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Prognostic impact of age and gender on patients with electrical storm

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Abstract

Background: *Electrical storm (ES) is a severe and life-threatening heart rhythm disorder. Age and male gender have been identified as independent risk factors for cardiovascular diseases. However, data regarding the prognostic impact of age and gender on ES patients is limited.*

Methods: *The present study included retrospectively consecutive patients presenting with ES from 2002 to 2016. Patients 67 years old or older were compared to patients younger than 67, males were also compared to females. Receiver operating characteristic analyses were performed to find the optimum age cut-off value. The primary endpoint was all-cause mortality at 3 years. The secondary endpoints were in-hospital mortality, rehospitalization rates, ES recurrences, and major adverse cardiac events (MACE) at 3 years.*

Results: *Eighty-seven ES patients with implantable cardioverter-defibrillators were included. Age ≥ 67 years was associated with increased all-cause mortality at 3 years (48% vs. 20%, hazard ratio = 3.046; 95% confidence interval 1.316–7.051; p = 0.008; log-rank p = 0.006). MACE, in-hospital mortality, re-hospitalization rates, and ES recurrences were not affected by age. Even after multivariate adjustment, age ≥ 67 years was associated with increased long-term mortality at 3 years, besides left ventricular ejection fraction < 35%. In contrast, gender was not associated with primary and secondary endpoints.*

Conclusions: *Patients 67 years old and older presenting with ES are associated with poor long-term prognosis. Increased long-term mortality was still evident after multivariate adjustment. In contrast, gender was not associated with primary and secondary endpoints.* (Cardiol J)

Key words: electrical storm, age, gender, long-term mortality

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Introduction

Electrical storm (ES) is a severe heart rhythm disorder defined as at least three distinct episodes of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) within 24 hours (separated by at least 5 min), requiring termination by an intervention [1, 2]. ES is associated with increased mortality of 40% at 1 year [3]. The clinical presentation varies between asymptomatic patients and those with severe hemodynamic instability or cardiac death [4]. Therefore, therapeutic options are diverse and include pharmacotherapy to reduce sympathetic system tension (first-line therapy beta-blockers), device therapy (overdrive stimulation, antitachycardia pacing, internal high voltage therapy), external cardioversion or defibrillation, rescue ablation of VT, and extracorporeal membrane oxygenation or intra-aortic balloon pump [1, 3]. Individually tailored therapy risk stratification is needed in this high-risk cohort and might improve patient outcomes [3].

The population of elderly patients is increasing in Europe [5]. Advanced age is the main risk factor for vascular disease [6]. The incidence of ventricular tachyarrhythmias (VTA) increases with age and is mostly attributed to higher rates of structural heart disease in the elderly, like ischemic or hypertensive cardiomyopathy [5, 7]. The treatment of VTA in elderly patients is a severe clinical challenge. Adverse effects of antiarrhythmic drugs have been frequently seen in elderly patients. These side effects are mostly attributed to decreased physiological function, side effects of polypharmacy, and geriatric syndromes [8, 9].

Male gender is an established risk factor for the future development of cardiovascular disease (CVD) [10]. Steroid hormones like estrogen and progesterone influence gender-related cardiovascular risk profiles [11]. It has been shown that steroid hormones affect blood pressure regulation, blood flow, vasodilatation, vascular inflammation, and atherosclerosis [11]. However, prior studies have reported an absence of these effects in postmenopausal women [12].

The prognostic impact of age and gender on ES patients has been investigated very little. Although advanced age is a known cardiovascular risk factor, elderly patients are usually excluded from most randomized controlled trials [13]. It is essential to identify clinical risk factors that impact ES patients' long-term prognosis to reduce morbidity and mortality.

Therefore, the present longitudinal, observational, registry-based, monocentric cohort study investigates the prognostic impact of age ≥ 67 years and gender on long-term all-cause mortality, major adverse cardiac events (MACE), in-hospital mortality, rehospitalization rates, and recurrences of ES (ES-R) in patients presenting with ES.

