

# Use of L'Abbé and pooled calibration plots to assess the relationship between severity of illness and effectiveness in studies of corticosteroids for severe sepsis

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## Editor's key points

- The role of corticosteroids in sepsis and pneumonia remains controversial.
- A factor in the differences between studies could be the severity of illness between groups.
- L'Abbé and pooled calibration plots were used to determine the interaction between illness severity and drug efficacy.
- Excessive mortality in placebo groups could explain the apparent benefit of corticosteroids in severe sepsis.

**Background.** The role of corticosteroids in severe sepsis and pneumonia remains controversial. This study described the use of L'Abbé and pooled calibration plots to assess the relationship between severity of illness and effectiveness of corticosteroids for severe sepsis.

**Methods.** Randomized controlled trials (RCTs) comparing corticosteroids and placebo from Cochrane Controlled Trial Register, MEDLINE, and EMBASE databases were retrieved. The observed and predicted mortality rates of the placebo groups were used as a measure of the severity of illness of the patients in L'Abbé and calibration plots.

**Results.** A total of 1089 patients from 10 RCTs fulfilled the inclusion criteria and were subject to further analysis. L'Abbé and calibration plots did not suggest significant interactions between the effectiveness of corticosteroids and severity of illness. The pooled calibration plot suggested that the mortality rates of the placebo groups from three studies were higher than predicted. After excluding these studies in the meta-analysis, there was a reduction in the point estimate of benefit of corticosteroids on mortality [odds ratio (OR) 0.97, 95% confidence interval (CI): 0.71–1.33,  $P=0.87$  by a fixed-effect model,  $P=0.59$  by a random-effects model vs OR 0.85, 95% CI: 0.66–1.10%].

**Conclusions.** The pooled calibration plot suggested that there were excessive deaths in the placebo groups of some RCTs that could explain the apparent benefit of corticosteroids on mortality of patients with severe sepsis. L'Abbé and pooled calibration plots might be useful as adjuncts to assess interactions between severity of illness and effectiveness of an intervention.

**Keywords:** clinical trials; predicted mortality; quality of study; standardized mortality ratio

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Randomized controlled trials (RCTs) are regarded as a gold standard to guide treatment decisions; their results are, however, often difficult to interpret and apply. Many RCTs in intensive care patients have not demonstrated the beneficial effects of the intervention under investigation, despite good previous preclinical and RCT evidence.<sup>1</sup> There are many reasons for these negative results, including problems with timing, endpoint selection, and heterogeneous study populations.<sup>1</sup>

Corticosteroids have been recommended for patients with sepsis, severe sepsis, and pneumonia,<sup>2–3</sup> but the results of RCTs and meta-analyses on benefits and risks of corticosteroids in these patients are conflicting and uncertain.<sup>3–5</sup> The possible explanations for the heterogeneity in the results of these studies include differences in corticotrophin responses, timing in the initiation of treatment, dose and duration of corticosteroids, co-treatments, and possible interactions

between effectiveness of corticosteroids and severity of illness.<sup>6–7</sup>

Evidence suggests that some treatments are more effective for patients who are at high risk of dying from a disease,<sup>8</sup> and possibly harmful for patients with a mild disease, for example, the use of activated protein C in sepsis.<sup>9</sup> Using mortality rates of the placebo groups of RCTs as a co-variate in the meta-regression, a recent meta-analysis suggested possible interactions between the effects of corticosteroids and severity of illness,<sup>7</sup> favouring corticosteroids in sicker patients. This approach has, however, a potential problem. If an RCT shows that corticosteroids are effective in reducing mortality but, at the same time, the mortality rate of the placebo group is unexpectedly high, it could lead to an apparent conclusion that corticosteroids are more effective in reducing mortality of patients with severe sepsis at high risk of mortality. Indeed, an

unexpectedly high mortality rate of the placebo or control group in an RCT is not uncommon and might, at least in part, explain why the results of a trial on tight blood glucose control in critically ill patients were not subsequently confirmed by a large RCT.<sup>10 11</sup>

