

## Clinical risk factors for the prediction of acute kidney injury post cardiac resynchronization therapy in an elderly population

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### ABSTRACT

**Background:** Data on the occurrence of acute kidney injury (AKI) in patients undergoing cardiac resynchronization therapy (CRT) implantation is limited and no previous studies investigated its impact in an elderly population. CRT implantation requires a relatively low quantity of contrast medium. Previous studies, however, focused primarily on contrast medium as etiological factor for AKI, reporting a high incidence (8–14%). The high incidence of AKI in absence of use of substantial amounts of contrast volume, suggests the existence of other factors that contribute to AKI.

**Objectives:** To determine the predictive value of patient and procedure-related risk factors for the occurrence of AKI post CRT, as well as the AKIs impact on length of in-hospital stay (LOS) and 1-year mortality. **Methods:** Retrospective observational study, including consecutive patients that underwent CRT implantation in a single center.

**Results:** 60 patients with a mean age of  $77 \pm 8.4$  years were included in the study and Twelve (20%) developed AKI. Prior renal insufficiency ( $p = 0.03$ ; OR = 15.4), larger procedure time ( $p = 0.02$ ; OR = 1.03), intra-operative hypotension ( $p < 0.01$ ; OR = 1.72) and bleeding ( $p = 0.01$  (OR = 7.86), showed to predict AKI significantly. AKI associated a significantly longer LOS (12 vs 3 days,  $p < 0.01$ ). No significant differences regarding 1-year mortality were observed ( $p = 0.19$ ; HR = 2.7 for patients with AKI).

**Conclusions:** AKI is a frequent complication of CRT implantation with an important impact on in-hospital stay, especially in the elderly. In addition to contrast administration, clinical factors could play a significant role in the occurrence of AKI.

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### 1. Introduction

Cardiac resynchronization therapy (CRT) has shown to reduce hospitalization and mortality and to improve cardiac function through biventricular pacing, in patients with symptomatic chronic heart failure (HF) with optimal medical treatment, severely depressed left ventricular ejection fraction (LVEF) and complete left bundle branch block. Although only a small proportion of HF patients is eligible (an estimated 5–10%) for this treatment, this represents still a large absolute number of patients [1].

In order to achieve optimal placement of the left ventricular lead, a detailed assessment of coronary sinus anatomy is required, being coronary venous angiogram considered the gold standard [2]. Injections of intravascular iodinated contrast medium associate the risk of contrast-induced acute kidney injury (CI-AKI), a syndrome defined as an increase of serum creatinine of  $\geq 25\%$  or  $\geq 0.5$  mg/dl within 48 h after contrast administration. Furthermore, advanced congestive heart failure is one of the most important risk factors of CI-AKI [3].

Thus, the detailed evaluation of acute kidney injury (AKI) is crucial in patients undergoing CRT implantation. However, only a few studies have investigated the occurrence of AKI after CRT, concluding that this complication is possibly an under-recognized entity,

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with an incidence of up to 14%, which may have a negative impact on morbidity and mortality [4–6]. All these studies focused on the administration of contrast medium as primary etiological risk factor for AKI. CRT implantation requires substantially less administration of contrast medium, compared with other invasive procedures, such as percutaneous coronary intervention (PCI) [6]. Therefore, the high incidence of AKI post CRT implantation, as described by the previously mentioned studies, suggests the existence of other patient or procedure-related factors that may contribute to AKI occurrence. Furthermore, none of the above mentioned studies investigated the impact of AKI post TRC in an elderly population.

### 1.1. Objectives

This study aims to assess the incidence of AKI post CRT implantation and its impact on length of in-hospital stay (LOS) and 1-year mortality. Furthermore, we investigated the predictive value of patient and procedure-related risk factors for the occurrence of AKI, beyond the administration of contrast medium.

## 2. Methods

### 2.1. Patients

Consecutive patients that underwent CRT implantation in our hospital between April 2014 and May 2019 were included for retrospective chart review. Inclusion and exclusion criteria are detailed in Supplementary Table A.1.

### 2.2. Procedure details

Indication for CRT implantation was made according to the current European guidelines on Cardiac pacing and Cardiac resynchronization therapy. [1] Implantation was performed according to our center's standard operating procedure, in agreement with standard transvenous techniques [2,7,8]. The procedure was carried out by a multidisciplinary team, including experienced interventional cardiologists, heart surgeons and anesthesiologists. Intra-operative non-invasive blood pressure was measured every 15 min and documented in the anesthesia record for all cases. We used standard, commercially available resynchronization systems (Quadra Assura; Abbott/St. Jude Medical, USA) and leads (Optisense, Durata, Quartet; Abbott/St. Jude Medical, USA) for pacing and sensing of the atrium, right ventricle and left ventricle.

