fold) between 2005 and 2018, the in hospital-mortality showed a significant downtrend during the same observational period. III) The highest number of hospitalizations for CA was seen in the 8th decade of life. IV) Although HF patients of other aetiologies revealed an unfavorable cardiovascular profile with higher frequency of cardiovascular risk factors as well as cardiovascular diseases such as coronary artery disease and AF, in-hospital mortality was comparable to CA patients (10.1% vs. 9.3%). V) While amyloidosis was not independently associated with in-hospital mortality, in general, this association became evident in the 5th to 8th decade of life, but was influenced by cancer. VI) Moreover, amyloidosis was an independent

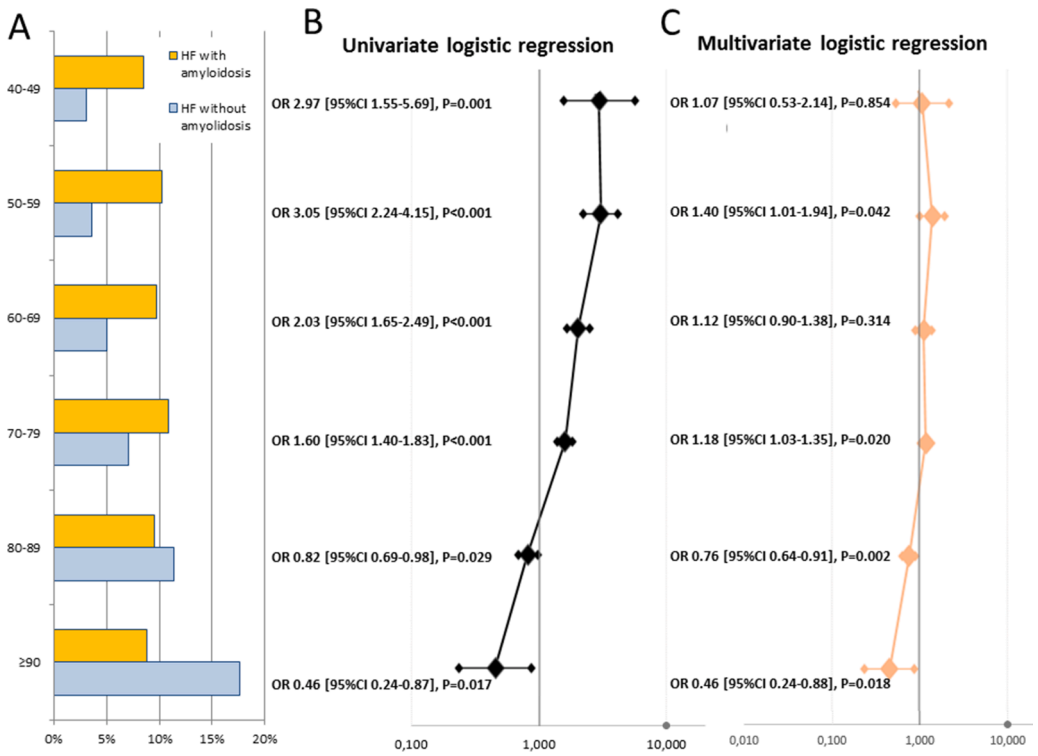

Fig. 2. Impact of amyloidosis on in-hospital mortality in HF patients stratified for age-decades. Panel A: In-hospital mortality rate in the different age-decades, Panel B: Univariate logistic regression model to identify the impact of amyloidosis on in-hospital mortality stratified by age-decades. Panel C: Multivariate logistic regression model to identify the impact of amyloidosis on in-hospital mortality stratified by age-decades independently of age, sex and comorbidities.

risk factor for adverse in-hospital events such as CPR, AKF, shock and ICB. VII) Cancer is an important co-factor regarding in-hospital death in CA patients.

