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ORIGINAL ARTICLE

Critical Illness-Related Corticosteroid Insufficiency (CIRCI) Among Patients with COVID-19 at a Tertiary Hospital: Clinical Characteristics and Outcomes*

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Abstract

Objectives. Among critically ill patients, there is usually impairment of the hypothalamic-pituitary-adrenal axis, leading to a condition known as critical illness-related corticosteroid insufficiency (CIRCI). This investigation aims to determine the incidence of and characterize CIRCI among patients with COVID-19 as well as to analyze the outcomes of these critically ill patients.

Methodology. This is a single-center, retrospective cohort study that investigated the occurrence of CIRCI among critically ill patients infected with COVID-19.

Results. In this cohort, there were 145 COVID-19-positive patients with refractory shock, which reflects that 22.94% of the COVID-19 admissions have probable CIRCI.

Patients who were given corticosteroids were found to have statistically significant longer median days on a ventilator (p=0.001). However, those on the corticosteroid arm were at higher risk of morbidity and mortality and a greater proportion had organ dysfunction. Multivariable logistic regression analysis revealed that SOFA score was a significant predictor of mortality in CIRCI (p=0.013).

Conclusion. CIRCI has a unique presentation among patients with COVID-19 because of the presence of a high level of inflammation in this life-threatening infection. It is possibly a harbinger of a markedly increased risk of mortality in these patients.

Key words: adrenal insufficiency, COVID-19, critical illness, shock

INTRODUCTION

Towards the end of 2019, the world was struck by a pandemic in the form of a disease known as COVID-19, brought about by SARS-CoV-2, which originated in Wuhan, Hubei Province, China. SARS-CoV-2 belongs to the betacoronavirus 2B lineage, distinct from Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Symptoms of COVID-19 infection include fever, cough, difficulty breathing, myalgia, fatigue, normal or low leukocyte counts or lymphopenia, and infiltrates on chest radiography indicative of pneumonia.[1] Indeed, COVID-19 is a serious global pandemic with a markedly high burden of disease.

In the Philippines, the total number of cases has reached 36,438, with 632 of these cases admitted at the Philippine General Hospital (PGH) at the time of this study's conclusion.[2] Severe cases of COVID-19 can present with organ dysfunction in the form of shock, acute respiratory distress syndrome, acute cardiac dysfunction, and acute kidney injury. In a cohort of 138 patients admitted at a hospital in Wuhan, as many as 26.1% of the patients were admitted to the intensive care unit (ICU) because of organ

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dysfunction.[1] Based on data from China, where the disease reportedly originated, about 13.2 to 21.3% of patients afflicted with COVID-19 had severe or fatal infections.[3] A significant number of patients afflicted with COVID-19 warrant intensive care. Septic shock occurred in about 4 to 8.7% of patients. The mortality is also high among critically ill patients reaching 61.7% at 28 days, with a median time from admission to death of 7 days.[4] On the other hand, international data showed that shock occurred in about 23 to 31% of patients in the ICU and that 70% of patients who succumbed to COVID-19 infection had septic shock.[1,5,6] Truly, a significant proportion of patients infected with COVID-19 present with critical illness in the form of septic shock or acute respiratory distress syndrome (ARDS), necessitating intensive care.

Among critically ill patients, there is usually impairment of the hypothalamic-pituitary-adrenal axis, leading to a condition known as critical illness-related corticosteroid insufficiency (CIRCI). This condition is characterized by a lack of corticosteroid response proportional to the level of stress. Patients afflicted with CIRCI usually present with refractory hypotension which may also be accompanied by hypoglycemia, electrolyte abnormalities, metabolic acidosis, and eosinophilia.[7] The incidence of CIRCI can be as high as 60% in patients with septic shock.[8] Analysis of different cohorts shows that the incidence of CIRCI among patients with sepsis ranged from 12% to as high as 75%.[9] Dysregulated systemic inflammation in the setting of CIRCI leads to organ dysfunction placing patients at high risk for prolonged vasopressor and ventilatory dependence and mortality. CIRCI is commonly found in a wide range of acute conditions such as sepsis, septic shock, severe community-acquired pneumonia, ARDS, cardiac arrest, head injury, trauma, burns, and after major surgery.[10] It has also been found that there is a twenty-fold higher incidence of symptomatic adrenal insufficiency in critically ill patients being managed in the ICU for more than two weeks,[11] which is a common scenario among patients afflicted with COVID-19. The diagnosis of CIRCI is established based on clinical findings of refractory hypotension unresponsive to fluid hydration, along with high or increasing requirements for vasopressors. According to the Society of Critical Care Medicine and European Society of Intensive Care Medicine, the diagnosis of CIRCI is confirmed through a random cortisol measurement of <10 mcg/dl or delta cortisol (change in baseline cortisol at 60 minutes of <9 mcg/dl) after cosyntropin or ACTH (250 mcg) administration.[12]