Assessing the relationship between event rates (or mortality) of the treatment and placebo groups by a L'Abbé plot is useful in exploring heterogeneity and identifying outlying trials in a meta-analysis.<sup>12 13</sup> On the other hand, comparing the rate of observed mortality against that of predicted mortality by a calibration curve is very useful to assess the accuracy of predictive models.<sup>14</sup> We hypothesized that L'Abbé and pooled calibration plots would be useful in assessing the relationship between severity of illness and effectiveness of an intervention, and describe how these plots can be used to assess the relationship between severity of illness and effectiveness of corticosteroids in sepsis, severe sepsis, or pneumonia requiring hospitalization.

## Methods

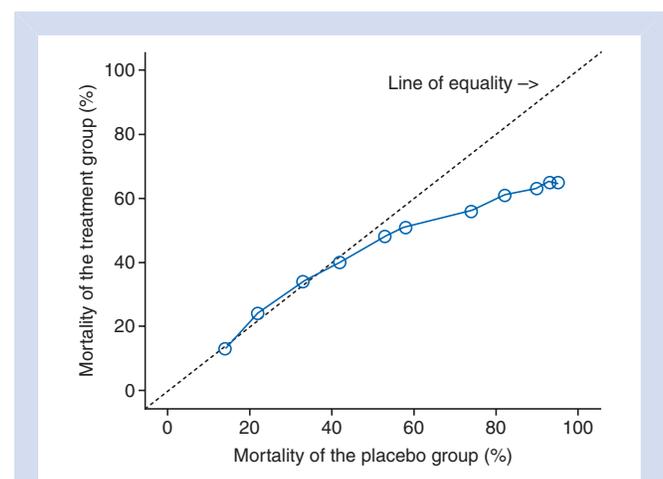
We searched for RCTs on effectiveness of corticosteroids in sepsis and severe pneumonia in the Cochrane controlled trial register (2010, issue 3) and the EMBASE (January 1990 to November 1, 2010) and MEDLINE databases (January 1990 to November 1, 2010). The use of a relatively restricted period of literature search aimed to include only studies that assessed low to medium doses of corticosteroids in severe sepsis or pneumonia. During the electronic database search, the following exploded Medical Subject Heading (MeSH) terms were used: 'sepsis', 'severe sepsis', 'septic shock', 'infection', or 'pneumonia' with 'steroid', 'corticosteroid', 'prednisolone', or 'prednisone'. The search was limited to clinical trials, RCTs, letters, editorial, and reviews without any language restrictions. The reference lists of related editorials, reviews, and original articles identified were further searched for relevant trials. Finally, the websites of the International Network of Agencies of Health Technology Assessment in Health Care were searched to ensure all suitable trials were included.

Only RCTs comparing corticosteroids with a placebo in critically ill adult patients (> 18 yr old) with sepsis, severe sepsis, or pneumonia requiring hospitalization were included. These trials were included so that the interactions between effectiveness of corticosteroids and a wide range of severity of illness related to infections can be assessed. RCTs that did not have any data on severity of illness of the patients [e.g. Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), or Pneumonia Severity Index (PSI)] or cross-over studies were excluded. These trials were excluded because construction of a pooled calibration plot is not feasible without data on severity of illness or predicted mortality rates of the subjects, and in cross-over studies, all subjects in the trials would have received corticosteroids. Mortality was the only endpoint in this descriptive study. The observed mortality rates of the treatment and placebo groups were retrieved, and the

