

**Review**

# Acute Kidney Injury in Cardiorenal Syndrome Type 1 Patients: A Systematic Review and Meta-Analysis

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**Key Words**

Cardiorenal syndrome · Type 1 · Acute kidney injury · Meta-analysis

**Abstract**

**Background:** We evaluated the epidemiology and outcome of acute kidney injury (AKI) in patients with cardiorenal syndrome type 1 (CRS-1) and its subgroups: acute heart failure (AHF), acute coronary syndrome (ACS) and after cardiac surgery (CS). **Summary:** We performed a systematic review and meta-analysis. CRS-1 was defined by AKI (based on RIFLE, AKIN and KDIGO), worsening renal failure (WRF) and renal replacement therapy (RRT). We investigated the three most common clinical causes of CRS-1: AHF, ACS and CS. Out of 332 potential papers, 64 were eligible – with AKI used in 41 studies, WRF in 25 and RRT in 20. The occurrence rate of CRS-1, defined by AKI, WRF and RRT, was 25.4, 22.4 and 2.6%, respectively. AHF patients had a higher occurrence rate of CRS-1 compared to ACS and CS patients (AKI: 47.4 vs. 14.9 vs. 22.1%), but RRT was evenly distributed among the types of acute cardiac disease. AKI was associated with an increased mortality rate (risk ratio = 5.14, 95% CI 3.81–6.94; 24 studies and 35,227 patients), a longer length of stay in the intensive care unit [LOS<sub>ICU</sub>] (median duration = 1.37 days, 95% CI 0.41–2.33; 9 studies and 10,758 patients) and a longer LOS in hospital [LOS<sub>hosp</sub>] (median duration = 3.94 days, 95% CI 1.74–6.15; 8 studies and 35,227 patients). Increasing AKI severity was associated with worse outcomes. The impact of CRS-1 defined by AKI on mortality was greatest in CS patients. RRT had an even greater impact compared to AKI (mortality risk ratio = 9.2, median duration of LOS<sub>ICU</sub> = 10.6 days and that of LOS<sub>hosp</sub> = 20.2 days). **Key Messages:** Of all included patients, almost one quarter developed AKI and approximately 3% needed RRT. AHF patients experienced the highest occurrence rate of AKI, but the impact on mortality was greatest in CS patients.

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## Introduction

Cardiorenal syndrome (CRS) is a pathophysiologic disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other organ. In 2008, Ronco et al. proposed five subtypes of CRS according to the temporal sequence of organ failure as well as the clinical context [1]. CRS type 1 or acute cardiorenal syndrome (CRS-1) is characterized by an acute cardiac disease leading to acute kidney injury (AKI). The most common aetiologies for an acute cardiac disease include acute decompensated heart failure (AHF), acute coronary syndrome (ACS) and cardiac surgery (CS) [2].

The number of studies in the medical literature on this topic is hampered by the fact that at least 37 different definitions for AKI are being used [3]. This obviously makes any comparison between different studies difficult. In recent years, interdisciplinary consensus groups have proposed standardized criteria to define and stage AKI. The RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) classification and its modifications by the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) group have been developed for the purpose of accurately diagnosing and assessing the severity and progression of AKI [4–7]. An alternative terminology and definition used, especially in publications on AHF, is worsening renal function (WRF).

The objective of this systematic review was to analyse the occurrence rate and outcome of CRS-1 according to the different definitions used for AKI, and for the three most frequent occurring aetiologies of CRS-1: AHF, ACS and CS.

## Methods

### *Study Design*

This is a systematic review and meta-analysis on CRS-1. The study was designed and is reported according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines and checklist [8].

### *Eligibility Criteria*

We included retrospective and prospective cohort studies on adult populations with AHF, ACS or CS, providing epidemiological data on the rate of AKI and mortality in the short and long term. Only papers in English, French or Dutch, published between 1960 till present, were included. Exclusion criteria were: studies on animals, studies including children, case reports, reviews, intervention studies evaluating a specific treatment and duplicate publications.