The cornerstone of the management of CIRCI is treatment with glucocorticoids. Various studies have demonstrated that the use of glucocorticoids at a stress dose (i.e., hydrocortisone at 200-300 mg/day) promoted hemodynamic function and improved survival of patients with septic shock by reducing organ system dysfunction, ventilatory support, and ICU days.[13] In terms of adverse effects, corticosteroids have been associated with hyperglycemia, myopathy, weight gain, easy bruisability, and osteopenia. However, these adverse effects are usually seen in patients with prolonged use of corticosteroids rather than in the critical care setting. A stress dose given over a short period - such as in refractory shock in critically ill patients is not expected to cause deleterious effects, such as immunosuppression. However, hyperglycemia and myopathy can still occur even with the short-term use of glucocorticoids.[14] Still, the current pool of evidence suggests that low-dose corticosteroids, i.e., hydrocortisone at 200-300 mg/day given for three days or more, contribute to improving survival and hemodynamic stability among critically ill patients without conferring a significant risk for adverse events.[12]

There is limited data on the use of glucocorticoids, which is the first-line treatment in CIRCI, in the setting of viral pneumonia. Several studies on patients with influenza A/H1N1 demonstrated the benefits of using glucocorticoids (methylprednisolone at 1 mg/kg/day or hydrocortisone at 300 mg/day) in patients with severe ARDS in terms of decreasing lung injury scores, multiple organ dysfunction scores, and mortality rate. However, other trials on patients afflicted with influenza A/H1N1 failed to detect any improvement in symptoms and even showed a trend towards an increase in mortality rate with glucocorticoid use.[13] In these trials though, patients in the glucocorticoid arm had a more severe illness which could possibly account for the increase in mortality rate observed in these cohorts.[15] For patients with SARS pneumonia, data from Guangzhou showed that 79.6% of patients who were given glucocorticoids had a lower mortality rate and shorter duration of hospitalization. However, it is worth noting that most trials on the use of glucocorticoids in patients with viral pneumonia were on patients with ARDS, rather than on those with septic shock. Therefore, further investigations on the benefit of glucocorticoids in patients with viral pneumonia and septic shock are indeed warranted.[13]

In cases of COVID-19, glucocorticoids were used for specific indications such as septic shock and ARDS. For instance, among the 138 admitted patients in a single center in Wuhan, as many as 44.9% received glucocorticoids. However, the outcomes of these patients were not fully analyzed.[1] In a cohort of 15 critically ill patients in Wuhan, the seven patients given glucocorticoids did not exhibit a survival benefit as they eventually expired. The study suggested that glucocorticoid treatment within the first 3 to 5 days of admission improved oxygen saturation and arterial oxygen tension/inspiratory oxygen fraction (PaO_2)/(FiO_2), thereby aiding in reducing organ dysfunction and shock. However, the small sample size of this cohort and the absence of a matched control group entail that such findings are interpreted with caution.[3] In another cohort of 201 patients at Jinyintan Hospital in Wuhan, it was shown that among patients with ARDS, methylprednisolone, which was given to 30.8% of the patients, reduced the risk of mortality (HR of 0.38, at 95% CI, 0.20-0.72). However, it was not specified how many of these patients suffering from ARDS were also in septic shock.[16] The recommendation for using dexamethasone for oxygen-requiring COVID-19 infection stems from the results of the Randomized

Evaluation of COVID-19 Therapy (RECOVERY) trial, which demonstrated that dexamethasone reduced 28-day mortality in these patients.[5] It can reduce mortality by up to a third.[17] There is an urgent need to investigate the development of CIRCI, its effect on clinical outcomes, and the response of COVID-19-positive patients to treatment with glucocorticoids.

Currently, there is a paucity of data on the incidence of CIRCI among COVID-19-positive patients, especially in the local setting. The extent to which CIRCI serves as a risk factor for poor outcomes among patients with COVID-19 and the effects of treatment with glucocorticoids on the clinical course of these patients are still crucial points of investigation. Extending the investigation of CIRCI to patients with COVID-19 will facilitate a deeper understanding of these two complex diseases. Addressing this knowledge gap will shape decision-making in the intensive care setting because CIRCI is a treatable condition. Glucocorticoid treatment when utilized in the appropriate context is potentially lifesaving. A better grasp of CIRCI in the context of COVID-19 infection is pivotal in improving the quality of intensive care management for COVID-19-positive patients.

This study had the following objectives: to describe the incidence of and characterize probable and definite CIRCI among patients with COVID-19; to determine the clinical outcomes (morbidity, mortality, ventilator days, number of days in shock, vasopressor dependent days, ICU days, length of hospitalization, recovery rate) among critically ill COVID-19-positive patients in shock who were given glucocorticoids and those who were not given glucocorticoids, and to detect the incidence of adverse events in those patients who were given glucocorticoids.

METHODOLOGY

Study design

This was a single-center, retrospective cohort study that investigated the occurrence of CIRCI among critically ill patients infected with COVID-19. A review of records among admitted patients was done.

Study duration

The retrospective chart review included patients admitted at the designated COVID-19 inpatient areas of the Philippine General Hospital from March 31, 2020 (which coincides with the assignment of the tertiary hospital as a COVID referral center) until June 30, 2020, thereby covering a total period of three months.

