Effect of serum γ-glutamyltransferase and albumin levels on the response to cardiac resynchronization therapy in the elderly

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Abstract

Background  Several liver function tests have been identified as predictors of hospitalization for heart failure (HF) and death in patients with chronic HF. The relationship between serum γ-glutamyltransferase (GGT) and albumin (SA) levels with the response to cardiac resynchronization therapy (CRT) has not been reliably determined. The aim of the study was to evaluate the impact of liver function tests on the results of CRT in the elderly. Methods  Baseline GGT and SA were assessed before CRT device implantation in the elderly (> 70-year-old) patients. The endpoints were: (1) CRT response defined as > 5% left ventricular ejection fraction improvement and no hospitalization for HF or cardiovascular death; (2) hospitalizations; and (3) mortality. Results  Eighty of 138 (58%) included patients were responders at nine months. Compared to responders, the SA levels were not significantly different (35.1 ± 5.4 vs. 33.6 ± 5.5 g/L, P = 0.103); but the GGT levels, higher (81.6 ± 69.3 vs. 54.7 ± 49.6 U/L, P = 0.013) in non-responders to CRT. GGT level was independently associated with non-response to CRT (P < 0.001, OR = 0.17; 95% CI: 0.08–0.38, P < 0.001). GGT cut-off value ≥55 U/L was highly predictive of non-response [AUC = 0.65, 64% Sensitivity, 69% Specificity (95% CI: 0.56–0.74)]. GGT ≥55 U/L was also associated with higher risk of hospitalization for atrial fibrillation (AF) (95% vs. 83%, P = 0.024). Both SA and GGT had no impact on overall (P = 0.220, P = 0.723) mortality. Conclusions  Higher level of GGT is an independent predictor of non-response to CRT in patients over age 70 years and is associated with higher risk of hospitalization for AF. Baseline serum levels of albumin and GGT and have no impact on mortality in elderly patients undergoing CRT.

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1 Introduction

Cardiac resynchronization therapy (CRT) has been shown to be an effective treatment option in patients with congestive heart failure (HF) with impaired left ventricular ejection fraction (LVEF) and large QRS complex.[1,2] However, a substantial proportion of patients do not respond to CRT.[3,4] Several demographic, electrocardiographic (ECG) and echocardiographic characteristics have been associated with non-response to the CRT.[5-7] Chronic HF has adverse effects on multiple organs including the liver.[8] Several liver function tests have been proposed as prognostic markers in patients with HF.[9-11] Serum γ-glutamyltransferase (GGT) has been identified as an independent predictor of fatal events including hospitalization for HF and death in patients with early stages HF,[10] and of mortality in patients with chronic HF.[9] However, the value of GGT as a marker of higher risk of HF and death in older population remains controversial.[12,13] Low serum albumin (SA) levels are common in the elderly.[11] Hypoalbuminemia has been reported as a predictor of mortality in patients with systolic HF[14] and as a predictor of outcomes after left ventricular assist device therapy in advanced HF.[15] Little is known about the liver function in elderly patients undergoing CRT. The aim of the present study was to evaluate the relationship between levels of GGT and SA and the response to CRT in patients included in the multicenter protocol evaluating the impact of frailty on clinical outcomes in elderly patients implanted with CRT devices.
2 Methods

2.1 Study population

This study was performed in the population enrolled in a larger multicenter protocol, which prospectively evaluated the impact of frailty on the response to CRT. The protocol was registered on the website Clinicaltrials.gov (Registration Number: NCT02369419). We included 138 patients with known baseline levels of GGT and serum albumin, who fulfilled the inclusion criteria of previously described protocol. Briefly, patients older than 70 years, with New York Heart Association (NYHA) II-IV functional class, LVEF ≤ 35%, QRS duration > 120 ms and left bundle branch block (LBBB) in sinus rhythm or in atrial fibrillation (AF) on optimal medical therapy were included. Were also included patients with conventional pacemaker indication and > 95% of ventricular pacing, LVEF ≤ 35%, and NYHA class II-IV. Patients with regular alcohol consumption (more than two drinks/day for men and more than one drink/day for women), were excluded. The investigation conforms to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients for CRT device implantation and follow-up. The study was approved by the local research ethics committee.

