Prognostic Value of Low Dose ACTH Test in Critically Ill patients

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Conflict of interests

The authors declare that there was no conflict of interest regarding the publication of this paper.

Declaration

No fund

Abstract

Background:

Previous trials evaluated the incidence of critical illness-related corticosteroid insufficiency (CIRCI) using 250 μg ACTH. However, this supra-physiological dose could result in false-positive levels. We aimed to determine the incidence of CIRCI in septic patients utilizing a 1 μg ACTH stress test.

Methods:

We conducted a prospective cohort study on 39 patients with septic shock. CIRCI was defined as a Δ max cortisol < 9 μg/dL following 1 μg ACTH stress test. The primary outcome of the study was death. Secondary outcomes included days of vasopressors, days of MV, amount of fluid per day, the incidence of AKI, and days of ICU stay.

Results:

The incidence of CIRCI in our cohort was 43.6 % using 1 μg ACTH. There were no significant differences between groups in terms of ICU scores, laboratory investigations, vasopressors, MV days, amount of fluid per day, and the ICU stay (P = NS). The CIRCI group had lower median survival and survival probability rates (5 days & 48.4 %, respectively) compared to the non-CIRCI group (7 days & 49.5%, respectively). In addition, the CIRCI group had a shorter time to develop AKI and a higher probability of developing AKI (4 days & 44.6 %, respectively) in comparison to the non-CIRCI group (6 days & 45.57%, respectively).

Conclusion:

We concluded that the CIRCI group had a lower mean survival rate and a higher incidence of AKI. We recommend the use of 1 μg ACTH test in septic shock patients to identify this subgroup of patients.

Keywords: CIRCI, relative adrenal insufficiency, sepsis, septic shock.

1 Introduction

In acute illness, endogenous glucocorticoids have a crucial role in maintaining endothelial cell integrity, vascular permeability, and vascular tone [1]. The term critical illness-related corticosteroid insufficiency (CIRCI) refers to the cellular corticosteroid activity that is non concordant to the disease severity [2].

Despite the rareness of absolute adrenal insufficiency in critical illness, relative adrenal insufficiency is significantly more prevalent [3]. Consequently, adrenal insufficiency in critical illness patients is also known as relative adrenal insufficiency. Despite a normal absolute cortisol level, there is either inadequate cortisol or inadequate tissue response to the severity of the illness. Therefore, cortisol levels considered normal in healthy subjects might be relatively low in severely ill patients [4].

The incidence of CIRCI is estimated to be between 20% and 60%, and trials on patients with septic shock yielded contradictory results [5]. Inappropriately low cortisol level has been linked to high mortality [1], and even slight impairment of the adrenal response may be associated with increased mortality [6].

The diagnosis of CIRCI is still controversial, and trials in septic shock patients showed mixed results [7-9]. Previous trials evaluated the benefits of testing for CIRCI with 250 μg ACTH [7, 10]; nevertheless, this supra-physiological dose, 250 μg ACTH, could result in false-positive glucocorticoid levels [10, 11]. Furthermore, Siraux and colleagues [10] suggested using 1 μg ACTH stress test in septic shock patients to identify CIRCI patients who would have been missed using 250 μg ACTH; however, the current practice depends on the use of 250 μg ACTH

in diagnosis of CIRCI. We aimed to determine the incidence of CIRCI in septic patients using 1 μg ACTH stress test as well as to investigate CIRCI patients' outcomes.

2 Materials and Methods

2.1 Study design

The current prospective observational study was carried out at a 36-bed medical Critical Care Unit of a university-affiliated hospital in the period from October 2019 to October 2020.

2.2 Ethical considerations

The study was approved by the Ethical Committee (No: 17101878 - October 18, 2016). Written informed consent was obtained from the patients or their legal guardians, as applicable.

2.3 Study Definition

Annane et al. defined CIRCI as a change in plasma cortisol level after 250 μg ACTH stimulation by less than 9 μg/dl [5]. Patients with normal or elevated basal plasma cortisol levels and a low cortisol response to ACTH stimulation were found to have a high mortality rate.

In the present study, CIRCI was defined as a Δ max cortisol less than 9 μg/dL following 1 μg ACTH stress test. The cortisol response to ACTH was determined as the difference between the baseline concentration and the highest level at one hour and two hours.

Patients were categorized as follows:

1. Patients with absolute adrenal insufficiency, defined as patients with baseline cortisol < 10 μg/dL [2], were excluded,

2. Patients with CIRCI: Δ max cortisol of < 9 μg/dL after 1 μg ACTH stress test,
3. Patients without CIRCI: Δ max cortisol of ≥ 9 μg/dL after 1 μg ACTH stress test.

Sepsis was defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. In the absence of hypovolemia, septic shock was clinically identified by the need for a vasopressor to maintain a mean arterial pressure of ≥ 65 mm Hg and serum lactate level greater than 2 mmol/L (>18 mg/dL) [12].

