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Elevated γ-glutamyltransferase in implantable cardioverter defibrillator patients

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Erhöhte γ-Glutamyltransferase bei ICD-Patienten

Zusammenfassung. *Hintergrund:* Erhöhte γ-Glutamyltransferase (GGT) Plasmaspiegel korrelieren mit kardiovaskulären Erkrankungen, aber nichts ist bekannt über eine mögliche Assoziation mit dem gehäuften Auftreten von ventrikulären Tachyarrhythmien. Weiters stellt sich die Frage, ob erhöhte GGT Werte auch bei ICD-Patienten mit einer erhöhten Sterblichkeit verbunden sind.

Methoden und Resultate: Aufgrund der geschlechtsspezifischen Normalwerte von GGT wurden nur männliche Patienten in die Analyse eingeschlossen. In einer retrospektiven Studie an 743 Patienten konnte gezeigt werden, dass erhöhte GGT Werte mit einer signifikant erhöhten Gesamtmortalität, nicht aber mit einer gehäuften Notwendigkeit von appropriater ICD-Therapie (antitachykardes Pacing, Schockabgabe) assoziiert sind. In einer Cox Regressionsanalyse bestätigte sich ein erhöhter GGT Wert (>56 U/L) als unabhängiger Risikofaktor für erhöhte Sterblichkeit, vor allem wenn dieser in Kombination mit einer eingeschränkten Nierenfunktion (GFR <60 ml/min/1,73 m^2) auftritt.

Zusammenfassung: Erhöhte GGT Werte sind trotz ICD Therapie mit einer erhöhten Gesamtsterblichkeit assoziiert. Es bleibt zu überprüfen, ob dieser Routineparameter in der verbesserten Patientenselektion zur ICD Therapie eine Rolle spielen kann.

Summary. *Background:* Elevated γ-glutamyltransferase (GGT) is a new risk factor for cardiovascular diseases, but its impact on ventricular tachyarrhythmia occurrence and survival in patients with an implantable cardioverter defibrillator (ICD) is unknown.

Methods and results: Considering that GGT levels are gender-dependent, female ICD recipients were excluded from our database because of the low incidence of events. In a retrospective analysis, appropriate ICD therapy (both shocks and antitachycardia pacing due to ventricular tachyarrhythmias) occurred in 31.9% of 320 male patients who had received an ICD for primary prevention (median follow-up of 2.3 years), and in 55.1% of 423 male patients who had received an ICD for secondary prevention (median follow-up of 3.9 years). Compared to normal low GGT plasma levels (below 28 U/L), total mortality but not risk for appropriate ICD therapy was elevated for higher GGT categories (p for trend = 0.004 in primary prevention and p for trend = 0.002 in secondary prevention, respectively). In Cox regression analysis, elevated GGT (>56 U/L) remained an independent predictor of death both in primary (p = 0.011) and in secondary prevention (p = 0.006). Patients with elevated GGT and renal insufficiency defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 suffered from excess total mortality jeopardizing the benefit of ICD therapy.

Conclusion: Elevation of GGT is an important adverse prognostic parameter in ICD patients. A possible role of GGT for improved patient selection for ICD therapy deserves further investigation.

Key words: γ-glutamyltransferase, heart failure, renal insufficiency, outcome, ventricular fibrillation, implantable cardioverter defibrillator.

Introduction

Treatment with an implantable cardioverter defibrillator (ICD) prolongs survival in patients with increased risk for sudden cardiac death (SCD) [1–3]. However, improved patient selection is still mandatory, considering that many ICD patients never suffer from ventricular tachyarrhythmias demanding ICD therapy. Furthermore, major comor-

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bidities such as advanced renal dysfunction may cause a high risk of short-term non-arrhythmogenic mortality despite ICD therapy [4].

