Prognosis and factors affecting mortality in patients with acute kidney injury due to cardiorenal syndrome type 1 treated with sustained low-efficiency dialysis

Thanapon Nilmoje, Dhipsukon Pongborriboon, Ussane Boonsrirat, Sirihatai Konwai, Suntornwit Praditau-Krit, Atthaphong Phongphithakchai

Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Abstract

Introduction: Cardiorenal syndrome (CRS) type 1 is linked to poor outcomes, particularly inhospital mortality. While diuretics are commonly used, their efficacy may be limited necessitating renal replacement therapy (RRT) often using continuous renal replacement therapy (CRRT). However, the cost and availability limit CRRT usage, prompting exploration of alternative therapies like sustained low efficiency dialysis (SLED).

Objectives: We conducted a retrospective analysis to explore significant factors affecting mortality rates in CRS type 1 patients treated with SLED.

Patients and Methods: This is a retrospective cohort study conducted in a tertiary hospital from 2012 to 2022, including 215 CRS type 1 patients treated with SLED. The patients were categorized into the survivors’ group and the nonsurvivors’ group. The clinical indicators and biochemical markers for each group were compared to identify any disparities. Additionally, multivariate logistic regression analysis was conducted to ascertain the independent risk factors.

Results: The in-hospital mortality was 49.3%. Hydralazine administration prior to admission (odd ratio [OR]: 0.39, 95% CI 0.18–0.86) serum creatinine at SLED initiation (OR: 0.86, 95% CI 0.77–0.96), intra-aortic balloon pumps (IABP) treatment (OR: 2.04, 95% CI 1.28–3.26), and urine output <400 mL/d in 24 hours prior discontinuing SLED (OR: 3.61, 95% CI 2.01–6.49) were associated with increased risk of in-hospital mortality.

Conclusion: SLED-based RRT for acute kidney injury in type 1 CRS is linked to higher in-hospital mortality for patients not previously administered hydralazine, having low serum creatinine, IABP usage, and experiencing oliguria.

Implication for health policy/practice/research/medical education: Incorporating assessments of pre-admission hydralazine administration, serum creatinine levels, intra-aortic balloon pump treatment, and oliguria into clinical guidelines may significantly enhance management strategies for cardiorenal syndrome type 1 patients treated with sustained low-efficiency dialysis.

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Introduction
Cardiorenal syndrome (CRS) is a pathophysiological condition involving both the heart and kidneys where the dysfunction of one organ, whether acute or chronic, triggers corresponding dysfunction in the other (1). CRS type 1 commonly observed in critical-care settings, is characterized by acute cardiac dysfunction, such as acute decompensated heart failure (ADHF) or acute coronary syndrome (ACS), resulting in cardiogenic shock subsequent with acute kidney injury (AKI) (2). The prevalence of CRS type 1 among hospitalized individuals is approximately 25.4%, with ADHF accounting for 24–45% of cases and ACS accounting for 9–19%, with the remainder resulting from cardiac surgery (2,3). More importantly, CRS type 1 is associated with poor outcomes. This was reported in previous studies finding a significant association between in-hospital mortality rate and rising creatinine levels in CRS type 1 patients on the admission day (4,5).

The pathophysiological mechanism behind CRS type 1 is that elevated venous pressures and congestion diminish the gradient of blood flow within the glomerular...
capillary system. This, in turn, leads to a reduction in intravascular circulation, functional impairment of the glomeruli, and a subsequent decrease in the production of urine (6). Management strategies for CRS type 1 aim to treat the possible causes and reduce congestion through the administration of diuretics. However, this may have limited efficacy in patients who have diuretic resistance often associated with low cardiac output. In such cases, renal replacement therapy (RRT) plays a crucial role in eliminating excess fluid from the body, thereby helping to restore normal cardiac and renal perfusion (7,8).

Continuous renal replacement therapy (CRRT) is the most-used RRT option because it is highly beneficial in hemodynamically unstable patients (9,10). However, CRRT is available only in limited critical-care units due to its high cost (11,12). Thus, an alternative hybrid therapy option using sustained low efficiency dialysis (SLED) is increasingly used to provide hemodynamic stability (13).

It is inferred that SLED offers enhanced hemodynamic tolerance, reduced exposure to anticoagulants, and shorter treatment durations, all while maintaining patient clinical outcomes and survival rates comparable to those achieved with CRRT (14,15). Moreover, previous studies report a lower cost compared with CRRT (16). However, there are no published studies on the effects of administration of SLED in AKI patients from type 1 CRS.

Objectives
We conducted a retrospective analysis to explore significant factors affecting mortality rates in CRS type 1 patients treated with SLED.