AKI was defined using the KDIGO guidelines as any of the following: 1) increase in serum creatinine (SCr) by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 h, or 2) increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or 3) urine volume < 0.5 mL/kg/h for 6 h [13].

2.4 Patients

The study included 39 septic shock patients. We excluded patients with low initial serum cortisol < 10 μg/dL (= 8 patients) and septic shock patients who needed steroids according to current recommendations for septic shock (= 55 patients) [12]. In addition, we excluded patients with COVID-19, patients with a known history of adrenal insufficiency, and patients who had received steroids in the three months prior to enrollment.

2.5 Data collection

We took the history from the patients – if applicable - or their legal guardians in addition to obtaining previous medical diseases and therapeutic history from patients' records. We recorded the reason for admission to the ICU and calculated the patients' admission APACHE II and

SOFA scores. In addition, we registered patients' vital signs, GCS, general examination, and cardiac, chest, and abdominal examinations. Initial investigations included complete blood count, serum lactate, serum creatinine, BUN, liver function test, serum sodium and potassium, prothrombin time, prothrombin concentration, activated partial thrombin time, and arterial blood gases.

2.6 ACTH stimulation test

The ACTH solution was prepared by pharmacists at the Critical Care Unit by dilution of 250 μg ACTH ampule (Cosyntropin 0.25 mg/vial, for diagnostic use only, Sandoz International GmbH, Industriestrasse 25, 83607 Holzkirchen, Germany Inc, Rancho Cucamonga, Calif) in 250 mL of 0.9 % NaCl to obtain a concentration of 1 μg/mL. One-milliliter syringes were used to withdraw 1 mL from the solution. Syringes were refrigerated between 2^{o}C to 8^{o}C.

For each patient, 5-10 ml of blood sample was collected in a sample tube, then it was allowed to clot for 30 minutes, and serum was separated from cells immediately after centrifugation and aliquot into a labeled polypropylene or similar plastic tube with a separate tube for each test ordered. Centaur XP (Siemens-healthineers, Germany) was used to determine the serum-free cortisol level.

The initial measurement of serum cortisol was performed at baseline, followed by an intravenous injection of 1 μg ACTH. Serum samples were then withdrawn after 1 hour and 2 hours of injection for serum cortisol levels.

2.7 Patients' treatment

All patients received 30 mL/kg of the crystalloid solution at admission. Blood cultures were withdrawn, along with other cultures, based on the suspected site of infection. Additionally, an empirical IV antibiotic therapy was initiated within the first hour according to the most common organism associated with the patient's condition.

Vasopressors were used to control hypotension which does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher. If hypotension persisted despite volume resuscitation or the initial lactate level was 4 mmol/L or higher, central venous pressure (CVP) would be measured, and the crystalloid solution would be added to achieve a CVP $\geq$ 8 mm Hg. Red blood cells (RBC) would be transfused to a target hemoglobin range of 7-9 g/dL if hemoglobin levels dropped below 7 g/dL. Patients with low baseline serum-free cortisol levels received 100 mg IV hydrocortisone and were excluded from the study.

2.8 Study Outcomes

The study's primary outcome was death, whereas days of vasopressors, days of MV, amount of fluid per day, the incidence of AKI, and days of ICU stay were secondary outcomes.

2.9 Statistical analysis

The statistical analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test normality. Continuous variables were presented as the means ± SD, and categorical variables were presented as frequency and percentage. The Chi-square test and Fisher Extract test were used to compare qualitative parameters. The paired t-test was used to compare continuous parameters in the case of parametric variables and the

Wilcoxon Signed-Rank test in the case of non-parametric variables. The Kaplan-Meier survival analysis was used to test the time to the event regarding mortality and incidence of AKI. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Demographic, clinical, and laboratory data

We identified 102 patients who met the septic shock criteria, whereas 55 patients who needed to add steroids to their septic shock management were excluded. In addition, we excluded eight patients who had absolute adrenal insufficiency. The clinical characteristics of 39 patients are presented in Table 1. Following 1 μg ACTH, we defined 17 CIRCI patients with Δ cortisol < 9 μg/dl and 22 non-CIRCI patients with a total incidence of 43.5 %. The mean APACHE II score was 23.5 ± 4.6 in the CIRCI group compared to 26.4 ± 6.2 in non-CIRCI patients with a P-value = 0.105. The SOFA score was 9.5 ± 2.2 in the CIRCI group compared to 9.9 ± 2.3 in the non-CIRCI group with a P-value = 0.607. Mechanical ventilation was used in 90.25 % of patients. At admission, patients with CIRCI had a mean PAO2 of 68.8 ± 9.9 mmHg and received a mean FIO2 of 32.6 ± 10.9 % compared to PAO2 of 67.6 ± 11.02 mmHg and mean of FIO2 31.7 ± 14.9 % in the non-CIRCI patients, P-values were 0.743 and 0.843 respectively. Other laboratory investigations are shown in Table 2.