CA is still considered as a rare disease [22,23]. Over the last decades the prevalence assessment of CA was hampered by the design of most studies investigating CA only in special subgroups such as HFpEF patients [9,24], patients with severe aortic valve stenosis [25,26] or focusing on special amyloidosis types (e.g. AL amyloidosis) [27,28]. Estimates of the annual incidence of AL amyloidosis were reported to range between 0.9 and 1.6 per 100,000 population [27,28]. In addition, the Tranthyretin Amyloidosis Outcomes Survey (THAOS) solely investigated genotype distribution, cardiac profile and the different phenotypes of ATTR amyloidosis including also ATTRwt patients [6]. The data of our study showed an annually prevalence of all amyloidosis types of 8.16 per 100,000 population in all hospitalizations in Germany (2005–2018).

Recently, Gilstrap et al. reported for the first time on incidence and prevalence of CA in hospitalized Medicare beneficiaries in the United States of America (US) [17]. Diagnosis of CA was based on a combination of International Diagnosis Codes (ICD-) for systemic amyloidosis and HF, comparable to our definition of CA in the present study. The authors reported a prevalence of CA of 18.0 per 100,000 patient years and an incidence of 8.0 per 100,000 patient years in 2005. Interestingly, both prevalence and incidence of CA increased significantly over time (2005 until 2012) resulting in a prevalence of 55.2 per 100,000 patient years and an incidence of 16.6 per 100,000 patient years in 2012 [17]. Notably, the prevalence of CA was significantly higher in men compared to women, with the highest prevalence noted among black men (174 per 100,000 patient years vs. 62.6 per 100,000 patient years in white men). Up to now, such epidemiological data for Europe are missing; thus, we aimed to close this gap.

In our present study, we observed a lower prevalence of CA of 1.87 per 100,000 population increasing from 0.91 in 2005 to 3.61 per 100,000 citizens in 2018 compared to the data of the US. Since it is well known that CA is a frequently overlooked disease [22,29], awareness of cardiac amyloidosis might have been better in the US than in Europe in the past years. Nevertheless, awareness of CA seems to grow in Germany, since it has to be hypothesized that the increasing prevalence of CA might predominantly be attributed to rather growing awareness for CA than primarily related to an increase regarding the total numbers of CA patients. Secondly, studies of the US show that there are large regional differences, which might also explain the country-by-country differences [17,29]. Prevalence of cardiac amyloidosis has been shown to increase with age and to be almost four times greater among blacks than among whites in the US [18]. In accordance with the study of Gilstrap et al. our study demonstrated also a higher prevalence of amyloidosis in male HF patients and an age-dependent peak prevalence of CA in older age (8th decade of life) [17].

CA is primarily categorized into two subtypes, transthyretin cardiac amyloidosis (ATTR-CA) and immunoglobulin light chain cardiac amyloidosis (AL-CA). Although several studies indicate that AL amyloidosis is still the most frequently diagnosed type of amyloidosis in western countries [10,30], ATTR might become the most common type of amyloidosis in an aging population [31,32]. Due to coding reasons, we were not able to differentiate between the subtypes of amyloidosis (i.e. ATTRh, ATTRwt and AL). However, we detected a prevalence of 14.8% of cancer, 10.6% of multiple myeloma, 5.2% of monoclonal gammopathy of undetermined significance (MGUS) and 0.5% of lymphoma in CA cases. In this context, it is well known, that AL amyloidosis is associated with myeloma as well as MGUS and transthyretin-related hereditary amyloidosis is related to lymphoma [33,34]. We found a rate of 9.5% CA cases treated with cytostatics and 1.7% treated with Bortezomib, which are treatment strategies of AL amyloidosis therapy [34–36]. As illustrated in Fig. S6 of the Supplementary Material, the proportion of CA patients examined with bone scintigraphy increased substantially in the years 2017 and 2018, while cardiac MRI and myocardial biopsy were widely stable over the years. Bone scintigraphy is one important examination modality in ATTR-CA beside cardiac MRI

and myocardial biopsy [22,23]. Thus, although we were not able to differentiate between the subtypes of amyloidosis due to coding in the German nationwide sample, the prevalence of precancer as well as cancer comorbidities, use of cytostratics and Bortezomib, and the time trends regarding diagnostics give hints regarding the proportions of different underlying amyloidosis forms of CA.

