

# The Impact of The [TIMP-2] × [IGFBP7]-Guided Checklist for Early Recognition and Treatment of Acute Illness on The Prevention of Acute Kidney Injury In Patients With Septic Shock

Jingjing Wang (✉ [wjj3531@163.com](mailto:wjj3531@163.com))

Tianjin First Central Hospital

Jing Li

Logistics University of of People's Armed Police Force

Dongqiang Wang

Tianjin First Central Hospital

Yongqiang Wang

Tianjin First Central Hospital

Lin Dou

Tianjin First Central Hospital

Hongmei Gao

Tianjin First Central Hospital

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## Research Article

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# Abstract

**Background:** Sepsis is the main aetiology of acute kidney injury (AKI) in critically ill patients, with high morbidity and mortality. The early identification of septic patients at high risk for AKI, followed by the timely implementation of appropriate interventions, is crucial for improving patient outcomes. Tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 ([TIMP-2] × [IGFBP7]) are promising biomarkers for AKI. Furthermore, the Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN) is a tool for evaluating and treating acute illness in a timely manner based on best practices. We hypothesized that the use of this biomarker-guided point-of-care tool would improve the prognosis of patients with sepsis-associated acute kidney injury (SA-AKI).

**Methods:** This was a single-centre prospective before-and-after study in the ICU of a comprehensive tertiary hospital. From June 2015 to December 2020, we assessed and managed patients with septic shock based on the biomarker-guided CERTAIN checklist. A checklist based on the Sepsis 3.0 bundle and urinary [TIMP-2] × [IGFBP7] > 0.3 (ng/mL)<sup>2</sup>/1000 within 12 hours were used as the inclusion criteria. The CERTAIN checklist includes the care bundles recommended in the Sepsis 3.0 bundle and Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines. The primary outcome was the incidence of moderate-to-severe AKI on the first day and within seven days after enrolment and mortality at 90 days after discharge from the hospital. The secondary outcomes were the ICU length of stay, non-mechanical ventilation duration, and the proportions of patients with the recovery of renal function and major adverse kidney events (MAKEs) at 90 days after exposure to events initiating AKI.

**Results:** At the end of the study, 124 patients had been treated based on the checklist. When compared to a cohort of 112 patients matched for disease, the CERTAIN group had a lower proportion of patients needing mechanical ventilation, a lower proportion of patients needing vasoactive agents, a shorter ICU length of stay, and a higher proportion of patients with recovered kidney function. Furthermore, there was a trend towards a higher 90-day survival rate in the CERTAIN group.

**Conclusions:** Implementation of the CERTAIN checklist was associated with improvements in the short-term recovery of kidney function, airway and haemodynamic management and mortality in patients with SA-AKI.

Trial registration: [NCT01973829](https://www.clinicaltrials.gov/ct2/show/study/NCT01973829); Date of registration: November 1, 2013.

## 1. Background

Acute kidney injury (AKI) is common in critically ill patients and is associated with progression to chronic kidney disease (CKD) and higher in-hospital mortality and cost of care [1]. Sepsis is a major aetiology of AKI in the intensive care unit (ICU). The kidney is the organ most commonly affected by sepsis. Sepsis-associated acute kidney injury (SA-AKI) contributes to the morbidity and mortality of critically ill patients. In the era of evidence-based medicine and management based on clinical practice guidelines, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were developed to promote the detection and

prevention of SA-AKI, thereby improving patient outcomes [1]. However, delayed diagnosis, inadequate diagnostic methods, and insufficient numbers of medical professionals capable of providing optimal management have contributed to adverse outcomes [2]. SA-AKI continues to impose a clinical burden on critically ill patients. Further study is needed to reduce the incidence of adverse consequences of SA-AKI.

Generally, patients with sepsis are at a higher risk for developing AKI and developing markedly worse outcomes. However, patients who survived SA-AKI had relatively high rates of recovery and survival 1 year after sepsis [3, 4]. The current core problem is the early identification of patients at a high risk for SA-AKI and the implementation of the most effective kidney-sparing treatment measures. The approach to the early detection of AKI based on the serum creatinine level and urine output is generally considered insufficient [5]. Urinary [TIMP-2] and [IGFBP7] are two markers of renal tubule injury involved in G1 cell cycle arrest. These two newer stress and damage biomarkers have shown good performance for the early detection of AKI [6]. Due to their strong performance, we used these biomarkers to screen sepsis patients to determine which patients were at a high risk for AKI and needed bundled care.

In the ICU, patients have complex conditions, and the staff are faced with time constraints, large amounts of clinical data and a heavy workload. In hospitals capable of performing advanced medical techniques, misjudgement and miscommunication can result in delayed treatment; failure to treat patients within the optimal therapeutic window can result in adverse events and even the death of the patients [7]. Checklists are a validated tool that can be used to standardize care models. Their use reduces certain types of adverse events in surgical departments [8–10]. However, delays in the updating of information, the incomplete usage of checklists, and the use of checklists only for monitoring purposes have meant that checklists have not led to clinical improvements [11]. Building upon these experiences and advances in modern technology, a novel electronic tool, the Checklist for Early Recognition and Treatment of Acute Illness and Injury (CERTAIN), is being developed to support the evaluation and treatment of critically ill patients in accordance with optimized clinical practices [12].