2.2 Pre-implantation examination

Before implantation all patients underwent an assessment of NYHA class, a 12-lead ECG, and a transthoracic echocardiogram. Ischemic heart disease was defined as one or more clinically documented (Q wave or enzyme positive) prior myocardial infarction or prior coronary artery bypass graft surgeries or percutaneous coronary interventions (balloon and/or stent angioplasty). Left ventricular end-diastolic diameter (LVEDD) was evaluated by two-dimensional transthoracic echocardiography. Simpson biplane method was used to evaluate LVEF. Cardiac magnetic resonance imaging, angiographic or radionuclide methods. Associated aortic valvulopathy was mentioned in the presence of moderate (valvular area < 1.5 cm²) to severe (valvular area < 1 cm²) aortic stenosis or an aortic regurgitation of grade ≥ 2. All mitral regurgitation of grade ≥ 2 was mentioned. QRS duration was evaluated in lead II (ms) using 12-lead ECG (25 mm/s) measurements (GE Marquette Mac 5000, USA). In patients with permanently paced ventriculograms, the QRS duration was measured from the onset of the spike to the end of the QRS complex. The typical LBBB was defined as QRS duration of ≥ 140 ms (men) or 130 ms (women), QS or rS in leads V1 and V2, and mid-QRS notching or slurring in ≥ 2 of leads V1, V2, V5, V6, I, and aVL. The atypical LBBB was defined as nonspecific intraventricular conduction delay and QRS widening > 150 ms without typical features of LBBB or right bundle branch block. Frailty was assessed in all patients prior to CRT implantation as described in the previous protocol. Pre-implantation analysis of GGT and serum AL were performed the day before device implantation.

2.3 Implantation and device programming

All enrolled patients underwent device implantation using standard transvenous techniques. Implantable cardioverter defibrillator (ICD) therapy was chosen following the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. The choice between a CRT-D and CRT-P devices was left to electrophysiologist discretion. Very high-risk patients (defined by blood urea nitrogen > 50 mg/dL and/or serum creatinine > 2.5 mg/dL) with expected attenuated efficacy of ICD were implanted with CRT-P devices. The RV lead was preferentially positioned in the RV septum if possible, or RV apex if septal positioning failed. The LV lead was preferentially placed in postero-lateral or lateral cardiac vein. Stimulation of basal LV segments was preferably programmed. The sensed atrioventricular delay was programmed at 100 ms with a 30 ms extension in patients in SR. The VV delay was initially programmed at 0 ms. Pacing rate was programmed at 50 beats/min in patients in SR and at 70 beats/min in patients in AF using rate adaptive mode.

2.4 Follow-up

Clinical-ECG evaluation and device testing were performed at three- and nine-month post-implant outpatient visits and echocardiographic evaluation was performed at nine months. All adverse events were documented: cardiovascular (sudden cardiac death or death due to HF) or non-cardiovascular deaths, specifying the causes. In patients who experienced no clinical or hemodynamical improvement (based on NYHA class and clinical examination) at the three-month visit, or for those who were hospitalized for HF, atrioventricular and VV delays were adjusted according to the optimal aortic ejection volume obtained using Doppler evaluation.

2.5 Definition of the CRT response

The response to the CRT was based a combined endpoint defined as the echocardiographic improvement of LVEF of more than 5% and the absence of major clinical event in relation with heart disease, including cardiovascular death or hospitalization for HF. The diagnosis of HF was based on symptoms and responsiveness to intravenous diuretic therapy observed by experienced cardiologists unaware of the study protocol.
2.6 Primary and secondary end points

The primary end point was to evaluate the relationship between GGT and SA levels and the response to CRT in patients over age 70 years implanted with biventricular devices. The secondary end point was the impact of GGT and SA levels on hospitalizations and deaths.

2.7 Statistical analysis

For all statistical analysis, we used the SPSS software package, version 9.0 (SPSS Inc., Chicago, IL, USA). Discrete variables were reported as percentages and continuous variables as mean ± SD. Differences between groups were tested with the $\chi^2$ test or Fisher exact test. For continuous variables, Student t test or Mann-Whitney $U$ test were used. A two-sided $P < 0.05$ was considered statistically significant. The absolute change in LVEF between baseline and nine-month follow-up was evaluated using paired-sample $t$ test. Event-free survival was compared using the Kaplan-Meier method and log-rank statistic.