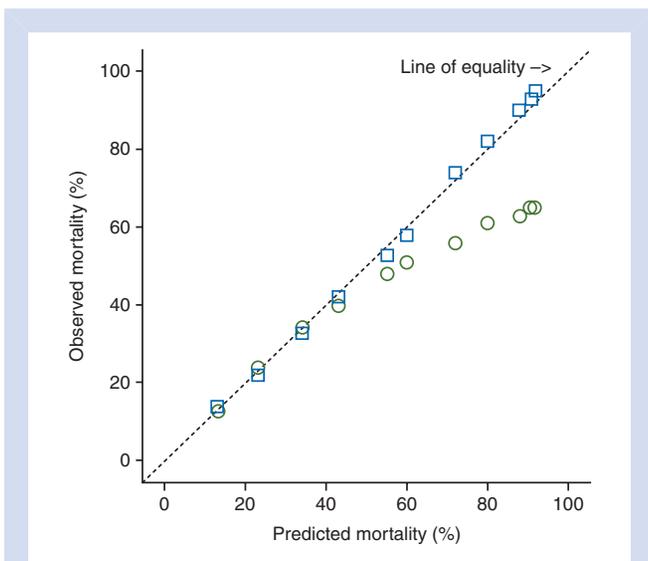
mean predicted mortality rates of the treatment and placebo groups were calculated using the mean severity of illness scores reported in the eligible studies together with the published weightings of the coefficients of sepsis or pneumonia of the severity of illness prognostic models used for the study.

A L'Abbé plot is constructed by plotting the observed mortality rates of the treatment groups against the observed mortality rates of the placebo groups. If corticosteroids are more effective in reducing mortality for patients at high risk of mortality, the mortality rates of the treatment groups will be lower than the placebo groups when the mortality rates of the placebo groups are high (Fig. 1). However, if the studies are distributed along the line of equality, significant interactions between severity of illness and effectiveness of corticosteroids are unlikely.

A pooled calibration plot is constructed by plotting the observed mortality rates against the predicted mortality rates of the placebo and treatment groups of the included trials. If corticosteroids were more effective in reducing mortality of subjects at high risk of mortality and the mortality rates of the placebo groups were not higher than predicted, the mortality data of the treatment groups will be distributed below the line of equality on the right-hand side of the graph, while the mortality data of the placebo groups will be distributed close to the line of equality (Fig. 2). However, if some trials have unexpectedly high mortality rates in their placebo groups, these studies will be distributed above the line of equality. Basically, the L'Abbé plot uses the observed risks of mortality of the placebo groups and the pooled calibration plot uses the ratio between observed and predicted risks of mortality of both placebo and treatment groups to assess the relationship between severity of illness and effectiveness of an intervention.



**Fig 1** The L'Abbé plot suggests that there are apparent interactions between an imaginary drug's treatment effect and severity of illness measured by mortality rates of the placebo groups. A curve parallel to the line of equality signifies lack of interaction between severity of illness and treatment effect.