As expected, the results of our present study confirm that the underlying pathomechanisms for development of HF are different between HF patients with and without amyloidosis. HF patients without amyloidosis revealed an unfavorable cardiovascular profile with higher frequency of cardiovascular risk factors and cardiovascular diseases such as coronary artery disease and AF, which might be causative and underlying conditions for the development of HF. Nevertheless, in-hospital mortality was non-significantly higher in CA patients (10.1% vs. 9.3%) probably caused directly by cardiac involvement of amyloidosis [22] resulting in aggressive forms of heart disease with cardiac failure largely resistant to many common heart failure therapies [21]. Our present study showed that amyloidosis was not independently associated with in-hospital mortality in general, but we identified an association of CA with increased in-hospital mortality in the 5th to 8th decade of life, but the in-hospital mortality was additionally strongly influenced by cancer. Cancer was an important co-factor regarding in-hospital death in CA patients.

Besides cardiac involvement subsequently leading to HF, extra-cardiac involvement is also frequently observed in amyloidosis. However, extracardiac involvement differs substantially between patients with AL- and ATTR amyloidosis. Renal involvement can be detected in up to 70% of patients with AL amyloidosis [37], whereas renal involvement is rarely detected in ATTR amyloidosis [38]. In our study amyloidosis was an independent risk factor for AKF (OR 1.4) and nephrotic syndrome was 24-fold more often detected in CA patients than in HF patients without amyloidosis. In addition, other typical diseases associated with amyloidosis like multiple myeloma were significantly more prevalent in patients with amyloidosis compared with patients without amyloidosis and studies reported that these extra-cardiac manifestations might precede cardiac involvement by years [39,40].

We found in our study that necessity for transfusion of blood constituents as well as incident ICB were affected by amyloidosis, thereby corroborating previous reports. It is well established, that among patients with AL amyloidosis deficiency of Factor X was detected, which was aggravated by additional hepatic involvement [41]. Thereby, the extent of Factor X deficiency was related to the severity of bleeding complications [42].

The higher rate of CPR and pacemaker implantations in HF patients with amyloidosis compared to those without might be explained by higher prevalence of conduction abnormalities and arrhythmias in patients with CA [43,44]. In this context, it is well known, that fatal outcome in patients with CA is often related to electromechanical dissociations as well as bradyarrhythmia and tachyarrhythmia [43]. Important conduction abnormalities including fascicular block and higher degree atrioventricular block are common in CA [45,46]. As an accepted prophylactic ICD-implantation strategy is currently not available in patients with CA, it is not surprising, that rates of implantable cardioverter-defibrillator implantations do not differ significantly between patients with amyloidosis and patients with HF without amyloidosis [1].

A recently published study of our group outlined an improvement regarding the outcome of HF patients during the observation period (2005 until 2016) in Germany. This improvement was at least in part attributable to increased rates of left heart catheterization and percutaneous coronary interventions [47]. As in our present study the in-hospital mortality rate decreased significantly during the observation period, whereas rates of interventional treatments (e.g. left heart catheterizations and percutaneous coronary interventions) remained almost stable and a recent study demonstrated that standard HF medication did not have a positive affect the survival of patients with ATTRh and ATTRwt [48], the documented decrease of in-hospital mortality in our present study must probably be attributable to other factors. In this context, the reduced mortality rate in the latest years might be explained by a growing incidence of ATTRwt CA and a better knowledge regarding amyloidosis in general. Additionally, a growing awareness concerning cardiac involvement of amyloidosis, as well as improvement in imaging modalities (i.e. strain imaging [49,50], MRI [51] and bisphosphonate scintigraphy [31]) enables an earlier diagnosis and might influence the outcomes of CA beneficially. Moreover, chemotherapy options have introduced and expanded in recent years resulting in significant improvements in survival of patients with AL amyloidosis, even in patients with significant cardiac involvement [52,53]. Although tafamidis has been demonstrated to reduce all-cause mortality and cardiovascular-related hospitalization rate in patients with ATTR-CA, its impact on the outcomes of the patients included in our present study might be neglectable, as only a very small number of patients were treated with tafamidis as part of the international multicenter double-blinded placebo-controlled phase III trial (21 patients receiving tafamidis were from Germany) [12]. In May 2019 it became the first therapy specifically designed for the treatment of ATTR-CA approved by the US Food and Drug Administration (FDA).