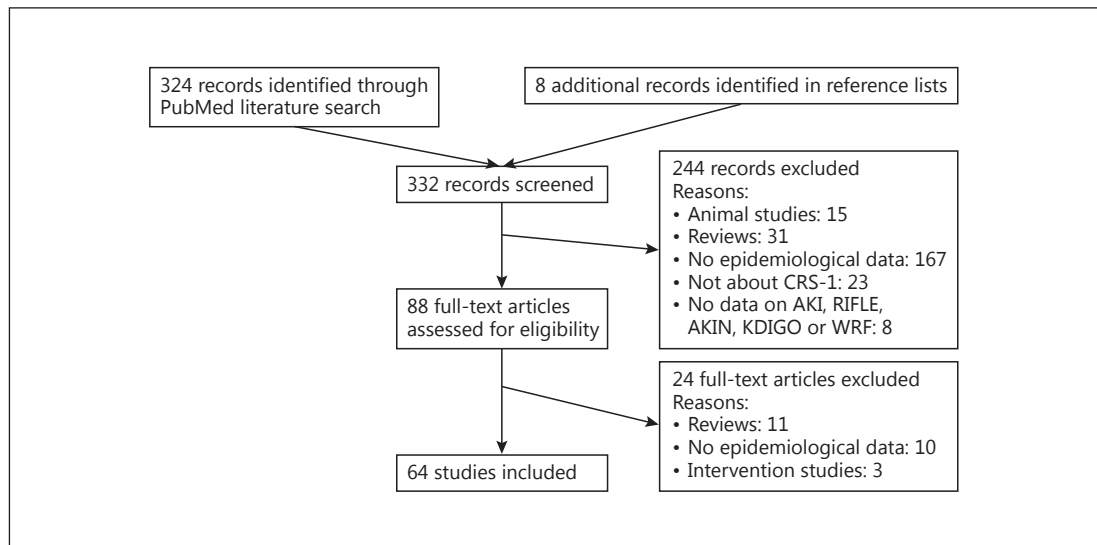
The primary outcome was mortality. Secondary outcomes that were collected were data on length of stay in the intensive care unit ( $LOS_{ICU}$ ), in the hospital ( $LOS_{hosp}$ ) and occurrence rate of renal replacement therapy (RRT).

### *Search Strategy*

The first selection of the search was performed by one investigator (W.V.), under supervision of the principal investigator (E.A.J.H.), who is a content expert. The scientific search engine PubMed was used, and included the period January 1, 1960 till February 28, 2015. The bibliographies of relevant papers were also consulted to retrieve further papers. For the PubMed search, we used the high-performance search filters for AKI as described by Hildebrand et al. [9], combined with the following medical subject headings (MeSH) terms: ‘cardiorenal syndrome’, ‘acute heart failure’, ‘acute coronary syndrome’ or ‘cardiac surgery’ (see online suppl. appendix 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000442300](http://www.karger.com/doi/10.1159/000442300)). Citations of included papers were collected using Reference Manager12 (Thomson Reuters®).

### *Data Extraction and Statistical Analysis*

We (W.V. and E.A.J.H.) collected basic study characteristics: first author, year of publication, study period, country, retrospectively or prospectively gathered data; and population characteristics: occurrence rate of AKI, definition of AKI, subgroups of CRS-1 (AHF, ACS and CS), inclusion and exclusion criteria of the



**Fig. 1.** Flow diagram of the study selection. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy.

study,  $LOS_{ICU}$  and  $LOS_{hosp}$ , use of RRT. The collected data were directly extracted to an excel database (Microsoft®). The subgroups of CRS-1 and the definition of AKI were used to define and analyse the subpopulations.

The statistical analysis was performed with the software program SPSS Statistics 22 (IBM Corporation and Others®). The meta-analysis was performed with the software package Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), using the Mantel-Haenszel test (risk ratio). Several subgroups of AKI were analysed. First, all AKI cases using the RIFLE consensus definition or its modifications (AKIN and KDIGO) were grouped as AKI. Second, all AKI cases defined by variations of WRF were grouped as WRF. The final AKI subgroup was AKI cases treated with RRT (grouped as RRT). The occurrence rate of AKI is reported by the different definitions of AKI. In addition, we report on mortality,  $LOS_{ICU}$  and  $LOS_{hosp}$ . A random effect model was used to combine the data. As a sensitivity analysis, we analysed the prospective studies separately. Heterogeneity was assessed using a forest plot and the  $I^2$  statistic. Bias was assessed by the risk of bias tool that is available in RevMan 5. Finally, a funnel plot was constructed for the assessment of heterogeneity and publication bias.

## Results

The systematic literature search yielded 332 potential studies (fig. 1). We excluded 268 studies: animal studies (15), reviews (42), no epidemiological data available (177), not about CRS-1 (23), no data about AKI or WRF (8) and studies evaluating a specific intervention (3). Finally, we included 64 papers ( $n = 509,766$  patients), containing data on AKI in AHF patients (18 studies; 29,202 patients) [4, 10–26], ACS (15 studies; 282,113 patients) [13, 27–40] and CS (32 studies; 198,451 patients) [41–72] (table 1). One study contained information about AHF as well as ACS and is therefore used in both groups [13].

AKI was defined by 10 different definitions (online suppl. table 1). AKI was used in 41 studies, subdivided into the RIFLE consensus definition in 30 studies, AKIN in 15 and KDIGO in 7. WRF, with 6 variants, was used in 25 studies, and RRT was used in 20 studies. A prospective study design was used in 29 (45%) studies (AHF 10, 56%; ACS 6, 40%, and CS 13, 41%).