Patients and Methods
Study design
This was a retrospective cohort study conducted in university hospital, which enrolled patients that admitted to the cardiac intensive care unit from January 2012 to December 2022. The inclusion criteria required patients to meet the following conditions: (a) age more than 18 years; (b) diagnosis of type 1 CRS; (c) diagnosis of AKI according to KDIGO 2012 criteria(17) (elevated serum creatinine level of more than 0.3 mg/dL) within 48 hours, urine output less than 0.5 mL/kg/h for 6 hours, or patients at risk of developing acute renal failure within one week of a 1.5-fold increase in baseline serum creatinine level; (d) CRS type 1 as the cause of AKI; and (e) treatment with SLED. Patients with stage 5 chronic kidney disease (CKD), a history of prior RRT within 3 months, AKI diagnosis from causes other than CRS type 1, or current pregnancy were excluded from the study.

SLED protocol
SLED was administered using a hemodialysis machine. We used the high-flux polysulphone hemofilter (REXEED-15L; Asahi Kasei Medical Co., Ltd.) and rinsed it with 2 L of pre-heparinized saline before applying it to the circuit. Temporary double lumen catheters were used for vascular access. The blood flow rate was prescribed in a range of 150–200 mL/min and dialysate flow rate were set at 300 mL/min. Heparin was used as an anticoagulant. However, in cases that contraindicated heparin, normal saline was flushed 200 mL every 1 hour to prevent circuit clotting. The duration of each SLED session was 8–12 hours. The total session was overseen by the attending nephrologist regarding of the improvement of the patient’s clinical conditions.

Data collection
The clinical and laboratory data of all eligible patients were collected from the electronic medical records of the hospital database. Age, gender, body weight, height, previous underlying diseases, current medication, underlying heart disease, baseline kidney function, and cause of cardiac dysfunction were reviewed. Additionally, the data prior to initiating SLED were collected, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), serum creatinine levels, blood urea nitrogen (BUN) levels, urine volume within 24 hours, vasopressors usage, and fluid balance status. The clinical cardiac parameters regarding the timing of SLED initiation were also extracted, and included left ventricular ejection fraction (LVEF), interventricular septum thickness (IVSD), left ventricular internal diameter end diastole (LVIDd), left ventricular posterior wall end diastole (LVPWd), right atrial pressure (RAP), right ventricular systolic pressure (RVSP), and history of cardiac interventions. The primary outcome of the study was in-hospital mortality. The secondary outcomes were the predictors of in-hospital mortality.

Statistical analysis
Statistical analyses were performed using R software version 4.2.1. Continuous data are presented as means ± standard deviations (SD), while categorical data are expressed as frequencies and percentages. Comparisons between continuous variables were performed using either the two-group t-test or the Wilcoxon rank-sum test, depending on the distribution of the data. Comparisons between categorical variables were analyzed using Fisher’s exact test. Multivariate logistic regression analysis was conducted to identify predictors of in-hospital mortality, with significant predictors from the univariate analysis included in the multivariate analysis. Statistical significance was defined as a P value < 0.05.

Results
During the study period, a total of 215 patients were included in this study. The baseline characteristic data are summarized in Table 1. Out of 215 patients, 112 (52.1%) were male, with a median age of 66 (55–77) years. The body mass index (BMI) was 22.8 (19–25) kg/m². The predominant comorbidities were hypertension (n = 128
Acute kidney injury

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 215</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (55–77)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>112 (52.1)</td>
</tr>
<tr>
<td>Female</td>
<td>103 (47.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8 (19–25)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>126 (58.6)</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>110 (51.2)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>91 (42.3)</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>27 (12.6)</td>
</tr>
<tr>
<td>Medications prior to admission</td>
<td></td>
</tr>
<tr>
<td>ACEi/ARBs, n (%)</td>
<td>45 (22.7)</td>
</tr>
<tr>
<td>CCBs, n (%)</td>
<td>75 (37.9)</td>
</tr>
<tr>
<td>Betablockers, n (%)</td>
<td>69 (34.8)</td>
</tr>
<tr>
<td>Hydralazine, n (%)</td>
<td>42 (21.2)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>90 (45.5)</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>109 (55.1)</td>
</tr>
<tr>
<td>Cause of cardiac dysfunction</td>
<td></td>
</tr>
<tr>
<td>Ischemic, n (%)</td>
<td>91 (42.3)</td>
</tr>
<tr>
<td>Non ischemic, n (%)</td>
<td>124 (57.7)</td>
</tr>
<tr>
<td>Baseline BUN (mg/dL)</td>
<td>29 (18–44)</td>
</tr>
<tr>
<td>Baseline serum Cr (mg/dL)</td>
<td>1.7 (1.1–2.5)</td>
</tr>
</tbody>
</table>

Note: Values are presented as number (%) or median and interquartile ranges.
Abbreviations: BMI, Body mass index; CKD, Chronic kidney disease; CVA, Cerebrovascular accident; ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CCBs, Calcium channel blockers; BUN, Blood urea nitrogen; Cr, Creatinine.