Inclusion criteria

All patients aged 19 years old and above, with confirmed COVID-19 infection documented on real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay, with an admitting diagnosis of shock or developed refractory hypotension during the admission (i.e., requiring at least 0.5 mcg/kg/min of norepinephrine or its equivalent dose with another vasopressor or with increasing vasopressor requirement) were included in the analysis. Refractory hypotension or shock was defined as systolic blood pressure of persistently <90 mmHg after adequate fluid resuscitation for at least 30 minutes in the presence of hypovolemia; need for vasopressors to maintain adequate organ perfusion; and signs of hypoperfusion such as tachycardia, altered mental status, confusion or encephalopathy, cold extremities, oliguria, and blood lactate >2 mmol/L.[18]

In this study, the case definitions used for CIRCI were the following: A probable case of CIRCI is a patient who exhibits clinical manifestations of CIRCI such as refractory hypotension responding poorly to fluid resuscitation and vasopressors or increasing vasopressor requirements, which may or may not be accompanied by other symptoms and signs of adrenal insufficiency such as weakness, fatigue, loss of appetite, abdominal pain, nausea, vomiting, hypoglycemia, hyperkalemia, hyponatremia, metabolic acidosis, and eosinophilia but without a random cortisol laboratory result to document hypocortisolism during the period of critical illness. A definite case of CIRCI is a patient exhibiting clinical findings of CIRCI as mentioned previously, with random serum cortisol of <10 mcg/dl or delta cortisol of <9 mcg/dl at 60 minutes after ACTH stimulation testing, which establishes an inadequate corticosteroid response for the level of stress. The ACTH stimulation test was done for patients with indeterminate baseline serum cortisol levels between 11-34 mcg/dl.[10] Serum cortisol levels were measured using the cortisol (125I) RIA kit (Ref: RK-240CT). The ACTH stimulation test was performed using Synacthen (tetracosactide acetate), which contains 250 mcg per ampule. Analytical validity standards were met. The conversion factor used to express serum cortisol levels from the unit nmol/L to mcg/dl was 1 mcg/dl = 27.59 nmol/L.[19]

The case definition for a COVID-19 confirmed case is based on the WHO Global Surveillance for Disease Interim Guidance.[20] A COVID-19 confirmed case is a patient with or without symptoms attributed to COVID-19, with documented SARS-CoV-2 infection. The laboratory test used to confirm the presence of COVID-19 infection is the rRT-PCR assay, where in SARS CoV-2 can be detected in nasal or pharyngeal samples, sputum, bronchoalveolar lavage fluid, and other bodily fluids.[4]

Exclusion criteria

The patients who were admitted as COVID-19 suspect cases but subsequently found to be negative on rRT-PCR COVID-19 testing and diagnosed as not afflicted with COVID-19 by the Infectious Disease service were excluded from the final analysis. Patients who were weaned off vasopressors immediately (within 4 hours from onset of shock) upon additional fluid resuscitation or loading of

antibiotics were excluded from the analysis because such patients are unlikely to have developed CIRCI. Other exclusion criteria were the use of systemic glucocorticoids in the form of at least 40 mg of prednisolone or equivalent per day for more than one week before admission for COVID-19, or the use of etomidate, ketoconazole, and other agents known to cause adrenal insufficiency.[21] Patients with a history of adrenal disease or adrenalectomy, pituitary surgery, or pituitary irradiation and pregnant individuals were also excluded from the analysis.

Outcomes

Relevant clinical characteristics such as the median age, proportion of males and females, median blood pressure, the top etiologies of shock, vasopressor dose, number of days on vasopressors, ventilator days, length of ICU stay, length of hospital stay and morbidity and mortality rates of patients with refractory shock and probable CIRCI were described. Laboratory values such as the serum cortisol levels of the subjects were also examined. The rate of corticosteroid utilization and the type and dose of corticosteroid administered were also obtained.

An in-depth analysis of the key clinical outcomes of the patients in refractory shock who were started on corticosteroids and those who were not started on corticosteroids was made. Outcomes included the number of days on vasopressors, ventilator days, vasopressor requirement, length of ICU stay, length of hospital stay, morbidity and mortality rate, and the ICU severity of illness score in the form of the Mortality Probability Model (MPM).

For the patients in the steroid group, a comparison of the clinical outcomes was made between patients given hydrocortisone and those who were given other types of corticosteroids such as dexamethasone, prednisone and methylprednisolone. The same clinical outcomes were examined for the patients who were started on different doses of hydrocortisone: at exactly 200 mg/day which is the recommended dose for patients with CIRCI,[10] at <200 mg/day, and >200 mg/day.

Statistical methods

The analysis of the data obtained from this retrospective chart review was performed using Stata Version 15.1. In determining the baseline characteristics of patients with CIRCI, the median and range were used as summary measures because almost all quantitative variables were not normally distributed. The distribution was tested using the Shapiro-Wilk test of normality. Qualitative variables were reported using count and proportion or rate. In making comparisons between the groups started on corticosteroids and those who were not started on corticosteroids, and between the hydrocortisone group and the non-hydrocortisone group, the Mann-Whitney U test of difference between medians of two groups, and the Z test of two proportions were employed.

The groups utilizing various doses of hydrocortisone were analyzed using the Kruskal-Wallis test of difference between medians of more than two groups and the Chi-square test of homogeneity (proportion) of more than two groups. The level of significance utilized for the statistical tests employed in this study was $\alpha = 5\%$.