**Table 1.** Baseline characteristics of the studies on patients with AHF, ACS and CS

| First author        | Year of publication | Type of data collection | CRS subgroup | AKI definition          | Participants, n | Mean age of patients ± SD, years | DM, % |
|---------------------|---------------------|-------------------------|--------------|-------------------------|-----------------|----------------------------------|-------|
| <b>AHF</b>          |                     |                         |              |                         |                 |                                  |       |
| 1 Smith [24]        | 2003                | Prospective             | AHF          | WRF                     | 412             | 72±11                            | NA    |
| 2 Cowie [12]        | 2006                | Prospective             | AHF          | WRF                     | 299             | 68.0±11.6                        | 32.8  |
| 3 Logaert [18]      | 2008                | Prospective             | AHF          | WRF                     | 416             | 71±13                            | 22.8  |
| 4 Metra [19]        | 2008                | Prospective             | AHF          | WRF                     | 318             | 68±11                            | 29.0  |
| 5 Aronson [10]      | 2010                | Prospective             | AHF          | WRF                     | 467             | 63±15                            | 49.5  |
| 6 Verdiani [25]     | 2010                | Prospective             | AHF          | WRF                     | 394             | 78±10                            | 33    |
| 7 Breidhardt [11]   | 2011                | Prospective             | AHF          | WRF                     | 657             | 79 (71–85)                       | 31.0  |
| 8 Metra [20]        | 2012                | Prospective             | AHF          | WRF                     | 594             | 69.1±10.8                        | 35.0  |
| 9 Mielniczuk [21]   | 2012                | Prospective             | AHF          | WRF                     | 34              | 67±15                            | 31    |
| 10 Roy [4]          | 2012                | Prospective             | AHF          | KDIGO, RIFLE, AKIN, WRF | 637             | 64.6±14.3                        | 23.7  |
| Total               |                     |                         |              |                         | 4,228           | Mean 70.0                        | 32.0  |
| <b>ACS</b>          |                     |                         |              |                         |                 |                                  |       |
| 1 Krumholz [16]     | 2000                | Retrospective           | AHF          | WRF                     | 1,681           | 80±8                             | 38.3  |
| 2 Nohria [22]       | 2008                | Retrospective           | AHF          | WRF                     | 433             | 56±14                            | 15.5  |
| 3 Hata [14]         | 2010                | Retrospective           | AHF          | RIFLE                   | 376             | 69±12                            | NA    |
| 4 Kociol [15]       | 2010                | Retrospective           | AHF          | WRF                     | 20,063          | NA                               | 38.9  |
| 5 Eren [13]         | 2012                | Retrospective           | AHF, ACS     | AKIN                    | 53 (AHF)        | NA                               | NA    |
| 6 Zhou [26]         | 2012                | Retrospective           | AHF          | RIFLE                   | 738             | 63±16                            | 36.6  |
| 7 Shirakabe [23]    | 2013                | Retrospective           | AHF          | RIFLE                   | 625             | 72±12                            | 37.7  |
| 8 Li [17]           | 2014                | Retrospective           | AHF          | KDIGO                   | 1,005           | 68.5±15.0                        | 32.7  |
| Total               |                     |                         |              |                         | 24,974          | Mean 68.1                        | 35.5  |
| <b>CS</b>           |                     |                         |              |                         |                 |                                  |       |
| 1 Marenzi [36]      | 2010                | Prospective             | ACS          | WRF                     | 97              | 66±11                            | 18.6  |
| 2 Bruetto [30]      | 2012                | Prospective             | ACS          | RIFLE                   | 828             | 65 (54–74)                       | 25.7  |
| 3 Lazaros [35]      | 2012                | Prospective             | ACS          | WRF                     | 447             | NA                               | 26.4  |
| 4 Alfaleh [27]      | 2013                | Prospective             | ACS          | WRF                     | 3,583           | 61.0±14.6                        | 55.1  |
| 5 Hsieh [32]        | 2013                | Prospective             | ACS          | RIFLE                   | 622             | NA                               | 32.2  |
| 6 Rodrigues [40]    | 2013                | Prospective             | ACS          | KDIGO, RIFLE            | 1,050           | 65 (55–74)                       | 24.9  |
| Total               |                     |                         |              |                         | 6,627           | Mean 64.3                        | 42.0  |
| 1 Goldberg [31]     | 2005                | Retrospective           | ACS          | WRF                     | 1,038           | 63±14                            | 24.5  |
| 2 Jose [33]         | 2006                | Retrospective           | ACS          | WRF                     | 1,854           | NA                               | 21.3  |
| 3 Latchamsetty [34] | 2007                | Retrospective           | ACS          | WRF                     | 1,417           | 63                               | 29.0  |
| 4 Newsome [38]      | 2008                | Retrospective           | ACS          | WRF                     | 87,094          | 77±8                             | 52.1  |
| 5 Parikh [39]       | 2008                | Retrospective           | ACS          | WRF                     | 147,007         | 47±9                             | 30.9  |
| 6 Amin [28]         | 2010                | Retrospective           | ACS          | WRF                     | 2,098           | 65±13                            | 28.8  |
| 7 Amin [29]         | 2012                | Retrospective           | ACS          | WRF                     | 31,532          | 68.6                             | 35.2  |
| 8 Eren [13]         | 2012                | Retrospective           | ACS, AHF     | AKIN                    | 236 (ACS)       | NA                               | NA    |
| 9 Marenzi [37]      | 2013                | Retrospective           | ACS          | AKIN                    | 3,210           | 71±16                            | 21.0  |
| Total               |                     |                         |              |                         | 275,486         | Mean 65.0                        | 37.9  |
| <b>CS</b>           |                     |                         |              |                         |                 |                                  |       |
| 1 Heringlake [54]   | 2006                | Prospective             | CS           | RIFLE                   | 29,623          | NA                               | NA    |
| 2 Kuitunen [57]     | 2006                | Prospective             | CS           | RIFLE                   | 808             | NA                               | NA    |
| 3 Lassnigg [58]     | 2008                | Prospective             | CS           | RIFLE, AKIN             | 7,241           | 63 (19–90)                       | 18.9  |
| 4 Haase [52]        | 2009                | Prospective             | CS           | RIFLE, AKIN             | 282             | 72±10                            | 27.0  |
| 5 De Santo [47]     | 2010                | Prospective             | CS           | RIFLE                   | 1,424           | 62±13                            | NA    |
| 6 Straugh [70]      | 2010                | Prospective             | CS, TAVI     | RIFLE                   | 28              | 82 (71–88)                       | 8     |
| 7 Ho [55]           | 2012                | Prospective             | CS           | KDIGO                   | 345             | 63±10                            | 8.1   |
| 8 Delgado [73]      | 2013                | Prospective             | CS           | RIFLE                   | 2,940           | 64.5±11.6                        | 8.2   |
| 9 Hansen [53]       | 2013                | Prospective             | CS           | RIFLE                   | 1,030           | 65.8 (79–75)                     | 16.1  |