The aim of this study was to use urinary [TIMP-2] × [IGFBP7] to select septic shock patients at a high risk of AKI, who were then treated based on the CERTAIN checklist. We hypothesized that the use of the biomarker-guided CERTAIN checklist, which addresses sepsis, AKI, and respiratory distress based on the updated guidelines and clinical experience, would improve clinicians' performance and improve the outcomes of patients with SA-AKI.

## 2. Methods

This was a single-centre prospective interventional before-and-after study performed in a comprehensive ICU in a tertiary public hospital in Tianjin. This study was carried out from June 1st, 2015, to June 1st, 2020. The study protocol was approved by the Ethics Committee of the Hospital of Tianjin First Centre Hospital. All patients provided informed consent. This trial was registered at ClinicalTrials.gov (NCT01973829).

## 2.1 Study participants

Participants were recruited from the patients admitted to the ICU with SA-AKI. Those 18 years or older were eligible to participate in this study. Patients had to simultaneously meet the criteria for the Sepsis 3.0 and have urinary  $[TIMP-2] \times [IGFBP7] > 0.3$  (ng/mL)<sup>2</sup>/1000 within 12 h after admission to the ICU [13, 14]. The exclusion criteria were advanced chronic kidney disease (CKD stage 4 and stage 5), hospitalization duration less than 72 hours, previous renal replacement therapy (RRT), renal transplantation, pregnancy, and non-infectious causes of AKI (obstructive diseases of urinary system, medications of nephrotoxic drugs and contrast induced nephropathy).

## 2.2 Protocol description

The protocol had 4 distinct phases. The first phase was the baseline phase (2015–2016). The second phase, which we called the training phase, involved 2 months of training for the entire clinical team. The training was based on the guidelines for the prevention of sepsis and AKI. The topics included the diagnosis and classification of SA-AKI based on the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2016) [14] and the KDIGO care bundles [15]. Moreover, the monitoring and therapeutic recommendations and treatment targets for resuscitation, antimicrobial therapy, vasoactive medications, RRT, fluid responsiveness assessments, and furosemide stress test were addressed [14–16]. The third phase was the checklist phase (2017–2020). In this phase, the medical staff used urinary  $[TIMP-2] \times [IGFBP7] > 0.3$  (ng/mL)<sup>2</sup>/1000 to select patients at a high risk for AKI and applied the checklist daily to evaluate and treat patients with septic shock. The decision-making team reviewed the checklist daily and discussed the effectiveness of the clinical decisions made based on the checklist. The last phase was the follow-up phase. All enrolled patients were tracked for 3 months after hospital discharge to monitor their prognosis and acute and chronic adverse events.

The urinary  $[TIMP-2] \times [IGFBP7]$  was measured with a sandwich immunoassay (NephroCheck™ Test, Astute Medical, San Diego, CA, USA) .

## 2.3 Outcomes

The primary outcome was mortality from any cause at 90 days after exposure to the event that precipitated AKI. The secondary outcomes included the number of days free of RRT; the numbers of ventilator-free and vasoactive-free days [17]; the length of hospitalization and number of hospitalization-free days at 90 days after discharge; the proportion of patients with a major adverse kidney event (MAKE), which was defined as death, dependence on RRT, or a sustained reduction in kidney function at 90 days after discharge (i.e., an estimated glomerular filtration rate [eGFR] of < 75% of the baseline value) [18]; and the proportion of patients with the recovery of renal function. The recovery of renal function after AKI before discharge was defined by the disappearance of oliguria (in the absence of diuretic treatment) and/or a reduction in the serum level of creatinine of at least 50% and/or a return of the serum level of creatinine to the baseline value in the absence of RRT. For patients with both oliguria and serum

creatinine changes indicating AKI, the correction of both the serum creatinine concentration and oliguria was needed to achieve recovery [19].

## 2.4 Statistical analysis

Data were analysed using SPSS version 18.0 software (IBM Corporation, USA) and GraphPad Prism software version 8.0 (GraphPad Software Inc, San Diego, CA, USA). Continuous variables were summarized using the means  $\pm$  SDs or the medians and interquartile ranges (IQRs), and categorical variables were summarized as numbers (%). The Mann-Whitney test and Fisher's exact test or the  $\chi^2$  test were used for two-group comparisons of continuous and categorical variables, respectively. Two-sided *P* values less than 0.05 were considered statistically significant in the final analyses.

## 3. Results

### Baseline characteristics

From June 1st, 2015, to December 1st, 2020, 250 patients were included in the study. Of these enrolled patients, 133 patients were included in the CERTAIN group, and 117 patients were included in the standard care group. Fourteen patients were excluded, 9 (6.8%) of whom were in the CERTAIN group and 5 (4.3%) of whom were in the standard care group. In the CERTAIN group, 5 (3.8%) patients withdrew consent, and 4 (3.0%) were lost to follow-up. In the standard care group, 5 (4.3%) patients were lost to follow-up. Thus, 236 patients (124 in the CERTAIN group and 112 in the standard care group) were included in the primary analysis (Fig. 1).

The baseline characteristics of patients in the CERTAIN group and standard care group are summarized in Table 1. There were no significant differences in age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, comorbidities, site of infection, or stage of AKI (*P* > 0.05).