Multiple logistic regression analysis was done to determine the predictors of mortality among patients with CIRCI infected with COVID-19. After conducting a literature review, the authors selected the following variables—severity of illness score, etiology of shock, timing of initiation of steroids relative to the number of days in shock, presence of hypoglycemia, and duration of steroid use—as co-variates or predictor variables in the regression analysis based on previous evidence demonstrating that such factors affect clinical outcomes in the setting of COVID-19 infection.[16,18] All these variables were included in the multivariate logistic regression model because these were hypothesized to be risk factors for increased mortality in CIRCI and were of interest to the authors.

Ethical issues

This research focusing on patients with COVID-19 was a sub-study of the mixed methods research project entitled, "The Development and Pilot Testing of a Protocol for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency for Patients Admitted with Shock at the Philippine General Hospital," approved by the University of the Philippines Manila Research Ethics Review Board, with the registration number 2020-297-01.

RESULTS

Study population characteristics

In this cohort, there were 145 patients with COVID-19 included in the final analysis. This corresponds to 22.94% of all the COVID-19-positive admissions at PGH (N= 632) during the study period, presenting with refractory shock, meeting the criteria for probable CIRCI. Twenty-two patients had available serum cortisol results. Thirteen of these patients were in the steroid group, with a median baseline cortisol level of 25.4 mcg/dl, and nine of these patients were in the non-steroid group, with a median baseline cortisol level of 25.08 mcg/dl. Four patients met the criteria for definite CIRCI based on initial serum cortisol results or ACTH stimulation testing. Two patients with indeterminate cortisol results underwent ACTH stimulation testing to ascertain the presence of CIRCI.

The median age of the patients was 63 years old and the majority were males (57.24%). Septic shock was the etiology of shock for 72.22% of the population. The average lactate level of the patients was 2.887 mmol/L, which is consistent with the presence of vasopressor-dependent shock.[22] Subjects were vasopressor dependent mostly on norepinephrine, with some patients requiring dopamine,

epinephrine, or dobutamine in addition to norepinephrine, for a median of 2 days with a range of 0 to 49 days. The median Sequential Organ Failure Assessment (SOFA) score was 13 which suggests that most of the patients included had a high mortality rate with a 40-50% risk of death.[23] Other ICU risk prognostic scores echoed this intensified risk. Majority of the patients suffered from acute respiratory failure, with 85.42% requiring a ventilator, and as much as 81.12% diagnosed with ARDS. There were also high rates of multiple organ dysfunction, with acute kidney injury in 67.59% of the subjects and central nervous system dysfunction in 79.17% of patients. The mortality rate of this cohort of patients was high at 90.34% (Table 1).

In terms of laboratory parameters, the median random cortisol level of the entire study population was 25.26 mcg/dl. This level is still way below the threshold of 34 mcg/dl and above which CIRCI is unlikely.[10] This strengthens the finding of CIRCI in this cohort of patients. For the patients with indeterminate cortisol level results who underwent ACTH stimulation testing, 50% had an increase in serum cortisol from baseline of more than 9 mcg/dl, while 50% did not exhibit an elevation in cortisol levels.

The patients were also screened for the presence of laboratory findings suggestive of adrenal insufficiency. Hyponatremia, i.e., a sodium level below 135 mEq/L, was present in 26.9% of the subjects in this cohort. On the other hand, hyperkalemia exemplified by a potassium value greater than 5.5 mEq/L, was seen in 16.55% of the participants. Hypoglycemia, defined as a capillary blood glucose level of less than 70 mg/dl, was found in 8.97% of the patients. Metabolic acidosis developed in 11.11%, and eosinophilia found in 2.10% of patients (Table 1).

Table 1. Baseline characteristics and outcomes of COVID-19 patients with CIRCI

Age, median (range)	63 (19-95)
Sex, count (percent)	
Males	83 (57.24%)
Females	62 (42.76%)
Top 3 etiologies of shock, count (percent)	
Septic	104 (72.22%)
Multifactorial	23 (15.97%)
Cardiogenic	9 (6.25%)
SOFA score, median (range)	13 (1-20)
APACHE II score, median (range)	29 (7-52)
MPM score, median (range)	82.7 (14.8-98.6)
On ventilator, count (percent)	123 (85.42%)
With ARDS, count (percent)	116 (81.12%)
With acute kidney injury, count (percent)	98 (67.59%)
With oliguria, count (percent)	36 (25.90%)
With CNS dysfunction (Glasgow Coma Scale of <15), count (percent)	114 (79.17%)
With hypoglycemia (CBG <70 mg/dl), count (percent)	13 (8.97%)
With metabolic acidosis, count (percent)	16 (11.11%)
With eosinophilia, count (percent)	3 (2.10%)
Baseline cortisol level (nmol/L), median (range)	696.06 (22-1668)
Dose of vasopressors (mcg/kg/min), median (range)	
On 1 vasopressor	0.5 (0.09-10)
On 2 vasopressors	0.4 (0.2-15)
On 3 vasopressors	10 (0.3-10)
Number of days on vasopressors, median (range)	2 (0-49)
Number of days on ventilator, median (range)	4 (0-76)
Length of ICU stay, median (range)	5 (0-56)
Length of entire hospital stay, median (range)	9 (1-81)
Morbidity, count (rate)	126 (86.90%)
Mortality, count (rate)	131 (90.34%)

