Critical Illness-related Corticosteroid Insufficiency is Common in Covid-19 and Treatment Provide Survival Benefit

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Abstract

Purpose

Covid-19 is a severe lethal disease characterized with pneumonia and acute respiratory distress syndrome. We aimed to analyze the prevalence of critical illness-related corticosteroid insufficiency (CIRCI) in Covid-19 patients treated in intensive care unit and whether treatment of it would create any survival benefit.

Methods

A total of 119 Covid-19 patients in intensive care unit were enrolled into the study. All patients received treatment for Covid-19 according to national guideline including hydroxychloroquine, favipiravir, antibiotics including azithromycin and oseltamivir in some patients. Basal cortisol below 10 µg/dl were accepted as CIRCI and above 34 µg/dl as intact HPA axis. Patients between them were introduced 1 µg cosyntropin stimulation test and delta cortisol below 9 µg/dl were also accepted as CIRCI. All patients who got diagnosis received hydrocortisone 300 mg/day until clinical condition stabilized. Mortality rate was recorded, then.

Results

CIRCI was detected in 50.4% of cases and mean plasma ACTH level was 14.8 ± 6.0 pg/ml. Patients below age 65 had a statistically higher risk (63.4 % vs. 40.2%, $p=0.012$). Presence of comorbidity did not increase the risk of CIRCI (47.3% vs. 62.5%, $p=0.18$). Also, severity of pulmonary involvement and intubation did not increase the risk of CIRCI. Total mortality rate was 49.5% and not different in patients with and without CIRCI (45.0% vs. 54.5%, $p=0.31$) indicating benefit of corticosteroid treatment.

Conclusion

CIRCI is common in Covid-19 patients treated in intensive care unit and treatment of CIRCI provide survival benefit.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), reached pandemic level with a high global mortality rate [1]. COVID-19 can cause severe illnesses such as acute respiratory distress syndrome (ARDS), multiorgan dysfunction syndrome (MODS), and death [2–4]. Most of the cases were mild (81%), while 14% were severe and 5% critical. The overall case-fatality rate was 2.3% [5].

Critical illness-related corticosteroid insufficiency (CIRCI) describes the impairment of the hypothalamic-pituitary-adrenal (HPA) axis during critical illness. Inadequate corticosteroid activity is the result of dysregulated systemic inflammation [6]. CIRCI can occur in a variety of acute conditions, such as sepsis

and septic shock, ARDS, severe community acquired pneumonia, and other shock states [6, 7]. Treatment with various doses of corticosteroid provide survival benefit in sepsis or septic shock [8].

Patients with adrenal insufficiency are at increased risk of infection due to their suppressed immunity which could facilitate the worsening of a SARS-CoV-2 infection into severe acute respiratory distress syndrome [9]. Patients with already known adrenal failure are advised to double the dose of original regimen in mild COVID-19. But in more severe or critical care patients, treatment should include higher doses like in adrenal crisis. Given that suggestions patients who had been diagnosed adrenal failure in critical care should be treated promptly to decrease morbidity and mortality related to that [6–8].

Data from SARS-CoV in the past indicate suppression of HPA axis. Study was done on survivors of SARS-Cov infection. Patients were evaluated 3 months after recovery of the disease and HPA axis suppression was detected in 40% of cases, majority of them resolved within a year [10]. In normal physiological response, immune reaction to an infection induces HPA axis and increased secretion of cortisol results in mild immunosuppression to control cytokine toxicity. However, in critical illnesses HPA activation was mostly blunted, leading to corticosteroid insufficiency [11]. Initial immune response to virus in COVID-19 induces an uncontrolled cytokine storm characterized by hyperinflammation and immunosuppression. Resultant reaction characterized by vasculitis, thromboembolism, and hypotensive shock resembles adrenal insufficiency.

Up to now, there is no study on assessment of adrenal function in COVID-19. The aim of this study was to determine the rate of adrenal failure in critical care patients and the effect of treatment on survival.

Materials And Methods

Subjects

Patients aged above 18 years (males and females) were recruited from the intensive care unit at the Bagcilar Training and Research Hospital, Istanbul, Turkey. A total of 119 patients with documented COVID-19 were included in the study.