### Initiation of CERTAIN checklist and therapy

The volumes infused into the patients increased on day 1 in the CERTAIN group compared with the standard care group. In contrast, the volumes infused into the patients decreased on day 7 in the CERTAIN group. The urinary output was lower in the standard care group than in the CERTAIN group on day 3 and day 7. The proportion of patients with KDIGO 2/3 was higher in the standard care group than in the CERTAIN group on day 7 (56.3% vs 40.3%, 95% CI 0.564–0.941). The CERTAIN group had lower proportions of patients receiving mechanical ventilation and RRT than the standard care group (83.1% vs 92.9%; 33.9% vs 48.2%). There were marginally fewer days on ventilation among patients in the CERTAIN group than among those in the standard care group (6 vs 7, 95% CI 1.501–4.387). Patients in the CERTAIN group had more ventilator-free days and vasoactive-free days (22 vs 17, 95% CI -9.486–5.060; 23 vs 19, 95% CI -5.538–0.075, respectively). Patients in the CERTAIN group had a shorter ICU stay than

those in the standard care group (95% CI 0.951–4.512,  $P < 0.01$ ). Patients in the two groups had similar durations of hospitalization. (Table 2)

Table 1  
Characteristics of the participants at baseline

| Characteristic                       | Standard care group | CERTAIN group   | <i>P</i> value |
|--------------------------------------|---------------------|-----------------|----------------|
|                                      | (N = 112)           | (N = 124)       |                |
| Age (years), mean $\pm$ SD           | 60.8 $\pm$ 15.2     | 57.6 $\pm$ 15.9 | 0.12           |
| Male sex, <i>n</i> (%)               | 67(59.8%)           | 73(58.9%)       | 0.88           |
| Severity scores in SA-AKI patients   |                     |                 |                |
| APACHE II, mean $\pm$ SD             | 24.2 $\pm$ 5.2      | 22.9 $\pm$ 4.7  | 0.05           |
| SOFA, mean $\pm$ SD                  | 10.5 $\pm$ 3.6      | 10.4 $\pm$ 2.9  | 0.67           |
| Comorbidities                        |                     |                 |                |
| Coronary heart disease, <i>n</i> (%) | 82(45.6)            | 98(54.4)        | 0.36           |
| Hypertension, <i>n</i> (%)           | 83(46.4)            | 96(53.6)        | 0.65           |
| COPD, <i>n</i> (%)                   | 45(43.7)            | 58(56.3)        | 0.36           |
| Diabetes mellitus, <i>n</i> (%)      | 67(53.2)            | 59(46.8)        | 0.07           |
| Stroke, <i>n</i> (%)                 | 37(49.3)            | 38(50.7)        | 0.78           |
| Malignancy, <i>n</i> (%)             | 24(43.6)            | 31(56.4)        | 0.54           |
| Immunosuppression, <i>n</i> (%)      | 50(43.1)            | 66(56.9)        | 0.2            |
| Site of infection                    |                     |                 | 0.62           |
| Pulmonary, <i>n</i> (%)              | 45(40.2)            | 56(45.2)        |                |
| Abdomen, <i>n</i> (%)                | 31(27.7)            | 26(21.0)        |                |
| Urinary system, <i>n</i> (%)         | 22(19.6)            | 24(19.4)        |                |
| Blood stream, <i>n</i> (%)           | 6(5.4)              | 11(8.9)         |                |
| Skin and soft tissue, <i>n</i> (%)   | 8(7.1)              | 7(5.6)          |                |
| AKI stage                            |                     |                 | 0.66           |
| KDIGO stage 1, <i>n</i> (%)          | 18(16.1)            | 15(12.1)        |                |
| KDIGO stage 2, <i>n</i> (%)          | 56(50.0)            | 63(50.8)        |                |
| KDIGO stage 3, <i>n</i> (%)          | 38(33.9)            | 46(37.1)        |                |

## Biomarker kinetics

According to the worst AKI stage within seven days after inclusion, the level of [TIMP-2] × [IGFBP7] decreased progressively over time in patients with all stages of AKI. Patients receiving RRT had the highest levels of [TIMP-2] × [IGFBP7] at all time points. Patients with stage 1 AKI had the lowest level of [TIMP-2] × [IGFBP7] at each time point (Fig. 2a).

Next, we evaluated the outcome of SA-AKI patients on the basis of the level of [TIMP-2] × [IGFBP7] within seven days after enrolment. According to course of AKI, patients were divided into four groups [24]: 1) stable AKI 1; 2) stable AKI 2/3; 3) AKI progression (from AKI 1 to AKI 2/3); and 4) AKI recovery (from AKI 2/3 to AKI 1). The distribution of patients across these groups is shown in Fig. 3. At baseline, the [TIMP-2] × [IGFBP7] levels in patients with stable AKI 2/3, AKI progression (AKI 1 to AKI 2/3), and AKI recovery (AKI 2/3 to AKI 1) were greater than that in patients with stable AKI 1. Patients with AKI progression had an increase in the level of [TIMP-2] × [IGFBP7] from baseline to 12 hours after inclusion. Patients with stable AKI 1 had median [TIMP-2] × [IGFBP7] levels below  $0.3 \text{ (ng/mL)}^2/1,000$ . The elevation of [TIMP-2] × [IGFBP7] was prolonged in patients with AKI progression (Fig. 2b).