Elevated GGT is related to incidence of and mortality from cardiovascular disease [5], but its impact on ventricular tachyarrhythmia occurrence and survival in patients with an implantable cardioverter defibrillator (ICD) is unknown. This study analysing retrospectively 743 male ICD recipients assessed the prognostic impact of GGT levels with respect to appropriate ICD therapies and mortality. In 690 male patients, elevated GGT levels defined as >56 U/L were correlated to established risk factors such as ischemic etiology, renal dysfunction, age, atrial fibrillation, broad QRS complex, advanced heart failure, severe left ventricular dysfunction and antiarrhythmic medical therapy [6–9].

Methods

Study population

Consecutive patients from the University Clinic of Innsbruck, Austria and from the University Clinic of Zürich, Switzerland, who had received an ICD in the years 1993–2009, were retrospectively analysed. Out of 1117 recipients, GGT values at the time of implantation were available in 945 patients. Considering that GGT levels are highly gender-dependent, female ICD recipients were excluded from our database because of the low incidence of events (4 deaths during follow-up in 76 women who had received an ICD for primary prevention of SCD, and 12 deaths during follow-up in 97 women who had received an ICD for secondary prevention of SCD). Furthermore, 32 male ICD recipients were excluded because of chronic alcoholism according to patients´ records. The underlying heart disease was coronary artery disease (CAD) in 459 (61.8%), dilated cardiomyopathy in 211 (28.4%), arrhythmogenic right ventricular dysplasia in 14 (1.9%), hypertrophic cardiomyopathy in 13 (1.7%), non-compaction cardiomyopathy in 12 (1.6%), valvular heart disease in 12 (1.6%), idiopathic VT/VF in 7 (0.9%), congenital heart disease in 7 (0.9%), Brugada syndrome in 4 (0.5%), cardiac sarcoidosis in 2 (0.3%), recurrent coronary vasospasm causing ventricular tachyarrhythmia in 1 (0.1%) and long QT syndrome in 1 (0.1%). The patients were routinely followed every 6 months, and appropriate or inappropriate ICD therapy was analysed by telemetry. Appropriate ICD therapy was defined as either antitachycardia pacing (ATP), cardioversion or defibrillation of ventricular tachycardia (VT) or ventricular fibrillation (VF) by analysis of the stored electrograms. Values reflect the highest New York Heart Association (NYHA) functional class recorded in the three-month period before ICD implantation. GGT concentrations from blood samples taken within one week before ICD implantation were measured at 37°C and were given as units per liter (U/L). Renal insufficiency was defined by an estimated glomerular filtration rate (eGFR) calculated according to the Modification of Diet in Renal Disease formula for men: $186 \times (\text{serum-creatinin}/0.95)^{-1.154} \times (\text{age})^{-0.203}$. The vast majority of patients received optimal neurohumoral medication as they were seen over years on a regular basis (6 months) in specialised outpatient units at University hospitals. Approximately 80% of all patients received betablocker therapy and ACE-inhibitors/angiotensin receptor blockers, respectively. At time of implantation, around 30% of patients received aldosterone inhibitors but their use increased with some delay after ICD implantation to more than 50% of all patients. CRT was indicated according to guidelines, usually including also class II indications (atrial fibrillation, high percentage of right ventricular pacing in heart failure patients). Around 20% of all CRT implantations were performed in NYHA II patients. Baseline characteristics of the cohort are shown in Table 1.