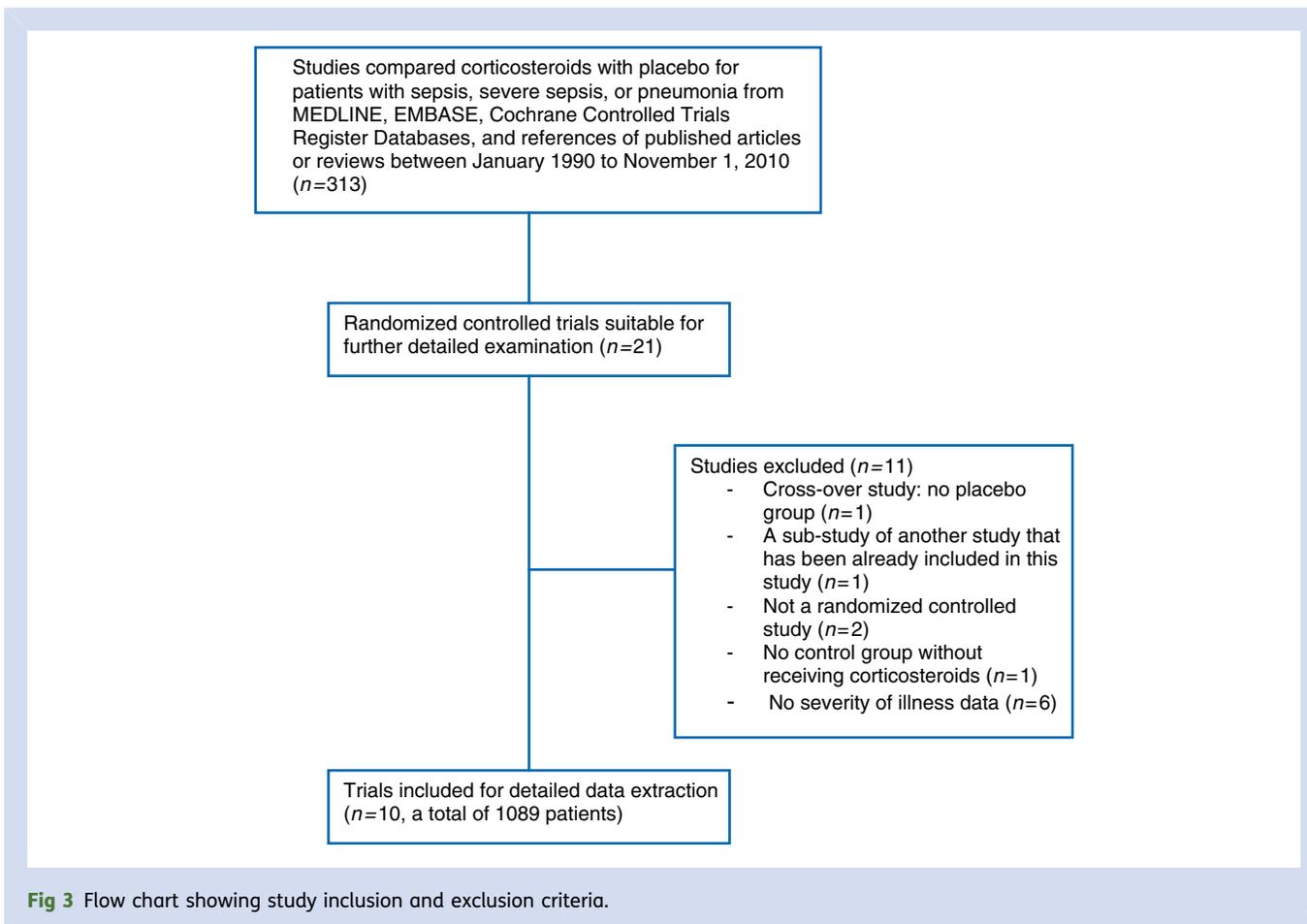
**Fig 2** The calibration plot suggests that the observed mortality of placebo groups are similar to those predicted by a risk prediction model, and that mortality rates of subjects who received an imaginary drug are lower than expected in subjects at high risk of mortality. This suggests that there are apparent interactions between the imaginary drug's treatment effect and severity of illness. Circles represent the patients in the treatment group and squares represent the patients in the placebo group.

Data were analysed using Review Manager (version 4.2.6 for Windows The Cochrane Collaboration, Oxford, UK, 2003), Comprehensive Meta Analysis (version 2.2.034, 2006, Englewood, NJ, USA), and SPSS (version 13.0, 2005, Chicago, IL, USA). A *P*-value of <0.05 was regarded as statistically significant in this study.

### Results

Of 313 studies identified from the literature search, a total of 1089 subjects from 10 RCTs fulfilled the inclusion criteria and were subjected to further analysis (Fig. 3).<sup>3 4 15-22</sup> Eight studies included subjects with sepsis or severe sepsis and two studies included subjects with severe community-acquired pneumonia.<sup>15 20</sup> The characteristics of the included studies are described in Table 1.

When all included trials were considered, the use of corticosteroids in sepsis, severe sepsis, or pneumonia was associated with a suggestion that it reduces mortality, although this was not statistically significant [odds ratio (OR) 0.85, 95% confidence interval (CI) 0.66-1.10, *P*=0.22 by a fixed-effect model, *P*=0.16 by a random-effects model; *I*<sup>2</sup>=23.2%] (Fig. 4). Using the mortality rate of the placebo group as a covariate in the meta-regression, there was a suggestion that the effectiveness of corticosteroids is related to the mortality rates of the placebo



