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Cortisol levels and adrenal response in severe community-acquired pneumonia: A systematic review of the literature☆,☆☆,★,★★

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Abstract

Objectives: Our aim was to review the literature on the prevalence and impact of critical-illness related corticosteroid insufficiency (CIRCI) on the outcomes of patients with severe community-acquired pneumonia (CAP).

Methods: We reviewed Cochrane, Medline, and CINAHL databases (through July 2008) to identify studies evaluating the adrenal function in severe CAP. Main data collected were prevalence of CIRCI and its mortality.

Results: We screened 152 articles and identified 7 valid studies. Evaluation of adrenal function varied, and most studies used baseline total cortisol levels. The prevalence of CIRCI in severe CAP ranged from 0% to 48%. Among 533 patients, 56 (10.7%) had cortisol levels of 10 μg/dL or less and 121 patients (21.2%) had cortisol levels of 15 μg/dL or less. In a raw analysis, there was no significant difference in mortality when patients with cortisol levels less than 10 μg/dL (8.6 vs 15.5%; $P = .55$) or less than 15 μg/dL (12.4 vs 16%; $P = .38$) were compared with those with cortisol above these levels. In the meta-analysis, relative risk for mortality were 0.81 (confidence interval, 0.39-1.7; $P = .59$; $\chi^2 = 1.04$)

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for cortisol levels less than 10 μg/dL and relative risk was 0.67 (confidence interval, 0.4-1.14; $P = .84$; $\chi^2 = 1.4$) for cortisol levels less than 15 μg/dL.
Conclusions: A significant proportion of patients with severe CAP fulfilled criteria for CIRCI. However, CIRCI does not seem to affect the outcomes. Noteworthy, the presence of elevated cortisol levels is associated with increased mortality and may be useful as a prognostic marker in patients with severe CAP.

1. Introduction

Community-acquired pneumonia (CAP) is associated with significant morbidity and mortality and is the most common cause of death from infectious diseases in critically ill patients [1]. Patients with severe CAP often require intensive care unit (ICU) admission, and despite major advances in supportive care, an exceedingly high mortality rate is observed [2]. A recent study evaluating factors associated with early death in patients with CAP reinforces the classical concept that some deaths are not only dependent on antibiotic efficacy but also on other factors, especially inadequate host response [3]. The hypothalamic-pituitary-adrenal axis plays a major role in the regulation of the host's response to infection [4], and a strong association between elevated cortisol levels and severity of illness and the risk of death have been demonstrated [5-7]. Moreover, the presence of an inadequate adrenal response or adrenal dysfunction or, as more recently defined, critical illness-related corticosteroid insufficiency (CIRCI) may also be helpful in identifying patients with severe infections at high risk of death [5,8-10].

Complex changes in the endocrine system have been described in critical illness [11]. Severe infections and the immune host response to microorganisms are frequently implicated in the pathogenesis of adrenal response present in critically ill patients. Clinical and experimental data have demonstrated that pro and antiinflammatory mediators lead to decreased production and delivery of cortisol, overcome local tissue regulation of cortisone/cortisol ratio, and induce down-regulation of glucocorticoids receptors [12]. Thus, it can be easily noticed that the adrenal response is a complex phenomenon in critical illness and its diagnosis can be misleading. Moreover, its epidemiology and impact on the outcomes of patients with severe CAP remains to be established.

In the present article, we reviewed the medical literature, identified, and analyzed studies that evaluated the adrenal function in patients with severe CAP. We describe the frequency of CIRCI and whether it plays a significant role on the outcomes of patients with severe CAP.