To the best of our knowledge, the present study provides for the time prevalence-estimates for amyloidosis, HF and CA in a large-scale population in Germany. Our data indicate that patients with amyloidosis represent a population at highest risk for adverse in-hospital events and in-hospital mortality (predominantly in younger age-groups).

5. Limitations

There are some limitations regarding our study that require consideration: First, the study results are based on ICD and OPS discharge codes of hospitalized patients, which might be under-reported or under-coded. Second, data about the administration of HF standard medications are not available in the dataset of the Federal Statistical Office of Germany. Third, we could provide only data for the in-hospital stay, but not for the later follow-up. Fourth, with these data of the Statistisches Bundesamt we could not distinguish between first and recurrent/repeat hospitalizations of the individual patient. This major limitation might lead to an over-estimated prevalence rate of amyloidosis patients, who are more likely to be re-hospitalized due to lack of a targeted disease specific therapy for ATTR amyloidosis during most of the investigated years of this study, and AL amyloidosis patients with cardiac involvement may also be more likely to be re-hospitalized. Fifth, a main limitation of our present study is, that we are not able to differentiate between the subtypes of amyloidosis (i.e. ATTRh, ATTRwt and AL) due to DRG coding. Sixth, we cannot provide information on the left ventricular ejection fraction and the underlying phenotypes of HF (i.e. HFpEF, HFmrEF and HFrEF).

6. Conclusion

The prevalence of hospitalized CA was low with 1.87 cases per 100,000 population. CA was identified as an independent risk factor for complications and in-hospital mortality in certain age groups of hospitalized HF patients. Despite younger age and favorable cardiovascular risk profile, we observed a similar case-fatality rate for HF patients with CA compared to those without. Thus, health care providers should be aware of this issue especially with respect to the requirements of treatment options and monitoring of patients with CA.

Declaration of Competing Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. SG, AD, TM, CR, and KK report no conflict of interest. LH reports having received lecture honoraria from MSD. PW reports having received consultancy and

lecture honoraria from Abbot Vascular, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Novartis. TG has received grant support (CARIMA study) and speaker's honoraria from Novartis, speaker's honoraria from Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer – Bristol-Myers Squibb and Astra Zeneca

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.05.013.