All patients were assessed for risk of CI-AKI according to the Mehran score and received the following preoperative prevention measures: 1) Pre- and postoperative intravenous hydration with isotonic saline (0.5 ml/kg/h 12 h before and 24 h after the procedure). 2) Acetylcysteine, 600 mg twice daily (pre- and postoperative for a total of 4 doses), was used in patients with a high risk of CI-AKI according to the Mehran score. 3) Metformin, as well as potentially nephrotoxic drugs, such as NSAIDs and diuretics, were discontinued according to our standard pre-operative protocol [3,9]. AKI was defined as an increase of serum creatinine of  $\geq 25\%$  or  $\geq 0.5$  mg/dl within 48 h after CRT implantation, in agreement with previous studies on AKI post CRT [3]. The estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation [10].

### 2.3. Contrast medium

Iomeprol 400, (Iomeron<sup>®</sup>, TiVo Corporations, Santa Clara, CA, USA, 50 ml per bottle), a low-osmolar, non-ionic contrast medium, was used in all procedures. Since increase of contrast induced

acute kidney injury in patients undergoing CRT implantation is correlated with the use of >100 ml of contrast medium, cases in which >2 bottles of Iomeprol (50 ml, each) were registered in the surgery material chart, were excluded from the study [6].

### 2.4. Statistical analysis

The distribution of data was tested with the Kolmogorov-Smirnov test. Descriptive statistics were used to summarize data, presenting medians and ranges for continuous non-parametric data, whereas mean and standard deviation are depicted for parametric data. Proportions were analyzed by generating cross-tables, using chi-square test to determine significant differences. Independent groups of non-parametric data were compared using the Mann-Whitney *U* test.

Univariate and multivariate binary inclusive logistic regression models were generated in order to identify independent predictors of AKI. We tested the following independent variables to determine their predictive value for the occurrence of AKI: 1) Patient-related risk factors: a) pre-operative eGFR < 60 ml/min/1.73 m<sup>2</sup>, b) Creatinine on admission, c) Hemoglobin on admission, d) NT-proBNP on admission. 2) Procedure-related risk factors: a) Procedure time, b) Intraoperative hypotension (defined as drop of systolic blood pressure (SBP) of  $\geq 20\%$  with regard to SBP at start of procedure for at least 15 min), c) Intraoperative bleeding (defined as  $\geq 2$  g/dl decrease in hemoglobin concentration or necessity of red blood cell transfusion). Each multivariate regression model included the variables age, gender, NYHA functional class and LVEF on admission, as co-variables.

We used Log-rank tests to compare Kaplan-Meier curves plotted for cumulative survival to evaluate 12-month mortality (each for all causes and HF). Multivariate Cox regression models were generated in order to determine the predictive value of the independent variable AKI on mortality.

All statistical analyses were performed using IBM SPSS (v21.0).

### 2.5. Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

## 3. Results

### 3.1. Patients' characteristics

A total of 65 consecutive patients that underwent CRT implantation in the period between April 2014 and May 2019 were included in the study. Three patients were excluded due to epicardial approach and two patients were excluded because of exceptional high (>100 ml) use of contrast medium. The remaining 60 patients were included in further analysis. The mean age was  $77 \pm 8.4$  years. Details concerning demographic data and clinical characteristics are shown in Table 1. No significant differences were found between patients that developed AKI and those who did not develop AKI, regarding demographic and clinical data. The median baseline eGFR was 57 ml/min/1.73 m<sup>2</sup>, and median baseline Creatinine was 1.15 mg/dl, with no significant differences between patients that developed AKI and those who did not develop AKI ( $p = 0.18$  and  $0.83$ , respectively).

### 3.2. Procedure details

Mean procedure time was 114.5 min, being significantly higher in patients that developed AKI than in patients that did not develop

**Table 1**  
Demographic data, clinical characteristics of overall population and of subgroups according to the occurrence of AKI.