Table 2. Use of corticosteroids for COVID-19 Patients with CIRCI

Corticosteroid Use, count (rate)	102 (70.83%)
Hydrocortisone	32 (31.37%)
<200 mg/day	3 (9.38%)
200 mg/day	16 (50.00%)
>200 mg/day	13 (40.62%)
Non-hydrocortisone	70 (68.63%)
Number of days in shock when corticosteroids were Initiated, median (range)	0 (0-12)
Days on corticosteroids, median (range)	4 (1-41)
Blood pressure after corticosteroids were initiated, count (percent)	
Improved	93 (70.45%)
Still hypotensive	39 (29.55%)
Dose of vasopressors (mcg/kg/min) after corticosteroids were initiated, median (range)	0.35 (0-7.8)

Use of corticosteroids for COVID-19 patients with CIRCI

For COVID-19 patients with refractory shock, there was a high rate of utilization of steroids at 70.83%. Half the population was given hydrocortisone at 200 mg/day, which is the recommended therapeutic regimen for CIRCI. As many as 68.63% were given steroids other than hydrocortisone, mostly as dexamethasone (71.57% of the non-steroid group). One patient received methylprednisolone. Corticosteroids were initiated after a median of less than one day in shock, with a range of 0 to 31 days. The duration of corticosteroid administration lasted for a median of 4 days. After corticosteroids were initiated, blood pressure improved in 70.45% of the patients (Table 2).

Use of corticosteroids and patient outcomes

Patients who were given corticosteroids were found to have statistically significant longer median days on a ventilator (p=0.001). However, those on the corticosteroid arm were at higher risk of morbidity and mortality as signified by statistically significant higher APACHE II scores (p=0.0233), MPM scores (p=0.006), and a greater proportion of patients with acute kidney injury (p=0.028), oliguria,(p=0.020) and CNS dysfunction (p=0.019). There were no significant differences between the length of hospital stay, morbidity, and mortality rates between the steroid and non-steroid groups. (Table 3).

Two out of the three patients with a baseline serum cortisol level of less than 10 mcg/dl died. Ten out of the fourteen patients with indeterminate serum cortisol levels, i.e., between 11-34 mcg/dl expired during the study. For the two patients who underwent ACTH stimulation testing, the non-responder died, and the responder who exhibited a greater than 9 mcg/dl increase in serum cortisol after ACTH administration, survived and was discharged.

There were no significant differences in morbidity (78.12% in the hydrocortisone group vs. 91.43% in the non-hydrocortisone group, p=0.062) and mortality (87.50% in the hydrocortisone group vs. 92.86% in the non-hydrocortisone group, p=0.376) rates among patients given hydrocortisone and those who received other types of steroids, albeit patients in the hydrocortisone arm had a slightly longer median length of hospital stay (13 days vs. 7.5 days, p=0.0231). This could likely be attributed to the greater severity of shock present in those on the hydrocortisone group (Table 5). Likewise, no significant differences in morbidity (p=0.279) and mortality (p=0.125) rates were detected among groups on varying doses of hydrocortisone (Appendix).

In terms of adverse events associated with corticosteroid use, steroid-induced hyperglycemia ensued in only 7 patients (6.8%) in the corticosteroid arm. One patient had documented hypernatremia, or a sodium level of more than 145 mEq/L after corticosteroid was initiated. There were no cases of steroid-induced myopathy, secondary infection, or bleeding detected in this cohort of patients. Overall, there was a low incidence of adverse events associated with corticosteroid use.

Predictors of mortality among COVID-19 patients with CIRCI

On univariable analysis, higher ICU risk prognostic scores, in terms of the SOFA (OR=1.31, CI 1.06 to 1.62, p=0.013 for the multivariable analysis and OR=1.37, CI 1.15 to 1.63, p=<0.001 for the univariable analysis) and MPM score (OR=1.03, CI 1.01 to 1.06, p=0.002) predict mortality among COVID-19 patients with CIRCI (Table 4). For every 1% increase in the SOFA score, the odds of mortality increase by 31%. The number of days in shock was also a significant predictor of mortality in this cohort of patients. For each day in shock since the steroid was initiated, the odds of mortality decreased by 18% as demonstrated in the unadjusted model. Logistic regression analysis also demonstrated that the duration of steroid use had an associated effect on mortality among patients with CIRCI and COVID-19.

Table 3. Comparison of clinical characteristics and outcomes of patients started on corticosteroids and patients not given corticosteroids

	With use of steroids	Without use of steroids	*p*
SOFA score, median (range)	13 (3-20)	12 (1-18)	0.1668
APACHE II score, median (range)	30 (11-52)	26 (7-41)	0.0233
MPM score, median (range)	89.45 (14.8-98.6)	66.25 (21.5-97.5)	0.0006
On ventilator, count (percent)	90 (88.24%)	33 (80.49%)	0.227
With ARDS, count (percent)	80 (80.00%)	35 (83.33%)	0.644
With acute kidney injury, count (percent)	75 (73.53%)	23 (54.76%)	0.028
With oliguria, count (percent)	31 (31.63%)	5 (12.50%)	0.020
With CNS dysfunction (Glasgow coma scale <5), count (percent)	85 (84.16%)	28 (66.67%)	0.019
With hypoglycemia (CBG <70 mg/dl), count (percent)	8 (7.84%)	5 (11.90%)	0.524
Baseline cortisol Level (nmol/L), median (range)	702.1 (22-1668)	691.92 (347.27-1427.2)	0.8673
Number of days on vasopressors, median (range)	3 (0-37)	2 (0-49)	0.4214
Number of days on ventilator, median (range)	5 (0-76)	2 (1-50)	0.0001
Highest vasopressor requirement, median (range)			
Vasopressor 1	0.5 (0.2-10)	0.415 (0.09-10)	0.5454
Vasopressor 2	0.4 (0.2-15)	1 (0.3-10)	0.4485
Vasopressor 3	10 (0.3-10)	-	-
Length of ICU stay, median (range)	6 (0-56)	3 (0-41)	0.0547
Length of entire hospital stay, median (range)	9 (1-76)	9.5 (2-81)	0.7050
Morbidity, count (rate)	89 (87.25%)	37 (88.10%)	0.890
Mortality, count (rate)	93 (91.18%)	37 (88.10%)	0.571