2. Methods

2.1. Search strategy, study selection, data collection, and analysis

We performed a systematic search of Medline, Cochrane database, and CINAHL (from 1966 to July 2008) to identify full-text English language publications that evaluated the adrenal function in adult hospitalized with severe CAP. Inclusion criteria were established a priori. Major MESH search terms included community-acquired infections, pneumonia, adrenal insufficiency, adrenal failure, cortisol, corticosteroids, and glucocorticoids. Additional published reports were identified through a manual search of citations from retrieved articles. Only original peer-reviewed studies evaluating the adrenal function in adult patients with CAP were selected and analyzed. The abstracts of all articles were used to confirm our target population, and the corresponding full-text articles were reviewed for the presence of data evaluating the adrenal function of adult nonimmunocompromised patients with CAP. Two investigators (JIFS and CRS) independently identified the eligible literature. Predefined variables were collected, including year of publication; study design (prospective/retrospective, cohort/clinical trial); number of patients included; and hospital mortality and length of stay, oxygenation, frequency of septic shock, mechanical ventilation, and pneumonia severity stratification. Additional unpublished data were obtained by electronic mail from most authors. Any inconsistencies between the 2 investigators (JIFS and CRS) in interpretation of data were resolved by consensus. Standard descriptive statistics were applied to describe and compare the populations.

For evaluated homogeneity of studies, using Q Cochran test and I^2, the measure of effect was relative risk calculated using Mantel-Haenszel approach. All meta-analytic procedures were performed using R software version 2.10.1 and the package r meta version 2.16. Statistical analyses were carried out with the open source statistical language and environment R 2.9.0 [R Foundation for Statistical Computing, www.r-project.org].)

3. Results

The initial literature search yielded 152 articles, and 145 studies were excluded based on their titles and abstracts. The reasons for exclusion are shown in Fig. 1. Eventually, we found and analyzed 7 studies that evaluated the adrenal function of patients with CAP.

3.1. Description of studies and patient's characteristics

Different design and patient selection were observed in most studies. Overall, 533 patients were enrolled in 7

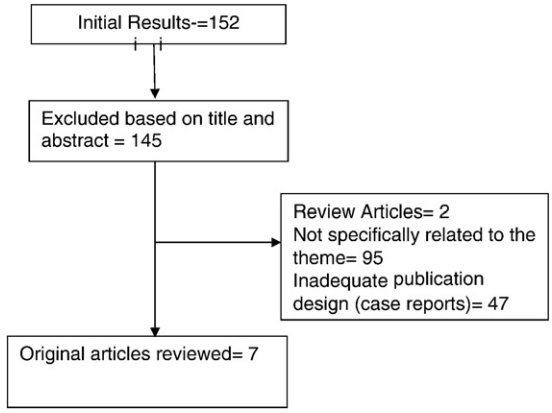

Fig. 1 Flow diagram of studies selected and reasons for exclusion.

studies that evaluated the adrenal function in patients with CAP (Table 1).

Overall, the studies evaluated a heterogeneous population of patients with CAP, ranging from mild CAP to those presenting with septic shock and respiratory failure (Table 1). Only 4 studies evaluated exclusively patients with severe CAP requiring ICU admission [8,13,17,20]. Feldman et al [13] included only critically ill patients with CAP, median Simplified Acute Physiology Score was 11.5 and ICU mortality was 33%. In the retrospective study performed by Salluh et al [20], 65% of the patients (n = 26) met the criteria for severe pneumonia according to the British Thoracic Society guidelines. These patients were severely ill as indicated by high Acute Physiology And Chronic Health Evaluation (APACHE) II scores (median, 16; 12-19; interquartile range, 25%-75%). In addition, a significant proportion of patients (70%; n = 28) received mechanical ventilation and were admitted in septic shock (47.5%; n = 19). The ICU and hospital mortality rates were 22.5% and 32.5%, respectively. Brivet et al [17] evaluated 38 patients, and 71% (n = 27) were diagnosed as severe CAP according to the American Thoracic Society criteria. Hospital mortality was 31.5%, and 27 patients (71%) needed mechanical ventilation. In the prospective study of Salluh et al [8], 72 CAP patients admitted to the ICU were evaluated. Patients were stratified with the CURB-65 [Confusion, Urea, Respiration, Blood pressure and Age 65 or more], median APACHE II score was 14 (11-17; interquartile range, 25%-75%), 27.8% of the patients received invasive mechanical ventilation, and 32% patients presented with septic shock. The ICU and in-hospital mortality were 13.8% and 16.7%, respectively. Among the studies that evaluated critically ill patients with CAP, median APACHE II ranged from 11 to 14, there was a high prevalence of mechanical ventilation (27.8%-71% of patients) and also a high prevalence of septic shock (32%-47.5% of patients). The ICU mortality varied from 13.8% to 22%, and hospital mortality ranged from 16.7% to 32.5%.