## Primary and secondary outcomes

The difference in 90-day mortality was marked (Table 3). The rates of mortality at 90 days were 45.6% and 55.4% in the CERTAIN group and standard care group, respectively ( $P = 0.039$ ). In-hospital mortality was higher in the CERTAIN group, but the difference was not significant (35.5% vs 33.9%,  $P = 0.909$ ). Patients in the CERTAIN group had significantly less RRT dependence at 90 days (36.3% vs 22.4%,  $P = 0.026$ ). Consistent with this finding, the proportion of patients with MAKEs in the CERTAIN group was lower than that in the standard care group (55.6% vs 76.8%,  $P = 0.001$ ). Patients in the CERTAIN group had a lower risk of rehospitalization (relative risk, 0.956; 95% CI, 0.673 to 1.358), but there was no difference between the two groups in the proportion of patients who were rehospitalized within 90 days (13.4% vs 13.8%,  $P = 0.953$ ). The impact of the spontaneous remission of AKI, which was mainly observed in those with mild AKI (stage 1), was excluded. Among those with moderate-to-severe AKI (stages 2 and 3), the CERTAIN group had a higher proportion of patients who recovered renal function than the standard care group (54.3% vs 38.2%,  $P = 0.029$ ). A Kaplan-Meier analysis of 90-day mortality showed tendency towards improved survival in the CERTAIN group, but there was no significant difference (Fig. 4).

Table 2  
Measures during the evaluation period in the CERTAIN and standard care groups

| Parameters                                                      | Standard care group | CERTAIN group | <i>P</i> value |
|-----------------------------------------------------------------|---------------------|---------------|----------------|
| Volume of infusion (ml), mean ± SD                              |                     |               |                |
| Day 1                                                           | 2660 ± 812          | 4124 ± 975    | < 0.01         |
| Day 2                                                           | 2912 ± 1016         | 2878 ± 919    | 0.79           |
| Day 3                                                           | 3048 ± 1000         | 2278 ± 765    | < 0.01         |
| Output of urine (ml), mean ± SD                                 |                     |               |                |
| Day 1                                                           | 1110 ± 975          | 962 ± 862     | 0.22           |
| Day 2                                                           | 1555 ± 1268         | 1611 ± 1189   | 0.73           |
| Day 3                                                           | 1764 ± 1448         | 2144 ± 1404   | 0.042          |
| Day 7                                                           | 1365 ± 894          | 1865 ± 1078   | 0.044          |
| AKI stage                                                       |                     |               | 0.019          |
| KDIGO stage 1, <i>n</i> (%)                                     | 49(43.8)            | 74(59.7)      |                |
| KDIGO stage 2/3, <i>n</i> (%)                                   | 63(56.3)            | 50(40.3)      |                |
| Median no. of ventilator-free days at 28 days (IQR)             | 17(0–23)            | 22(21–23)     | < 0.01         |
| Median no. of days free from vasoactive agents at 28 days (IQR) | 19(0–20)            | 23(0–25)      | 0.04           |
| Length of ICU stay, days                                        | 10(6–21)            | 10(6–13)      | < 0.01         |
| Length of hospital stay, days                                   | 17.5(12–22)         | 17(14–22)     | 0.76           |

Table 3  
Primary and secondary outcomes

|                                                                                                                                     | Standard care  | CERTAIN        | Relative risk          |
|-------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|------------------------|
|                                                                                                                                     | group          | group          | or difference (95% CI) |
| Primary outcome                                                                                                                     |                |                |                        |
| Death from any cause at 90 days, n (%)                                                                                              | 62/112 (55.4%) | 52/124 (45.6%) | 1.294 (1.009 to 1.660) |
| Secondary outcomes                                                                                                                  |                |                |                        |
| RRT dependence at 90 days, n (%) <sup>a</sup>                                                                                       | 37/102 (36.3%) | 26/116 (22.4%) | 1.618 (1.063 to 2.479) |
| MAKES at 90 days, n (%)                                                                                                             | 86/112 (76.8%) | 69/124 (55.6%) | 1.525 (1.211 to 1.921) |
| Death from any cause, n (%)                                                                                                         |                |                |                        |
| In-hospital mortality, n (%)                                                                                                        | 38/112(33.9%)  | 44/124 (35.5%) | 0.956 (0.673 to 1.358) |
| Rehospitalization at 90 days, n (%)                                                                                                 | 8/58 (13.8%)   | 9/67 (13.4%)   | 1.027 (0.424 to 2.488) |
| Recovery of renal function after AKI <sup>a</sup>                                                                                   | 39/102 (38.2%) | 63/116 (54.3%) | 0.715 (0.526 to 0.959) |
| a. The number of patients with AKI progression and stable AKI 2/3 were 102 in the standard care group and 116 in the CERTAIN group. |                |                |                        |

## 4. Discussion

In this before-and-after randomized controlled trial, we examined the combined impact of screening with urinary [TIMP-2] × [IGFBP7] and the implementation of the CERTAIN checklist on patients with SA-AKI. This study showed that use of urinary [TIMP-2] × [IGFBP7] as a screening tool promoted the implementation of the CERTAIN checklist in patients with SA-AKI, with the aim of improving the outcomes and lowering the risk of death at 90 days. Moreover, the group of patients with SA-AKI who were managed based on the [TIMP-2] × [IGFBP7]-guided checklist had a lower proportion of patients dependent on RRT and a higher proportion of patients who recovered renal function within 90 days.