Table 4. Multiple logistic regression analysis of predictors of mortality among COVID-19 positive patients with CIRCI

Factors	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Steroid use	1.40	[0.44, 4.44]	0.572	0.39	[0.08, 1.99]	0.258
MPM score	1.03	[1.01, 1.06]	0.002	1.02	[0.99, 1.06]	0.111
SOFA score	1.37	[1.15, 1.63]	<0.001	1.31	[1.06, 1.62]	0.013
APACHE II score	1.13	[1.05, 1.22]	0.001	1.03	[0.94, 1.14]	0.476
Etiology of shock						
Septic	Reference			Reference		
Cardiogenic	0.25	[0.04, 1.45]	0.123	2.16	[0.16, 29.35]	0.563
Hypovolemic	0.07	[0.01, 0.43]	0.004	0.05	[0.004, 0.51]	0.012
Multifactorial	0.76	[0.15, 3.91]	0.740	2.05	[0.27, 15.24]	0.484
Days in shock when steroids were started	0.82	[0.68, 0.99]	0.041	-		
Days on steroids	0.94	[0.85, 1.05]	0.274	-		
Hypoglycemia	0.55	[0.11, 2.78]	0.469	0.65	[0.003, 1.90]	0.118

Table 5. Comparison of patient characteristics and outcomes between patients given hydrocortisone and patients given other forms of steroids

	Hydrocortisone	Non-Hydrocortisone	*p*
SOFA score, median (range)	12 (3-18)	14 (5-20)	0.0847
APACHE II score, median (range)	31.5 (11-47)	30 (14-52)	0.8551
MPM score, median (range)	90 (14.8-98.6)	89.2 (21.6-98.5)	0.9196
On ventilator, count (percent)	25 (78.12%)	65 (92.86%)	0.032
With ARDS, count (percent)	21 (65.62%)	59 (86.76%)	0.014
With acute kidney injury, count (percent)	24 (75.00%)	51 (72.86%)	0.820
With oliguria, count (percent)	8 (25.81%)	23 (34.33%)	0.399
With CNS dysfunction (Glasgow coma scale <15), count (percent)	26 (81.25%)	59 (85.51%)	0.586
With hypoglycemia (with CBG <70 mg/dl), count (percent)	4 (12.50%)	4 (5.71%)	0.237
Baseline cortisol level (nmol/L), median (range)	655.05 (34-1668)	957.13 (22-1349.4)	0.7697
Number of days on vasopressors, median (range)	3 (0-37)	4 (0-32)	0.4817
Number of days on ventilator, median (range)	4.5 (0-76)	6 (1-26)	0.9683
Highest vasopressor requirement, median (range)			
Vasopressor 1	0.5 (0.2-10)	0.445 (0.2-2)	0.1456
Vasopressor 2	0.575 (0.3-10)	0.4 (0.2-15)	0.3902
Vasopressor 3	5.15 (0.3-10)	10 (10-10)	0.1573
Length of ICU stay, median (range)	6 (0-56)	5 (0-36)	0.5669
Length of entire hospital stay, median (range)	13 (1-76)	7.5 (1-51)	0.0231
Morbidity, count (rate)	25 (78.12%)	64 (91.43%)	0.062
Mortality, count (rate)	28 (87.50%)	65 (92.86%)	0.376

DISCUSSION

COVID-19 is a systemic disease with a complex form of management. Most patients with severe and critical COVID-19 infection present with multiple organ dysfunction. Shock is also prevalent among patients with COVID-19, with a significant proportion dependent on vasopressors, reaching 22 to 67% according to several studies.[24] In this cohort of patients at the PGH, a notable proportion of 22.94% of COVID-19 admissions qualify as probable CIRCI, thus representing a serious disease burden.

This population cohort consisted of individuals with a high risk for morbidity and mortality because of the presence of critical COVID-19. Several reliable ICU prognostic scores, namely MPM and APACHE II scores, validated that this cohort had a high risk for adverse outcomes. Such an inherent characteristic of this population accounts for the mostly poor outcomes seen in this population. COVID-19-positive patients with refractory shock who were started on steroids were found to have statistically significant longer days on a ventilator. This is likely because most of the patients on the steroid arm also had ARDS, thus entailing a longer period of ventilatory support. There were also statistically significant higher rates of baseline acute kidney injury, oliguria, and CNS dysfunction among patients in the steroid group. The presence of multiple organ dysfunction is a significant barrier to weaning off the ventilator, thus accounting for the longer time of dependence on the ventilator for patients in this arm.