Christ-Crain et al [16] included 278 consecutive patients with suspected CAP admitted to the hospital, and 60% of patients (n = 167) were classified as severe CAP (pneumonia severity index [PSI] IV and V). Patients with PSI class IV and V had in-hospital mortality rates of 16% and 21%, respectively. Only 4 patients were hypotensive at presentation, and there is no available information about the use of mechanical ventilation or vasopressors or the need for ICU admission. Mikami et al [15] evaluated all patients admitted to the hospital with CAP but excluded those with septic shock and who needed mechanical ventilation or ICU admission. Seventeen patients (54.8%) were diagnosed as severe CAP (PSI classes IV and V), and only one patient died (3.2%). In the study conducted by Gotoh et al [18], all CAP patients admitted to the hospital were evaluated. Most patients (69%;

Table 1 Clinical studies evaluating the adrenal function in patients admitted with severe CAP

Reference	No. of patients	Patient category	Study design	End points
Feldman et al [13]	18	Severe CAP	Prospective single center cohort	Frequency of endocrine changes
Fine et al [14]	40	Severe CAP	Retrospective single center cohort	Evaluate cortisol levels
Mikami et al [15]	23	Moderate to severe CAP	Prospective single center cohort within an open-label prospective randomized controlled trial	Hospital length of stay, antimicrobial therapy duration, and time to stabilize vital signs
Christ-Crain et al [16]	278	CAP at emergency department presentation	Prospective cohort study	Correlation of adrenal function with survival
Brivet et al [17]	38	Severe CAP	Retrospective single center cohort	Correlation of cortisol levels with survival
Gotoh et al [18]	64	Moderate to severe CAP	Prospective single center cohort	Correlation of ACTH, cortisol and cortisol after cosyntropin-stimulation test with survival, and length of hospital stay
Salluh et al [8]	72	Severe CAP	Prospective single center cohort	Correlation of baseline cortisol levels and cortisol after cosyntropin stimulation with survival

n = 44) had severe CAP (PSI classes IV and V). There is no available information on septic shock, mechanical ventilation, or ICU admission, and 7 patients (10.9%) died during hospitalization. Among the studies that evaluated a non-ICU population of patients admitted with CAP, hospital mortality ranged from 3.2% to 21% of patients and was significantly lower than the critically ill population, as expected.