[58.6%] followed by CKD (n = 110 [51.2%]). Diuretics were widely used (n = 109 [55.1%]), while hydralazine was used only in 42 patients (21.2%). The main cause of cardiac dysfunction was non-ischemic etiologies (n =124 [57.7%]). The median BUN and serum creatinine at baseline were 29 (18–44) mg/dL and 1.7 (1.1–2.5) mg/dL, respectively. The main indication for SLED initiation was pulmonary edema (n = 121 [56.2%]). The median duration of SLED was 8d (4.1–12.8). A total of 102 patients (96.2%) required at least one vasoactive agent during SLED. Of the 215 adult patients with AKI caused by CRS type 1 who received SLED, 106 died in the hospital (in-hospital mortality: 49.3%).

When comparing survivors with nonsurvivors, there were no significant differences observed across the categories of age, gender, BMI, and comorbidities. A high proportion of survivors were found to be administered hydralazine prior to admission (P<0.001) prior to admission in the survivors. Nonsurvivors tended to have a higher proportion of non-ischemic causes of cardiac dysfunction (P=0.076), whereas a higher prevalence of ischemic causes was observed in survivors (P=0.001). Of interest, patients in the non-survival group had significantly lower baseline serum BUN and Cr levels than the survival group (P<0.001). Survivors had significantly better LVEF than nonsurvivors (P=0.008). No significant differences were found in RAP, RVSP, LVIDd, or TAPSE (Table 2). Survivors required significantly lower levels of vasoactive agents, including norepinephrine (P<0.001), epinephrine (P<0.001), and dobutamine (P<0.001) at RRT initiation compared with nonsurvivors. Moreover, SBP, DBP and MAP were significantly higher in survivors (P<0.001). Nonsurvivors had significantly higher proportions of intra-aortic balloon pumps (IABP) (P<0.001) and VA-ECMO (P<0.001). Although urine output at 24h after SLED initiation showed no significant difference between the two groups, survivors had significantly better urine output 24h after SLED cessation. Furthermore, survivors had significantly higher BUN and creatine at SLED initiation (P<0.001). There was also significantly positive cumulative fluid balance in nonsurvivors both at SLED initiation (P=0.009) and at SLED cessation (P<0.001).

Four variables remained significant in the final model of multivariable logistic regression analysis, as shown in Table 3. For CRS type 1 patients with AKI who received RRT, predictors of in-hospital mortality included hydralazine usage prior to admission (adjusted OR: 2.04, 95% CI 1.28–3.26), and urine output <400 mL in 24 hours prior to RRT cessation (adjusted OR: 3.61, 95% CI 2.01–6.49).

Discussion
In this retrospective cohort study, we found that nearly half of CRS type 1 patients who received SLED died during hospital admission. The survivors had higher proportions of hydralazine usage prior to admission, ischemic heart disease, and baseline serum BUN and creatinine. Furthermore, at SLED initiation, survivors had higher LVEF, SBP, DBP, and MAP; higher urine output within 24 hours at SLED cessation; lower levels of vasoactive agent usage at the time of SLED initiation; more prevalent history of IABP and ECMO treatments; and lower levels of positive cumulative fluid balance after SLED cessation. Finally, the independent risk factors in the prognosis of patients were hydralazine usage prior to admission, serum creatinine at SLED initiation, IABP treatment, and urine output <400 mL within 24 hours at SLED cessation.

A high incidence of AKI manifestation in patients suffering from type 1 CRS has been reported worldwide (2). Furthermore, if patients in this group require RRT, the likelihood of mortality will significantly increase; it has been observed that the rate of RRT in these patients has steadily increased over the past 10 years (2,18).
Because CRS type 1 patients often experience fluctuating hemodynamic variables and require continuous fluid removal due to the presence of diuretic resistance, which limits their ability to produce adequate urine, CRRT is therefore commonly chosen. Several studies have reported less favorable outcomes of using CRRT in patients within this group (19,20). Prins et al (19) reported high in-hospital mortality, especially in older patients and in those who had used vasoactive agents; these results are similar to those of a study from Japan that found the same poor prognosis factors in type 1 CRS receiving CRRT (20). However, to our knowledge, no study has described the