3 Results

The baseline characteristics of 138 included patients are shown in Table 1. Comparison between CRT responders and non-responders according to the implantation data is shown in Table 2. One hundred and sixteen (84%) patients were on a-blockers, 95 (69%) on angiotensin converting enzyme inhibitors, 21 (15%) on angiotensin receptor blockers, 122 (88%) on loop diuretic, 58 (42%) on aldosterone

| Table 1. Baseline demographic, echographic characteristics and ECG characteristics of the study population. |
|---------------------------------------------------------------|
| VARIABLE                        | ALL PATIENTS (N = 138) | RESPONDERS (N = 80) | NON-RESPONDERS (N = 58) | P-VALUE |
|---------------------------------|------------------------|---------------------|------------------------|---------|
| Age, yrs                        | 78.4 ± 5.3             | 78.6 ± 5.7          | 78.0 ± 4.7             | 0.489   |
| Male                            | 107 (77%)              | 59 (74%)            | 48 (83%)               | 0.211   |
| Ischemic cardiomyopathy         | 73 (53%)               | 45 (56%)            | 28 (48%)               | 0.354   |
| LVEF, %                         | 27.3 ± 6.8             | 27.7 ± 7.2          | 26.7 ± 6.0             | 0.366   |
| NYHA class                      | 2.8 ± 0.5              | 2.7 ± 0.5           | 2.9 ± 0.4              | 0.023   |
| Persistent/permanent AF         | 53 (38%)               | 23 (28%)            | 30 (52%)               | 0.006   |
| History of cardiac surgery      | 33 (24%)               | 21 (26%)            | 12 (21%)               | 0.450   |
| CABG                            | 14 (10%)               | 9 (11%)             | 5 (9%)                 | 0.777   |
| Valvular surgery                | 16 (12%)               | 9 (11%)             | 7 (12%)                | 0.882   |
| Hypertension                    | 99 (72%)               | 58 (72%)            | 41 (71%)               | 0.816   |
| Diabetes mellitus               | 47 (34%)               | 26 (32%)            | 21 (36%)               | 0.650   |
| BMI, kg/m²                      | 26.6 ± 4.6             | 26.6 ± 4.4          | 27.1 ± 4.8             | 0.269   |
| Frailty (Score G8 < 14)         | 84 (61%)               | 42 (52%)            | 42 (72%)               | 0.018   |
| Glomerular filtration rate, mL/mm| 56.5 ± 24.9            | 59.1 ± 26.2         | 53.0 ± 22.8            | 0.156   |
| BNP, ng/L                       | 666 ± 638              | 561 ± 584           | 832 ± 689              | 0.020   |
| Serum albumine, g/L             | 34.2 ± 5.5             | 33.6 ± 5.5          | 35.1 ± 5.4             | 0.103   |
| Gamma-glutamyltransferase, U/L  | 66.0 ± 59.9            | 54.7 ± 49.6         | 81.6 ± 69.3            | 0.013   |
| Echographic characteristics     |                        |                     |                        |         |
| LVEDD, mm                       | 63.5 ± 8.2             | 62.7 ± 7.8          | 64.6 ± 8.6             | 0.186   |
| Moderate aortic stenosis or regurgitation | 23 (17%) | 13 (16%) | 10 (17%) | 0.877 |
| Mitral regurgitation            | 29 (21%)               | 12 (15%)            | 17 (29%)               | 0.056   |
| ECG characteristics             |                        |                     |                        |         |
| QRS duration, ms                | 179 ± 27               | 180 ± 28            | 178 ± 26               | 0.691   |
| LBBB                            | 66 (48%)               | 39 (49%)            | 27 (47%)               | 0.799   |
| Atypical LBBB                   | 23 (17%)               | 10 (12%)            | 13 (22%)               | 0.123   |
| Paced QRS                       | 49 (35%)               | 31 (39%)            | 18 (31%)               | 0.350   |

Data are presented as means ± SD or n (%). AF: atrial fibrillation; BMI: body mass index; BNP: brain natriuretic peptide; CABG: coronary artery bypass graft; ECG: electrocardiographic; LBBB: left bundle branch block; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.
antagonist, and 74 (54%) on oral anticoagulants.