	A: Overall Population	B: AKI, n = 12	C: No AKI, n = 48	P value (B vs C)
<b>Clinical characteristics</b>				
Age - years	77.0 (SD 8.4)	78.0 (SD 5.2)	76.6 (SD 9.0)	0.69
Male gender - no (%)	50 (83.3)	9 (75)	41 (85.4)	0.38
History of atrial fibrillation - no (%)	36 (60)	9 (75)	27 (56.3)	0.32
Arterial hypertension - no (%)	54 (90)	11 (91.7)	43 (89.6)	0.83
Diabetes mellitus - no (%)	25 (41.7)	5 (41.7)	20 (41.7)	1.00
Prior CABG - no (%)	5 (8.3)	3 (25)	2 (4.2)	0.05
Ischemic cardiomyopathy - no (%)	39 (65)	9 (75)	30 (62.5)	0.41
NYHA class on admission	3 (2-4)	3 (2-4)	3 (2-3)	0.91
Left ventricle ejection fraction - %	31 (21-45)	33 (21-40)	30 (18-45)	0.86
NT-proBNP on admission - pg/mL	6893 (800-20452)	6991 (1727-19575)	5325 (800-20452)	0.37
<b>Medication</b>				
Beta-adrenergic blocker - no (%)	56 (93.3)	12 (100)	44 (91.7)	0.57
ACE-Inhibitor / ARB - no (%)	53 (88.3)	10 (83.3)	43 (89.6)	0.62
Spirolactone/Epleronone - no (%)	42 (70)	9 (75)	33 (68.8)	0.67
Loop diuretics - no (%)	48 (80)	10 (83.3)	38 (79.2)	0.74
Digoxin - no (%)	7 (11.7)	1 (8.3)	6 (12.5)	0.68
Statin - no (%)	54 (90)	11 (91.7)	43 (89.6)	0.83
Neprilisin inhibitor - no (%)	9 (15)	2 (16.7)	7 (14.6)	0.85
<b>Biochemical analysis</b>				
Creatinine on admission - umol/L	1.15 (0.52-4.19)	1.20 (0.52-1.98)	1.12 (0.64-4.19)	0.83
GFR on admission - ml/min/1.73 m <sup>2</sup>	57 (14-102)	51 (29-94)	58 (14-102)	0.18
Hemoglobin on admission - g/dl	12.8 (8-17.5)	12.4 (9.3-15.6)	12.9 (8-17.5)	0.78

ACE Angiotensine converting enzyme, ARB angiotensin receptor blocker, CABG coronary artery by-pass grafting, AKI acute kidney injury, GFR glomerular filtration rate, NT-proBNP N-terminal prohormone of brain natriuretic peptide, NYHA New York Heart Association.

AKI (135.9 vs 109.5 min respectively,  $p = 0.03$ ). Mean SBP at the beginning of the intervention was 136.3 mmHg, with no significant differences between the two subgroups. Drop in SBP of  $\geq 20\%$  with regard to SBP at the beginning of the procedure occurred in 8 (16.3%) patients. Patients that presented intra-operative drop of SBP were significantly more likely to develop AKI than patients without SBP drop (62.5 vs 7.3%, respectively,  $p < 0.01$ ). Intra-operative bleeding occurred in 9 (15%) patients, those being significantly more likely to develop AKI than patients that did not present this complication (55.6 vs 13.7%, respectively,  $p = 0.012$ ). See Table 2 for details.

### 3.3. Incidence of AKI and impact on LOS

Overall, 12 (20%) out of the 60 enrolled patients developed AKI; none of them required hemodialysis or hemofiltration. AKI was associated with a significantly longer LOS (median of 12 days in patients that developed AKI vs 3 days in patients without AKI,  $p < 0.01$ ). Details are depicted in Table 2.

### 3.4. Predictors of AKI

#### 3.4.1. Patient related risk factors

Occurrence of AKI was significantly higher in patients with eGFR  $< 60$  ml/min/m<sup>2</sup> at baseline than in patients without prior renal dysfunction (30.6% vs 4.2%, respectively,  $p = 0.01$ ). See Table 1 for details. Furthermore, prior deterioration of the renal function showed to be a significant independent predictor for the occurrence of AKI, as determined by univariate and multivariate binary inclusive logistic regression models ( $p = 0.033$  (OR 10.1),  $p = 0.026$  (OR 15.4)). The other patient-related independent variables (Creatinine, Hemoglobin and NT-proBNP on admission) did not predict AKI. Details are shown in Table 3.