### Table 2. Comparing parameters at SLED initiation between survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survivors (n=109)</th>
<th>Nonsurvivors (n=106)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular parameters at SLED initiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49 (35–60)</td>
<td>36 (22–60)</td>
<td>0.008*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>11.4 (8.5–16)</td>
<td>12.6 (8.4–17)</td>
<td>0.302</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>50 (38–60)</td>
<td>54.5 (40–64)</td>
<td>0.558</td>
</tr>
<tr>
<td>LVIDd (mm Hg)</td>
<td>51 (44–56)</td>
<td>51 (45–59)</td>
<td>0.318</td>
</tr>
<tr>
<td>TAPSE (mm Hg)</td>
<td>15.8 (5.3)</td>
<td>13.4 (5.8)</td>
<td>0.300</td>
</tr>
</tbody>
</table>

**Vasoactive drugs at SLED initiation**

- Norepinephrine n (%): 34 (31.2) vs. 70 (66), <0.001*
- Epinephrine, n (%): 5 (4.6) vs. 24 (22.6), <0.001*
- Dopamine, n (%): 37 (33.9) vs. 71 (67), <0.001*
- Dobutamine, n (%): 17 (15.6) vs. 22 (20.8), 0.421

**SBP at SLED initiation (mm Hg)**

- 132 (117–150) vs. 110 (100–124), <0.001*

**DBP at SLED initiation (mm Hg)**

- 70 (61–80) vs. 60 (53–69), <0.001*

**MAP at SLED initiation (mm Hg)**

- 89 (80–100) vs. 77 (69–84.8), <0.001*

**Intervention at SLED initiation**

- IABP, n (%): 8 (7.3) vs. 31 (29.2), <0.001*
- VA-ECMO, n (%): 1 (0.9) vs. 10 (9.4), <0.001*

**Urine output 24 h at SLED initiation**

- 650 (300–1240) vs. 595 (200–1196), 0.227

**Fluid balance at SLED initiation**

- 743 (380–1420) vs. 1106 (468–1967), 0.009*

**BUN at SLED initiation**

- 99 (69–119) vs. 66 (47–98), <0.001*

**Serum Cr at SLED initiation**

- 5.4 (3.8–8.6) vs. 3.3 (2.2–4.8), <0.001*

**Duration of SLED, day**

- 6 (4–12) vs. 9 (6–13), 0.483

**Urine output 24 h prior to SLED cessation**

- 820 (400–1130) vs. 52 (0–227), <0.001*

**Fluid balance at SLED cessation**

- 515 (270–940) vs. 1519 (526–2367), <0.001*

**Note:** Values are presented as number (%) or median and interquartile ranges.

**Abbreviations:** SLED, Sustained low-efficiency dialysis; LVEF, Left ventricular ejection fraction; RAP, Right atrial pressure; RVSP, Right ventricular systolic pressure; LVIDd, Left ventricular internal diameter end diastole; IVSD, Interventricular septum thickness; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; IABP, Intra-aortic balloon pump; VA-ECMO, Venoarterial extracorporeal membrane oxygenation; BUN, Blood urea nitrogen; Cr, Creatinine.

*P < 0.05 means a statistically significant difference.

### Table 3. Multivariate logistic regression analysis for in-hospital mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine usage prior to admission</td>
<td>0.24 (0.12–0.49)</td>
<td>0.39 (0.18–0.86)</td>
<td>0.011</td>
</tr>
<tr>
<td>Serum Cr at SLED initiation</td>
<td>0.77 (0.68–0.86)</td>
<td>0.86 (0.77–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IABP treatment</td>
<td>3.23 (2.12–4.93)</td>
<td>2.04 (1.28–3.26)</td>
<td>0.004</td>
</tr>
<tr>
<td>Urine output &lt;400 mL in 24 h prior to SLED cessation</td>
<td>6.42 (3.92–10.51)</td>
<td>3.61 (2.01–4.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** Cr, Creatinine; IABP, Intra-aortic balloon pump; SLED, Sustained low-efficiency dialysis.
effect of hybrid therapy employing SLED in AKI from type 1 CRS.

We reported the high in-hospital mortality of CRS type 1 patients receiving SLED as an RRT option. These results do not differ much from those of those of patients with type 1 CRS who received CRRT (19,20). This may be explained by a comparable baseline demographic, and by cardiac parameters at admission that influence the prognosis of patients. However, even though total fluid removal was significantly greater in our survivors, none of the patients truly achieved a negative fluid balance. These findings contradict previous studies that demonstrated the attainment of a negative volume status in all patients with CRRT treatment (20). By way of explanation, we note that although SLED can be extended in duration, the issue of fluid overload persists, with fluid accumulation often exceeding the hourly removal rate due to variations in the number of hours per session. Another hypothetical consideration is that patients may experience an exacerbation of heart failure after completing SLED, resulting in increased body fluid volume during the non-SLED periods. These factors set SLED apart from CRRT in its ability to provide real-time control over ultrafiltration rates. However, this problem may be mitigated by lengthening the duration of treatment according to patients’ fluid status.