3.1 Response to CRT

After nine-month follow-up, 80 of 138 (58%) patients were responders. Mean increase in LVEF in the entire population was 9.4% ± 10.3%. Ten patients (7%) were hospitalized for HF and nine patients (6.5%) died of cardiovascular death. Non-responders to CRT had similar SA (35.1 ± 5.4 vs. 33.6 ± 5.5 g/L, P = 0.103), but higher GGT (81.6 ± 69.3 vs. 54.7 ± 49.6 U/L, P = 0.013) levels compared to responders. GGT ≥ 55 U/L correctly predicted non-response to CRT [AUC = 0.65, 64% Sensitivity, 69% Specificity (95% CI: 0.56–0.74)] (Figure 1). Higher level of GGT ≥ 55 U/L (OR = 0.17, 95% CI: 0.08–0.38, P < 0.001) and frailty (OR = 0.38, 95% CI: 0.16–0.91, P = 0.030) were identified as independent predictors of non-response to CRT. The percentage of biventricular pacing was not significantly different in patients with GGT ≥ 55 U/L as compared to patients with GGT < 55 U/L (95% ± 8% vs. 97% ± 11%, P = 0.234). The percentage of biventricular pacing was not different in frail compared to non-frail patients (96% ± 12% vs. 96% ± 5%, P = 0.826). Distribution of left ventricular lead positions was similar in patients with GGT ≥ 55 U/L as compared to patients with GGT < 55 U/L (P = 0.660). Quadri-polar leads were used respectively in 15 (21%) and 16 (24%) patients (P = 0.660). Changes in NYHA class, LVEF, LVEDD and QRS duration at nine-month in patients with GGT < 55 U/L compared to those with GGT ≥ 55 U/L are shown in Table 3. The non-response to CRT was accurately predicted with GGT ≥ 55 U/L in men [AUC = 0.62, 60% Sensitivity, 70% Specificity (95% CI: 0.51–0.73)] (Figure 2B). The cut-off level of GGT to accurately predict the CRT non-response in women was ≥ 59 U/L [AUC = 0.73, 70% Sensitivity, 71% Specificity (95% CI: 0.55–0.92)] (Figure 2A). Higher GGT level remained associated with a higher risk of nonresponse to CRT, when stratified by gen-

| Variable | GGT < 55 U/L (n = 76) | GGT ≥ 55 U/L (n = 62) | P-value |
|----------|-----------------------|------------------------|---------|
| NYHA class | –0.7 ± 0.7 | –0.7 ± 0.6 | 0.565 |
| LVEF, % | 11.7 ± 10.1 | 6.7 ± 10.0 | 0.005 |
| LVEDD, mm | –3.9 ± 7.8 | –1.2 ± 5.5 | 0.037 |
| QRS, ms | –26 ± 25 | –31 ± 28 | 0.307 |

Data are presented as means ± SD. GGT: γ-glutamyltransferase; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.
Figure 2. ROC curves of GGT levels in women (A) and men (B) to predict non-response to CRT. Sex-specific cut-off level for GGT were 59 U/L in women, $AUC = 0.73$, 70% Sensitivity, 71% Specificity (95% CI: 0.55–0.92); and 55 U/L in men, $AUC = 0.62$, 60% Sensitivity, 70% Specificity (95% CI: 0.51–0.73). $AUC$: area under the curve; CRT: cardiac resynchronization therapy; GGT: γ-glutamyl-transpeptidase; ROC: receiver operating characteristic.

3.2 Hospitalizations

Compared to patients who were not hospitalized during the follow-up, baseline serum albumin levels were not significantly different in patients hospitalized for any cause ($n = 44$, $34.0 \pm 5.2$ vs. $34.3 \pm 5.7$ g/L, $P = 0.715$), in patients hospitalized for HF ($n = 10$, $33.2 \pm 3.9$ vs. $34.3 \pm 5.6$ g/L, $P = 0.580$) and in patients hospitalized for AF ($n = 14$, $34.2 \pm 4.9$ vs. $34.3 \pm 5.7$ g/L, $P = 0.936$).

| Gender   | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|----------|--------------|--------------|-------------|-----------|------------------------|
| Women    | 14/16        | 7/15         | 0.12 (0.02–0.75) | 0.023     | 0.406                  |
| Men      | 41/60        | 18/47        | 0.29 (0.13–0.64) | 0.002     |                        |

| Age, yrs | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|----------|--------------|--------------|-------------|-----------|------------------------|
| 70–80    | 37/53        | 15/41        | 0.25 (0.11–0.59) | 0.002     | 0.988                  |
| 81–95    | 18/23        | 10/21        | 0.25 (0.07–0.94) | 0.039     |                        |