3.2. Diagnosis and prevalence of CIRCI

Diagnostic criteria of CIRCI have only recently been defined as a random total cortisol of 10 mg/dL or less or a δ serum cortisol of 9 μg/dL or less after adrenocorticotropic hormone (ACTH) administration of 250 μg [21]. As a result, several different criteria to address the adrenal function were used in each the selected studies. Among all, only total random cortisol levels were available for all patients. From 533 patients, 121 patients (21.2%) had baseline cortisol levels of 15 μg/dL or less and 56 (10.7%) had cortisol levels of 10 μg/dL or less. Christ-Crain et al [16] evaluated total and free cortisol levels in patients with CAP. In the whole study cohort, 54 patients (19.4%) had random total cortisol levels of 15 μg/dL or less and 30 patients (10.8%) had total cortisol levels of 10 μg/dL or less. Assessing only patients with PSI class IV and V (n = 147), 22 patients (14.9%) had total cortisol levels of 15 μg/dL or less, and 9 patients (6%) had total cortisol levels of 10 μg/dL or less [16]. Corticotropin stimulation test was not performed. Feldman et al [13] in an earlier study could not observe any case of CIRCI in patients with lobar pneumonia requiring ICU admission. Only baseline cortisol and ACTH levels were evaluated. The ACTH levels were nonsignificantly lower in nonsurvivors than in survivors, but values were not reported. Salluh et al [19] evaluated 40 patients with severe CAP. Random plasma cortisol levels were obtained, 5 patients (12.5%) had levels of 10 μg/dL or less and 19 patients (48%) had levels of 15 μg/dL or less. The ACTH levels or a corticotropin stimulation test were not obtained. Mikami et al [15] evaluated the adrenal function of 23 patients with CAP. One patient (4.3%) had baseline cortisol of 10 μg/dL or less, and 7 patients (40.3%) had levels of 15 μg/dL or less. A corticotropin (250 μg) stimulation test was performed, and the diagnostic criteria were fulfilled by 10 patients (43%). Critical illness-related corticosteroid insufficiency was not a predictive factor for either hospital length of stay or duration of intravenous antibiotic administration. No data on disease severity of this subgroup is available; only, there was no difference in disease severity or other clinical background between patients with or without CIRCI [15]. Gotoh et al [18] evaluated 64 patients hospitalized due to severe CAP and found that 2 patients (3%) had cortisol levels of 10 μg/dL or less and 12 patients (19%) had cortisol levels of 15 μg/dL or less. When corticotropin test was used as a diagnostic criterion of CIRCI, 13 patients (20%) fulfilled the diagnostic criterion [18]. Brivet et al [17] evaluated 38 severe CAP patients, 1 patient (2.7%) had cortisol levels of 10 μg/dL or less and 9 patients (25%) had cortisol levels of 15 μg/dL or less. A corticotropin test was not performed. Finally, Salluh et al [8] enrolled 72 patients with CAP admitted to the ICU. Seventeen (23.6%) had baseline cortisol levels of 10 μg/dL or less, and 20 patients (27.7%) had cortisol levels of 15 μg/dL or less. Corticotropin stimulation test was performed in all patients, and 13 (18%) were diagnosed as having CIRCI based on this criterion. Overall, the prevalence of CIRCI varied from 2.7% to 48% of patients, ranging from 2.7% to 23.6% when cortisol level of less than 10 μg/dL was used as CIRCI criteria and from 14.9% to 48% when cutoff was cortisol level of less than 15 μg/dL. Only 3 studies performed corticotropin stimulation test, and the prevalence of CIRCI according to these criteria were 18% and 43% [8,15,18] (Table 2).

3.3. Adrenal response and mortality

A total of 81 patients (15.2%) died during hospital stay. In a crude analysis, there was no significant difference in mortality between patients with CIRCI when compared to the non-CIRCI group (7/56 [8.6%] vs 74/477 [15.5%]; P =

Table 2 Prevalence of CIRCI and mortality in the clinical studies according to different CIRCI criteria

	No. of patients	Cortisol < 10 μg/dL	Cortisol ≥ 10 μg/dL	Cortisol < 15 μg/dL	Cortisol ≥ 15 μg/dL
Feldman	18	0	18 (33.3%)	0	18 (33.3%)
Salluh, 2006	40	5 (40%)	35 (22.8%)	19 (26.3%)	21 (38%)
Christ-Crain	278	30 (6.6%)	248 (11.7%)	54 (19.4%)	224 (12.5%)
Mikami	23	1 (0%)	22 (4.5%)	7 (0%)	16 (6.25%)
Brivet	38	1 (0%)	37 (32.4%)	9 (33.3%)	29 (31%)
Gotoh	64	2 (0%)	62 (11.3%)	12 (.8%)	52 (11.5%)
Salluh, 2008	72	17 (17.6%)	55 (16.4%)	20 (15%)	52 (17.3%)
Pooled studies	533	56 * (12.5%)	75 (15.7%)	121 ** (12.3%)	412 (18.3%)

In the study by Feldman et al [13], no patients presented low cortisol levels. Numbers in parenthesis represent mortality in the groups of patients with cortisol level of less than 10 and 10 μg/dL or greater and less than 15 and 15 μg/dL or greater.

* P = .55 (comparing mortality between cortisol < 10 μg/dL and ≥ 10 μg/dL).