Methods

Study population

All consecutive patients with implantable cardioverter-defibrillator (ICD) referred to our institution with an ES diagnosis between 2002 and 2016 were included. ES was defined as three or more episodes of VTA, delimited by at least 5 minutes, leading to appropriate ICD therapy during a single 24-hour time period [1]. Only ICD recipients were included. All relevant clinical data were documented using the electronic hospital information system, ICD protocols, discharge letters, daily charts, patient files, and reports from diagnostic testing, including 12-lead electrocardiogram (ECG) and Holter ECG assessed during the clinical routine.

In detail, data documentation included baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies like coronary angiography and electrophysiological examination, and imaging modalities like echocardiography or cardiac magnetic resonance imaging. The documentation period lasted from the index event until 2016. Independent cardiologists blinded to final data analyzes performed all medical data documentation at the time of the patient's individual clinical presentation period.

The present study is derived from a retrospective analysis of the Registry of Malignant Arrhythmias and Sudden Cardiac Death–Influence of Diagnostics and Interventions (RACE-IT) and represents a single-center registry that includes consecutive patients presenting with VTA and aborted cardiac arrest and acutely admitted to the University Medical Center Mannheim, Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 until 2016. The registry was carried out according to the principles of the Declaration of Helsinki. It was approved by the medical ethics committee II of the Faculty of Medicine Mannheim, University of Heidelberg, Germany.

Definition of study groups, inclusion and exclusion criteria

Risk stratification was performed according to age and gender. Only patients who already had an ICD and presented with ES were analyzed. Receiver operating characteristic (ROC) analyzes were performed to find the highest Youden index. The Youden index, defined as the maximum of sensitivity + specificity –1, was used to find the optimum age cut-off for the present study [14, 15]. Furthermore, males were compared to females. Each patient was counted only once for inclusion when presenting with the first episode of ES.

Study endpoints

The primary endpoint was all-cause mortality at a follow-up of 3 years. Secondary endpoints were in-hospital mortality, first cardiac rehospitalization, MACE, and ES-R at long-term follow-up of 3 years. First cardiac rehospitalization was related to recurrent VT and VF, excluding ES-R, and to cardiopulmonary resuscitation, acute heart failure, or acute myocardial infarction (AMI). AMI patients included those with both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction according to current guidelines [16]. In addition, the coronary angiography results at index stay were retrieved to update these patients' coronary artery disease diagnoses. MACE was defined as the composite of AMI, target vessel revascularization by percutaneous coronary intervention or coronary artery bypass grafting, and the primary endpoint of all-cause mortality [16]. ES-R was defined as the recurrence of further ES episodes at follow-up beyond the initial 24 hours of prior ES [2]. The follow-up period lasted until 2016. All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices (Bureau of mortality statistics) across Germany. Patient identity was verified by name, surname, date of birth, and registered living address.

Statistical methods

Quantitative data are presented as mean ± standard error of mean, median, and interquartile range and ranges, depending on the data distribution, and were compared using the Student t-test for normally distributed data or the Mann–Whitney U test for nonparametric data. The Kolmogorov–Smirnov test tested deviations from a Gaussian distribution. The Spearman rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as appropriate and relative frequencies and were compared using the χ^2 test or the Fisher exact test.

Multivariate Cox regression models were developed using the "forward selection" option, where only statistically significant variables ($p < 0.05$) were included and analyzed simultaneously (see below). The following analyzes were applied stepwise to evaluate the prognostic value of predefined variables for all-cause mortality: Kaplan-Meier survival curves were calculated with log-rank testing for statistical significance. Univariate hazard ratios (HR) are given with 95% confidence intervals (CI). Multivariate Cox regressions were applied for age analyzes only because of an assumed higher event rate for the primary endpoint. Predefined variables used for the multivariate Cox regressions included age ≥ 67 years, male gender, coronary artery disease, atrial fibrillation, left ventricular ejection fraction (LVEF) < 35%, beta-blocker, and, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). The result of a statistical test was considered significant for $p < 0.05$. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistics.