| Cardiomyopathy | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|----------------|--------------|--------------|-------------|-----------|------------------------|
| Ischemic       | 33/45        | 12/28        | 0.27 (0.10–0.74) | 0.011     | 0.920                  |
| Non-ischemic   | 22/31        | 13/34        | 0.25 (0.10–0.72) | 0.010     |                        |

| Diabetes mellitus | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|-------------------|--------------|--------------|-------------|-----------|------------------------|
| Yes               | 19/27        | 20/7         | 0.23 (0.07–0.78) | 0.019     | 0.818                  |
| No                | 16/49        | 18/42        | 0.27 (0.11–0.65) | 0.004     |                        |

| Persistent/permanent AF | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|-------------------------|--------------|--------------|-------------|-----------|------------------------|
| Yes                     | 14/22        | 9/31         | 0.23 (0.07–0.75) | 0.014     | 0.629                  |
| No                      | 41/54        | 16/31        | 0.34 (0.13–0.87) | 0.024     |                        |

| GFR, ml/min | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|-------------|--------------|--------------|-------------|-----------|------------------------|
| < 40        | 15/21        | 11/28        | 0.26 (0.08–0.87) | 0.029     | 0.907                  |
| ≥ 45        | 40/55        | 14/33        | 0.28 (0.00–0.70) | 0.007     |                        |

| LVEF, %       | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|---------------|--------------|--------------|-------------|-----------|------------------------|
| LVEF < 27%    | 27/37        | 11/30        | 0.21 (0.08–0.61) | 0.004     | 0.628                  |
| LVEF ≥ 27%    | 28/39        | 14/32        | 0.31 (0.11–0.82) | 0.019     |                        |

| Frailty       | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|---------------|--------------|--------------|-------------|-----------|------------------------|
| Yes           | 29/43        | 13/41        | 0.22 (0.09–0.56) | 0.001     | 0.541                  |
| No            | 26/33        | 12/21        | 0.36 (0.11–1.21) | 0.095     |                        |

| Summary       | GGT < 55 U/L | GGT ≥ 55 U/L | OR (95% CI) | $P$-value | $P_{\text{max}}$-value |
|---------------|--------------|--------------|-------------|-----------|------------------------|
|               | 62/76        | 30/52        | 0.26 (0.20–0.34) | < 0.0001 |                        |

**Figure 3.** Odds ratios of the response to CRT according to different levels of serum GGT stratified by gender, age, type of cardiomyopathy, presence of diabetes mellitus, persistent/permanent AF, renal dysfunction, level of LVEF and frailty. AF: atrial fibrillation; CRT: cardiac resynchronization therapy; GFR: glomerular filtration rate; GGT: γ-glutamyl-transpeptidase; LVEF: left ventricular ejection fraction.
32.2 ± 6.0 vs. 34.4 ± 5.4 g/L, \( P = 0.173 \). Compared to patients not hospitalized, GGT levels were not significantly different in patients hospitalized for any cause (70.7 ± 68.5 vs. 64.2 ± 54.3 U/L, \( P = 0.473 \)) and in patients hospitalized for HF (53.5 ± 31.1 vs. 67.0 ± 61.6 U/L, \( P = 0.495 \)), but higher in patients hospitalized for AF (97.5 ± 72.4 vs. 62.5 ± 57.6 U/L, \( P = 0.038 \)). The GGT \( \geq 55 \) U/L correctly predicted hospitalization for AF [AUC = 0.69, 79% Sensitivity, 57% Specificity (95% CI: 0.56–0.82)]. Mean survival without hospitalization for AF was significantly better in patients with lower GGT level (95% vs. 83%, log-rank \( P = 0.024 \)) (Figure 4A).

3.3 Outcome analyses

A total of 14 (10%) deaths occurred during the follow-up; of these, nine (64%) were cardiovascular related (HF). The causes of five non-cardiovascular deaths were: one colon cancer, one esophageal cancer, one pneumonia, one septic shock and one unexplained death without preceding cardiovascular symptoms. Serum albumin level was not associated with all-cause mortality (log-rank \( P = 0.220 \)). There was no association between GGT level and all-cause mortality (log-rank \( P = 0.723 \)).

4 Discussion

This study gives an insight into the relationship of impaired hepatic function tests with the results of CRT in the elderly. The main findings are as follows: (1) higher level of GGT (\( \geq 55 \) U/L) is an independent predictor of non-response to CRT; (2) elevated GGT is associated with higher risk of hospitalization for AF; and (3) serum levels of albumin and GGT have no impact on overall mortality.