Table 1. Baseline characteristics of patients

	All patients (*N* = 743)	Primary prevention (*N* = 320, 43.1%)	Secondary prevention (*N* = 423, 56.9%)
Ischemic etiology	459 (61.8%)	183 (57.2%)	276 (65.2%)
GFR < 60 ml/min/1.73 m²	319 (42.9%)	147 (45.9%)	172 (40.7%)
LVEF < 30%	452 (60.8%)*	260 (81.3%)	192 (45.4%)
Age > 70 years	149 (20.1%)	47 (14.7%)	102 (24.1%)
Atrial fibrillation	289 (38.9%)	121 (37.8%)	168 (39.7%)
QRS > 120 ms	369 (49.7%)**	178 (55.6%)	191 (45.2%)
NYHA > II°	277 (37.3%)	161 (50.3%)	116 (27.4%)
β-blocker	582 (78.3%)	256 (80.0%)	326 (77.1%)
Amiodarone	233 (31.4%)	78 (24.4%)	155 (36.6%)
GGT > 56 U/L	266 (35.8%)	109 (34.1%)	157 (37.1%)
Mean follow-up (years) ± SD	3.65 (±3.20)	2.42 (±1.99)	4.58 (±3.60)
Median ± 25/75 percentiles	2.92 (1.19/5.10)	2.26 (0.84/3.38)	3.85 (1.68/6.92)
Device			
Single chamber	380 (51.1%)	141 (44.1%)	239 (56.5%)
Dual chamber	178 (24.0%)	47 (14.7%)	131 (31.0%)
CRT-D	185 (24.9%)	132 (41.3%)	53 (12.5%)

*data from 737 patients available; **data from 695 patients available.

Statistical analysis

Categorical data are presented as absolute numbers with percentages; continuous parameters are shown as mean ± standard deviation or median ± range as indicated. Kaplan Meier curves and Log-Rank test were used to compare GGT levels with the incidence of appropriate ICD therapy and survival in primary and secondary prevention ICD patients. Cox proportional hazards regression was used to identify independent predictors for appropriate ICD therapy and survival. Tarone Ware test was used when comparing subgroups concerning GGT and eGFR levels. Follow-up started after implantation of the device and ended at appropriate ICD therapy, death or censoring. The proportional hazards assumption was checked using Schoenfeld residuals and visual inspection of the hazard plots. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 17.0 statistical software (Chicago, Illionois).

Results

Risk stratification for appropriate ICD therapy and total mortality in primary and secondary prevention of SCD: Comparison of established risk factors with elevated GGT levels.

As shown in Tables 2 and 3, compared to normal low GGT plasma levels (below 28 U/L), total mortality but not risk for appropriate ICD therapy was elevated for higher GGT categories (p for trend = 0.004 in primary prevention and p = 0.002 in secondary prevention, respectively). As

Table 2. Elevated GGT does not predict appropriate ICD therapy

	Normal low (<27.99 U/L) *N* = 198	Normal high (28–55.99 U/L) *N* = 279	Elevated (56–111.99 U/L) *N* = 156	Highly elevated (>112 U/L) *N* = 110
Primary prevention	*N* = 82	*N* = 129	*N* = 60	*N* = 49
Events (%)	24 (29.3)	43 (33.3)	22 (36.7)	13 (26.5)
HR (95% CI)	1.00 (Ref)	1.38 (0.83 – 2.29)	2.13 (1.18 – 3.87)	1.33 (0.67 – 2.63)
p for trend			0.096	
Secondary prevention	*N* = 116	*N* = 150	*N* = 96	*N* = 61
Events (%)	66 (56.9)	87 (58.0)	51 (53.1)	29 (47.5)
HR (95% CI)	1.00 (Ref)	1.35 (0.97–1.86)	1.15 (0.79–1.66)	1.15 (0.74–1.78)
p for trend			0.351	

Table 3. Elevated GGT predicts total mortality in ICD patients

	Normal low (<27.99 U/L) *N* = 198	Normal high (28–55.99 U/L) *N* = 279	Elevated (56–111.99 U/L) *N* = 156	Highly elevated (>112 U/L) *N* = 110
Primary prevention	*N* = 82	*N* = 129	*N* = 60	*N* = 49
Events (%)	9 (11)	11 (8.5)	13 (21.7)	11 (22.4)
HR (95% CI)	1.00 (Ref)	0.79 (0.33–1.92)	2.56 (1.09–6.01)	2.80 (1.15–6.79)
p for trend			0.004	
Secondary prevention	*N* = 116	*N* = 150	*N* = 96	*N* = 61
Events (%)	28 (24.1)	31 (20.7)	35 (36.5)	18 (29.5)
HR (95% CI)	1.00 (Ref)	1.24 (0.74–2.07)	2.34 (1.42–3.87)	2.21 (1.21–4.02)
p for trend			0.002	