3.2 Baseline cortisol levels

The initial mean serum cortisol level for the entire study population was 22.6 ± 14.5 μg/dl, with a range of 10.7-74 μg/dl. CIRCI patients had significantly lower serum cortisol levels, with a mean of 13.1±2.3 μg/dl, ranging from 10.7-20 μg/dl compared to the mean initial serum cortisol level

of non-CIRCI patients, which was 30.9 ± 14.6 μg/dl, ranging from 10.9-74 μg/dl, with a P-value of < 0.001.

3.3 Response to low-dose ACTH stimulation testing

Following 1 μg ACTH, the mean increases in plasma cortisol at 1 hour and 2 hours were 18.7 ± 4.7 and 14.5 ± 5.2 in the CIRCI group, which were significantly lower than the non-CIRCI group, whose mean increases were 55.7 ± 8.8, and 37.4 ± 6.1 respectively, with a P-value of < 0.000.

3.4 Clinical outcomes

The Kaplan Meier survival analysis revealed that the incidence of mortality is significantly higher in the CIRCI group by 3.01 times than in the non-CIRCI patients (HR: 3.01, P < 0.05). Moreover, the CIRCI group had lower median survival and survival probability (5 days & 48.4 %, respectively) compared to the non-CIRCI group (7 days & 49.5%, respectively), as demonstrated in Figure 1. After a mean-ICU stay of 6.1 ± 1.1 days, 9 (52.9 %) of CIRCI patients died while in non- CIRCI patients, 10 (45.5 %) died after a mean-ICU stay of 5.1 ± 2.4 days (P > 0.05). The most common cause of death was electro-mechanical dissociation (7, 41.1% in CIRCI patients and 9, 40.9 % in non-CIRCI patients; P > 0.05), followed by VT storm (2, 11.7 % in CIRCI patients and 1, 4.5 % in non-CIRCI patients; P = 0.001) unresponsive to defibrillation, Table 3. In addition, The 9 CIRCI deaths have a mean of 14.89 ± 2.35 μg/dl, ranging from 13.1-20 μg/dl, while the 8 CIRCI survivors, have a mean of 11.15 ± 0.31 μg/dl, ranging from 10.7-11.6 μg/dl, with a P-value of < 0.031.

The incidence of AKI was significantly higher in the CIRCI group (3.62 times more than the group without CIRCI), with an HR of 3.62 and a P-value of < 0.05. In addition, the CIRCI group had a shorter time to develop AKI and a higher probability of AKI (4 days & 44.6 %, respectively) in comparison to the non-CIRCI group (6 days & 45.57%, respectively), Table 4, Figure 2. The blood urea nitrogen/Creatinine ratio (BCR) of the cohort is 14.5 ± 2.32 (13.9 ± 2.48 in CIRCI patients and 14.6 ± 3.14; p > 0.05). Urine analysis showed trace proteinuria and RBCs in 3, 17.6 % in CIRCI patients and 4, 18.1 % in non-CIRCI patients; P > 0.05). Other outcomes demonstrated insignificant group differences, Table 5.

4 Discussion

The main findings of the current study are 1) The incidence of CIRCI in our cohort was 43.6 % by using 1 μg ACTH stress test, 2) There are no significant differences between CIRCI and the non-CIRCI group regarding ICU scores, laboratory investigations, days of vasopressors, days of MV, amount of fluid per day, and days of ICU stay, 3) The CIRCI group had a lower mean survival rate, 4) The CIRCI group had a higher incidence of AKI.

The diagnosis of CIRCI remains controversial, with trials in the septic shock population yielding contradictory results [7-9], which could be explained by 1) the lack of universally accepted diagnostic criteria, 2) different cohort characteristics, and 3) the difference in the used ACTH dose. Dynamic testing with ACTH has previously been evaluated in the critical care setting, with some data suggesting the degree of change following ACTH is indicative of outcome and response to corticosteroid therapy [5, 6, 14]. The administration of 250 μg ACTH results in serum levels that are 100 times greater than a normal ACTH stress response and may lead to a cortisol response in patients who would not normally generate one under stress [10, 11, 15]. In

addition, this extra physiologic dose could result in increased blood glucose and sodium levels in patients with normal adrenal function [16].

The 250 μg ACTH dose is popular because it is easier to perform than 1 μg ACTH test which requires preparation at the bedside as the commercial ampoules contain 250 μg of ACTH [17]. However, in terms of accuracy, both adult and children prospective studies concluded similar accuracy of both doses in predicting outcomes [17], and some, although sparse, suggested that a dosage of 1 μg ACTH is more sensitive to diagnosing adrenal insufficiency [18, 19].

In the current study, the incidence of CIRCI was 43.6%. The literature revealed that the incidence of CIRCI in the ICU ranges from 32% to 70.6% [7, 20-22].

As previously reported [23], the CIRCI group had significantly lower cortisol levels than the non-CIRCI group.