Results

Study population by age < 67 years and ≥ 67 years

Eighty-seven consecutive patients with ES at index were included in the present study. The maximum Youden index was 0.353 for a cut-off at 67 years. Therefore, patients 67 years old and older were compared to patients younger than 67 years old. Of these, 40% were younger than 67, and 60% were 67 or older. As outlined in Table 1, most patients were male, and significantly more patients 67 years old or older suffered from arterial hypertension (73% vs. 49%; $p = 0.020$). Furthermore, patients 67 years old or older had a significantly lower LVEF (79% vs. 53%, $p = 0.042$) and higher rates of ischemic cardiomyopathy (52% vs. 46%, $p = 0.016$). Notably, all patients 67 years old and older were treated with beta-blockers at discharge (100% vs. 87%, $p = 0.015$). No other differences were seen between these patient groups (Table 1).

Study population in patients by gender

Of the 87 patients included in this study, 15% were female, and 85% were male. As outlined in Table 2, in-hospital cardiac arrest was more frequent in females (15% vs. 1%, $p = 0.010$). Differences

Table 1. Baseline characteristics of patients presenting with electrical storm by age < 67 years and ≥ 67 years.

Characteristic	Age < 67 years (n = 35; 40%)	Age ≥ 67 years (n = 52; 60%)	P
Age, [year] median (range)	56 (22–67)	77 (68–85)	**0.001**
Male gender	28 (80%)	46 (89%)	0.278
Cardiopulmonary resucitation:	2 (6%)	3 (6%)	0.991
Out-of-hospital	1 (3%)	2 (4%)	0.999
In-hospital	1 (3%)	1 (2%)	0.775
Cardiovascular risk factors:			
Arterial hypertension	17 (49%)	38 (73%)	**0.020**
Diabetes mellitus	6 (17%)	16 (31%)	0.152
Hyperlipidemia	11 (31%)	26 (50%)	0.086
Smoking	9 (26%)	6 (12%)	0.086
Cardiac family history	2 (6%)	5 (10%)	0.512
Comorbidities:			
Acute myocardial infarction	0 (0%)	0 (0%)	–
Chronic kidney disease	8 (30%)	22 (51%)	0.076
Atrial fibrillation	12 (34%)	24 (46%)	0.270
Liver cirrhosis	1 (3%)	2 (4%)	0.804
COPD	3 (9%)	12 (23%)	0.079
Prior stroke	6 (17%)	6 (12%)	0.917
Cardiomyopathy:			
Ischemic cardiomyopathy	16 (46%)	27 (52%)	**0.016**
Non-ischemic cardiomyopathy	3 (9%)	5 (10%)	0.868
Not documented	15 (14%)	20 (39%)	0.681
Channelopathies:			
Long-QT syndrome	1 (3%)	0 (0%)	0.402
Brugada syndrome	1 (3%)	0 (0%)	0.402
Short-QT syndrome	0 (0%)	0 (0%)	–
Coronary angiography:	24 (69%)	43 (83%)	0.124
No coronary artery disease	8 (33%)	6 (14%)	0.257
Coronary one vessel disease	4 (17%)	7 (17%)	
Coronary two vessel disease	6 (25%)	12 (28%)	
Coronary three vessel disease	6 (25%)	18 (27%)	
Electophysiological examination:	10 (29%)	11 (21%)	0.428
VT ablation	9 (26%)	9 (17%)	0.343
Laboratory data:			
Hemoglobin [g/dL]	13.7 ± 0.3	12.7 ± 0.3	0.778
Potassium [mmol/L]	3.9 ± 0.1	4.1 ± 0.1	0.282
Creatinine [mg/dL]	1.2 ± 0.08	1.5 ± 0.1	0.403
Urea [mg/dL]	83.0 ± 12.0	88.0 ± 14.0	0.673
C-reactive protein [mg/dL]	20.9 ± 6.6	35.2 ± 8.7	0.197
Troponin I [μg/L]	0.4 ± 0.1	0.2 ± 0.0	0.128
Medication at discharge:			
Beta-blocker	31 (87%)	49 (100%)	**0.015**
ACE inhibitor/ARB	28 (80%)	39 (80%)	0.963
Statin	19 (54%)	31 (63%)	0.408
Amiodarone	16 (46%)	29 (59%)	0.222

→

Table 1 (cont.). Baseline characteristics of patients presenting with electrical storm by age < 67 years and ≥ 67 years.