Table 4. Cox regression analysis for appropriate ICD therapy

Risk factor	Primary prevention *N* = 305			Secondary prevention *N* = 385		
	HR	CI	*p*	HR	CI	*p*
Ischemic etiology	0.888	0.58–1.36	0.587	1.282	0.95–1.74	0.108
LVEF < 30%	1.388	0.75–2.57	0.297	1.122	0.83–1-53	0.467
GFR < 60 ml/min/1.73m²	1.405	0.92–2.16	0.120	0.779	0.58–1.05	0.102
Age > 70a	1.157	0.66–2.02	0.607	1.241	0.89–1.74	0.206
Atrial fibrillation	1.588	1.04–2.43	0.033	1.083	0.81–1.61	0.598
QRS > 120 ms	1.380	0.85–2.25	0.195	1.265	0.95–1.69	0.112
NYHA > II°	1.209	0.77–1.89	0.404	1.150	0.82–1.61	0.417
β-blocker	1.495	0.84–2.65	0.168	1.251	0.89–1.75	0.191
Amiodarone	1.690	1.07–2.67	0.024	1.602	1.21–2.13	0.001
GGT > 56 U/L	1.239	0.78–1.96	0.360	0.933	0.69–1.26	0.648

assessed in Cox regression analysis and shown in Table 4 and Fig. 1, elevated GGT (>56 U/L) had no impact on occurrence of appropriate ICD therapy. As assessed in Cox regression analysis and shown in Table 5 and Fig. 2, elevated GGT (>56 U/L) showed a significant prognostic impact on survival in patients who had received an ICD for both primary and secondary prevention. Excess mortality was found in particular in patients suffering both from elevated GGT (>56 U/L) and renal insufficiency (eGFR <60 ml/min/1.73 m²) as shown in Fig. 4.

Discussion

The main findings of our retrospective analyses of 743 male ICD recipients are as follows: (a) Compared to normal low GGT plasma levels (below 28 U/L), total mortality but not the risk for appropriate ICD therapy was elevated for higher GGT categories; (b) in Cox regression analysis, elevated GGT (>56 U/L) showed a significant prognostic impact on survival in patients who had received an ICD for both primary and secondary prevention; (c) excess mortality was found in patients suffering both from elevated GGT (>56 U/L) and renal insufficiency (eGFR <60 ml/min/1.73 m²) jeopardizing the benefit of ICD therapy.

Despite several well-designed prospective randomised clinical studies, improved patient selection for ICD therapy is still mandatory. More complex tests such as electrophysiological stimulation testing inducibilty of VT, microwave T-wave alternans, signal-averaged electrocardiography, derivates of heart-rate variability or genetic testing did not gain major impact on the clinical routine in the last years and are unlikely to do so in the near future. Therefore, risk factors more easily to assess may be taken into consideration in the selection of patients for ICD therapy.