Sari et al. studied CIRCI in COVID-19 patients admitted to the ICU. They detected a total CIRCI incidence of 50.4% of their cohort. It was found that 25 patients were diagnosed with basal cortisol below 10 μg/dl, and 35 of them with Δ cortisol below 9 μg/dl after a 1 hour of 1 μg ACTH test [24]. We excluded patients with COVID-19 as their treatment, which was controversial at the time of the current study. Additionally, the majority of these patients received steroids following the adopted ICU protocol based on patients' lung affection.

In the current study, the APACHE II score, SOFA score, and all parameters related to vital signs showed insignificant differences between study groups. Kwon et al. investigated CIRCI in

Korean septic shock patients, using a Δ 9 μg/dl cut-off value after the injection of 250 μg ACTH, and found both mean SAPS II score and the SOFA score were significantly higher in patients with CIRCI compared to those without CIRCI [22]. Other studies on cardiogenic shock patients concluded that SOFA score was the only variable increased in CIRCI patients according to the Bagate et al. definition [20]. This finding indicates that different cohort characteristics and methodologies reveal different results.

Regarding laboratory findings, our study revealed insignificant differences between the study groups in all laboratory measurements. Kwon et al. found that prothrombin concentration and lactate levels were significantly higher among the CIRCI group than the non-CIRCI group [22]. This result may signify that CIRCI patients have a specific cytokine profile that varies according to the pathogen and site of infection. In addition, patients' demographics could play a role in that profile's final theme.

Sepsis represents a dysregulated immune response to infection that leads to organ dysfunction [25], and biomarkers help clinicians in both early diagnosis and prognosis assessment of sepsis patients.

In a retrospective study conducted by De Jong et al., the results showed that laboratory data such as a low pH/bicarbonate were independent predictors of relative adrenal insufficiency in critically ill patients [26]. However, this study included patients receiving glucocorticoids, antifungal agents, and etomidate, which can interfere with the hypothalamic-hypophysial axis. In addition, the short corticotropin stimulation test was performed only in patients with suspicious symptoms or signs of adrenal insufficiency.

The Kaplan-Meier survival analysis demonstrated that the incidence of mortality is significantly higher in the CIRCI group than in the group without CIRCI. However, due to the small sample size, concluding that VT storm is the CIRCI pattern of death could be misleading. Burry et al. retrospectively identified 219 CIRCI patients with septic shock with 1 μg ACTH test. They concluded that patients with CIRCI had similar ICU mortality whether or not they received corticosteroids (46% vs. 25% P = 0.1666), and that patients with high baseline cortisol and those who did not respond appropriately to ACTH had the highest mortality rates. In addition, corticosteroid administration was not associated with decreased mortality [27]. In the current study, CIRCI patients had a significantly lower mean serum cortisol levels, compared to the mean initial serum cortisol level of non-CIRCI patients, and the 9 CIRCI deaths have a significantly higher mean of baseline cortisol level than CIRCI survivors. The lack of response to steroid administration could be explained by that CIRCI patients have reached an irreversible state of vasoplegia due to the late enrollment time [28]. Although vasoplegia in sepsis is usually attributed to the impairment of vascular reactivity by a combination of endothelial injury, arginine-vasopressin system dysfunction, release of other vasodilatory inflammatory mediators, and muscle hyperpolarization [29], it is physiologically known that corticosteroids in lesser amounts are essential for maintenance of peripheral vascular resistance. Corticosteroids enhance the vasoconstrictor action of vasoconstrictor hormones including α-adrenergic with agonists (norepinephrine), angiotensin II, arginine vasopressin, endothelin and thromboxanes. This is explained by the enhanced sensitivity of the vascular smooth muscle to these potent vasoconstrictor by corticosteroids [30]. So, physiologically, vasoplegia in sepsis could be expected to be partially contributed to the relatively lower production of corticosteroids in sepsis [31]. Another explanation is that their adrenal insufficiency is related to an end-organ resistance state that makes the patients unresponsive to steroids, or their sepsis-related inflammatory storm

being NF-κB independent [31]. Future studies on transcriptomic signatures in sepsis may enable us to identify which sepsis profile will gain the advantage of the early introduction of Corticosteroid in sepsis. In studies using 250 μg, ACTH showed conflicting results of associated mortality. De Jong et al. found statistically higher mortality in the CIRCI group than the other group [32], while Ducrocq et al. concluded no association between CIRCI and mortality [20]. Yang et al. also investigated the outcome of CIRCI patients with multiple injuries. They prospectively found that the CIRCI patients had a significantly higher 28-day mortality (39.3%) compared with those with a baseline cortisol level of less than 10 μg /dL (10%) and non-CIRCI patients (6.3%) [33].

In our study, the incidence of AKI was significantly higher in the CIRCI group than in the group without CIRCI, even though baseline differences in serum creatinine were insignificant. According to our knowledge, no prior study has examined this issue. This phenomenon could be explained by the unique cytokine profile of CIRCI patients, which makes them more susceptible to AKI. Sepsis is a dysregulated host immune response caused by infectious or noninfectious factors characterized by the over-production of multiple pro-inflammatory cytokines and associated with multiorgan dysfunction.