** P = .38 (comparing mortality between cortisol < 15 μg/dL and ≥ 15μg/dL).

.55). When a baseline cortisol cutoff level of 15 μg/dL to define CIRCI was applied, again there was no difference in mortality (15/121 [12.4%] vs 66/412 [16.0%]; P = .38) (Table 3). When ICU vs non-ICU patients were compared, no significant difference in mortality was found in CIRCI patients when a cortisol cutoff level of less than 10 μg/dL was applied (5/23 [21.8%] vs 2/33 [6%]; P = .11). However, when a cortisol cutoff level of less than 15 μg/dL was used to define CIRCI, there was a significant difference in mortality between ICU vs non-ICU patients with adrenal dysfunction (11/48 [22.9%] vs 4/69 [5.8%]; P = .009) (Table 4). Only 3 studies have used corticotropin test to define CIRCI [8,15,18]. According to this criteria, when CIRCI vs non-CIRCI patients were compared, there was no significant difference in mortality (5/30 [16.6%] vs 15/121 [12.3%]; P = .55).

In the meta-analysis, when a cuttoff of basal cortisol level of less than 10 μg/dL was applied, we computed data for only 3 studies [8,16,20], due to the small number of CIRCI patients in the other studies. Relative risk for mortality was 0.81 (IC, 0.39-1.7; P = .59; χ^2 = 1.04) (Fig. 2). When cortisol of less than 15 μg/dL was used as criteria, 5 studies were included [8,16-18,20]. Relative risk was 0.67 (IC, 0.4-1.14; P = .84; χ^2 = 1.4) (Fig. 3).

4. Discussion

The current systematic review and meta-analysis comprehensively evaluates the role of cortisol levels and the diagnosis of CIRCI on mortality in patients with CAP. Analyzing the 7 selected studies, we could conclude that a diagnosis of CIRCI has no significant effect on mortality even when different cutoffs (baseline cortisol levels < 10 μg/dL or < 15 μg/dL) are considered. Our meta-analysis also has demonstrated no significant difference between CIRCI vs non-CIRCI patients. However, it suggests a possible association between high cortisol levels and mortality, which could make cortisol a useful biomarker for assessing prognosis in patients with severe CAP.

Regarding the impact of adrenal response on the outcomes, 2 of the evaluated studies thoroughly investigated and found an association between plasma cortisol and mortality [16,19]. These results are in accordance with those obtained from patients with severe sepsis [5-7]. Christ-Crain et al [16] observed that cortisol levels were directly associated with disease severity (as measured by the PSI score) and hospital mortality and concluded that cortisol levels are good predictors of severity and outcome in CAP. In this study, the prognostic accuracy of free cortisol for patients with CAP was not better than total cortisol. A total cortisol cutoff value of 34.8 μg/dL was superior to that of leukocyte count, C-reactive protein, and procalcitonin to predict death and improve the prognostic accuracy compared with the PSI alone [16]. Salluh et al [8] reported in a prospective study that there was no difference in ICU and hospital mortality between patients diagnosed with CIRCI and those who were not. Nonetheless, in this ICU population of patients with severe CAP, baseline total cortisol levels were significantly higher in nonsurvivors than in survivors. Also, baseline cortisol was the best predictor of death when compared with other laboratorial parameters (D-dimer and C-reactive protein) and scores (APACHE II, CURB-65, and SOFA). In this study, δ cortisol or postcorticotropin cortisol were not able to distinguish survivors from nonsurvivors. These data support the notion that although the presence of CIRCI is not associated with worse outcomes, elevated cortisol levels are associated with disease severity and in-hospital mortality.

Finally, it should be acknowledged that, despite the finding that low cortisol levels are not associated with worse outcomes in severe CAP, it does not mean that patients with severe CAP will not benefit from corticosteroids. Despite recent literature that challenges the role of adrenal function status in relation to the response to corticosteroids [21], there is also evidence of benefit of corticosteroids in patients with septic shock [22] and in selected patients with severe CAP [23]. Therefore, this issue is still a source of intense debate that should be evaluated in future clinical trials.