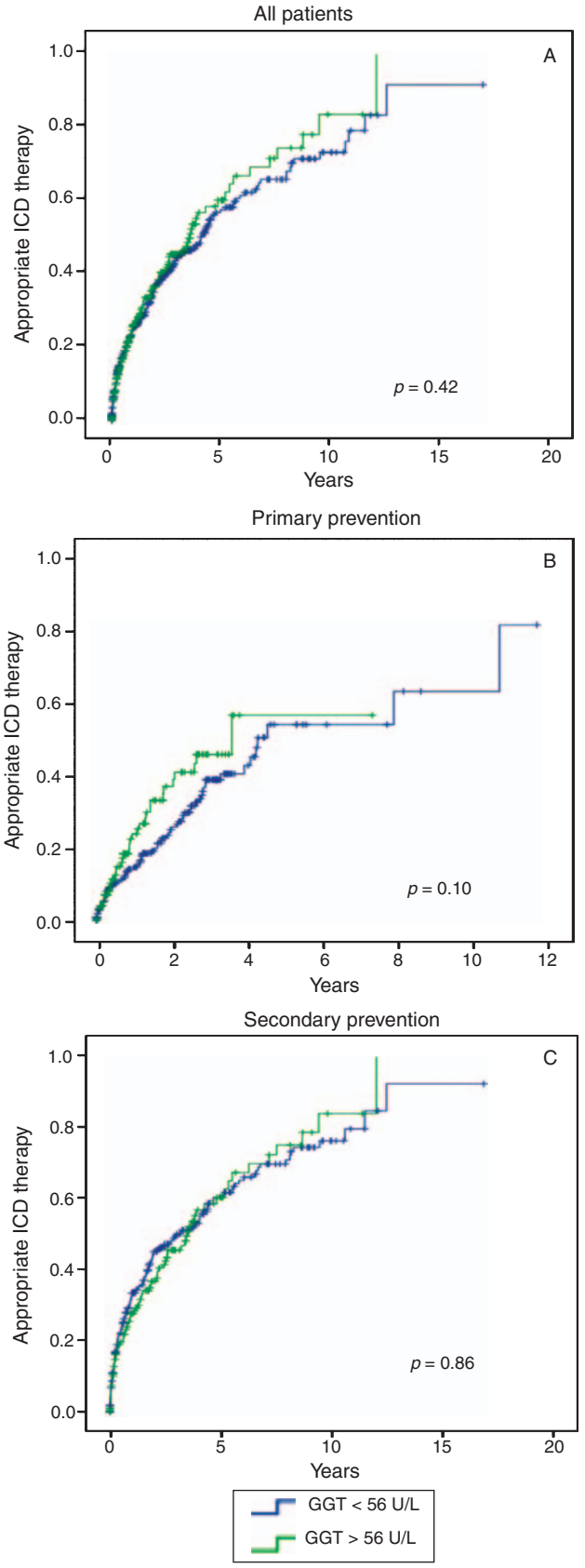

Fig. 1. Kaplan Meier curves showing that elevated GGT (>56 U/L) does not predict appropriate ICD therapy (panel A), although there was a trend for increased appropriate ICD therapy in whom the device had been implanted for primary (panel B) or secondary (panel C) prevention of SCD ($p = 0.098$)

Table 5. Cox regression analysis for total mortality in ICD patients

Risk factor	Primary prevention *N* = 302			Secondary prevention *N* = 385		
	HR	CI	*p*	HR	CI	*p*
Ischemic etiology	0.811	0.42–1.56	0.532	1.983	1.19–3.30	0.008
LVEF < 30%	1.504	0.51–4.42	0.458	1.270	0.79–2.03	0.320
GFR < 60 ml/min/1.73 m²	2.635	1.24–5.59	0.012	1.681	1.08–2.63	0.023
Age > 70a	0.614	0.25–1.52	0.291	2.128	1.36–3.32	0.001
Atrial fibrillation	1.863	0.97–3.57	0.061	0.834	0.62–1.47	0.955
QRS > 120 ms	2.837	1.27–6.34	0.011	1.725	1.09–2.73	0.019
NYHA > II°	0.964	0.49–1.91	0.917	1.734	1.11–2.71	0.015
β-blocker	1.267	0.52–3.07	0.601	0.806	0.52–1.26	0.343
Amiodarone	1.91	1.01–3.62	0.048	1.132	0.74–1.73	0.565
GGT > 56 U/L	2.280	1.21–4.30	0.011	1.844	1.19–2.85	0.006

Multiple factors interact with a reduced left ventricular ejection fraction to influence the risk of arrhythmogenic mortality. As recently shown in a retrospective analysis of the MADIT II cohort, CAD patients below 70 years have a relatively low mortality rate despite a highly reduced ventricular function, as long as additional risk factors such as atrial fibrillation, advanced heart failure (NYHA functional class III and IV), wide QRS or renal dysfunction are not present [4]. Our study confirms the importance of these established risk factors, but suggests that GGT levels may provide additional information for risk stratification as well.