The pathophysiology of AKI in sepsis remains unclear. In the past few decades, renal hypoperfusion and associated ischemia were believed to be the main culprits of AKI in sepsis; however, animal experiments have not fully supported this notion.

Several animal studies demonstrated that the subjects with Gram-negative bacteremia had significantly increased renal blood flow compared with the control group. In histology findings, the degree of tubular injury was mild, and there was no significant difference between the sepsis and the non-sepsis groups [34]. Therefore, instead of the traditional concept, inflammatory cascade, macrovascular and microvascular dysfunction, and cell response abnormality are now believed to be the three cornerstones of the underlying pathophysiological mechanism of AKI in sepsis [35]. In the current study, the BCR of our cohort does not stand clearly for renal hypoperfusion as a soul cause of AKI . This suggests a renal origin of AKI induced by the sepsis related inflammatory environment in addition to an element of hypoperfusion. As there is no significant difference in the BCR between groups, we infer that relative adrenal insufficiency could have a role in augmenting AKI in sepsis.

The length of ICU stay, fluid (L/Day), vasopressors, and MV days did not show any significant differences between both groups. De Jong et al. found significantly lower hospital stay in patients without CIRCI [32]. On the contrary, most other studies showed an insignificant difference [20, 22, 23]. These contradictory results could be attributable to the characteristics of the cohort.

The administration of ACTH in an extra physiologic dose could result in a falsely normal cortisol response in septic shock patients who cannot generate an adequate response to stress [10, 11, 15], or could result in metabolic abnormalities in patients with normal adrenal function [16]. Hence, it is reasonable to use a near physiologic dose of ACTH (1 μg) to detect this critically ill group of patients. This finding could help improve the management of sepsis by early introduction of steroids even if their hemodynamics were stabilized with fluids and vasopressor.

5 Limitations and Recommendations

This study has limitations; the sample size interfered with conducting regression analysis to test the independent predictors of mortality and AKI. Adequate sample size help avoids committing type II error regarding testing other outcomes. The authors do believe that, although a small study with minimal difference in outcome, it raises multiple questions, had answering them would change the septic shock management practice. The 2-day difference in mortality and incidence of AKI between 17 CIRCI patients and 22 non-CIRCI septic shock with a mean ICU stay of 6.1 ± 1.1 days should not be discarded and should provoke the scientific society to conduct a larger study at a wide scale to validate this result.

This study highlights the need to investigate the early introduction of steroids, even if their hemodynamics are stabilized with fluids and vasopressors. This type of study should be randomized and controlled to provide precise results regarding the effects of corticosteroids on critically ill patients. A large multicenter trial including a wide spectrum of sepsis origin, age, ethnic group, and using different doses of ACTH may enable us to identify the best dose for different patients.

More studies should be conducted to investigate the cytokine profile in this patient subgroup to gain a deeper understanding of the underlying mechanisms of CIRCI. Using other serum and urinary AKI biomarkers could help detect the early incidence of AKI instead of relying on serum creatinine.

6 Conclusion

We concluded that the CIRCI group had a lower mean survival rate and a higher incidence of AKI. Based on our observations, we recommend using 1 μg ACTH test in septic shock patients who do not need steroids in their septic shock management protocol to identify this subgroup of patients with subnormal test response to improve the management of sepsis.

Acknowledgment

The authors would like to acknowledge the nursing staff at the ICU for their help in timely withdrawing blood samples.

Conflict of Interest

No conflict of interest.

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Figure 1: The Kaplan-Meier survival analysis shows that the mortality rate in the CIRCI group was significantly higher by 3.01 times the non-CIRCI patients (HR: 3.01, P-value < 0.05).

Figure 2: The Kaplan-Meier survival analysis shows that the incidence of AKI was significantly higher in the CIRCI group by 3.62 times the non-CIRCI patients (HR of 3.62, P-value < 0.05).