**Table 1** (continued)

| First author        | Year of publication | Type of data collection | CRS subgroup | AKI definition   | Participants, n | Mean age of patients ± SD, years | DM, % |
|---------------------|---------------------|-------------------------|--------------|------------------|-----------------|----------------------------------|-------|
| 10 Kallel [74]      | 2013                | Prospective             | CS           | RIFLE            | 136             | 55±14                            | 28.0  |
| 11 Sampaio [68]     | 2013                | Prospective             | CS           | KDIGO,RIFLE,AKIN | 321             | 62 (53–71)                       | 30    |
| 12 Elmistekawy [48] | 2014                | prospective             | CS           | AKIN             | 3,869           | NA                               | NA    |
| 13 Rydén [67]       | 2014                | Prospective             | CS           | AKIN             | 27,929          | 67.1±9.1                         | 23.0  |
| Total               |                     |                         |              |                  | 75,976          | Mean 65.6                        | 21.0  |
| 1 Dasta [46]        | 2008                | Retrospective           | CS           | RIFLE            | 3,741           | 70±10                            | 39.9  |
| 2 Aregger [41]      | 2009                | retrospective           | CS, TAVI     | RIFLE            | 58              | 83±5                             | 12.0  |
| 3 Benedetto [44]    | 2009                | Retrospective           | CS           | AKIN             | 705             | 68 (59–73)                       | 39.2  |
| 4 Machado [61]      | 2009                | Retrospective           | CS           | AKIN             | 817             | 61±9                             | 34.8  |
| 5 Argaliouis [42]   | 2010                | Retrospective           | CS           | RIFLE            | 10,648          | NA                               | 17.6  |
| 6 Robert [66]       | 2010                | Retrospective           | CS           | RIFLE, AKIN      | 24,747          | 66±11                            | 31.9  |
| 7 Testani [71]      | 2010                | Retrospective           | CS           | RIFLE            | 3,914           | NA                               | 36.2  |
| 8 Englberger [49]   | 2011                | Retrospective           | CS           | RIFLE,AKIN       | 4,836           | 64.4±14.2                        | 20    |
| 9 Mariscalco [63]   | 2011                | Retrospective           | CS           | RIFLE            | 414             | 62.5±11.5                        | 8.7   |
| 10 Schneider [69]   | 2012                | Retrospective           | CS           | RIFLE            | 1,504           | 67.9                             | 29.9  |
| 11 Tolpin [72]      | 2012                | Retrospective           | CS           | RIFLE            | 3,914           | NA                               | 36.2  |
| 12 Bastin [43]      | 2013                | Retrospective           | CS           | RIFLE,AKIN       | 1,881           | 66 (56–74)                       | NA    |
| 13 Dardashti [45]   | 2013                | Retrospective           | CS           | RIFLE            | 5,742           | 67.3±9.7                         | 22.1  |
| 14 Englberger [50]  | 2013                | Retrospective           | CS           | RIFLE            | 951             | 67±13                            | 20.4  |
| 15 Liotta [59]      | 2014                | Retrospective           | CS           | WRF              | 25,665          | 67.0±9.2                         | 24.0  |
| 16 Nina [65]        | 2013                | Retrospective           | CS           | RIFLE, AKIN      | 169             | 63±9                             | NA    |
| 17 Engoren [51]     | 2014                | Retrospective           | CS           | KDIGO            | 1,543           | NA                               | NA    |
| 18 Machado [62]     | 2014                | Retrospective           | CS           | KDIGO            | 2,804           | 59 (49–66)                       | 23    |
| 19 Ng [64]          | 2014                | Retrospective           | CS           | WRF              | 28,422          | Mean 66                          | NA    |
| Total               |                     |                         |              |                  | 122,475         | Mean 66.5                        | 27.0  |

Values in parentheses are interquartile ranges. DM = Diabetes mellitus; NA = not available.

