Comparison of cumulative incidence analysis and Kaplan-Meier for analysis of shock reversal in patients with septic shock☆,☆☆

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Abstract
Introduction: Kaplan-Meier (KM) has become the most used method to evaluate time-to-event analysis, although it is unsuitable in competing event situations such as death and shock reversal. Despite that the use of this methodology is not widely disseminated, cumulative incidence analysis (CIA) is more appropriate in these situations. We used CIA and KM (with 2 different techniques of censoring) to compare shock reversal in a cohort of patients with septic shock after steroid therapy. Furthermore, we have analyzed shock reversal in responders and nonresponders to high-dose cortrosyn test (250 μg).

Methods: Analysis of shock reversal in a cohort of 74 patients with septic shock at a university hospital was done.

Results: Shock reversal by the 28th day was estimated to be 88% and 72% by KM methods and 59% by CIA. In nonresponders to cortrosyn test (Δ ≤ 9 μg/dL), shock reversal was estimated in 80% and 56% according to KM and 47% according to CIA. As for responders to cortrosyn test, shock reversal was estimated in 90% and 77% according to KM and 64% according to the CIA method.

Conclusion: Kaplan-Meier overestimates shock reversal. Cumulative incidence analysis seems to be a more appropriate method to analyze shock reversal. Future trials intended to analyze shock reversal should apply CIA.

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1. Introduction

In some medical situations, the main outcome is the time to an event, such as shock reversal in patients with septic shock. There are many methods to evaluate time-to-event...
data. Instead of “time-to-event,” the word “survival” is commonly used to designate these methods, although the words are not synonymous. In common, these techniques estimate the probability of occurrence of events at every follow-up period for the population cohort [1,2].

Also known as “product-limit method,” Kaplan-Meier (KM) has become the most conventional method to assess time-to-event analysis; besides, it is executable in most statistical software packages. In the scope of critical care, some trials have applied this methodology for the purpose of assessing the influence of steroid therapy in patients with sepsis and septic shock on shock reversal [3-6]. These trials and their respective meta-analysis allowed concluding that steroids decrease vasopressor dependence [7,8].

Shock reversal is currently the only consensual clinical benefit of steroids in patients with septic shock, mainly in patients with critical illness–related corticosteroid insufficiency that can be diagnosed as baseline serum cortisol concentration less than 10 μg/d or cortisol variation (Δ) 9 μg/dL or less [9]. Although it has been ideally suited to analyze several time-to-event situations, KM is inadequate to analyze vasopressor withdrawal because it works with time set to a single type of event; thus, assuming independence between event and censoring. This assumption is not confirmed when analyzing shock reversal, as this is a competing event. Kaplan-Meier method is a “2-state model” [10]; in this example, at the beginning of the observation, all patients were in shock, whereas during follow-up, the curve showed a step-down as the patient exhibited shock reversal as an outcome. The problem is that some patients will exhibit the competing event “death” but before the main outcome (shock reversal) is disclosed during the follow-up period. Yet, there are different ways to deal with this limitation in KM techniques. The 2 most common ways are (1) at the moment the patient dies, he or she is censored, and; (2) the patients who die in shock during the follow-up are considered to have been in shock (alive) until the end of the follow-up period. These corrections induce bias in the interpretation of curves and may overestimate the incidence of shock reversal.

In scenarios where there are competing events, methodologies that correct the probability of 1 event to the competing event are more accurate and should be used. These methods bring into question the assumption the probability of another outcome (death), thereby correcting the probability of the main outcome regarding the competing event. One of the terms used in the literature to designate such methodologies is “cumulative incidence analysis” (CIA). Unfortunately, researchers have only recently become aware of the benefits of this methodology [11].

In this study, both CIA and KM methodologies have been applied to compare estimates of shock reversal in a cohort of patients with septic shock after steroid therapy. We have also analyzed estimates of shock reversal based on the responses to cortrosyn test.