Patients were admitted to critical care unit mostly for severe pneumonia and related ARDS. Other indications were MODS and myocardial infarction. Indications for admission to critical care were determined by advisory board committee of ministry of health in Turkey [12]. According to that in addition to pulmonary infiltrates on thorax computerized tomography, patients with (a) respiratory rate >30/minute, (b) dyspnea and respiratory failure, (c) patient with oxygen saturation <90% and PaO₂ <70mmHg (despite nasal oxygen supply of 5 liters/minutes), (d) PaO₂/FiO₂ <300, (e) lactate>4mmol/L, (f) bilateral infiltration or multilobar involvement in lung CT, (g) hypotension, (h) skin perfusion disorder, (i) kidney and liver function test disorder, thrombocytopenia and organ dysfunction, (j) immunosuppressive patients, (k) uncontrolled comorbidity, (l) elevated troponin, arrhythmia.

All of the patients needed assisted ventilation either by intubation (n=60) or noninvasive mechanical ventilation (NIMV) (n=59). MODS was described as change in consciousness, respiratory failure, low oxygen saturation, low urine output, increase in creatinine, increase in heart rate, filiform pulses, cold extremities, low blood pressure, coagulopathy, thrombocytopenia, acidosis, increase in lactate level and hyperbilirubinemia.

According to national COVID-19 treatment protocol(12), besides standard supportive care, all of the patients received hydroxychloroquine at a dose of 200mg/day, 98.3% favipiravir 200 mg/day, 37.8% azithromycin 500 mg/day, 17.6% oseltamivir 200 mg/day, 97.4% antibiotics either as piperacillin-tazobactam, meropenem, linezolid or daptomycin. Also, all patients received enoxaparin sodium 6000 IU twice daily and 15-gram parenteral vitamin C infusion every day.

Concomitant diseases were recorded. Subjects with any disease that can affect cortisol secretion such as brain tumors, pituitary diseases, and adrenal diseases were excluded. Patients who were pregnant or have alcohol abuse were also not included. Patients on treatment with drugs that can directly or indirectly cause or affect cortisol metabolism were also excluded. But, medications that patient on treatment for chronic diseases were recorded and included into the study such as antihypertensive medications, antidiabetics etc.

This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki and was approved by the ethical committee of Bagcilar Training and Research Hospital (2020.05.1.10.042). All subjects or legal representative gave informed consent before entrance into the study.

Study design

All patients were seen in intensive care units. After collection of demographic data, laboratory results used in evaluation and follow-up of a COVID-19 was recorded from patient file e.g. complete blood count, lymphocyte count, C-reactive protein (CRP), fibrinogen, D-dimer, lactate dehydrogenase (LDH), ferritin, triglyceride, troponin-I, creatine kinase (CK), blood urea, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These laboratory tests were a part of routine assessment and we did not add any other test than those.

Assessment of Adrenal Function

For the diagnosis of adrenal insufficiency in patients in critical care, Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017 recommendations were used [13]. The task force recommended delta cortisol (change in baseline cortisol at 60 min of $< 9 \mu\text{g/dL}$) after cosyntropin (250 μg) administration and a random plasma cortisol of $< 10 \mu\text{g/dL}$ to be used for diagnosis.

Initially blood drawn from all patients for random cortisol. Patients with random cortisol level below $10 \mu\text{g/dL}$ were directly accepted as adrenal insufficiency and values above $34 \mu\text{g/dL}$ were accepted as intact adrenal gland. If random cortisol was between $10\text{-}34 \mu\text{g/dL}$, patients were directed to cosyntropin

stimulation test. But instead of 250 µg which is thought to be supra-physiologic for assessment of these patients, we used 1 µg test. Both tests are equally accurate to identify mortality and time of vasopressor therapy (14). Delta cortisol (change in baseline cortisol at 30 or 60 min of < 9 µg/dL) after cosyntropin (1 µg) administration was accepted as adrenal insufficiency.

Patients who had diagnosed as CIRCI were administered intravenous hydrocortisone at a dose of 100 mg three times daily during ICU stay. If patient recovered from COVID-19 and clinically stabilized hydrocortisone dose was steadily tapered to maintenance dose of 30 mg/day and until reassessment of adrenal function they were suggested to continue hydrocortisone after discharge. Other patients who had initial cortisol level above 34 µg/dL or patients who had > 9 µg/dL increase in cosyntropin test were not given any corticosteroid therapy. All patients also received standard supportive care and COVID-19 specific medications.