Characteristic	Age < 67 years (n = 35; 40%)	Age ≥ 67 years (n = 52; 60%)	P
ECG data			
PQ [ms]	240 ± 60	216 ± 10	**0.015**
QRS [ms]	120 ± 20	129 ± 15	0.401
QT [ms]	435 ± 19	442 ± 19	0.090
LVEF:			**0.042**
≥ 55%	7 (21%)	2 (4%)	
45–54%	4 (13%)	3 (6%)	
35–44%	4 (13%)	5 (10%)	
< 35%	17 (53%)	38 (79%)	
Type of ICD:			0.170
ICD	32 (91%)	44 (85%)	
CRT-D	1 (3%)	7 (14%)	
s-ICD	2 (6%)	1 (2%)	
ICD indication:			0.071
Primary prevention	17 (49%)	15 (29%)	
Secondary prevention	18 (51%)	36 (71%)	
ICD programming [bpm], median (IQR):			
VT detection threshold	169 (128–220)	165 (133–188)	0.382
VF detection threshold	217 (200–250)	219 (200–250)	0.486

Data are shown as number (%), mean ± standard error of mean, median and interquartile range (IQR); ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blocker; COPD — chronic obstructive pulmonary disease; CRT-D — cardiac resynchronisation therapy defibrillator; ECG — electrocardiogram; ICD — implantable cardioverter- defibrillator; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 2. Baseline characteristics of female and male patients presenting with electrical storming.

Characteristic	Female (n = 13; 15%)	Male (n = 74; 85%)	P
Age [year], median (range)	65 (52–83)	72 (22–85)	0.414
Cardiopulmonary resucitation:	3 (23%)	5 (7%)	0.744
Out-of-hospital	1 (8%)	4 (5%)	0.743
In-hospital	2 (15%)	1 (1%)	**0.010**
Cardiovascular risk factors:			
Arterial hypertension	11 (85%)	44 (60%)	0.083
Diabetes mellitus	4 (31%)	18 (24%)	0.622
Hyperlipidemia	7 (54%)	30 (40%)	0.371
Smoking	0 (0%)	15 (20%)	0.074
Cardiac family history	2 (15%)	5 (7%)	0.292
Comorbidities:			
Acute myocardial infarction	0 (0%)	0 (0%)	–
Chronic kidney disease	6 (46%)	24 (32%)	0.337
Atrial fibrillation	7 (54%)	29 (39%)	0.322
Liver cirrhosis	1 (8%)	3 (4%)	0.563
COPD	2 (15%)	13 (18%)	0.847
Prior stroke	2 (15%)	12 (16%)	0.940

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Table 2. Baseline characteristics of female and male patients presenting with electrical storming.