#### 3.4.2. Procedure related risk factors

A higher procedure time, resulted to be a significant predictor for AKI ( $p = 0.011$  (OR: 1.03) and  $p = 0.024$  (OR: 1.03), respectively). Univariate and multivariate regression models indicated that an intra-operative drop in SBP of  $\geq 20\%$  predicted occurrence of AKI ( $p = 0.001$  (OR: 1.77) and  $p = 0.003$  (OR: 1.72), respectively).

**Table 2**  
Procedure details and Outcomes of overall population and of subgroups according to the occurrence of AKI.

	A: Overall Population	B: AKI, n = 12	C: No AKI, n = 48	P value (B vs C)
<b>Procedure details</b>				
Procedure time - min	114.5 (SD 32.14)	135.9 (SD 34.0)	109.5 (SD 29.9)	0.03
SBP at the beginning of intervention - mmHg	136.3 (SD 17.9)	143.1 (SD 20.2)	135.0 (SD 17.4)	0.24
<b>Renal parameters</b>				
Creatinine post OP - umol/L	1.29 (0.66-3.85)	1.76 (1.13-3.19)	1.26 (0.66-3.85)	<0.01
GFR post OP - ml/min/1.73 m <sup>2</sup>	40 (11-113)	27 (14-113)	41 (11-88)	<0.01
<b>Biochemical analysis</b>				
Hemoglobin post OP - g/dl	12.6 (7.3-13.9)	11.6 (7.6-14.2)	13.0 (7.3-13.9)	0.05
<b>LOS and Mortality</b>				
LOS - days	3 (2-28)	12 (4-28)	3 (2-11)	< 0.001
12 month mortality (all cause) - %	7 (11.7)	3 (25)	4 (8.3)	0.10
12 month mortality (cardiac) - %	3 (5)	1 (8.3)	2 (4.2)	0.55

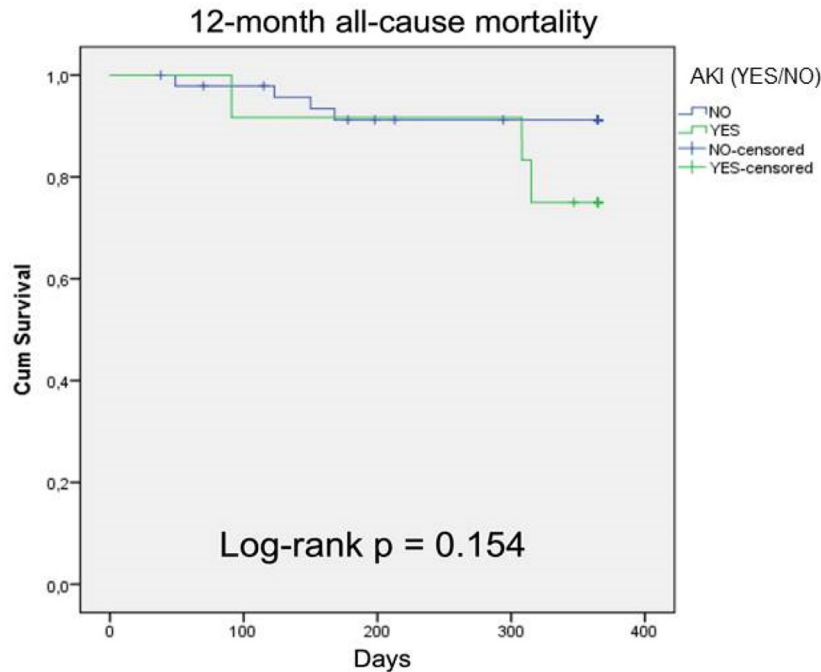
ACE Angiotensine converting enzyme, ARB angiotensin receptor blocker, CABG coronary artery by-pass grafting, AKI acute kidney injury, GFR glomerular filtration rate, LOS length of in-hospital stay, NT-proBNP N-terminal prohormone of brain natriuretic peptide, NYHA New York Heart Association, SBP systolic blood pressure.

**Table 3**  
Evaluation of independent predictors for the occurrence of AKI.

Independent variables	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Prior deterioration of renal function*	10.1 (1.3–15.8)	0.033	15.4 (1.3–17.8)	0.026
Procedure time	1.03 (1.05–3.5)	0.011	1.03 (1.04–3.8)	0.024
Intra-operative drop in SBP of ≥20%	1.77 (1.2–4.7)	0.001	1.72 (1.1–5.1)	0.003
Intra-operative bleeding‡	7.86 (1.6–8.9)	0.009	5.45 (0.95–6.6)	0.081

CI Confidence interval, AKI acute kidney injury, GFR glomerular filtration rate, NT-proBNP N-terminal prohormone of brain natriuretic peptide, SBP systolic blood pressure. Non-significant co-variables included in each regression model were: 1) Age on admission, 2) Gender, 3) LVEF on admission, 4) NYHA functional class on admission.