However, significant heterogeneity in study design and patient selection is observed among the studies and could

Table 3 Pooled analysis of mortality in patients with severe CAP according to different criteria of adrenal dysfunction

	Nonsurvivors	Survivors	Total	P
Cortisol < 10 μg/dL	7	49	56	.55 [a]
Cortisol > 10 μg/dL	74	403	477	
Cortisol < 15 μg/dL	15	106	121	.38 [b]
Cortisol > 15 μg/dL	66	346	412	

[a] For comparisons between survivors and nonsurvivors using cortisol level of less than 10 μg/mL as CIRCI criteria.
[b] For comparisons between survivors and nonsurvivors using cortisol level of less than 15 μg/mL as CIRCI criteria.

Table 4 Pooled analysis of mortality in ICU and non-ICU patients with severe CAP diagnosed with CIRCI according different criteria

	Nonsurvivors	Survivors	Total	P
Cortisol < 10 μg/dL				
ICU patients	5	18	23	.11 [a]
Non-ICU patients	2	31	33	
Cortisol < 15 μg/dL				
ICU patients	11	37	48	.009 [b]
Non-ICU patients	4	69	73	

[a] For comparisons between survivors and nonsurvivors using cortisol level of less than 10 μg/dL as CIRCI criteria.
[b] For comparisons between survivors and nonsurvivors using cortisol level of less than 15 μg/dL as CIRCI criteria.

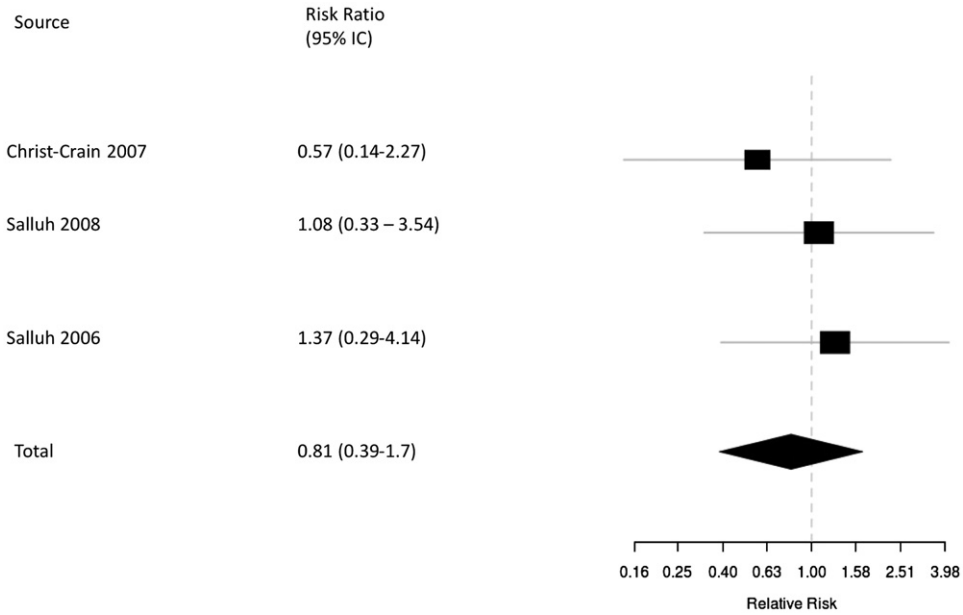

Fig. 2 Mortality based on basal cortisol levels of less than 10 μg/dL. CI indicates confidence interval. Size of the data markers indicates weight of the study.

explain the differences in the frequency of CIRCI and in its implications on clinical outcomes observed in the few studies currently available [5,7,10].

Selection bias is usually implicated as a plausible explanation for the results observed in clinical studies involving small patient population. Stratification for disease severity varied, and in only 2 studies [15,16], the same criteria was used. As disease severity varied among the studies, nonresponders to ACTH may have been underrepresented, and its influence on mortality may not been adequately recognized [24]. Unfortunately, adequate characterization and detailed data on subgroups as acute respiratory distress syndrome and septic shock were not available for all studies and could not be systematically evaluated. However, to overcome this, we obtained additional data from direct contact with the authors. Adrenal function was evaluated by many different methods including total cortisol [8,13,16], corticotropin test [15], and free cortisol [16], and different diagnostic criteria were applied by the investigators [5,25,26]. Currently, the diagnosis of