Characteristic	Female (n = 13; 15%)	Male (n = 74; 85%)	P
Cardiomyopathy:			
Ischemic cardiomyopathy	5 (38%)	36 (48%)	0.443
Non-ischemic cardiomyopathy	1 (8%)	8 (11%)	0.733
Not documented	7 (54%)	30 (41%)	0.370
Channelopathies:			
Long-QT syndrome	1 (8%)	0 (0%)	1.000
Brugada syndrome	0 (0%)	1 (1%)	1.000
Short-QT syndrome	0 (0%)	0 (0%)	–
Coronary angiography at index:	12 (92%)	54 (73%)	0.132
No coronary artery disease	4 (33%)	10 (18%)	0.664
Coronary one vessel disease	2 (17%)	9 (16%)	
Coronary two vessel disease	3 (25%)	15 (27%)	
Coronary three vessel disease	3 (25%)	21 (39%)	
Electophysiological examination:	1 (8%)	20 (27%)	0.133
VT ablation	1 (8%)	17 (23%)	0.210
Laboratory data:			
Hemoglobin [g/dL]	12.3 ± 0.5	13.3 ± 0.2	0.194
Potassium [mmol/L]	4.0 ± 0.2	4.0 ± 0.08	0.513
Creatinine [mg/dL]	1.4 ± 0.1	1.4 ± 0.08	0.861
Urea [mg/dL]	87.2 ± 6.5	87.2 ± 13.7	0.289
C-reactive protein [mg/dL]	61.9 ± 18.5	24.5 ± 6.0	0.187
Troponin I [μg/L]	0.3 ± 0.1	0.3 ± 0.06	0.462
Medication at discharge:			
Beta-blocker	13 (100%)	68 (94%)	0.403
ACE inhibitor/ARB	10 (83%)	57 (79%)	0.739
Statin	7 (58%)	43 (60%)	0.928
Amiodarone	6 (50%)	39 (54%)	0.789
ECG data:			
PQ [ms]	220 ± 40	220 ± 10	0.055
QRS [ms]	113 ± 13	134 ± 18	0.256
QT [ms]	400 ± 0	448 ± 15	**0.002**
LVEF:			0.727
≥ 55%	2 (15%)	7 (10%)	
45–54%	2 (15%)	5 (8%)	
35–44%	1 (8%)	8 (12%)	
< 35%	8 (62%)	47 (70%)	
Type of ICD:			0.654
ICD	11 (85%)	65 (88%)	
CRT-D	1 (8%)	7 (10%)	
s-ICD	1 (8%)	2 (3%)	
ICD indication:			0.919
Primary prevention	5 (39%)	27 (37%)	
Secondary prevention	8 (61%)	46 (63%)	
ICD programming [bpm], median (IQR):			
VT detection threshold	171 (136–220)	165 (128–188)	0.410
VF detection threshold	217 (200–250)	218 (200–250)	0.703

Data are shown as number (%), median and interquartile range (IQR); ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blocker; COPD — chronic obstructive pulmonary disease; CRT-D — cardiac resynchronisation therapy defibrillator; ICD — implantable cardioverter- defibrillator; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 3. Primary and secondary endpoints of patients with electrical storm, by age < 67 and ≥ 67 years.

Characteristic	Age < 67 years (n = 35; 40%)	Age ≥ 67 years (n = 52; 60%)	P
Primary endpoint			
All-cause mortality at 3 years	7 (20%)	25 (48%)	**0.008**
Secondary endpoints			
In-hospital mortality	0 (0%)	2 (4%)	0.513
First cardiac rehospitalization	18 (51%)	20 (38%)	0.231
Major adverse cardiac event	10 (29%)	25 (48%)	0.069
Electricial storm-recurrence	6 (17%)	16 (31%)	0.152