\* Defined as GFR < 60 ml/min/1.73 m2 on admission, †Defined as defined as ≥2 g/dl decrease in hemoglobin concentration or necessity of red blood cell transfusion.



No. at Risk		0	100	200	300	400
AKI		12	11	11	11	9
NO AKI		48	45	41	39	39

**Fig. 1.** Kaplan-Meier curve presenting cumulative surviving concerning 12-month all-cause mortality.

Furthermore, intra-operative bleeding showed to be a significant predictor in univariate regression models, with a tendency towards statistical significance in multivariate regression models ( $p = 0.01$  (OR: 7.86) and  $p = 0.08$  (OR: 5.45), respectively). See Table 3 for details.

### 3.4.3. Interaction between co-variables

Generating a multivariate logistic regression model, including the variables that showed to be significant predictors of AKI, only prior deterioration of the renal function and intra-operative drop in SBP remained statistically significant ( $p = 0.048$  and  $p = 0.012$ , respectively).

### 3.5. Impact on 1-year mortality

Cumulative surviving concerning 12-month all-cause mortality is presented in a Kaplan-Meier curve (Fig. 1). The differences in mortality (all-cause and cardiac) did not reach statistical significance, as determined by Log-rank test. Multivariate Cox-regression analysis that included demographic and clinical charac-

teristics, such as age, gender, LVEF and NYHA functional class, evaluated the value of AKI for the prediction of mortality, presenting a hazard ratio of 2.7 for the outcome of 12-month all-cause mortality ( $p = 0.19$ ) and 2.1 ( $p = 0.55$ ) for cardiac mortality. See Table A.2 for details.

## 4. Discussion

### 4.1. Study population and incidence of AKI

Our study demonstrates that acute kidney injury is a frequent complication of CRT implantation, which has a negative impact on LOS, especially in the elderly. CI-AKI has previously been described as a major complication with significant impact on long-term survival in patients undergoing coronary angiography and PCI [11–13]. Despite the abundance of studies, investigating the incidence of AKI in patients undergoing coronary angiography and PCI, there is only limited data available on the AKI occurrence after CRT implantation. Furthermore, no studies investigated the impact of AKI post TRC in an elderly population [4–6]. The patients'

mean age in our study was  $77 \pm 8.4$  years, whereas Kowalczyk et al. presented in their subanalysis of a randomized trial a significantly younger group of patients (61 (IQR: 39–82) years). This subanalysis of the TRUST CRT trial revealed a 10.2% incidence (however, applying a different definition of AKI: rise in serum creatinine of at least  $26.5 \mu\text{mol/L}$  (0.3 mg/dL) within 48 h after contrast exposure, or at least 50% increase from the baseline value during index hospital stay), whereas in a study by Cowburn et al. AKI occurred in 14% of patients that underwent CRT implantation [4–6]. In comparison to the previously mentioned studies, we found a higher incidence of AKI (20%). This may be explained by the significantly older and therefore more vulnerable study population, which is underlined by a worse baseline clinical status of our study population (high prevalence of patients with  $\text{GFR} < 60 \text{ ml/min/m}^2$  on admission (60%) and higher NT-proBNP on admission).

#### 4.2. Impact of AKI on LOS

Furthermore, we showed that LOS was significantly longer in patients that developed AKI than in patients that did not present this complication. This finding is in line with previous findings of Cowburn et al. and stands in contrast to the results of the TRUST CRT trial, where no significant difference could be found [4,5]. Future prospective studies are needed to confirm the negative impact of AKI on the length of hospital stay.

#### 4.3. Predictors of AKI

CRT implantation usually requires substantially less administration of contrast medium than PCI. Therefore, the high incidence of AKI post CRT implantation, as described by the previously mentioned studies, suggests the existence of other patient or procedure-related factors that may contribute to AKI occurrence. Nevertheless, all previous studies investigating AKI after CRT implantation focused primarily on the administration of contrast medium as the main etiological risk factor. Our study, on the other hand, investigated the predictive value of patient and procedure-related risk factors. We present an elderly study population, in which the prevalence and impact of these factors may be even more important than in a younger subgroup of patients.