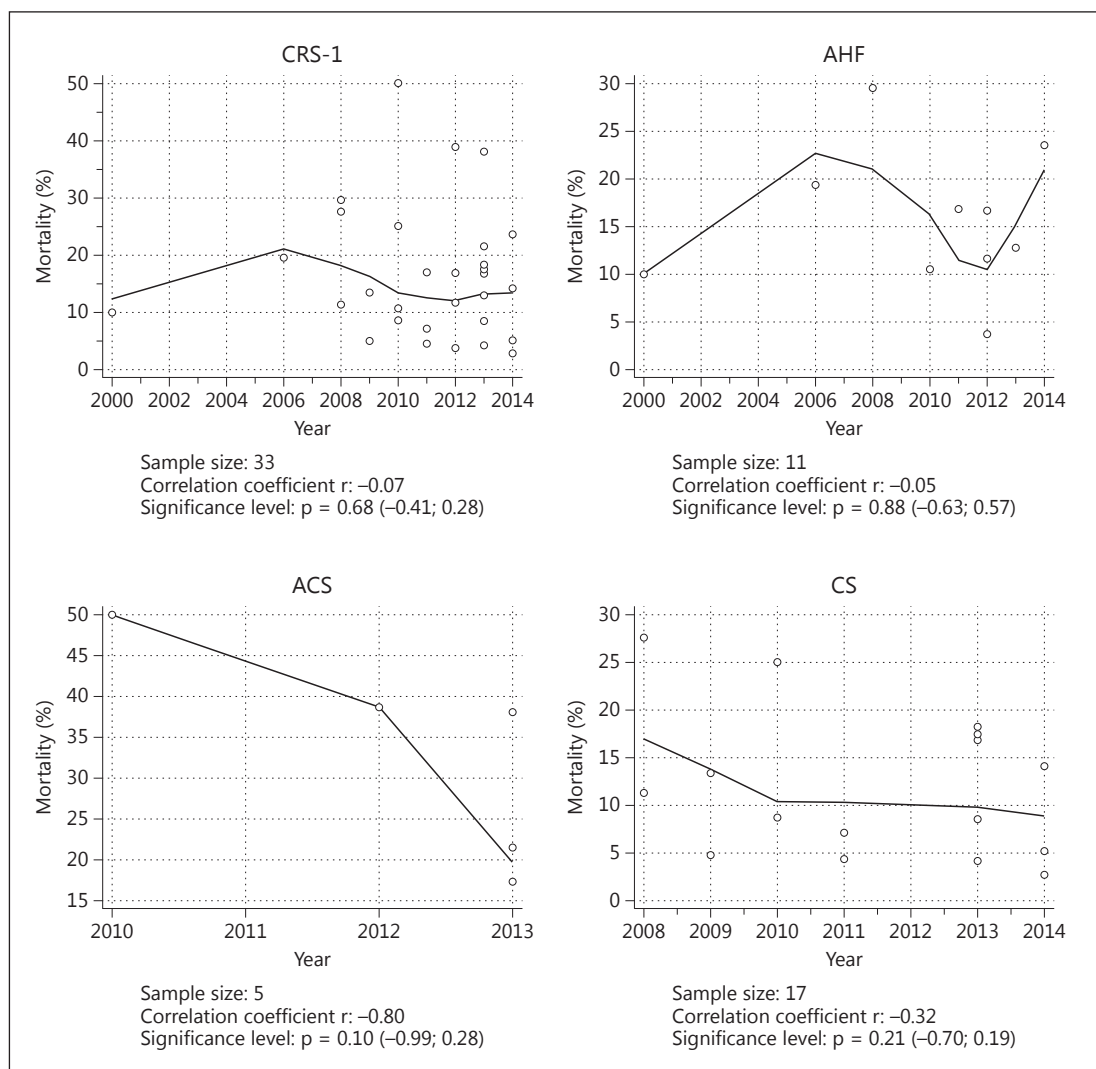
**Table 2.** Occurrence rate of AKI in CRS-1 patients

|                       | All AKI, %       | Studies/<br>Patients | AKI, %           | Studies/<br>Patients | WRF, %           | Studies/<br>Patients | RRT, %        | Studies/<br>Patients |
|-----------------------|------------------|----------------------|------------------|----------------------|------------------|----------------------|---------------|----------------------|
| <i>CRS-1 subgroup</i> |                  |                      |                  |                      |                  |                      |               |                      |
| All CRS-1             | 24.4 (12.9–36.6) | 64/509,766           | 25.4 (14.3–38.9) | 40/153,744           | 22.4 (11.8–33.1) | 24/356,022           | 2.6 (1.8–4.7) | 23/71,313            |
| AHF                   | 35.3 (25.2–46.2) | 18/29,202            | 47.4 (39.1–63.3) | 6/3,434              | 30.4 (24.2–35.9) | 12/25,768            | 4.3 (1.0–8.8) | 4/1,525              |
| ACS                   | 12.7 (10.7–17.0) | 15/282,113           | 14.9 (13.2–20.7) | 5/5,946              | 12.0 (8.8–14.1)  | 10/276,167           | 1.7 (1.3–2.2) | 2/3,446              |
| CS                    | 22.1 (13.5–32.9) | 32/198,451           | 22.1 (13.7–32.9) | 30/144,364           | 6.4 (6.4–6.4)    | 2/54,087             | 3.1 (1.9–4.5) | 17/66,342            |