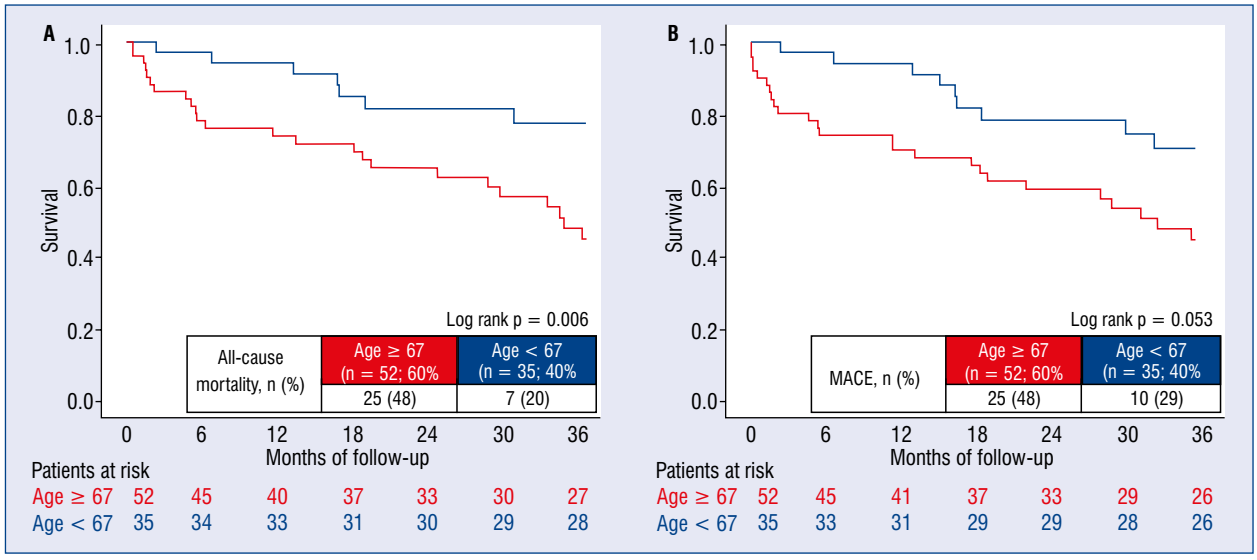

Figure 1. Prognostic impact of age on long-term all-cause mortality at long-term follow-up of 3 years (**A**) and major adverse cardiac events (MACE) (**B**).

between males and females were found in ECG data. Female patients showed a significantly longer QT interval (400 ± 0 vs. 448 ± 15, p = 0.002) (Table 2). No other differences were seen between the two groups (Table 2).

Primary and secondary endpoints by age < 67 years and ≥ 67 years

Follow-up for all patients regarding the primary endpoint of all-cause mortality was performed at 3 years (median 2.45 years, interquartile range 1.01–4.77 years), with at least one ICD check-up regularly every 6 to 12 months. Patients 67 years old and older were associated with the primary endpoint of all-cause mortality at 3 years (48% vs. 20%, HR = 3.046; 95% CI 1.316–7.051; p = = 0.008; log-rank p = 0.006) (Table 3; Fig. 1A) but not with MACE (48% vs. 29%, HR = 2.034; 95% CI 0.976–4.238; p = 0.069; log-rank p = 0.053) (Table 3; Fig. 1B), in-hospital mortality (4% vs. 0%, p = 0.513), first cardiac rehospitalization (38% vs. 51%, p = 0.231), or ES-R (31% vs. 17%, p = 0.152) (Table 3).

Primary and secondary endpoints by gender

The primary and secondary endpoints were not affected by gender (Table 4; Fig. 2).

Multivariate Cox regression by age < 67 years and ≥ 67 years

Even after multivariate adjustment, age ≥ 67 years was associated with increased long--term mortality at 3 years (HR = 4.267, 95% CI 1.057–8.277, p = 0.039), besides LVEF < 35% (HR = 10.341, 95% CI 2.127–50.26, p = 0.004). The presence of beta-blockers (HR = 0.119, 95% CI 0.017–0.825, p = 0.031) and ACE inhibi-

Table 4. Primary and secondary endpoints in female and male patients with electrical storm.

Characteristic	Female (n = 13; 15%)	Male (n = 74; 85%)	P
Primary endpoint			
All-cause mortality	5 (39%)	27 (37%)	0.892
Secondary endpoints			
In-hospital mortality	0 (0%)	2 (3%)	0.549
First cardiac rehospitalization	5 (38%)	33 (45%)	0.680
Major adverse cardiac event	6 (46%)	29 (39%)	0.637
Electricial storm-recurrence	2 (15%)	20 (27%)	0.376