2. Materials and methods

Our study used data from a trial designed to compare low- and high-dose cortrosyn tests (to be published). The trial included 74 patients older than 18 years sequentially submitted to both tests at a medical-surgical intensive care unit (ICU) of a tertiary university hospital; patients were prospectively enrolled from November 2006 to February 2009. Patients who were eligible for enrollment into the study were those who met the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Conference Consensus Committee [12] for septic shock; have systolic blood pressure less than 90 mm Hg, despite of adequate fluid replacement and use of vasopressor for at least 1 hour for a period inferior to 96 hours at the ICU; and were under invasive mechanical ventilation. The decision concerning low-dose hydrocortisone therapy after the cortrosyn test and other therapeutic decisions was taken at the discretion of the patient’s physician without influence of researchers. The following were considered as exclusion criteria: previous use (short or long term) of cortisone; use of drugs known to suppress adrenal function, such as etomidate, spironolactone, oral contraceptives, or antifungals; AIDS; history of previous adrenal failure; pathology of hypothalamic-pituitary-adrenal axis; pregnancy; and shock due to other etiologies. All patients were submitted to high-dose (250 μg) cortrosyn test (tetracosactide, Synacthen; NOVARTIS, Rueil-Malmaison, France). Serum cortisol concentration was measured at baseline 30 and 60 minutes after cortrosyn infusion. Cortisol variation (Δ) was calculated as the difference between peak serum cortisol concentration (30 or 60 minutes) and the baseline cortisol concentration before the cortrosyn test. Patients were considered non-responders to the high-dose test when Δ cortisol is 9 μg/dL or less. Because of the overlap of results between responders and nonresponders to the low- and high-dose cortrosyn tests, the analysis of the low-dose test was suppressed in this study. Serum cortisol analysis was performed by chemiluminescence (Modular E-170; Roche, Vasel, Switzerland). The protocol was approved by the ethics committee. The following variables were recorded: age, sex, admission category (medical or surgical), source of infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score [13], serum albumin, and glycemia. Patients were followed up for 28 days. Shock reversal was defined as systolic blood pressure more than 90 mm Hg without vasopressor support for at least 24 hours.

3. Statistical analysis

Statistical analyses were conducted using SPSS 17.0 statistical package software (SPSS Incorporation, Chicago, IL). The results of continuous variables are expressed as the mean ± SD. Shock reversal was estimated by KM and CIA methods. Cumulative incidence analysis was conducted as
described by Ludbrook and Royse [14], and groups were compared by Cox proportional hazards to competing events [15]. Kaplan-Meier method allows different censoring applications. Two different approaches to KM have been performed. In the first approach (KM1), the occurrence of death before shock reversal resulted in censoring in the moment of death. In the second approach (KM2), the competing event death was ignored, that is, they were considered to be in shock until the end of the follow-up period.

Mortality was estimated by the KM method, and results were compared between groups using the log-rank test. Furthermore, \( P < .05 \) was considered statistically significant.

### 4. Results

In this cohort of 74 patients, 57% were men. Mean age was 62 ± 16 years, and APACHE score was 25.7 ± 8.5. Fifty-three percent were medical ICU admissions, and 47% were surgical admissions. In 46% of admissions, the source of infection was respiratory, whereas in 42% the source, it was abdominal, and in 12%, other sources were observed. Only 6 patients (8%) have not received hydrocortisone. This decision was taken at the discretion of the patient’s physician without influence of researchers and was not related to serum cortisol concentration or response to cortrosyn test. Analysis performed with exclusion of these 6 patients has not influenced results. Blood glucose was 137 ± 45 mg/dL. Mean serum albumin was 2.0 ± 0.5 g/dL, and there was no difference between responders or nonresponders to cortrosyn. Baseline cortisol before conduction of cortrosyn test was 31.8 ± 20.3 \( \mu \text{g/dL} \). In this cohort, 24% (18/74) of patients were nonresponders to the test. Cortisol variation is shown in Table 1. The variation was not related to baseline cortisol.

In the entire cohort, shock reversal was estimated in 88% of patients when KM1 method was used and 72% when KM2 method was adopted. Estimate was only 59% when CIA was used. Responders to the cortrosyn test had shock reversal estimated in 90%, according to KM1, 77% according to KM2, and 64% when analysis was performed with CIA. Among nonresponders to cortrosyn test, KM1 estimated shock reversal in 80% and 56% with KM2. The estimate was 47% when CIA was applied (Table 2 and Fig. 1).

Overall mortality on the 28th day was 57%. Mortality in nonresponders to the cortrosyn test was 61%, whereas in responders, it was 55% (log-rank \( P = .39 \)). Table 3 shows the difference in estimates of shock reversal between both KM methods used and CIA and its relation to mortality. The difference is greater when KM1 is applied. In addition, it has reached 33% among nonresponders to cortrosyn, which was the group with the highest mortality rate (61%). The discrepancy between both methods is smaller (9%) when comparison is conducted between CIA and KM2.