Data are presented as proportions and interquartile ranges. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy.

A risk of bias analysis showed a low risk for selection bias in 55% of the studies, and the funnel plot could not indicate publication bias (fig. 2).

The use of different definitions resulted in a wide range of reported rates of AKI in CRS-1 patients. Table 2 summarises the occurrence rates of AKI according to the definition used and the CRS-1 subgroup. The median occurrence rate of AKI defined by any definition was 24.4%. A comparison of the AKI definition groups in CRS-1 reveals that AKI and WRF have a similar occurrence rate (25.4 and 22.4%,  $p = 0.478$ ).



**Fig. 2.** Reported mortality rates over time, grouped by the year of publication in CRS-1 patients, AHF, ACS and after CS.

The subgroup of CRS-1 patients who had AHF had a higher occurrence rate of AKI (35.3%) in comparison to those with ACS and CS (12.7 and 22.1%,  $p < 0.001$  and  $p = 0.09$ ). This trend is similar when AKI was defined by AKI or WRF. In contrast, RRT was evenly distributed among all CRS-1 subtypes ( $p = 0.611$ ; table 2), with a median occurrence rate of 2.6%.

The sub-analyses of AKI stages for patients classified as AKI demonstrated that the majority of patients had less severe AKI (table 3). The analysis of the subgroups of CRS-1 showed a similar trend for AKI severity.

#### Outcomes of CRS-1 and Its Subgroups

##### CRS-1: Whole Cohort

Most papers reported data on mortality after an observation period of 28 days (33 studies; table 4). Although, only a few papers reports long-term follow-up data on mortality, these included large patient cohorts and are therefore still informative.

**Table 3.** Occurrence rate of AKI according to the 3 stages of AKI and subclasses of CRS-1

|       | Risk/stage 1,<br>% | Studies/<br>patients | Injury/stage 2,<br>% | Studies/<br>patients | Failure/stage 3,<br>% | Studies/<br>patients |
|-------|--------------------|----------------------|----------------------|----------------------|-----------------------|----------------------|
| CRS-1 | 17.9 (9.1–24.0)    | 27/99,561            | 4.4 (3.5–6.9)        | 28/101,442           | 3.6 (1.9–5.3)         | 17/99,561            |
| AHF   | 34.2 (27.6–39.6)   | 5/2,797              | 11.7 (10.4–18.6)     | 5/2,797              | 9.1 (5.7–9.3)         | 5/2,797              |
| ACS   | 9.2 (8.2–9.6)      | 5/5,763              | 4.3 (3.7–4.5)        | 5/5,763              | 3.2 (1.0–3.8)         | 5/5,763              |
| CS    | 17.9 (9.6–22.0)    | 19/93,858            | 4.4 (3.5–5.6)        | 19/93,858            | 3.5 (1.9–4.5)         | 19/93,858            |

Data are presented as proportions and interquartile ranges. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications.

**Table 4.** Outcomes of CRS-1 according to the definition of AKI

|                     | Period   | All definitions  | Studies/<br>Patients | AKI              | Studies/<br>Patients | WRF              | Studies/<br>Patients | RRT                 | Studies/<br>Patients |
|---------------------|----------|------------------|----------------------|------------------|----------------------|------------------|----------------------|---------------------|----------------------|
| Mortality           | 28 days  | 4.90 (3.68–6.52) | 33/56,860            | 5.14 (3.81–6.94) | 24/35,227            | 5.19 (2.78–9.70) | 12/51,805            | 9.16 (2.71–30.98)   | 5/6,556              |
|                     | 1 year   | 2.08 (1.27–3.42) | 9/13,723             |                  |                      |                  |                      |                     |                      |
|                     | ≥5 years | 1.90 (1.50–2.41) | 3/31,108             |                  |                      |                  |                      |                     |                      |
| LOS <sub>ICU</sub>  | 28 days  | 1.46 (0.52–2.39) | 10/10,855            | 1.37 (0.41–2.33) | 9/10,758             | 3.00(0.04–5.96)  | 1/97                 | 10.63(3.51–17.74)   | 3/5,799              |
| LOS <sub>hosp</sub> | 28 days  | 3.51 (1.78–5.24) | 13/8,733             | 3.94 (1.74–6.15) | 8/6,649              | 2.65 (0.75–4.54) | 5/2,084              | 20.20 (12.17–28.23) | 3/6,045              |

Data are presented as risk ratio (95% CI) for mortality and weighted mean difference (95% CI) for LOS. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy; CI = confidence interval.