Elevated GGT and hypoalbuminemia in patients of our series are consistent with severe congestive HF, due to chronic left ventricular systolic dysfunction. Elevated GGT resulting from hepatic venous congestion has been identified as an independent predictor of incidental HF in younger populations.\[^{[10,24,25]}\] Elevated GGT has been proposed as a prognostic marker in patients with HF.\[^{[9,10,26,27]}\] Our study shows that higher GGT levels in elderly patients are associated with non-responsiveness to CRT. Although GGT level had no effect on mortality at nine months, the improvement of LVEF and reduction of LVEDD were significantly more limited in elderly patients with GGT \( \geq 55 \) U/L implanted with CRT devices. The cut-off value of 55 U/L can reflect the stage of HF beyond which the improvement of hemodynamic parameters may be more difficult to obtain with biventricular pacing. Patients with severely impaired hepatic function resulting from prolonged left ventricular systolic impairment may represent a cohort in whom reversibility of left ventricular systolic dysfunction with CRT is unlikely to occur. Along with the RV function and the pulmonary hypertension, GGT level appears as a marker of more advanced stage of systolic HF. The GGT level can be easily obtained and the cut-off value of 55 U/L could be integrated into the clinical decision-making process in candidates to CRT. A higher cut-off value of GGT (\( \geq 59 \) U/L) in women could be consistent with a better reserve of systolic dysfunction being reversible at a different threshold compared to men. Higher predictive value of GGT for adverse outcomes in men compared to women has been previously reported.\[^{[10,28]}\] Moreover, female gender has been associated to better response to CRT.\[^{[2]}\] The reported above cut-off values of GGT can be easily obtained and incorporated in pre-implantation evaluation.

In our study, higher GGT level had no impact on hospitalizations for HF. This finding is consistent with a previous
report, which demonstrated that GGT was not significantly associated with HF in patients older than 70 years. Interestingly, our study showed that elevated GGT was associated with higher risk of hospitalization for AF. Hepatopathy resulting from chronic congestion typically observed in patients with low cardiac output is associated with inflammation and oxidative stress. Serum GGT is a marker of oxidative stress related to glutathione metabolism. Involvement of chronic inflammation and oxidative stress in the pathophysiology of AF have been reported. Previous studies have demonstrated a linear association of GGT with AF risk after adjustment for established predictors in younger populations. Our study extends these results to patients over age 70 years with severe HF. In patients with GGT ≥ 55 U/L, the probability of hospitalization for AF was significantly higher during a shorter nine-month period (compared with twelve- and twenty-two-year follow-up in previous series). Accordingly, reinforcement of antiarrhythmic therapy should be considered in patients with higher GGT in AF.

Serum albumin level had no impact on hospitalizations in our study. Reduced SA results from the cholestasis induced through chronic hepatic congestion and is an established marker of inadequate nutrition. Lower SA has been reported as a prognostic marker in patients with HF. The lack of impact on the results of CRT in our series is consistent with previous studies showing no effect of baseline SA on worsening of HF.

Our study did not demonstrate prognostic value of GGT level in the elderly with severe left ventricular systolic dysfunction implanted with CRT devices. Our findings are consistent with previous reports, which have failed to show a prognostic role of GGT in older patients. The reason for limited prognostic value of GGT is not completely understood, but the reduction in hepatic clearance of xenobiotic in the elderly resulting in different GGT levels than in younger ages has been reported. Furthermore, our study failed to demonstrate prognostic value of hypoalbuminemia in spite of a similar follow-up duration as in previous report showing its prognostic role in patients with systolic HF. The difference could be explained by the fact that patients in that study were much younger (52 years) compared to our study (78 years). Accordingly, there is limited evidence supporting the use of serum GGT and SA levels to assess mortality risk in elderly patients over age 70 years.

4.1 Limitations

RV function, right-sided pressures and a history of chronic obstructive pulmonary disease were not analyzed. Our analysis was limited to GGT and SA, and did not assess other liver function tests. Changes in a serum levels of GGT and SA overtime after CRT device implantation were not evaluated.

4.2 Conclusions

Higher level of GGT (≥ 55 U/L) is an independent predictor of non-response to CRT in the elderly. Elevated GGT is associated with higher risk of hospitalization for AF. GGT should be integrated in decision-making process in candidates to CRT. Pre-implantation serum levels of albumin and GGT have no impact on overall mortality in elderly patients undergoing CRT.

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