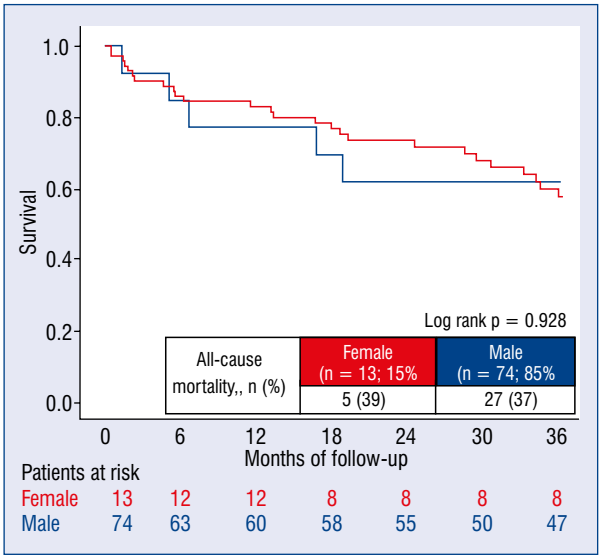

Figure 2. Prognostic impact of gender on long-term all--cause mortality at long-term follow-up of 3 years.

Table 5. Multivariable Cox regression analyses.

Endpoint	All-cause mortality at 3 years		
	HR	95% CI	P
Age ≥ 67 years	4.267	1.057–8.277	**0.039**
Male gender	0.407	0.135–1.223	0.109
CAD	0.977	0.398–2.494	0.995
Atrial fibrillation	1.115	0.523–2.377	0.778
LVEF < 35%	10.341	2.127–50.26	**0.004**
Beta-blocker	0.119	0.017–0.825	**0.031**
ACE-inhibitor/ARB	0.345	0.143–0.831	**0.018**

Level of significance p < 0.05, statistical trend p < 0.1; ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blockers; CAD — coronary artery disease; CI — confidence interval; HR — hazard ratio; LVEF — left ventricular ejection faction

tors or ARBs at discharge (HR = 0.345, 95% CI 0.143–0.831, p = 0.018) was beneficial (Table 5).

Discussion

The present study evaluates the prognostic impact of age and gender in consecutive high-risk patients presenting with ES on admission. The data suggest that ES patients 67 years old or older have higher long-term mortality at 3 years than younger patients. In-hospital mortality rates, risk of first cardiac rehospitalization, ES-R, and MACE were not affected by age. Gender was not associated with increased long-term mortality at 3 years or the secondary endpoints.

The causative pathology for the development of ES is yet not fully understood. However, severe systolic dysfunction, chronic renal failure, and age are clinical predictors for the development of ES [17]. A meta-analysis showed a 3-fold higher risk of death in ES patients compared to VTA patients without ES [18]. However, in this meta-analysis, advanced age and gender were not associated with an increased prevalence of ES [18]. According to available research, the prognostic impact of age and gender on the long-term mortality of ICD patients who have already survived ES has never been investigated.

Age is a widely discussed risk factor for cardiovascular morbidity and mortality [8]. The incidence of VTA increases with age and is mainly attributed to structural heart diseases like ischemic or hypertensive cardiomyopathy [7, 19].

However data for elderly ES patients are very rare [8]. Most studies concentrate on conventional cardiovascular risk factors, such as arterial hypertension, diabetes mellitus, and hyperlipoproteinemia [20]. Elderly patients are frequently excluded from randomized controlled trials [8].

Studies on age are usually confronted with the argument that elderly patients, in general, are at greater risk of all-cause mortality than younger patients. In daily clinical routine, advanced age influences therapeutic decisions, as it is assumed

that elderly patients are, per se, at greater risk of all-cause mortality than younger patients. In triage especially, one must be able to make the influence of advanced age objective to give the appropriate priority to chronological age. The general mortality statistics from Germany in 2015 showed that the risk of mortality per year for elderly patients (age > 60 years) was 12 times higher than that for middle-aged patients (40–60 years) (0.97% ÷ 0.08% = 12) [21]. All-cause mortality rates in the present preselected cohort of critically ill patients with ES are overall higher, but the rate for elderly patients is only 2.4 times higher than for patients under 67 (48% ÷ 20% = 2.4). The present data suggest that increasing age is associated with increased mortality in ES patients but with a weaker influence than in the general population.