CRS-1 is correlated with an approximately 5-times increased risk for mortality after 28 days – confirmed by AKI as well as WRF (table 4). The mortality risk in RRT patients is almost twice as high as that of AKI. The risk for mortality after initial hospital survival is 2 times higher 1 and 5 years after CRS-1.

CRS-1 is associated with an increased LOS<sub>ICU</sub> and LOS<sub>hosp</sub> (1.5 and 3.5 days, respectively). When CRS-1 was defined by RRT, LOS<sub>ICU</sub> and LOS<sub>hosp</sub> dramatically increased by 11 and 20 days.

A higher severity stage of AKI is associated with a stepwise worsening of all outcomes (table 5). The outcome of CRS-1 also varies according to the underlying clinical condition. Table 6 illustrates the different outcomes in the CRS-1 subtypes, subdivided according to the definition of AKI.

A correlation analysis of mortality over time, grouped by the year of publication, indicate no significant change in CRS-1 (correlation coefficient –0.07, p 0.68) and its subgroups AHF, ACS and CS (correlation coefficient: –0.05, p = 0.88; –0.80, p = 0.10; –0.32, p = 0.20, respectively; fig. 2).

#### Acute Heart Failure

We observed a significant increased mortality (risk ratio 2.89), but the impact was less in this cohort compared to ACS and CS patients. When defined as WRF, CRS-1 was associated with a longer LOS<sub>ICU</sub>. LOS<sub>hosp</sub> was increased for CRS-1 defined by WRF and AKI defined by the KDIGO classification. We found no studies that reported on CRS-1 defined as RRT in this cohort.

#### Acute Coronary Syndrome

We found important differences in the mortality rate associated with CRS-1 in ACS patients. CRS-1 defined by AKI was associated with a 3.5-times increased risk for mortality, while WRF was associated with a 17-times increased risk. This may be explained by the differences in

**Table 5.** Outcomes of CRS-1 according to the severity of AKI when defined as AKI

|                     | Risk/stage1      | Studies/<br>Patients | Injury/stage2     | Studies/<br>Patients | Loss/stage 3        | Studies/<br>Patients |
|---------------------|------------------|----------------------|-------------------|----------------------|---------------------|----------------------|
| Mortality           | 3.45 (2.25–5.31) | 16/53,066            | 9.57 (6.31–14.50) | 13/39,644            | 20.37 (13.19–31.48) | 12/38,575            |
| LOS <sub>ICU</sub>  | 0.99 (0.65–1.33) | 8/16,348             | 2.22 (0.89–3.55)  | 7/12,479             | 8.32(3.39–13.24)    | 7/12,479             |
| LOS <sub>hosp</sub> | 3.51 (2.63–4.39) | 10/17,713            | 8.32 (5.87–10.78) | 9/13,844             | 18.41 (14.74–22.09) | 9/13,844             |

Data are presented as risk ratio (95% CI) for mortality and weighted mean difference (95% CI) for LOS. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy; CI = confidence interval.

**Table 6.** Mortality, LOS<sub>ICU</sub> and LOS<sub>hosp</sub> in the subtypes of CRS-1 according to the definition of AKI

| Outcome             | Sub-group | AKI               | Studies/<br>Patients | WRF                 | Studies/<br>Patients | RRT                 | Studies/<br>Patients |
|---------------------|-----------|-------------------|----------------------|---------------------|----------------------|---------------------|----------------------|
| Mortality           | AHF       | 2.89 (2.14–3.89)  | 5/4,018              | 2.37 (1.65–3.38)    | 8/5,050              |                     |                      |
|                     | ACS       | 3.53 (2.04–6.10)  | 3/5,088              | 16.95 (12.00–23.93) | 2/4,621              | 2.72 (1.52–4.88)    | 1/97                 |
|                     | CS        | 7.51 (5.58–10.11) | 16/26,121            | 17.11 (9.53–30.73)  | 2/42,134             | 7.55 (1.28–44.39)   | 4/5,605              |
| LOS <sub>ICU</sub>  | AHF       | 0.35 (–0.80–1.51) | 3/2,119              | 3.00 (0.04–5.96)    | 1/97                 |                     |                      |
|                     | ACS       | 2.00 (1.88–2.12)  | 1/3,210              |                     |                      |                     |                      |
|                     | CS        | 1.68 (0.38–2.97)  | 5/5,429              |                     |                      | 10.63 (3.51–17.74)  | 3/5,799              |
| LOS <sub>hosp</sub> | AHF       | 5.79 (1.21–10.37) | 4/2,172              | 2.65 (0.75–4.54)    | 5/2,084              |                     |                      |
|                     | ACS       | 2.08 (1.01–3.15)  | 1/236                |                     |                      |                     |                      |
|                     | CS        | 3.56 (–1.05–8.16) | 4/4,241              |                     |                      | 20.20 (12.17–28.23) | 3/6,045              |

Data are presented as risk ratio (95% CI) for mortality and weighted mean difference (95% CI) for LOS. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy; CI = confidence interval.

definition and the variant of WRF used, but probably more importantly also the differences in baseline characteristics of the patients. The association of RRT and mortality was only reported in 1 study (including 97 patients), limiting the strength of the observed risk ratio. CRS-1 defined by AKI was associated with a 2 days longer LOS in the ICU as well in the hospital.