GGT, present on the external surface of most cells and in serum, is the enzyme responsible for the extracellular catabolism of the antioxidant glutathione. Despite its well established clinical use as an indicator of hepato-biliary diseases and marker of excessive alcohol intake, in recent years several epidemiological studies have sparked further interest in elevated GGT as an independent predictor for morbidity and mortality from causes other than liver disease, in particular heart disorders [10–15]. Prevalence of elevated GGT is high in patients with chronic heart failure and GGT levels are associated with disease severity and survival. Hepatic congestion is an obvious mechanistic explanation for the elevation of GGT in heart failure, but other causative factors for the worse prognosis of heart failure patients with GGT elevation have to be considered.

Based on findings in rats that GGT interacts with redox regulation of potassium channels in the postmyocardial infarction heart, we speculated that elevated GGT may predispose to ventricular tachyarrhythmia [16]. Our study, however, does not support this notion, as appropriate ICD therapy did not correlate with GGT levels.

Patients with advanced renal insufficiency have a considerably higher mortality from non-arrhythmogenic causes. Accordingly, several studies suggest that patients with advanced kidney disease have little benefit from prophylactic ICD therapy and suffer from higher device com-

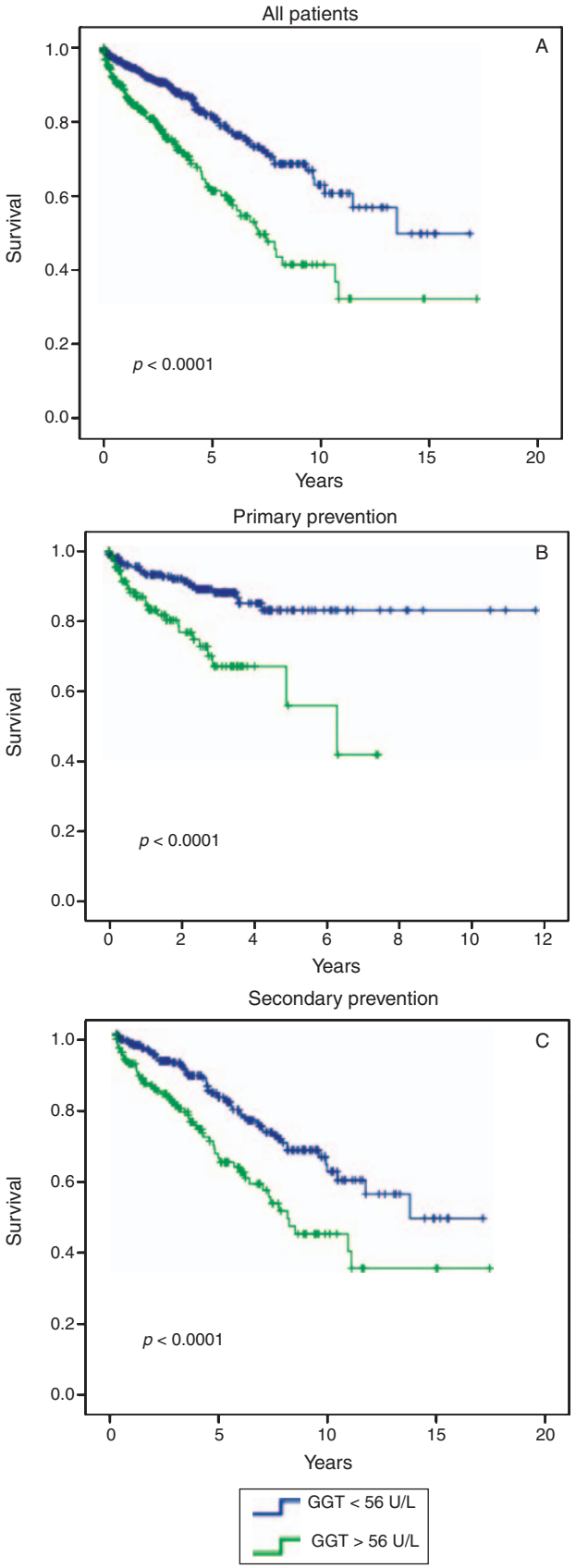

Fig. 2. Kaplan Meier curves showing that elevated GGT (>56 U/L) predicts survival in ICD patients (panel A). This association was found in all ICD recipients regardless of whether the device had been implanted for primary (panel B) or secondary (panel C) prevention of SCD