In addition to chronological age, biological or vascular age might worsen prognosis in ES patients. Biological age is influenced by chronic diseases like heart failure and chronic kidney disease [6]. The present study showed that heart failure (LVEF < 35%), in addition to age ≥ 67 years, was associated with increased mortality in ES patients. Furthermore, patients 67 years old or older showed a numerically higher rate of chronic kidney disease (CKD) than patients younger than 67. Prior studies have demonstrated that severe heart failure, CKD, and age increase the risk of developing ES for ICD patients, and that elderly patients have a lower survival rate after ICD implantation (mean survival 1.5 years) when both CKD and LVEF < 35% were present [7, 17]. These findings underline that chronological age alone should not be used to estimate prognosis in ES patients, but rather that it should be evaluated in the context of a patient's biological age.

There are several potential mechanisms in the pathogenesis of cardiac diseases and aging. The aging heart is associated with myocardial inflammation that might lead to calcium channel dysfunction, reduced cardiomyocyte density, and altered formation of collagen fibers [5, 22]. These processes have been associated with a higher risk of VTA, and they might be accelerated by VTA [23]. Laboratory experiments have investigated the effect of recurrent VTA like ES on the myocardium [24]. It has been shown that recurrent VTA are associated with increased intracellular calcium, which ultimately leads to a decreased systolic LVEF [24]. In addition, repeated ICD shocks lead to myocardial injury with consecutive myocardial inflammation and fibrosis [24]. Myocardial aging processes may encourage VTA, and VTA and ICD shocks by themselves worsen the myocardial damage of the aging heart. These kinds of myocardial damage are associated with a decreased LVEF [24] and, therefore, with poorer long-term mortality in ES patients [7].

Male gender is an established risk factor implemented in guideline-recommended risk charts that estimate future CVD development risk in an individual [1]. Prior studies have shown that steroid hormones like estrogen and progesterone are associated with lower blood pressure, vasodilatation, and lower vascular inflammation and atherosclerosis [11]. However, these differences are not found in postmenopausal women due to lower steroid hormone levels [12]. Female patients included in the present study had a mean age of 65 and were most likely postmenopausal, which might explain the findings. However, only 13 female patients were included in the present study. Therefore, a gender-dependent influence on long-term all-cause mortality in ES patients must be investigated in further studies.

In conclusion, elderly patients represent a population at the highest risk of mortality. However, in patients with ES, chronological age impacts the mortality less than in the general population. Therefore, in risk stratification the influence of chronological age of ES patients must be considered in connection with their biological age. Adequate time must be spent within a multidisciplinary team to evaluate chronic diseases, geriatric syndromes, and the optimal individual pharmacological and interventional therapy. Therapeutic goals must be determined to prevent hospitalizations and maintain patients' quality of life [5, 21]. Male gender is an established risk factor in the development of CVD. Unfortunately, a small number of female postmenopausal patients were included in the present study. More extensive studies investigating this important risk factor are desirable. This study demonstrates the adverse prognostic impact for ES patients of age ≥ 67 years on long-term all-cause mortality at 3 years. However, the prognosis for males at 3 years was no worse than that for females.

Limitations of the study

The present observational study is based on a small sample size with retrospective data documentation. All-cause mortality was documented using an electronic hospital information system and directly contacting state resident registration offices across Germany. The mode of death could, therefore, not be verified, which is one of the main limitations of this study apart from the small sample size. Rehospitalization rates were

documented only within the present institution. The management of ES has changed in recent years, which is reflected in the present study cohort. The improvements in catheter ablation for ES during the last years might have influenced survival rates in these patients, and the improvements in catheter ablation, in particular, may have affected survival rates in ES patients over time. Furthermore, ICD programming changed during the last years, mainly due to the knowledge of the MADIT-RIT study in 2012, which might have influenced the endpoints in the present study. Moreover, recent studies reported that a percutaneous stellate ganglion blockade effectively attenuates ES and might have effects on prognosis. However, stellate ganglion blocade was not performed in any of the current patients.

This paper's low percentage of women might be underpowered for detecting differences among males and females.

Conclusions

Age ≥ 67 years was associated with increased long-term mortality in ICD patients presenting with ES. Male gender was not associated with an impaired prognosis.

Conflict of interest: None declared

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