Unlike NGAL, the levels of which are elevated not only in patients with sepsis but also in those with severe inflammation, urinary [TIMP-2] × [IGFBP7] is an independent factor that can be used to identify septic shock patients at high risk of progression to severe AKI over the next 24 hours [20]. The cut-off for [TIMP-2] × [IGFBP7] for the identification of patients at high risk for developing moderate-to-severe AKI within 24 h was [TIMP-2] × [IGFBP7] > 0.3 (ng/mL)<sup>2</sup>/1000 [21]. Maizel et al found that urinary [TIMP-2] × [IGFBP7] > 0.3 (ng/mL)<sup>2</sup>/1000 was associated with a diagnosis of AKI stage 3 within 24 h in patients with septic

shock, with a sensitivity of 78% and a specificity of 81% [20]. Because moderate-to-severe AKI (corresponding to KDIGO stages 2 and 3) is associated with a poor prognosis [1], this trial used  $[TIMP-2] \times [IGFBP7] > 0.3(\text{ng/mL})^2/1000$  within 12 h as the threshold for enrolment. The incidence of all stages of AKI in patients with sepsis in this study was 75.3%, and 35.1% of the patients had moderate-to-severe AKI. Moreover, the performance of  $[TIMP-2] \times [IGFBP7]$  with regard to the prediction of AKI in septic patients is reliable even in the absence of renal organ failure [22]. Thus, we used urinary  $[TIMP-2] \times [IGFBP7] > 0.3(\text{ng/mL})^2/1000$  as a screening tool to identify patients at high risk for AKI. Regardless of the stage of AKI, the level of  $[TIMP-2] \times [IGFBP7]$  declined within 48 hours after inclusion. Patients who received RRT had the highest levels of  $[TIMP-2] \times [IGFBP7]$ . These results suggested that SA-AKI patients who met the criteria for RRT had prolonged renal damage. Moreover, an elevated level of  $[TIMP-2] \times [IGFBP7]$  persisted for longer in patients with AKI progression. These results are consistent with those of a previous report [23].

It is noteworthy that the implementation of the Surviving Sepsis Campaign and KDIGO care bundles improved the short- and long-term outcomes of sepsis and AKI, respectively[24, 25]. However, in clinical practice, these interventions have been shown to have poor performance. Bundle fatigue was one of the main issues affecting their implementation [26]. Moreover, in the absence of sufficient support for decision making and the inappropriate selection of medical interventions, medical errors are the leading cause of death in hospitals [27, 28]. The CERTAIN checklist is intended to ensure that the evaluation and treatment of acute critically ill patients is based on best practices. The use of accurate and up-to-date information, as well as key point-of-care information, when making clinical decisions are the cornerstones of CERTAIN [12]. In the highly stressful environment of the ICU, early structured treatment plans can decrease the risk of task omission and provide care for patients with sepsis and myocardial infarction based on the best standardized practices.

The Sepsis 3.0 and KDIGO care bundles were used when patients were identified as being at high risk for SA-AKI based on the urinary  $[TIMP-2] \times [IGFBP7]$ . To avoid fluid overload, we used dynamic measures of volume responsiveness assessed by transthoracic Doppler to guide resuscitation. In our trial, we adapted the de-resuscitation strategy. Early aggressive resuscitation is necessary to recover the intravascular volume and ensure tissue perfusion. However, later conservative approaches protect against oedema in the brain, myocardium, pulmonary tissue, gut and other organs [29]. In our trial, the CERTAIN group had significantly lower proportions of patients who needed mechanical ventilation and RRT. Patients in the CERTAIN group had more ventilator-free days and vasoactive-free days at 28 days than those in the standard care group. These results are in contrast with the findings of a study that investigated the impact of the implementation of the Surviving Sepsis Campaign care bundles on SA-AKI, which showed no reduction in the incidence of AKI within the first week after the development of sepsis[30].

RRT is the only specific intervention for AKI[31]. Spontaneous renal recovery was observed in up to 49% of patients with AKI[32], and RRT has many complications. Clinicians should avoid unnecessary RRT. In this trial, the use of the biomarker-guided CERTAIN checklist decreased the proportion of patients receiving RRT. We assume that the positive effect of the use of the CERTAIN checklist was due to the early

selection of the patients with sepsis at high risk for AKI. After this early identification of the high-risk group, the decision-making team could initiate appropriate interventions before the development of kidney injury [33].

Our study has a few limitations. First, it was a single-centre study. Second, this study was not blinded, which resulted in measurement bias. Further trials with a larger multicentre cohort of patients with septic shock are warranted.

## 5. Conclusions

To our knowledge, this is the first report of the use of the [TIMP-2] × [IGFBP7]-guided CERTAIN checklist in septic patients with AKI. This trial showed that biomarker-guided interventions can decrease the need for RRT and improve the rate of the recovery of renal function in patients with SA-AKI. Moreover, [TIMP-2] × [IGFBP7]-guided CERTAIN checklist can decrease the mortality at 90 days after exposure to the event that precipitated AKI.

## Declarations

### Ethical Approval and Consent to participate

The study was approved by the Ethics Committee of the Hospital of Tianjin First Centre Hospital.

### Consent for publication

Not applicable.