References

[1] Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. Arch Intern Med 2006;166(17):1805–13.
[2] Steiner I, Hajkova P. Patterns of isolated atrial amyloid: a study of 100 hearts on autopsy. Cardiovasc Pathol 2006;15(5):287–90.
[3] Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, Koch A, Sack FU, Katus HA, Linke RP, Dengler TJ. High prevalence of amyloid in 150 surgically removed heart valves–a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. Cardiovasc Pathol 2010;19(4):228–35.
[4] Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641–54. 10038.
[5] 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, Investigators T. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (transthyretin amyloid outcome survey). J Am Coll Cardiol 2016;68(2):161–72.
[6] Damy T, Kristen AV, Suhr OB, Maurer MS, Plante-Bordeneuve V, Yu CR, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the transthyretin amyloidosis outcomes survey (THAOS). Eur Heart J 2019;43(5):391–400. https://doi.org/10.1093/eurheartj/ehz173.
[7] Falk RH, Alexander KM, Liao R, AL DorbalaS. Light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016;68(12):1323–41.
[8] Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ, Riley SJ, Subramanya V, Brown EE, Hopkins CD, Ononogbu S, Perzel Mandell K, Halushka MK, Steenbergen C, Rosenberg AZ, Tedford RJ, Judge DP, Shah SJ, Russell SD, Kass DA, Sharma K. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. JACC Heart Fail 2020;8(9):712–24.
[9] Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36(38):2585–94.
[10] Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, Grogan M, Hayman SR, Kapoor P, Leung N, Fonder A, Hobbs M, Hwa YL, Gonsalves W, Warsame R, Kourelis TV, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Kyle RA, Rajkumar SV, Dispenzieri A. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood 2017;129(15):2111–9.
[11] Yilmaz A, Bauersachs J, Bengel F, Buchel R, Kindermann I, Klingel K, Knebel F, Meder B, Morbach C, Nagel E, Schulze-Bahr E, Aus dem Siepen F, Frey N. Diagnosis and treatment of cardiac amyloidosis: position statement of the German cardiac society (DGK). Clin Res Cardiol 2021;110(4):479–506.
[12] 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, Investigators A-AS. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379(11):1007–16.
[13] Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. Adv Ther 2015;32(10):920–8.
[14] Bishop E, Brown EE, Fajardo J, Barouch LA, Judge DP, Halushka MK. Seven factors predict a delayed diagnosis of cardiac amyloidosis. Amyloid 2018;25(3):174–9.
[15] Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, Rowczenio DM, Gilbertson JA, Hutt DF, Rezk T, Strehina SG, Caringal-Galima J, Manwani R, Sharpley FA, Wechalekar AD, Lachmann HJ, Mahmood S, Sachchithanantham S, Drage EPS, Jenner HD, McDonald R, Bertolli O, Calleja A, Hawkins PN, Gillmore JD. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation 2019;140(1):16–26.
[16] Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, Basset M, Hawkins P, Merlini G, Wechalekar AD. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126(5):612–5.
[17] Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, Falk RH, Dorbala S. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service medicare beneficiaries in the United States. Circ Heart Fail 2019;12(6):e005407.
[18] Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Buck FS, Buxbaum JN. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. N Engl J Med 1997;336(7):466–73.
[19] Internet Page of the InEK GmbH, Institut für das Entgeltsystem im Krankenhaus vanO. Deutsche kodierrichtlinien 2018 druckversion A4 (PDF). https://www.g-drg.de/inek_site_de/layout/set/standard/Media/Files/G-DRG-System/G-DRG-System_2018/Deutsche_Kodierrichtlinien_2018_Druckversion_A4_PDF 2018 (assessed 10th April 2019).
[20] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
[21] Liao R, Ward JE. Amyloid cardiomyopathy: disease on the rise. Circ Res 2017;120(12):1865–7.
[22] Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, Grogan M, Kristen AV, Lousada I, Nativi-Nicolau J, Cristina Quarta C, Rapezzi C, Ruberg FL, Witteles R, Merlini G. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail 2019;12(9):e006075.
[23] Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL, American Heart Association Heart F, Transplantation Committee of the Council on Clinical C. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American heart association. Circulation 2020;142(1):e7–22.
[24] Bennani Smires Y, Victor G, Ribes D, Berry M, Cognet T, Mejean S, Huart A, Roussel M, Petermann A, Roncalli J, Carrie D, Rousseau H, Berry I, Chauveau D, Galinier M, Lairez O. Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. Int J Cardiovasc Imaging 2016;32(9):1403–13.
[25] Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, Wollenweber T, Ahmed N, Thornton GD, Kelion AD, Sabharwal N, Newton JD, Ozkor M, Kennon S, Mullen M, Lloyd G, Fontana M, Hawkins PN, Pugliese F, Menezes LJ, Moon JC, Mascherbauer J, Treibel TA. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. J Am Coll Cardiol 2021;77(2):128–39.
[26] Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, Hartman N, Hawkins PN, Menezes LJ, Moon JC. Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. J Am Coll Cardiol 2018;71(4):463–4.
[27] Kyle RA, Larson DR, Kurtin PJ, Kumar S, Cerhan JR, Therneau TM, Rajkumar SV, Vachon CM, Dispenzieri A. Incidence of AL amyloidosis in Olmsted county, Minnesota, 1990 through 2015. Mayo Clin Proc 2019;94(3):465–71.
[28] Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018;2(10):1046–53.
[29] Alexander KM, Orav J, Singh A, Jacob SA, Menon A, Padera RF, Kijewski MF, Liao R, Di Carli MF, Laubach JP, Falk RH, Dorbala S. Geographic disparities in reported US amyloidosis mortality from 1979 to 2015: potential underdetection of cardiac amyloidosis. JAMA Cardiol 2018;3(9):865–70.
[30] Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, Westermark P. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification international society of amyloidosis 2016 nomenclature guidelines. Amyloid 2016;23(4):209–13.
[31] Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133(24):2404–12.
[32] Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, Berk JL, Plante-Bordeneuve V, Schmidt HHJ, Merlini G. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. J Am Coll Cardiol 2015;66(21):2451–66.
[33] Hemminki K, Li X, Forsti A, Sundquist J, Sundquist K. Cancer risk in amyloidosis patients in Sweden with novel findings on non-Hodgkin lymphoma and skin cancer. Ann Oncol 2014;25(2):511–8.
[34] Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. Blood 2020;136(23):2620–7.