##### 4.3.1. Patient related risk factors

Pre-existing renal impairment, as defined as  $\text{GFR} < 60 \text{ ml/min/m}^2$ , showed to be a significant independent predictor for the occurrence of AKI in patients that underwent CRT-implantation. This finding is in line with previous trials on CI-AKI risk factors [3]. Creatinine, hemoglobin and NT-proBNP on admission did not predict CI-AKI occurrence.

##### 4.3.2. Procedure related risk factors

Our study demonstrates that procedure-related factors play a significant role in the development of AKI after CRT implantation. The predictive value of these factors has not been studied before in CRT patients. A larger procedure time, intraoperative hypotension and intraoperative bleeding, showed to significantly predict AKI in CRT patients, as assessed by binary logistic regression models.

#### 4.4. Impact on 1-year mortality

Among the few studies, that investigated the incidence of AKI in patients undergoing CRT implantation, to our best knowledge, only one of them studied the impact on long-term outcomes. A subanalysis of the TRUST CRT trial, which studied a relatively young group of HF-patients (median of 61 years), revealed a significant impact of AKI occurrence on long-term mortality, with almost

three-fold higher 30-month mortality in the AKI group [5]. Our findings on long-term outcomes of elderly patients are in line with those presented by Kowalczyk et al. regarding the higher 12-month hospitalization rate and mortality, however, our results did not reach statistical significance. This lack of statistical significance may be explained by the lower number of patients included in our study and the shorter follow-up period. Future prospective studies are needed to evaluate the negative impact of AKI on long-term mortality.

#### 4.5. Clinical implications of this study

Our findings provide deeper insight and knowledge about the possible mechanisms and preventive strategies of AKI post CRT. Furthermore, our study contributes real-life data in an elderly (>75 years old) CRT-HF population, thus shedding light on a category of patients which is commonly under-represented in CRT trials. Our study suggests that AKI is a frequent complication with an important impact on LOS and long-term mortality. The effort of minimizing this complication should, therefore, hold a high priority when CRT implantation is performed. Some of the procedure-related factors share a common pathophysiologic pathway and could interact with each other. Intra-operative bleeding may lead to hypotension and eventually cause renal hypoperfusion. A longer procedure time may be due to these complications and may also be associated with a higher use of contrast medium. This is underlined by the fact that 2 of 3 procedure-related factors did not maintain statistical significance when included in a multivariate logistic regression model that incorporated all variables that showed to be significant predictors in univariate models. However, prior impairment of the renal function showed predict AKI in all models and consequently seems to be an independent risk factor. Thus, a thorough patient selection and the avoidance of factors that could lead to *peri-procedural* renal hypoperfusion are crucial to reduce the high incidence of AKI.

#### 4.6. Study limitations

The most important limitations of our study are the single centre retrospective design and the insufficient data on total contrast volume used in all patients. Furthermore, the relatively low number of patients is a limiting factor concerning the interpretation of multivariate regression models.

#### 4.7. Conclusions

In conclusion, we found that AKI is a frequent complication of CRT implantation with an important negative influence on in-hospital stay, especially in the elderly. In addition to the administration of contrast medium, patient and procedure-related factors, such as prior renal dysfunction, larger procedure time, intraoperative hypotension and -bleeding, could play a significant role in the occurrence of AKI.

#### CRediT authorship contribution statement

**Alexander Marschall:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing - original draft, Writing - review & editing. **Hugo del Castillo Carnevali:** Investigation, Methodology, Resources, Validation, Writing - review & editing. **José Carlos de la Flor Merino:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Miguel Rubio Alonso:** Resources, Validation, Writing - review & editing. **Ramón de Miguel Gómez:** Resources,



Validation, Writing - review & editing. **Jorge Palazuelos Molinero:** Validation, Writing - review & editing. **María de Fatima Goncalves Sánchez:** Resources, Validation, Writing - review & editing. **Eduardo López Soberon:** Validation, Writing - review & editing. **Concepción Fernández Pascual:** Validation, Writing - review & editing. **Ricardo Concepción Suárez:** Validation, Writing - review & editing. **Dámaris Carballeira Puentes:** Validation, Writing - review & editing. **Freddy Andrés Delgado Calva:** Validation, Writing - review & editing. **Salvador Álvarez Antón:** Resources, Validation, Writing - review & editing. **David Martí Sánchez:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing.

#### Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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None.

#### Statement of Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

#### Disclosure Statement

The authors have no conflicts of interest to declare.

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None declared

#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100594>.

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