Assessment of Pulmonary Involvement

All patients presenting with dyspnea or symptoms like coughing were directed to computerized tomography of thorax [12]. In order to assess the severity of pulmonary involvement, we stratified patients into three groups: patients who had involved pulmonary surface area on CT scan less than 25% were accepted as mild, 25-50% moderate, >50% severe. All scans were assessed by same radiologist.

Treatment of Comorbidities

If patients were stable in concomitant diseases, we did not change their therapy unless clinical condition created a contraindication for the use of medications such renal dysfunction or hepatic failure. For the treatment of diabetes, oral antidiabetics were stopped, and insulin infusion was introduced to control glycaemia. Antihypertensive treatment was continued unless contraindicated or patient becomes hypotensive. All other medications were continued.

Assessment of mortality

In-hospital mortality was recorded with the exact reason.

Assays

All laboratory assays were studied at the central laboratory of Bagcilar Training and Research Hospital. Serum LDH, AST, ALT, Urea, creatinine, CRP, CK, triglyceride was studied with photometric method in Beckman Coulter AU4800, Fibrinogen, D-dimer, was studied in Succeeder sf-8200. Complete blood count was studied with absorption photometry and flow cytometry in Sysmex XN-900.

Statistical analysis

Statistical analyses were performed using SPSS software version 25. Descriptive analyses were presented using means and standard deviations for continuous data and frequencies and percentages for categorical data. Since the variables were normally distributed, independent samples t-test was used

to compare the groups. The Chi-Square and Fisher's exact test, where appropriate, were used to compare the percentages in the groups. For the multivariate analysis, the possible risk factors identified statistically significant with the univariate analyses were further entered into linear regression analysis to determine independent predictors of adrenal insufficiency. A 5% type-I error level was used to infer a statistical significance.

Results

Diagnosis of CIRCI

Critical illness-related corticosteroid insufficiency was detected in 60 (50.4%) patients in intensive care unit with Covid-19 infection. Twenty-five of them were diagnosed with basal cortisol below 10 µg/dl and 35 of them with delta cortisol below 9 µg/dl at 60th minute of 1 µg cosyntropin test. There were differences in some parameters between either group whether diagnosed with basal cortisol or cosyntropin test (Table 1).

Mean plasma ACTH level was 14.8 ± 6.0 pg/ml (range 6.4-22.1) and 36.3% of patients had an ACTH level below 10 pg/ml.

Demographic characteristics

Demographic characteristics of study population were presented in Table 2. Although men (63.8%) dominated study population, the rate of diagnosis was similar in both sex (47.3% vs. 55.8%, $p=0.37$).

Age is accepted as an important risk factor for Covid-19, especially patients above age of 65 have a higher risk. On the other hand, in this study population younger patients below age 65 had a statistically higher risk of CIRCI (63.4 % vs. 40.2%, $p=0.012$). We also looked at young patients and 8 patients were below age of 45 and all of them had CIRCI.

Ninety-five patients (79.8%) had at least one comorbidity. But comorbidity also did not increase the risk of CIRCI, even patients without comorbidity had a relatively higher rate of CIRCI (47.3% vs. 62.5%, $p=0.18$).

Pulmonary involvement was moderate (35.5%) to severe (65.5%). Again, the severity of pulmonary involvement did not change the possibility of diagnosis (51.2 % vs. 48.7%, $p=0.79$).

All the patients required assisted ventilation. Among them, 67 (56.3%) were intubated and 52 patients received noninvasive mechanical ventilation (NIMV). Intubation did not increase the possibility of CIRCI compared to NIMV (47.7% vs. 53.8%, $p=0.51$).

Laboratory results

Basal cortisol level was correlated with CRP ($p=0.006$, $r=0.352$) and LDH ($p=0.006$, $r=0.350$) in patients with CIRCI and CRP ($p=0.005$ $r=0.256$) in total group. Mean cortisol level was also calculated. It was 18.2 ± 7.0 mcg/dl in patients with CIRCI and 38.9 ± 10.9 mcg/dl in patients without CIRCI ($p<0.0001$). Mean

cortisol was correlated with CRP ($p=0.005$, $r=0.360$), LDH ($p=0.007$, $r=0.346$) and mortality ($p=0.003$, $r=0.375$).