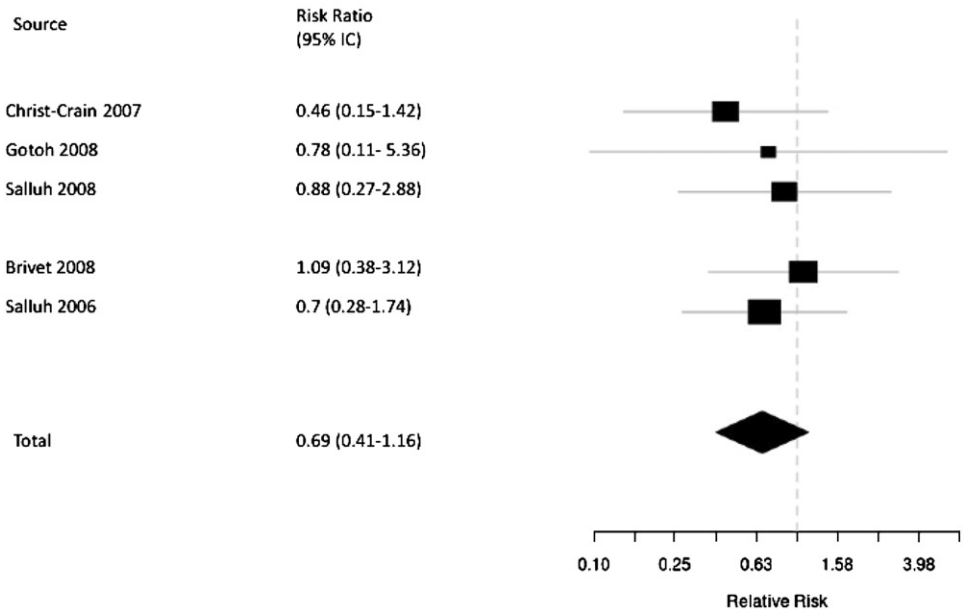

Fig. 3 Mortality based on basal cortisol levels of less than 15 μg/dL. CI indicates confidence interval. Size of the data markers indicates weight of the study.

adrenal dysfunction or CIRCI and its impact on the outcomes of severely ill patients are still matters of controversy [27,28], and the 250-μg ACTH infusion test is usually considered for the diagnosis of adrenal insufficiency [29]. In a landmark study, Rothwell et al [30] demonstrated that a failure to increase basal cortisol levels by greater than 9 μg/dL (nonresponse) after a 250-μg ACTH infusion was associated with increased mortality in patients with septic shock ($P < .001$). These findings were confirmed by a French multicenter study almost a decade later [5]. Despite these compelling data, several authors argue that the ACTH test is not appropriate for the diagnosis of CIRCI [8,17,31]. Hamrahian et al [32] have suggested the use of free cortisol concentrations to diagnose CIRCI. In addition, the question of what is an adequate baseline cortisol level continues to be debated, and several proposed baseline cortisol concentrations were evaluated. A baseline cortisol level of 15 μg/dL or less [33,34], or 10 μg/dL or less according to some authors, is considered sufficient to diagnose CIRCI [35]. To date, no single study evaluated exclusively patients with severe CAP by using simultaneously free and total cortisol, ACTH test, and methyrapone test.

5. Conclusions

In conclusion, the current evidence regarding the frequency and significance of adrenal dysfunction in patients with severe CAP is modest. Critical illness-related corticosteroid insufficiency is present in a variable number of patients with severe CAP (0%-48%) depending on the diagnostic methods and criteria applied in the different studies. Considering the present results, we cannot conclude that adrenal function tests are mandatory for the clinical management of patients admitted to the hospital with severe CAP. However, total cortisol levels may be useful as biomarkers for the assessment of disease severity and in-hospital outcomes.

After systematic review and meta-analysis, the authors, concerned about the quality of evidence available of effect the adrenal dysfunction in severe CAP, suggest that additional evidence based in prospective study with good sample size and well-defined end points is needed.

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