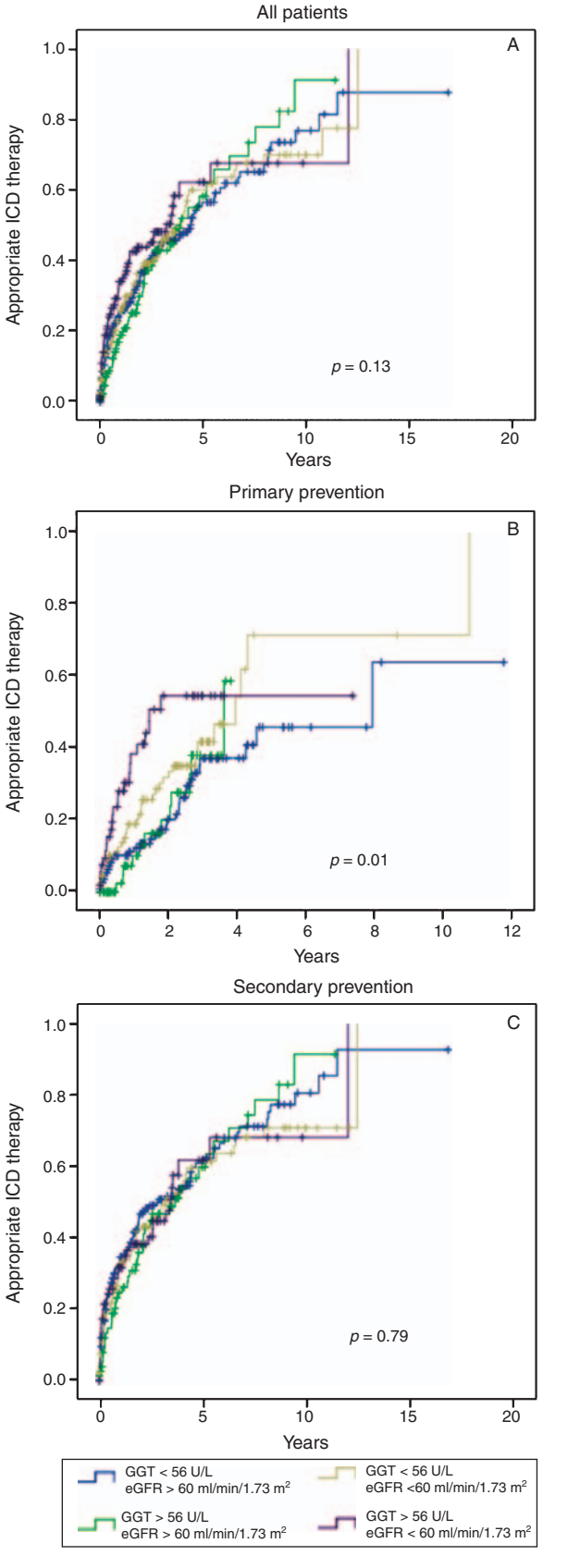

Fig. 3. Kaplan Meier curves showing subgroup analysis concerning elevated GGT (>56 U/L) and/or renal insufficiency (eGFR < 60 ml/min/1.73 m²). In patients who had received an ICD for primary prevention of SCD, appropriate therapy occurred more often in patients with both elevated GGT and decreased eGFR (panel B, $p = 0.01$)