Frequency of Comorbidities and Effect on Diagnosis

The most common comorbidities were hypertension (51.2%), diabetes mellitus (39.4%), coronary artery disease (33.6%), chronic renal failure (17.6) and chronic obstructive pulmonary disease (15.1%). Other comorbidities and rate of diagnosis of CIRCI were presented in Table 2.

The Effect of Medications on CIRCI

Eighty-one (68.0%) of patients were on chronic treatment with some medications while hospitalized. None of the patients were on treatment that influences cortisol metabolism. Whether the patient on treatment with any medication or not did not differ the possibility of CIRCI (46.9% vs 57.8%, $p=0.26$). Medication list and their effect on CIRCI rate was presented in Table 2.

Laboratory tests

Laboratory results were presented in Table 3. As expected, cortisol levels either basal or in ACTH stimulation test were lower in patients with CIRCI ($p<0.0001$). All other inflammatory markers related to SARS Covid-19 infection were not different between groups. Although disease severity was described as an increased inflammatory markers and pulmonary involvement, there were no correlation between severity of pulmonary involvement and inflammatory markers such as CRP, fibrinogen, leukocytosis etc.

Pulmonary involvement

Pulmonary involvement increased with age ($p=0.04$, $r=0.188$). There was a positive correlation between severity of pulmonary involvement and intubation ($p<0.0001$, $r=0.716$) and mortality ($p<0.0001$, $r=0.542$).

Mortality

Total mortality rate was 49.5%. There was no difference in patients with and without CIRCI (45.0% vs. 54.5%, $p=0.31$). Main reason for mortality was respiratory failure in 84.7% of patients, multiorgan failure in 13.5% and myocardial infarction in 1.7% of cases. Mortality risk was correlated with basal ($p=0.02$, $r=0.209$) and mean cortisol level ($p=0.01$, $r=0.224$). Among laboratory tests only CRP level was correlated with mortality ($p=0.003$, $r=0.274$). Severity of pulmonary involvement ($p<0.0001$, $r=0.542$) and intubation ($p<0.0001$, $r=0.501$) were correlated with mortality. In linear regression analysis, only basal cortisol level had effect on mortality ($p=0.02$ $R^2=0.044$). Comorbidities did not have any effect on mortality.

Other Correlation Analysis

There was a positive correlation between age and severity of pulmonary infiltration ($p=0.04$, $r=0.188$) and presence of any comorbidity ($p=0.0001$, $r=0.321$).

Presence of comorbidity increased risk of intubation ($p=0.03$, $r=0.191$).

Intubation risk was increased with severity of pulmonary infiltration ($p=0.0001$, $r=0.716$), CRP ($p=0.04$, $r=0.183$), blood urea level ($p=0.02$, $r=0.210$), creatinine ($p=0.03$, $r=0.198$) and hemoglobin ($p=0.02$, $r=-0.207$).

Discussion

The results of this study showed that adrenal insufficiency is common among patients with COVID-19 treated in critical care units. Compared to other studies, the prevalence was similar to patients with severe sepsis reported by Annane et al. [15]. Treatment with corticosteroids decreased mortality in these patients.

CIRCI was first introduced in 2008 by a task force convened by the Society of Critical Care Medicine to describe the impairment of the HPA axis during critical illness [16]. Severity of the critical illness causes inadequate cellular corticosteroid activity resulting in dysregulated systemic inflammation. Three major pathophysiologic events are considered to constitute CIRCI: dysregulation of the HPA axis, altered cortisol metabolism, and tissue resistance to glucocorticoids [7, 17]. Plasma clearance of cortisol is markedly reduced during critical illness, due to suppressed expression and activity of the primary cortisol-metabolizing enzymes in the liver and kidney. Furthermore, despite the elevated cortisol levels during critical illness, tissue resistance to glucocorticoids is believed to occur because of insufficient glucocorticoid receptor alpha-mediated anti-inflammatory activity.

The clinical spectrum of COVID-19 varies from asymptomatic form to clinical conditions characterized by respiratory failure that requires mechanical ventilation to sepsis, septic shock, and MODS. Direct injury to the lung tissue from a viral infection-mediated local inflammatory response is one of the proposed mechanisms behind the pulmonary manifestations of COVID-19 [18]. Cytokine storm syndrome (CSS) is an accentuated immune response to viral infection. CSS is characterized by unremitting fever and multiorgan involvement, including ARDS and acute cardiac and renal injury.