### Availability of supporting data

Not applicable.

### Competing interests

All the authors have no conflicts of interest to declare.

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### Author contributions:

L.D and H.M.G conceived of the project and designed the study. J.J.W, D.Q.W and Y.Q.W performed the trial. J.J.W and J.L analysed the data. J.J.W wrote the manuscript. All authors read and approved the

final manuscript.

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None.

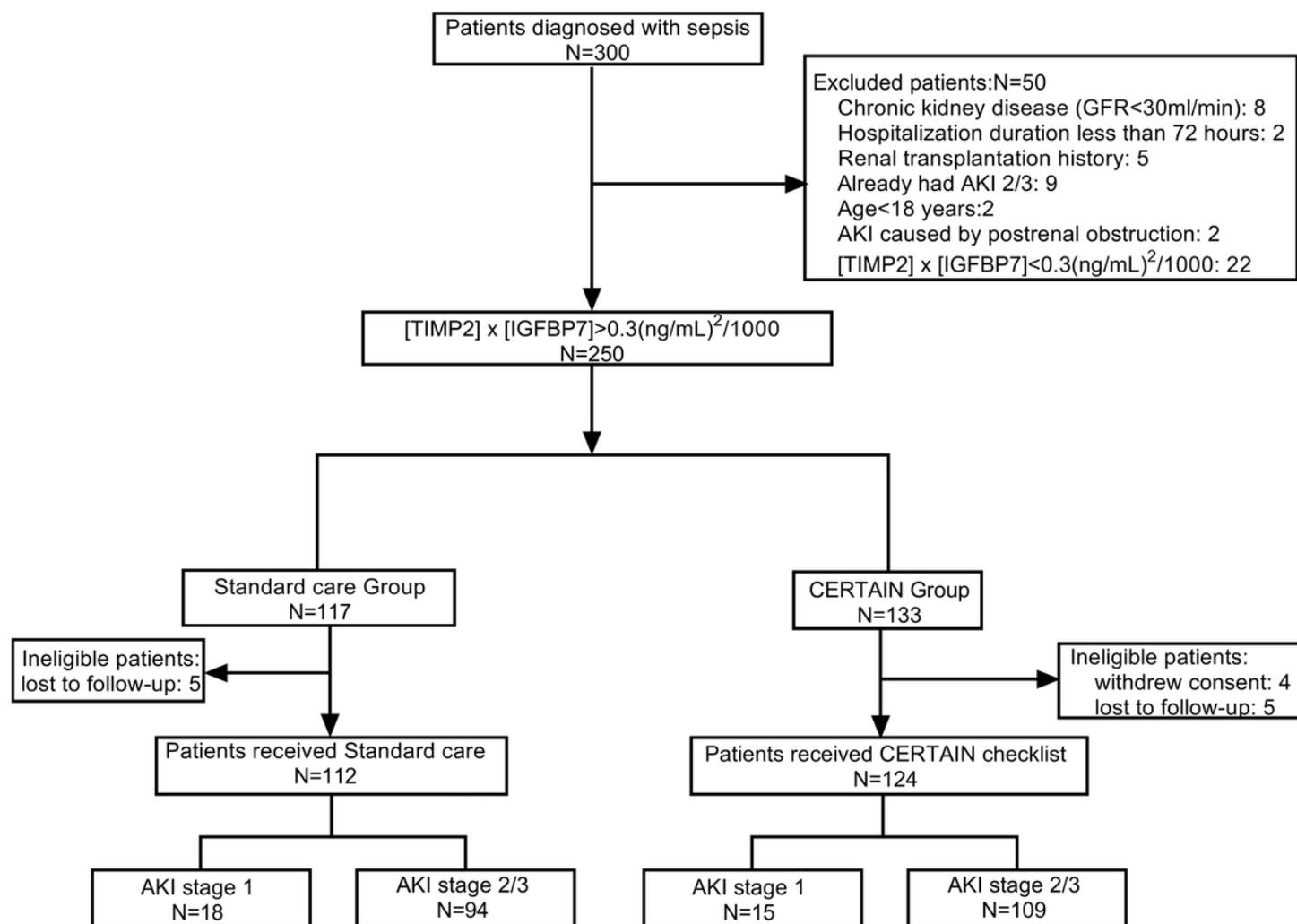
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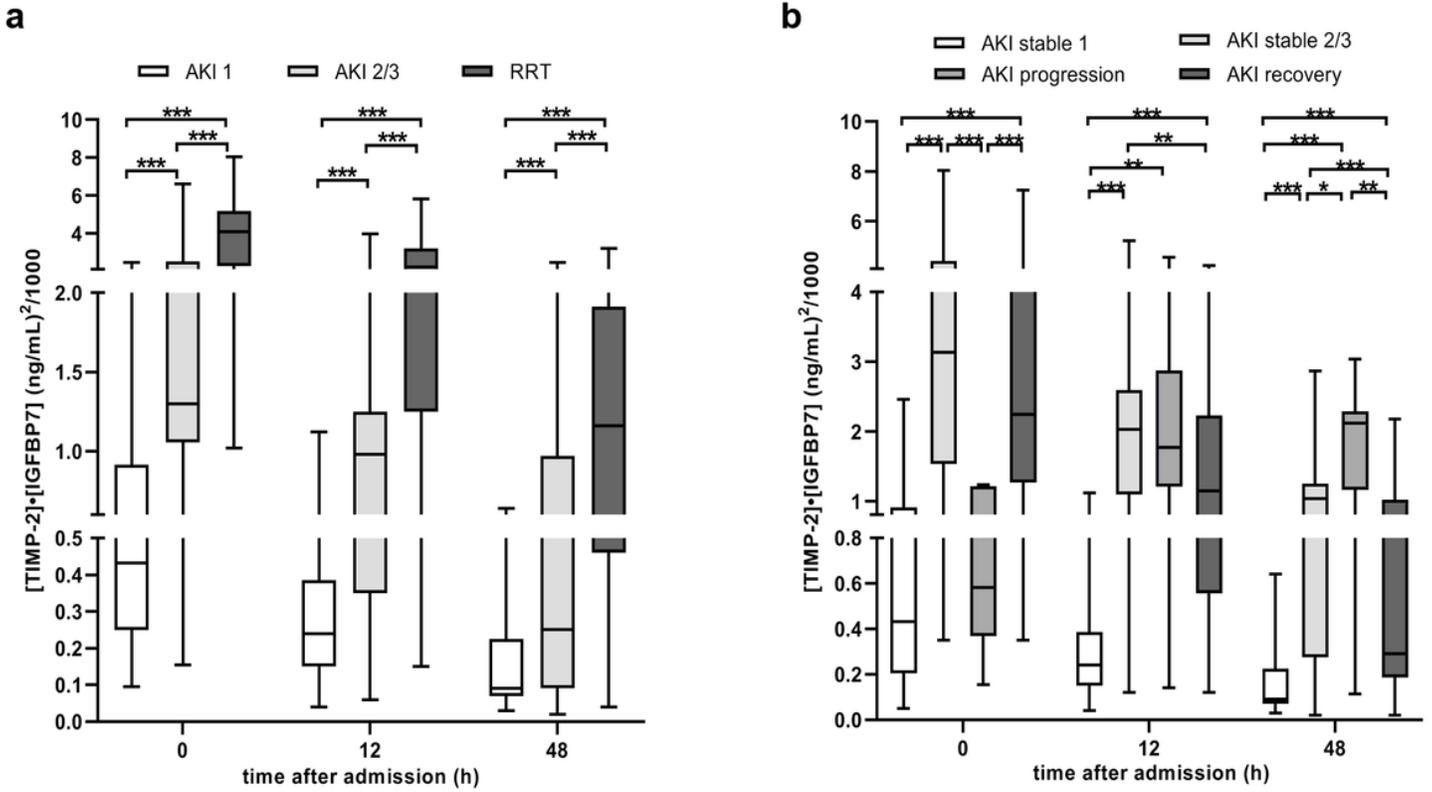
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## Figures