[35] Al Hamed R, Bazarbachi AH, Bazarbachi A, Malard F, Harousseau JL, Mohty M. Comprehensive review of AL amyloidosis: some practical recommendations. Blood Cancer J 2021;11(5):97.
[36] Bianchi G, Zhang Y, Amyloidosis ComenzoRLAL. Current chemotherapy and immune therapy treatment strategies: JACC: cardiooncology state-of-the-art review. JACC CardioOncol 2021;3(4):467–87.
[37] Rubin J, Maurer MS. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annu Rev Med 2020;71:203–19.
[38] Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol 2012;7(8):1337–46.
[39] 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(17):2040–50.
[40] Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, Koyama J, Yanagisawa S, Ikeda S. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid 2016;23(1):58–63.
[41] Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in primary amyloidosis: resolution after splenectomy. N Engl J Med 1979;301(19):1050–1.
[42] Choufani EB, Sanchorawala V, Ernst T, Quillen K, Skinner M, Wright DG, Seldin DC. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood 2001;97(6):1885–7.
[43] Falk RH, Dubrey SW. Amyloid heart disease. Prog Cardiovasc Dis 2010;52(4):347–61.
[44] Boldrini M, Salinaro F, Mussinelli R, Raimondi A, Alogna A, Musca F, Palladini G, Merlini G, Perlini S. Prevalence and prognostic value of conduction disturbances at the time of diagnosis of cardiac AL amyloidosis. Ann Noninvasive Electrocardiol 2013;18(4):327–35.
[45] Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol 2005;95(4):535–7.
[46] Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RM, 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: disease profiles and clinical courses of the 3 main types. Circulation 2009;120(13):1203–12.
[47] Keller K, Hobohm L, Ostad MA, Gobel S, Lankeit M, Konstantinides S, et al. Temporal trends and predictors of inhospital death in patients hospitalised for heart failure in Germany. Eur J Prev Cardiol 2021;28(9):990–7. https://doi.org/10.1177/2047487320936020.
[48] Aus dem Siepen F, Hein S, Bauer R, Katus HA, Kristen AV. Standard heart failure medication in cardiac transthyretin amyloidosis: useful or harmful? Amyloid 2017;24(sup1):132–3.
[49] Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, Gaudron PD, Knop S, Ertl G, Bijnens B, Weidemann F. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6(6):1066–72.
[50] Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98(19):1442–8.
[51] Vogelsberg H, Mahrholdt H, Deluigi CC, Yilmaz A, Kispert EM, Greulich S, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 2008;51(10):1022–30.
[52] Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, Greipp PR, Witzig TE, Lust JA, Rajkumar SV, Fonseca R, Zeldenrust SR, McGregor CG, Jaffe AS. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004;22(18):3751–7.
[53] Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012;30(9):989–95.