People with COVID-19 and ARDS have classical serum biomarkers of CRS, including elevated CRP, LDH, D-dimer, and ferritin [19]. This clinical history is similar to other infections resulting in ARDS and respiratory failure. For this reason, adrenal gland dysfunction is possible in patients with COVID-19. This study is an example for this relationship.

Proposed mechanisms for the development CIRCI are fulfilled in COVID-19. This study, for the first time, demonstrated the possibility of compromised adrenal function in severe COVID-19 treated in ICU. CIRCI is commonly seen in patients admitted to intensive care units for different reasons. CIRCI occurred in 54.3% of the patients with multiple injuries [20] and 0–48% in severe community-acquired pneumonia [21]. Mortality among patients with CIRCI was higher than normal adrenal function especially patients with abnormal response to cosyntropin had a higher mortality risk [20]. Similar finding was also observed in our study. Patients who had basal cortisol level less than 10 mcg/dl had a mortality rate 28.0% while

patients who had abnormal response to cosyntropin (< 9 mcg/dl increase) had a mortality rate of 57.1%. This shows that baseline cortisol is not enough to assess adrenal function and response to cosyntropin may have a predictive role in assessing mortality.

In contrast to low cortisol levels in CIRCI group, ACTH level was inappropriately low or below 10 pg/ml indicating suppression at hypothalamic or pituitary level. Cortisol insufficiency during critical disease may result in structural damage in any point of the HPA axis from hypothalamus to adrenal gland itself. In physiological states, acute phase of stress causes an increase in cortisol level and either due to inflammatory reaction or negative feedback suppression ACTH levels were found relatively low. If patients survive the acute phase of disease but do not recover from the disease, they will enter chronic phase of critical disease, which is characterized by atrophy of the adrenal gland due to inadequate stimulation, by the pituitary with a resultant secondary adrenal failure [22].

According to WHO data on 31st May 2020 confirmed cases of COVID-19 throughout the world was 5,934,936 with 397,166 deaths and mortality rate of 6.6%. Main reasons for mortality were hypoxic respiratory failure, MODS and septic shock. Independent from each other every etiology has a potential to induce CIRCI [17, 23]. It may be speculated here that CIRCI might play a role in at least some of those deaths. In our study, mortality rate was comparable in patients with and without adrenal dysfunction. This was probably related to the corticosteroid replacement after diagnosis of adrenal insufficiency. This shows that detection of adrenal insufficiency early after admission to intensive care unit and proper treatment may be lifesaving.

Except age, all other baseline demographic characteristics including comorbidities, drug use, need for mechanical ventilation in the form of intubation or NIMV and severity of pulmonary infiltration were similar in patients with or without adrenal insufficiency. Patients with adrenal insufficiency were younger like in previous studies [24]. Prognosis in patients with adrenal insufficiency was worse in subgroup of delta cortisol below 9 mcg/dl compared to basal cortisol below 10 mcg/dl both in ours and previous studies [24]. In delta cortisol group, patients were even younger than basal cortisol and normal adrenal function group. These patients also had higher CRP and LDH levels compared to basal cortisol group. These findings indicate a more severe disease in this subgroup. Even they were treated with corticosteroid; mortality was higher than basal cortisol group but similar to normal adrenal function group. Only patients who had a basal cortisol level below 10 mcg/dl had a benefit over mortality according to our results if they are treated with steroid.

COVID-19 was related to increase in inflammatory (CRP, Fibrinogen, LDH, ferritin, leukocytosis, lymphopenia), thrombotic (D-dimer, thrombocytopenia, hypertriglyceridemia), and myocardial injury (Troponin-I and CK) markers [3]. These are specific markers to the disease itself and there was no difference in any parameters. But, in subgroups, CRP and LDH level were higher in patients with adrenal insufficiency diagnosed with delta cortisol level compared to basal cortisol level. This finding might indicate a more severe disease in this group. This may explain why the mortality rate was higher in those patients.