Overall, patients in both groups did not exhibit statistically significant differences in morbidity and mortality rates, though the logistic regression analysis suggested an association between a longer duration of steroid treatment and a decrease in mortality for COVID-19 patients with refractory shock. The power achieved on the analysis of steroid use as a predictor variable (OR = 0.39) in a multivariable regression with other co-variates (Pseudo-R2 = 0.3140) and two-tailed alpha=5% level of significance is 77%. Given that power should ideally be at 80%, the study may have not established sufficient evidence that steroid use is a significant predictor of mortality because it falls short of a few more samples. The relatively small sample size of this cohort could have affected the detection of a stark contrast in terms of morbidity and mortality between the two groups.

In this study which was done during the early days of the pandemic, the patients received the type of treatment appropriate for the presentation of their COVID-19 infection. Some of the patients had refractory shock but no hypoxemia and predominantly exhibited weakness, fatigue, or gastrointestinal symptoms instead. Yet, a substantial number of the patients with refractory shock also presented with acute respiratory failure (85.42%); thus, dexamethasone was widely utilized because it is the recommended treatment for oxygen-requiring severe and critical COVID-19 infection.[25] One patient was given methylprednisolone for acute respiratory distress syndrome. However, compared to hydrocortisone, dexamethasone and methylprednisolone do not have significant mineralocorticoid activity, and this phenomenon could explain why some patients remained in shock even after corticosteroids were initiated, thus accounting for the lack of statistically significant reduction in mortality seen in this cohort. Moreover, in contrast to the patients in the RECOVERY trial who were treated with corticosteroids for a median of 7 days, the patients in this study were given corticosteroids for a median of 4 days. The relatively shorter duration of treatment brought about by the high rates of early demise from critical COVID-19 infection may have also contributed to the lack of reduction in mortality seen in this cohort.

The results of this study done in the Philippines are also consistent with the trends found in other countries like China. The study of Yiming et al. also had a population similar to the Philippine cohort with most of the subjects receiving non-hydrocortisone steroid therapy and with high rates of organ dysfunction among the non-survivors.[26]

The presentation of CIRCI among patients with COVID-19 is unique. Individuals present with refractory shock, but the cortisol levels may be higher than those patients without COVID-19 infection because of the intense level of inflammation present in COVID-19 infection.[27] In this cohort of COVID-19-positive patients, the median cortisol level was at 25.26 mcg/dl compared to 24.15 mcg/dl for the non-COVID subgroup in the same institution.[28] However, a notable factor that ought to be considered is that not all patients in this cohort had random serum cortisol results because, in most of the patients, CIRCI was diagnosed based on the presence of refractory shock and subsequent therapeutic response to corticosteroids. The small sample size of patients with cortisol results could have served as a barrier in detecting significantly low cortisol levels in this cohort. Still, cortisol levels relatively higher than those seen in patients without COVID-19 infection were also observed in other studies.

In a case report of a 69-year-old male admitted for critical COVID-19, the median total cortisol level was 12 mcg/dl,[29] which was higher than the usual cortisol level of less than 10 mcg/dl for those with definite CIRCI.[10] High cortisol levels can be associated with increased mortality as well, in the setting of a dysregulated inflammatory response amidst the cytokine storm.[27,30] The ongoing massive systemic inflammation activates the stress response, accounting for the increase in cortisol levels that is somehow still seen. Therefore, the diagnosis of CIRCI is not dependent on cortisol levels alone. Across studies, the levels of cortisol among COVID-19-positive patients with CIRCI are varied. Interindividual variability when it comes to fluctuations in cortisol levels in response to stress may also account for this phenomenon.[27] CIRCI is more reliably determined by the inability of the cortisol level to address the extensive inflammation and metabolic demand.[31] Even if elevations of cortisol levels are seen, the action of cortisol is still insufficient to maintain hemodynamic stability during critical illness which can be due to the presence of tissue resistance to glucocorticoids.[24] Amidst the limitations of utilizing cortisol levels in diagnosing CIRCI, the determination of random serum cortisol levels is still valuable in guiding the course of therapy and future management strategies.

The pathophysiologic mechanisms surrounding the complex phenomenon of CIRCI in COVID-19 infection are multi-faceted. During critical illness in the context of COVID-19 infection, despite the increase in cortisol levels seen in some cases, this response is still not enough to meet the high demand for cortisol. Extremely high levels of inflammatory makers such as interleukins 1 and 6, and tumor necrosis factor α (TNF-α) disrupt the hypothalamic-pituitary-adrenal (HPA) axis. The release of ACTH stimulated by corticotrophin-releasing hormone (CRH) is blunted by TNF-α, thereby inhibiting the action of ACTH and angiotensin 2 on adrenal cells.[32-34] Therefore, the cytokine storm itself inhibits the hypothalamic-pituitary-adrenal axis. Another plausible mechanism is the production of amino acid sequences mimicking ACTH by SARS viruses, thereby resulting in the generation of antibodies that ultimately lead to central adrenal insufficiency.[35]