### 5. Discussion

Despite that KM became the most popular method to assess time-to-event analysis in situations with competing events, it is no longer considered the most appropriate method. Our study shows that KM overestimates shock reversal in scenarios with competing events like death.

The use of stress dose steroids in patients with septic shock is partially supported by the results of trials that allowed concluding that steroids increase shock reversal [3-6]. Kaplan-Meier method has been applied in these trials, thereby leading to such conclusion. Briegel et al [3] used KM “ignoring the deaths” method; patients who died using vasopressor during follow-up were therefore considered to be alive and using vasopressor during all the follow-up period; thus, performing an estimative described in our trial as KM2. This way of censoring is the one that reaches results closer to those of CIA, but it is an “actuarial” estimated vasopressor withdrawal, and it actually estimates how many patients would exhibit shock reversal if no patients had died during the follow-up. Indeed, the most influent trials analyzing steroids and shock reversal do not mention how

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( 62 \pm 16 )</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, %</td>
<td>Male</td>
<td>53</td>
</tr>
<tr>
<td>APACHE score</td>
<td>25.7 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>Source of infection</td>
<td>Respiratory, %</td>
<td>46</td>
</tr>
<tr>
<td>Others, %</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>2.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>137 ± 45</td>
<td></td>
</tr>
<tr>
<td>Baseline cortisol, ( \mu \text{g/dL} )</td>
<td>31.8 ± 20.3</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) Cortisol after cortrosyn test, ( \mu \text{g/dL} )</td>
<td>All patients: 16.3 ± 10.1</td>
<td>Nonresponders: 4.8 ± 2.8</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of patients

Data are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Shock reversal</th>
<th>KM1 (%)</th>
<th>KM2 (%)</th>
<th>CIA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>88</td>
<td>72</td>
<td>59</td>
</tr>
<tr>
<td>( \Delta ) Cortisol ≤9 ( \mu \text{g/dL} )</td>
<td>80</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>( \Delta ) Cortisol &gt;9 ( \mu \text{g/dL} )</td>
<td>90</td>
<td>77</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 2: Estimates of shock reversal according to KM methods with different censoring schemes (KM1 and KM2) and CIA in the entire cohort according to the response to cortrosyn test
patients were censored. Bollaert et al [4], Annane et al [5], nor Sprung et al [6] have described how patients were censored at time of death. The authors were contacted to inform how they have censored dead patients in every trial. The authors of CORTICUS (Corticosteroid Therapy of Septic Shock) [6] have declared that they used the same methods of censoring of Briegel et al [3]. In Bollaert et al [4], authors have censored patients in the moment of death the same way we have performed in KM1 analysis. Our study shows that this technique (KM1) is the one that most overestimates shock reversal and that the higher the mortality, the higher is the bias estimated by this technique. We did not have access to data of Annane et al [5].

Although patients can be censored in different ways [16], KM is believed to be proper for working with time for a single type of event. In this technique, the assumption of independence between event and censoring is pivotal, and it fails in scenarios with competing events. To correct the prediction of the number of patients who have actually exhibited shock reversal, it is necessary to apply a multistate model, that is, a model that deals with more than a single event and that does not assume independence between main and competing events; hence, allowing patients to present 1 event (in this case, shock reversal) without being censored to a competing event (in this case, death).

These methods are usually designated not only as CIA but also as expressions such as actual CIA or conditional probability estimation, which can be found in the medical literature. Such designations have been used by physicians in areas where competing events are usual; this can be observed in cardiac surgery (death competes with valve durability) [17,18] or oncology (death competes with disease relapse). Although competing events are common in critical care and emergency medicine, CIA has surprisingly not been as frequently applied as it should have been; recommendations support that this methodology is more appropriate though [19].

6. Conclusion

Steroid therapy in septic shock is partially supported by the statement that steroids increase shock reversal. The trials that lead to this conclusion have been applied using the KM method, and different censoring schemes were therefore used for this purpose. Our trial exemplifies that, mainly, when patients are censored in the moment of death, KM overestimates steroid influence on shock reversal. Cumulative incidence analysis is more accurate in addressing shock reversal because it addresses the actual risk of shock reversal. We hence suggest that future trials intended to analyze competing events, such as shock reversal and death, should apply CIA instead of KM.

References

Comparison of CIA and KM for analysis of shock reversal