Comorbidities were more likely detected in severe patients [25]. In Chinese case series, preexisting comorbid conditions increased mortality by 5.6–10.5% [5]. Also, according to Italian Higher Health Institute (Istituto Superiore di Sanità) report, patients without any comorbidities accounted for only 2.8% of those died from COVID-19 [26]. On the other hand, although 79.8% of our study population had at least one comorbid disease, mortality was not increased. The presence of disease may be a confounding factor in previous studies since other factors such as disease treatment and control rate before hospitalization, severity or grade of the disease and in-hospital treatment are also important. There were no data about them both in previous studies and ours.

There is no standard treatment of COVID-19. Corticosteroids were widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome. But their efficacy is controversial. Although critical patients were more likely to require corticosteroids therapy, its use was associated with higher mortality, longer length of stay, a higher rate of bacterial infection and hypokalemia [27]. For this reason, empirical treatment with corticosteroids may be harmful in COVID-19. Instead, assessment of adrenal function and proper treatment makes more sense.

There are some limitations of this study. First, study includes limited number of patients. But, by being the first example, sample size is acceptable. Second, we used 1 mcg cosyntropin test instead of 250 mcg. Standard recommendation was 250 mcg cosyntropin test. But comparative studies report equal value of both tests for the evaluation of critical cases. We can estimate that if we used 250 mcg test, the prevalence possibly would be higher. Third, our mortality rate was similar to patients with intact adrenal function, which we attribute it to corticosteroid replacement. We did not have an arm that is not treated for adrenal insufficiency due to ethical reasons. So, we don't know whether mortality will be higher if not treated. Four, although chronic medications that patients were using and the ones that started for the treatment for COVID-19 as far as we know does not influence adrenal function, separately, we cannot exclude the interaction of polypharmacy.

In conclusion, adrenal insufficiency is very common in COVID-19. Treatment of these patients with corticosteroids help to decrease mortality to the level of normal adrenal function patients. For this reason, all patients admitted to intensive care unit whether the clinical picture resembling adrenal insufficiency or not has to be assessed for adrenal function and if diagnosed treated properly.

Declarations

Conflicts of interest/Competing interests

All of the authors here declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported; or declare any financial or other potential conflict of interest.

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Availability of data and material

Data about the results obtained are available and ready for evaluation in part of transparency.

Code availability

Not applicable

Ethics approval

Local ethical committee with approval number 2020.05.1.10.042 approved the study

Authors' Contributions

Hakan Sari: helped to the design of the study, performed collection of data, helped in draft of data, participated in manuscript writing

Mehmet Salih Sevdı: participated in the follow-up of study subjects, performed cosyntropin test, helped to draft the manuscript and writing process

Kerem Erkalp: participated in the follow-up of study subjects, performed cosyntropin test, participated in collection of data, helped in writing

Hasan Aydin: designed and coordinated the study, performed the statistical analysis, write manuscript

Consent to participate

All authors gave consent to participate to this study

Consent to publication

All authors gave consent to participate to this study

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Tables

Table 1. Important differences between diagnostic methods.

	Delta cortisol group (n=35)	Basal cortisol group (n=25)	p
Blood cortisol (µg/dl, mean±SD)	23.0±4.7	7.6±2.3	<0.0001
Age (years, mean±SD)	60.4±2.4	67.9±3.3	0.06
Co-morbidity (%)	72.2	76.0	0.88
Mortality (%)	57.0	28.0	0.02
Intubation (%)	60.0	44.0	0.22
Pulmonary infiltration (moderate/severe)	9/16	11/24	0.72
CRP (mg/L, mean±SD)	152.1±18.5	82.8±13.1	0.006
LDH (U/L, mean±SD)	581.7±56.4	386.3±31.9	0.008