**Figure 1**

Study flow diagram



**Figure 2**

Kinetics of  $[TIMP-2] \times [IGFBP7]$  over time. a. Kinetics of  $[TIMP-2] \times [IGFBP7]$  based on the maximum acute kidney injury stage within 7 days after inclusion. AKI 1= mild AKI, AKI 2/3=moderate or severe AKI without the need for RRT, RRT= AKI with the need for RRT. b. Kinetics of  $[TIMP-2] \times [IGFBP7]$  in relation to the maximum acute kidney injury stage at day 1 and day 7. AKI progression= AKI 1 to AKI 2/3. AKI recovery= AKI 2/3 to AKI 1. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

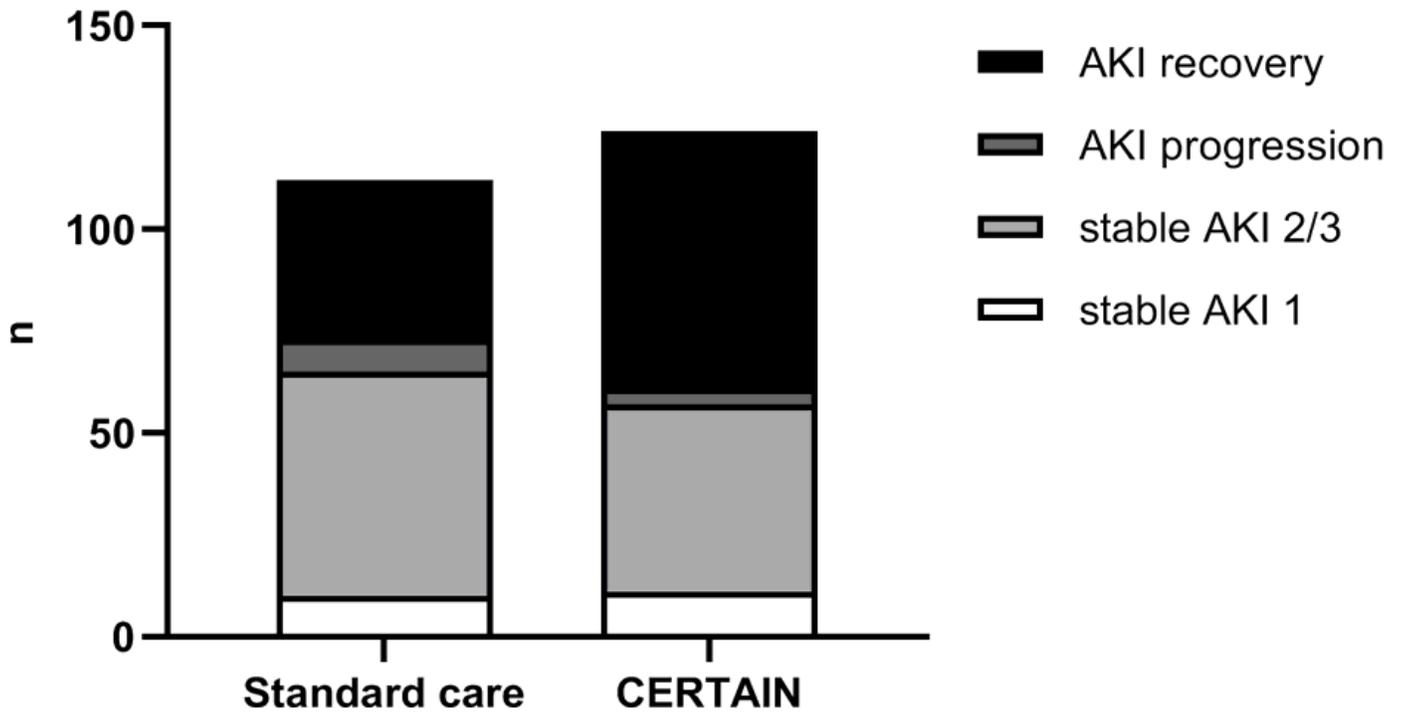


Figure 3

The number of patients with changes in acute kidney injury stage within seven days after inclusion

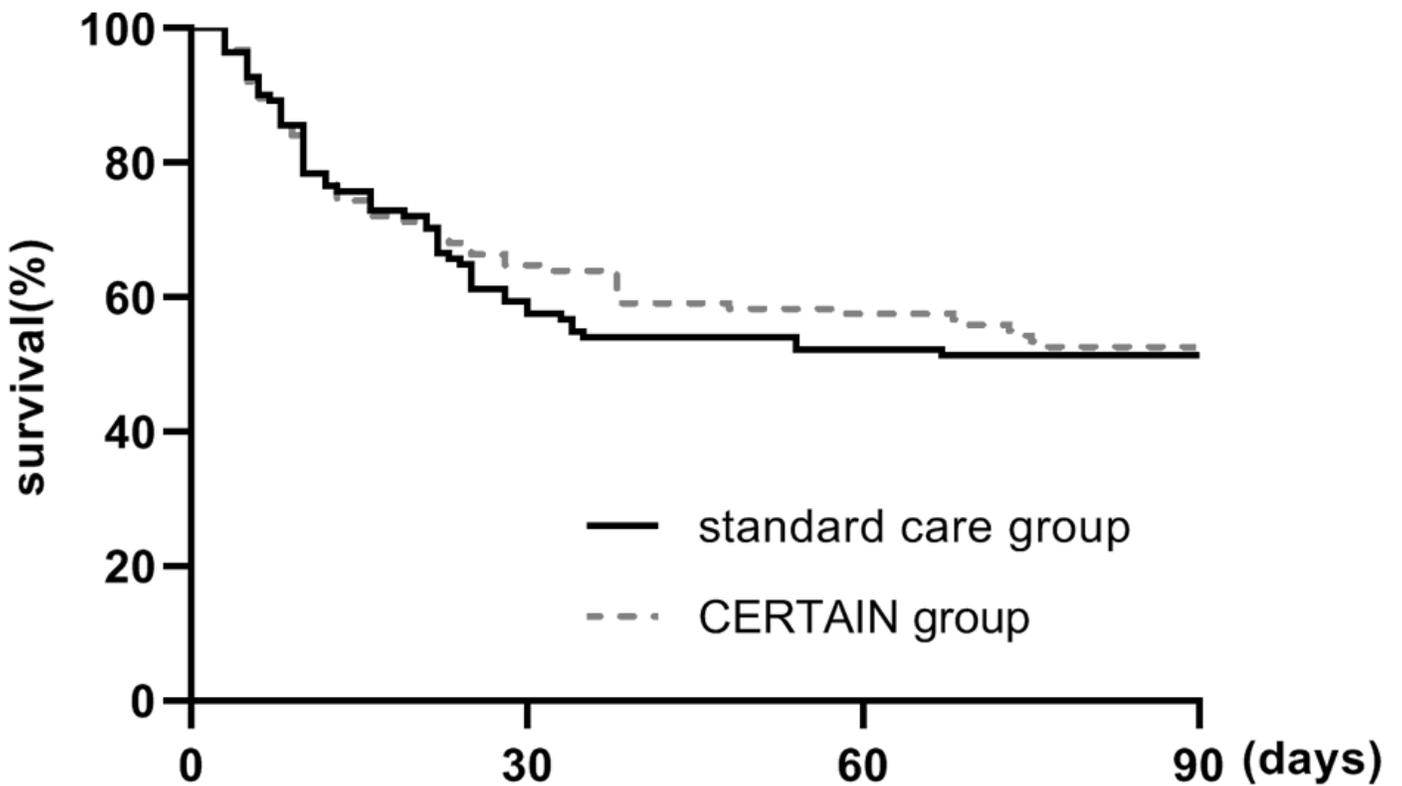


Figure 4

Kaplan-Meier curve for 90-day mortality