Interestingly, we found that hydralazine administration prior to admission was associated with good prognostic outcomes. The reason for this is not entirely clear; hydralazine was reported to have an effect on increase in renal blood flow, increased cardiac output, and decreased systemic vascular resistance (21,22), collectively resulting in more favorable hemodynamic parameters that can affect patient’s survival. However, further studies are required to establish the mechanisms involved and quantify the cardiac parameter changes. Our findings showed that a decrease in serum creatinine was associated with an increased risk of in-hospital death. We hypothesize that most heart failure patients experience reduced lean muscle mass and consequently lower serum creatinine levels (23). Unfortunately, we did not have a specific data tool for assessing muscle mass. IABP is a therapeutic device widely used as a supportive treatment tool in the clinical context of cardiogenic shock. In a randomized controlled trial, 600 patients with cardiogenic shock complicating myocardial infarction were assigned to receive IABP. Thiele et al found that IABP treatment did not significantly reduce the 30-day mortality rate vs. the control group (24). Another single-center, retrospective cohort study involving 536 patients reported that IABP emerged as a predictor of in-hospital mortality, a result that is similar to that of our study (25). Nevertheless, there are no clear guidelines for when to initiate IABP, resulting in clinical practice that is still characterized by a diversity of decision-making approaches relying on the evaluating physician. This variability can impact the outcomes of patients with varying degrees of severity. Oliguria (urinary output less than 400 mL/d) was known as an important factor associated with increased risk of death in critically patients receiving RRT in ICU (25). These results align with our study, which found an association between oliguria prior to SLED cessation and in hospital death. This might be explained by the fact that none of the nonsurvivors experienced kidney recovery, and thus their oliguria was persistent at the time of in-hospital death.

Conclusion
This study emphasized the challenges and high mortality associated with CRS type 1 treated with SLED. Hydralazine usage prior to admission, baseline serum creatinine levels, IABP treatment, and urine output <400 mL in 24 hours before SLED cessation were identified as independent risk factors for in-hospital mortality. Our results can predict the correlations between variables and outcomes without ascertaining causal relationships. Our findings hold clinical significance in the management and prognosis of CRS type 1 patients, helping clinicians assess the risks and benefits before opting for SLED treatment.

Limitations of the study
We acknowledge some limitations. First, the study was conducted in retrospect using data from a single center with one machine and a hemofilter platform. However, we utilize a standardized SLED protocol, ensuring the correct and appropriate administration of treatment. Moreover, no ascertainment bias was found, as all data were obtained from the unalterable electronic records of the hospital. Second, our study was limited by its small sample size and nonrandomized nature. However, data are scarce regarding outcomes in type 1 CRS patients who require SLED for AKI. Finally, there are potential confounders, such as actual ultrafiltration rate, sterilization of dialysis fluid, and filter type. Unfortunately, we do not have details on these factors. However, we demonstrated the substantial influence of factors that can have implications for the treatment in clinical practice.

Authors’ contribution
Conceptualization: Thanapon Nilmoje, Dhipsukon Pongborriboon, Atthaphong Phongphithakhchai.
Data curation: Dhipsukon Pongborriboon, Sirihatai Konwai, Suntornwit Praditau-Krit.
Formal analysis: Atthaphong Phongphithakhchai, Ussane Boonsrirat, Dhipsukon Pongborriboon.
Investigation: Thanapon Nilmoje, Dhipsukon Pongborriboon, Atthaphong Phongphithakhchai.
Methodology: Thanapon Nilmoje, Atthaphong Phongphithakhchai.
Writing–original draft: Dhipsukon Pongborriboon, Atthaphong Phongphithakhchai.
Writing–review & editing: Thanapon Nilmoje, Dhipsukon Pongborriboon, Atthaphong Phongphithakhchai, Sirihatai Konwai, Suntornwit Praditau-Krit, and Ussane Boonsrirat.
Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Human Research Ethics Committee of the faculty the study protocol was approved by the Research Ethics committee of Prince of Songkla University (REC.64-441-14-4). Before participating in the study, all participants provided their written informed consent. This study was part of Dhipsukon Pongborriboon M.D.’s thesis at the university. Moreover, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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None.

References


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