Table 2. Demographic and medical history of patients

	Total group (n=119)	Patients with CIRCI (n=60)	Patients without CIRCI (n=59)
Age (year, mean±SD)	67.5±14.1	63.5±15.7*	71.5±11.0*
Sex (n, M/F)	76/43	36/24	40/19
Comorbidity (n, %)	95 (79.8)	45 (75)	40 (67.7)
Diabetes mellitus	47 (39.4)	24 (40.0)	23 (38.9)
Hypertension	61 (51.2)	26 (43.3)	35 (59.3)
Coronary artery disease	40 (33.6)	18 (30.0)	22 (37.2)
Cerebrovascular disease	10 (8.4)	5 (8.3)	5 (8.4)
Malignancy	9 (7.5)	5 (8.3)	4 (6.7)
Chronic renal failure	21 (17.6)	9 (15.0)	12 (20.3)
Congestive heart failure	2 (1.6)	0 (0)	2 (3.3)
Dementia	4 (3.3)	4 (6.6)	6 (10.1)
Parkinson's disease	3 (2.5)	2 (3.3)	1 (1.6)
COPD	19 (15.9)	8 (13.3)	10 (16.9)
Atrial fibrillation/arrhythmia	4 (3.3)	2 (3.3)	2 (3.3)
Medication use (n, %)	81 (68.0)	38 (63.3)	43 (72.8)
ACE-I	22 (18.4)	10 (16.6)	12 (20.3)
ARB	14 (11.7)	7 (11.6)	7 (11.8)
Oral antidiabetic	37 (31.0)	19 (31.6)	18 (30.5)
Insulin	8 (6.7)	5 (8.3)	3 (5.0)
Calcium channel blocker	28 (23.5)	10 (16.6)	18 (30.5)
Diuretic	18 (15.1)	6 (10.0)	12 (20.3)
Isosorbide-5-mononitrate	7 (5.8)	3 (5.0)	4 (6.7)
Alpha blocker	7 (5.8)	3 (5.0)	4 (6.7)
Beta blocker	9 (7.5)	5 (8.3)	4 (6.7)
Acetylsalicylic acid	19 (15.9)	7 (11.6)	12 (20.3)

Acetylcysteine	5 (4.2)	0 (0)	5 (8.4)
Salbutamol	5 (4.2)	2 (3.3)	3 (5.0)
Levodopa	3 (2.5)	2 (3.3)	1 (1.6)
Assisted ventilation (n, %)			
Intubation	67(56.3)	32 (53.3)	35 (59.3)
NIMV	52 (43.6)	28 (46.6)	24 (40.6)
Pulmonary infiltration (n, %)			
Moderate	41 (34.5)	20 (33.3)	21 (35.5)
Severe	78 (65.5)	40 (66.6)	38 (64.5)
Mortality (n, %)	59 (49.5)	27 (45)	32 (54.5)

M, Male, F, Female, COPD, Chronic Obstructive Pulmonary Disease, ACE-I, Angiotensin Converting Enzyme Inhibitor, ARB, Angiotensin Receptor Blocker

*p=0.0018

Table 3. Laboratory results

	Total group (n=119)	Patients with CIRCI (n=60)	Patients without CIRCI (n=59)
ACTH stimulation test			
Basal cortisol (µg/dl)	26.6±13.8	17.9±6.7*	35.5±13.5*
30 min. cortisol (µg/dl)	29.1±8.9	24.2±6.0*	35.0±8.3*
60. min. cortisol (µg/dl)	27.7±8.6	22.3±5.7*	34.2±7.1*
Leucocyte (10³/µL)	12597±9093	12462±8139	12734±10039
Lymphocyte (10³/µL)	1073±881.2	1144±763.2	1001±988.4
Lymphocyte/Leucocyte	0.10±0.07	0.11±0.06	0.09±0.08
Hemoglobin (g/dL)	10.9±2.3	10.7±2.6	11.1±1.9
Platelets (10³/µL)	313400±140400	324300±149300	302200±131200
CRP (mg/L)	138.2±112.7	123.2±99.5	153.5±123.7
Fibrinogen (g/L)	475.5±154.8	469.2±142.2	482.1±167.8
D-dimer (µg/mL)	2.5±6.9	2.0±2.0	3.1±9.7
Troponin-I (pg/mL)	561.4±2740	967.0±382.1	155.8±461.8
Creatine kinase (U/L)	282.9±621.1	351.3±813.0	213.4±320.8
Ferritin (ng/mL)	393.2±377.9	379.4±352.6	406.8±403.9
Triglyceride (mg/dL)	140.7±67.5	138.3±67.5	143.1±67.9
Lactate dehydrogenase (U/L)	473.9±252	500.3±289.8	445.7±202.7
AST (U/L)	73.0±196.9	94.0±272.1	51.8±51.6
ALT (U/L)	44.2±93.1	46.8±112.5	41.5±68.9
Urea (mg/dL)	75.8±53.9	71.5±58.7	80.1±48.6
Creatinine (mg/dL)	1.4±1.5	1.4±1.6	1.5±1.3

*p<0.0001