Figure 1

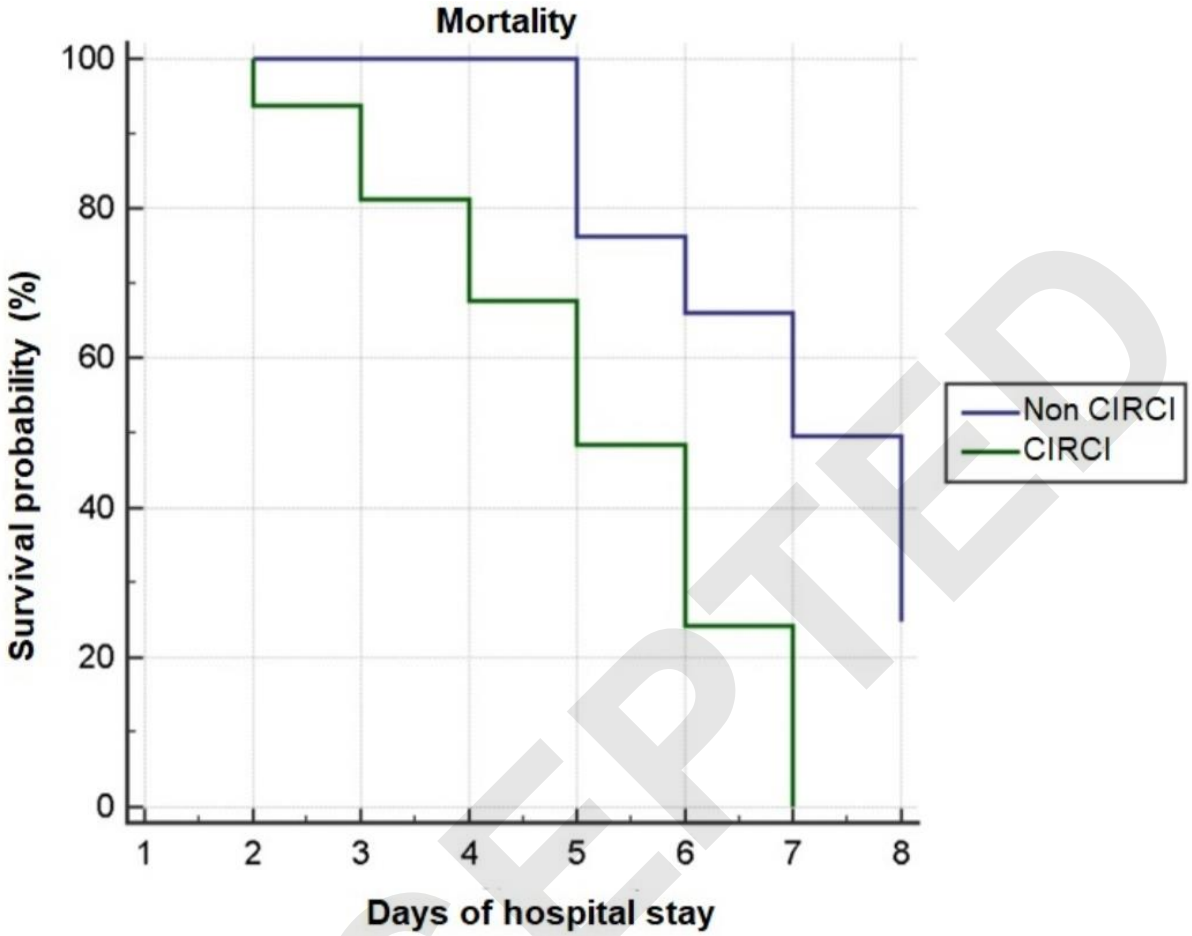

Figure 2

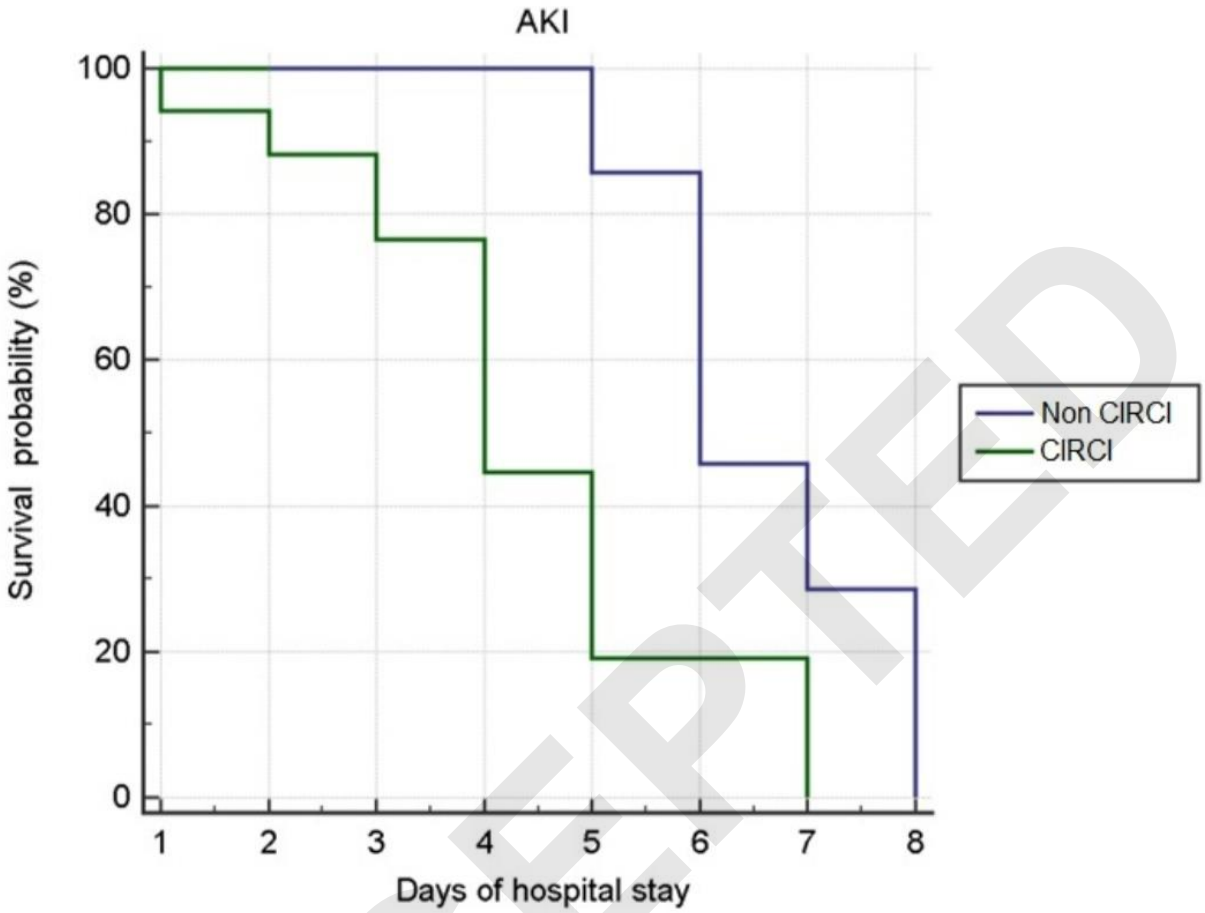

TABLE (1) DEMOGRAPHIC DATA OF THE STUDY COHORT

Characteristics	All patients (n=39)	CIRCI group (n=17)	No CIRCI group (n=22)	*P-VALUE*
Age* years	62.5 ± 14.3	59.9 ± 14.4	64.4 ± 14.2	***0.221***[1]
— Male	18 (46.2%)	9 (52.9%)	9 (40.9%)	
— Female	21 (53.8%)	8 (47.1%)	13 (59.1%)	***0.460***[2]
Comorbidities				
— DM	14 (35.9%)	5 (29%)	9 (40.9%)	
— HTN	9 (23.1%)	4 (23.5%)	5 (22.7%)	
— COPD	2 (5.8%)	1(5.8%)	1 (5.8%)	
— CVD	6 (17.6%)	3 (16.7%)	3 (16.7%)	
— CKD	6 (17.6%)	3 (16.7%)	3 (16.7%)	
— Drug addiction	1 (2.9%)	0 (0%)	1(5.9%)	
— Cancer	1 (2.9%)	1 (5.9%)	0 (0%)	***0.972***[3]
Site of infection				
— Pneumonia	22 (56.4%)	11(64.7%)	11(50%)	
— DF	5 (12.8%)	4 (23.5%)	2 (9.1%)	
— Pyelonephritis	3 (8.8%)	2 (11.8%)	1 (5.9%)	
— Peritonitis	3 (8.7%)	0 (0%)	3 (16.7%)	