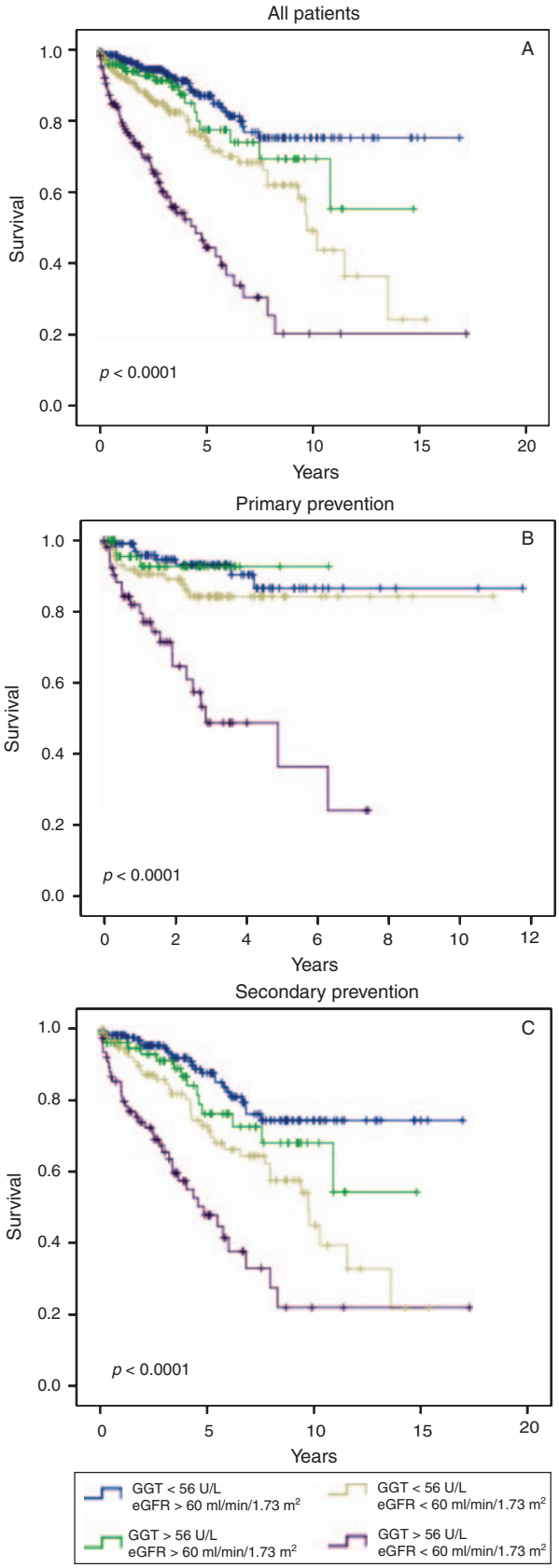

Fig. 4. Kaplan Meier curves showing that ICD patients with both elevated GGT (>56 U/L) and an eGFR < 60 ml/min/1.73 m² suffer from excess mortality (panel A). This association was found in all ICD recipients regardless whether the device had been implanted for primary (panel B) or secondary (panel C) prevention of SCD

plication rates such as infection [4, 17–19]. On the other hand, renal insufficiency was found to be a predictor of appropriate ICD therapy [20, 21]. Considering these possible benefits and risks, further studies are needed to assess the potential impact of ICD therapy in patients with chronic kidney disease. Our findings suggest that patients with both elevated GGT > 56 U/L and an eGFR below 60 ml/min/1.73 m² suffer from such an excess mortality which makes life-prolonging effects of ICD therapy questionable, in particular in primary prevention.

In conclusion, elevated GGT levels have prognostic impact on survival in ICD patients. Because of its wide availability and inexpensive cost for screening, GGT levels might help in adequate patient selection for ICD therapy in clinical routine. Highly elevated GGT levels indicate patients at very-high risk and extensive mortality despite ICD therapy, in particular in case of concomitant severe renal dysfunction. Furthermore, our data confirm the importance of other risk factors indicating increased mortality in ICD patients, such as a broad QRS complex, advanced age or ischemic etiology of heart failure. Certainly, additional studies are needed to test the correlation of GGT and outcome in ICD patients, in particular in females and in large prospective trials.

Conflict of interest

None declared.

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