Indeed, the presence of CIRCI among COVID-19-positive patients is associated with significant morbidity and mortality. Thus, consensus-building on the optimal management strategies for COVID-19 patients with refractory shock is paramount, especially in light of the variability seen in diagnosing and treating CIRCI currently. Ideally, the use of hydrocortisone for COVID-19 infected patients with refractory shock should be incorporated into management protocols of institutions, as it is the corticosteroid with significant mineralocorticoid action that could address the hypotension. Currently, there is strong evidence suggesting that the use of hydrocortisone would produce the same extent of benefit as dexamethasone and methylprednisolone in reducing inflammation amidst respiratory damage, as well as mortality because of a class effect.[36,37] Hydrocortisone has also been shown to protect the endothelium against damage in the presence of severe inflammation.[35] The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial demonstrated that hydrocortisone at a dose of 200 mg per day, comes with an 80% probability of benefit.[38] Likewise, Liu et al., found that hydrocortisone can reduce mortality at 28 days even for patients suffering from ARDS, thus reinforcing the postulation of a class effect.[39]

The use of hydrocortisone for COVID-19-positive patients experiencing shock is consistent with the recommendations of several expert bodies, such as the Surviving Sepsis Guidelines for COVID-19,[40] the China National Commission[39] and the Philippine Living Clinical Practice Guidelines for COVID-19.[25] Even amidst the COVID-19 infection, corticosteroid administration has been deemed safe because it does not significantly affect the rates of secondary infection[41] nor the rates of clearance of the SARS-CoV-2 virus.[26]

This study performed at a tertiary referral center for COVID-19-positive patients was able to characterize CIRCI in the setting of COVID-19 infection. However, a significant limitation of this study is the small number of patients who had cortisol level determinations and subsequent ACTH stimulation testing due to constraints in resources in the local setting. Also, the impact of steroid use on mortality was not fully demonstrated because of the relatively small sample size. The study was also conducted at a time when the protocol on CIRCI was newly launched and was still undergoing pilot testing at the tertiary hospital, accounting for the gap in the consistent performance of cortisol testing

for patients suspected to have CIRCI. Thus, the findings from this research underscore the need to incorporate the diagnosis and management of CIRCI in critically ill COVID-19-positive patients in institutional protocols to guide clinical practice, especially since early detection and treatment of the condition can be lifesaving.

CONCLUSION

Among COVID-19-positive patients, CIRCI has a likely substantial disease burden. CIRCI has a unique presentation among COVID-19 patients because of the presence of a high level of inflammation in this life-threatening infection. It is possibly a harbinger of increased risk of poor clinical outcomes and mortality.

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Statement of Authorship
All authors certified fulfillment of the ICJME authorship criteria.

CRediT Author Statement
AEA: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **KWL:** Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization; **MA:** Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization; **CJ:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision.

Author Disclosure
Dr. Anna Arcellana is a junior manuscript editor at JAFES. Dr. Cecilia Jimeno is the Vice Editor-in-Chief of JAFES. The other authors did not declare any conflicts of interest.

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APPENDIX

Appendix. Comparison of patient characteristics and outcomes of patients given different doses of hydrocortisone

	Hydrocortisone <200 mg/day	Hydrocortisone 200 mg/day	Hydrocortisone >200 mg/day	*p*
SOFA score, median (range)	16 (9-18)	11 (8-18)	12 (3-18)	0.5851
APACHE II score, median (range)	29 (19-47)	29.5 (15-40)	35 (11-47)	0.5102
MPM ccore, median (range)	52.2 (37.2-97.2)	92.5 (14.8-98.6)	78 (17.3-98.1)	0.6954
On ventilator, count (percent)	2 (66.67%)	11 (68.75%)	12 (92.31%)	0.279
With ARDS, count (percent)	2 (66.67%)	8 (50.00%)	11 (84.62%)	0.153
With acute kidney injury, count (percent)	3 (100%)	11 (68.75%)	10 (76.92%)	0.728
With Oliguria, count (percent)	-	3 (18.75%)	5 (38.46%)	0.443
With CNS dysfunction (Glasgow coma scale <15), count (percent)	2 (66.67%)	13 (81.25%)	11 (84.62%)	0.667
With hypoglycemia (CBG <70 mg/dl), count (percent)	-	3 (18.75%)	1 (7.69%)	0.740
Baseline cortisol level (nmol/L), median (range)	784.22 (784.22-784.22)	655.05 (311.5-1668)	34 (34-34)	0.2826
Number of days on vasopressors, median (range)	2 (1-19)	5.5 (0-26)	1 (0-32)	0.1316
Number of days on ventilator, median (range)	14 (4-24)	14 (2-76)	3 (0-42)	0.0603
Highest vasopressor requirement, median (range)				
Vasopressor 1	0.4 (0.3-2)	0.52 (0.2-10)	0.5 (0.2-3)	0.9711
Vasopressor 2	10 (10-10)	0.35 (0.3-2.2)	0.75 (0.3-10)	0.1649
Vasopressor 3	0.3 (0.3-0.3)	-	10 (10-10)	0.3173
Length of ICU stay, median (range)	14.5 (4-25)	6 (0-56)	2 (1-41)	0.3432
Length of entire hospital stay, median (range)	30 (3-53)	21 (5-76)	6 (1-43)	0.0112
Morbidity, count (rate)	2 (66.67%)	11 (68.75%)	12 (92.31%)	0.279
Mortality, count (rate)	2 (66.67%)	13 (81.25%)	13 (100%)	0.125