— Cellulitis	2 (5.8%)	0 (0%)	1 (5.9%)	
— UTI	1 (2.9%)	0 (0%)	1 (5.9%)	
— Bedsore	1 (2.9%)	0 (0%)	1 (5.9%)	
— IO	1(2.9%)	0 (0%)	1 (5.9%)	
— IE	1 (2.9%)	0 (0%)	1(5.9%)	***0.062***[3]
Temperature*	38.4 ± 0.8	38.6 ± 0.8	38.3 ± 0.8	***0.306***[1]
HR*	111.5 ± 17.6	114.2 ± 16.3	109.4 ± 18.6	***0.407***[1]
RR*	28.8 ± 5.4	29.5 ± 4.1	28.2 ± 6.3	***0.448***[1]
GCS*	13.2 ± 2.1	13.6 ± 1.9	12.8 ± 2.2	***0.294***[1]
MAP*	49.7 ± 8.6	51.6 ± 8.8	48.2 ± 8.3	***0.222***[1]
GCS*	13.2 ± 2.1	13.6 ± 1.9	12.8 ± 2.2	***0.294***[1]

**DATA IS PRESENTED AS MEAN ± SD*

ABBREVIATIONS: DM=DIABETES MELLITUS, HTN=HYPERTENSION, COPD=CHRONIC OBSTRUCTIVE PULMONARY DISEASE, CVD=CARDIOVASCULAR DISEASE; CKD=CHRONIC KIDNEY DISEASE; DF=DIABETIC FOOD; UTI=URINARY TRACT DISEASE; IO= INTESTINAL OBSTRUCTION; IE=INFECTIVE ENDOCARDITIS.

INDEPENDENT T TEST; 2. CHI SQUARE TEST; 3. FISHER EXACT TEST.