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CS patients who had CRS-1 had the highest mortality risk of all 3 subtypes of CRS-1. The 2 studies that reported on WRF revealed a 17-times increased risk for mortality. Similar to AHF patients, the most obvious explanation for this important difference may be the differences in baseline characteristics between the study cohorts. LOS was only moderately increased in the ICU, and remarkably, LOS<sub>hosp</sub> was similar to CS patients without CRS-1.

**Discussion**

A total of 64 studies, including 509,766 patients, were analysed in this systematic review on the epidemiology of CRS-1. We found that 10 different definitions for AKI were used in these publications. These could be grouped in AKI, WRF and RRT. AKI and WRF occurred in



approximately one-fifth of the patients with acute cardiac disease, and they were associated with a 5-times increased risk for death and a 1–4 days longer LOS. RRT occurred in 2.6% of the patients with acute cardiac disease, and it was associated with a 9-times increased risk for death. These patients had a 10 and 20 days longer LOS in the ICU and hospital, respectively.

We found important differences between the occurrence rate of CRS-1 and outcomes in the 3 subgroups of acute cardiac disease. AHF patients experienced the highest rates of AKI (defined by the KDIGO guidelines) and WRF, but the rate of RRT was similar among the 3 different acute cardiac diseases. CRS-1, defined by any definition, had the greatest impact on mortality in CS patients.

There may be several explanations for the higher occurrence of CRS-1 in AHF patients. First, heart failure patients do more likely have decreased renal perfusion as a consequence of forward and/or backward failure. This is less frequently occurring in patients who develop CRS-1 as a consequence of ACS or CS. Second, a considerable number of patients who had AHF may also have suffered from chronic heart failure, a condition associated with chronic impairment of kidney function. Third, the therapy for AHF includes potential nephrotoxic drugs, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Finally, unmeasured differences in the baseline characteristics of the AHF patients may also explain the higher occurrence rate of CRS-1.

Although, the occurrence rate of AKI is highest in AHF patients, the impact of AKI on mortality is more pronounced in patients who underwent CS. Several explanations are possible. First, AKI could be a surrogate marker of severe complications after CS, for example peri-operative blood loss, AHF, ACS, stunning of the heart due to multiple episodes or a prolonged period on cardiopulmonary bypass, post-operative infections or thrombo-embolic processes. All these events can result in an additional deterioration of kidney function, and some of these have an important impact on outcome. Second, the higher severity of AKI in the CS group may explain the worse outcome. We found that RRT occurred more frequently in CS patients. On the other hand, AKI stage 3 was less frequent, although peri-operative fluid loading, resulting in a dilution of serum creatinine and false low AKI staging, could bias this.

#### *Study Strengths and Limitations*

This review includes over 60 studies with more than half a million patients and presents a comprehensive overview of all studies reporting on AKI in patients with CRS-1, defined according to the different definitions of AKI used, including the newest KDIGO variant. In addition, we evaluated in a sub-analysis, the 3 most important categories of acute cardiac disease leading to CRS-1. Although we searched for studies published between 1960 till present, we could only include studies published since 2000. This guarantees that the data presented in this study are contemporary and valid for present-day practice.

We would like to mention several limitations. First, we did not include studies on AKI caused by contrast agents during coronary interventions, because in these patients, AKI is a toxic reaction secondary to contrast exposure, rather than a consequence of acute cardiac disease. Second, studies have used different durations of observation time for the ascertainment of AKI. These variations in ascertainment for AKI have the potential to introduce bias and misclassification. The most common definition for AKI has been at any time during hospital admission. Third, despite of grouping the AKI definitions, there is still considerable heterogeneity within each group. We found 6 variants of WRF, and AKI was also defined according to the different modifications of the original RIFLE classification – AKIN and KDIGO. Additionally, the indications and exclusion criteria for RRT are diverse, resulting in a heterogeneous cohort. Fourth, none of the studies used the urine output criteria for AKI. Fifth, bias and heterogeneity may limit this systematic review. To assess the quality of the collected

papers, we performed a risk of bias analysis. This showed a low risk for selection bias in only 55% of the papers and prospective data collection in 45%. The  $I^2$  statistic of 87% (fig. 1) also indicates an important statistical heterogeneity among the studies. Finally, the 5-year mortality rate was based on only 3 studies, limiting the strength of this observation.

## Conclusions

Almost one quarter of the patients included had AKI, and RRT was used in approximately 3%. AKI was associated with significantly worse outcomes. AHF patients experienced the highest occurrence rate of AKI, but the impact on mortality was greatest in CS patients.

## Disclosure Statement

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