TABLE (2) LABORATORY INVESTIGATIONS OF THE STUDY COHORT

	All patients (n=39)	CIRCI group (n=17)	No CIRCI group (n=22)	*P-VALUE*
WBCs	16.1 ± 7.4	15.4 ± 7.6	16.6 ± 7.5	***0.610***[1]
HG	9.6 ± 1.9	9.4 ± 1.9	9.8 ± 1.39	***0.537***[1]
HCT	28.9 ± 5.8	28.3 ± 5.9	29.4 ± 5.8	***0.551***[1]
PLT	210.6 ± 99.3	198.94 ± 86.77	219.6 ± 109.1	***0.526***[1]
AST	155.4 ± 351.1	110.4 ± 256.1	190.2 ± 412.5	***0.489***[1]
ALT	118.9 ± 229.1	99.9 ± 190.2	133.5 ± 258.6	***0.656***
Albumin	22.8 ± 11.9	24.1 ±10.4	21.7 ± 13.1	***0.547***
Total bilirubin	1.6 ± 3.4	1.25 ± 0.81	1.96 ± 4.56	***0.457***[1]
PT	13.7 ± 4.8	13.01 ± 2.3	16 ± 5.8	***0.054***[1]
PC	74.5 ± 24.8	85.6 ± 24.9	75.9 ± 21.7	***0.072***[1]
INR	1.2 ± 0.5	1.4 ± 0.1	1.3 ± 0.9	***0.099***[1]
Urea	26.9 ± 18.8	27.3 ± 20.8	26.6 ± 17.6	***0.914***[1]
Creatinine	376.8 ± 332.2	391.5 ± 345.01	364.9 ± 329.6	***0.810***[1]
Na	134.6 ± 8.04	135.2 ± 7.4	134.08 ± 8.9	***0.653***[1]
K	4.4 ± 0.8	4.5 ± 0.7	4.3 ± 0.9	***0.497***[1]
CRP	118.9 ± 57.03	115.2 ± 58.4	121.8 ± 56.8	***0.726***[1]
PH	7.2 ± 0.1	7.2 ± 0.08	7.2 ± 0.2	***0.573***[1]
Lactate	8.12 ± 2.15	8.32 ± 4.75	7.92 ± 3.72	***0.487***

ALL DATA IS PRESENTED AS MEAN ± SD

ABBREVIATIONS: WBCS=WHITE BLOOD CELLS, HG=HEMOGLOBIN, HCT= HEMATOCRIT, PLT= PLATELETS, ALT=ALANINE AMINOTRANSFERASE, AST= ASPARTATE AMINOTRANSFERASE, INR= INTERNATIONAL NORMALIZED RATIO, CRP= C REACTIVE PROTEIN, PT=PROTHROMBIN TIME, PC=PROTHROMBIN CONCENTRATION.

1 INDEPENDENT T TEST.

TABLE (3) MORTALITY		
Mortality	CIRCI group (n=17)	NON- CIRCI GROUP (N=22)
Number (%)[1]	9 (52.9%)	10 (45.5%)
EMD[2] Number (%)	7 (41.1%)	9 (40.9 %)
VT3 Number (%)	2 (11.7 %)	1 (4.5 %)
Mean survival. days	5.153	6.917
Median survival days	5	7
Survival probability %	48.4 %	49.5 %
Hazard ratio (HR)[4]	3.01	0.33

1 CHI SQUARE TEST, P VALUE = 0.6471
2 EMD: ELECTRO-MECHANICAL DISSOCIATION, CHI SQUARE TEST, P VALUE = 0.451
3 VT: VENTRICULAR TACHYCARDIA, CHI SQUARE TEST, P = 0.001
4 95% CONFIDENT INTERVAL = 1.0342 TO 8.7574, P = 0.0046

TABLE (4) INCIDENCE OF AKI AND AKI PROBABILITY

AKI	CIRCI group (n=17)	NON- CIRCI GROUP (N=22)
Number (%)[1]	14 (82.3%)	15 (68.2%)
Mean survival. days	4.4	6.6
Median survival. days	4	6
AKI probability %	44.6 %	45.7%
Hazard ratio (HR)[2]	3.62	0.31

1 CHI SQUARE TEST, P VALUE = 0.3211.
2 95% CONFIDENT INTERVAL = 1.3599 TO 7.8283, P VALUE = 0.0001.

TABLE (5) CLINICAL OUTCOMES

Outcome	All patients (n=39)	CIRCI group (n=17)	Non-CIRCI group (n=22)	P-VALUE
ICU stay (days)	5.2 ± 1.6	6.1 ± 1.1	5.1 ± 2.4	**0.071**[1]
Fluid (L/Day)	4.1 ± 1.4	5.8 ± 1.2	4.4 ± 2.9	**0.097**[1]
Vasopressors (days)	6.3 ±1.5	7.3 ± 3.2	6.7 ± 4.9	**0.081**[1]
MV (days)	7.5 ± 2.3	8.2 ± 3.1	6.5 ± 4.2	**0.067**[1]
AKI n (%)	29 (74.3%)	15 (68.2%)	14 (82.3%)	**0.154**[2]

ALL DATA IS PRESENTED AS MEAN ± SD

ABBREVIATIONS: MV: MECHANICAL VENTILATION

1 INDEPENDENT T TEST.

2 CHI SQUARE TEST.