**Fig 3** Flow chart showing study inclusion and exclusion criteria.

**Table 1** Characteristics of the included studies. APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score

Author, country of origin, year of publication [reference number]	Characteristics of the included patients	Interventions	Observed and predicted hospital mortality	Adequate, blinding, analysis by intention to treat, % of subjects completed the study
Annane and colleagues, France, 2002 [3]	Septic shock with a definite source of infection. Mean SAPS II score of the corticosteroid and placebo groups was 60 and 57, respectively	Hydrocortisone 50 mg i.v. every 6 h with 50 µg fludrocortisones orally daily ( $n=150$ ) or placebo ( $n=149$ ) for 7 days	Observed mortality of the corticosteroid and placebo groups was 95 (63%) and 103 (69%), respectively. Predicted mortality of the corticosteroid and placebo groups was 68.1% and 61.9%, respectively	Adequate, double-blinded, analysis by intention to treat, 0.3% did not complete the study
Sprung and colleagues, multi-national, 2008 [4]	Septic shock. Mean SAPS II scores of the corticosteroid and placebo groups was 49.5 and 48.6, respectively	Hydrocortisone 50 mg i.v. every 6 h for 5 days then 50 mg every 12 h for 3 more days and then 50 mg every 24 h for 3 more days ( $n=251$ ) or placebo ( $n=248$ )	Observed mortality of the corticosteroid and placebo groups was 111 (44.2%) and 100 (40.8%), respectively. Predicted mortality of the corticosteroid and placebo groups was 46.1% and 43.8%, respectively	Adequate, double-blinded, analysis by intention to treat, 0.2% did not complete the study
Mikami and colleagues, Japan, 2007 [15]	Severe community-acquired pneumonia requiring hospitalization but without other underlying medical illness. Mean PSI of the corticosteroid and placebo groups was 94.8 and 85.9, respectively	40 mg of prednisolone i.v. ( $n=15$ ) for 3 days or placebo ( $n=16$ )	Observed mortality of the corticosteroid and placebo groups was 1 (6.7%) and 0 (0%), respectively. Predicted mortality of the corticosteroid and placebo groups was 9.5% and 0.9%, respectively	Unclear, no blinding, analysis by intention to treat, all completed the study
Oppert and colleagues, Germany, 2005 [16]	Early hyperdynamic septic shock. Mean APACHE II of the corticosteroid and placebo groups was 25 and 25.5, respectively	50 mg of hydrocortisone bolus followed by infusion $0.18 \text{ mg kg}^{-1} \text{ h}^{-1}$ which was reduced to $0.06 \text{ mg kg}^{-1} \text{ h}^{-1}$ after cessation of vasopressor for more than 1 h and then it was further reduced by $0.02 \text{ mg kg}^{-1} \text{ h}^{-1}$ every day ( $n=18$ ) or placebo ( $n=23$ )	Observed mortality of the corticosteroid and placebo groups was 7 (39%) and 11 (48%), respectively. Predicted mortality of the corticosteroid and placebo groups was 56.1% and 59.7%, respectively	Adequate, double-blinded, analysis not by intention to treat, 14% did not complete the study
Rinaldi and colleagues, Italy, 2006 [17]	Severe sepsis. Mean SAPS II score of the corticosteroid and placebo groups was 54 and 57, respectively	Hydrocortisone infusion $300 \text{ mg day}^{-1}$ for 6 days ( $n=20$ ) or placebo ( $n=20$ )	Observed mortality of the corticosteroid and placebo groups was 10.8% and 11.1%, respectively. Predicted mortality of the corticosteroid and placebo groups was 55.3% and 61.9%, respectively	Adequate, un-blinded, analysis not by intention to treat, 23% did not complete the study
Cicarelli and colleagues, Brazil, 2007 [18]	Septic shock. Mean APACHE II of the corticosteroid and placebo groups was 20 and 19, respectively	Dexamethasone $0.2 \text{ mg kg}^{-1}$ 3 doses at 36 h interval ( $n=14$ ) or placebo ( $n=15$ )	Observed 28 day mortality of the corticosteroid and placebo groups was 7 (50%) and 12 (80%), respectively. Predicted mortality of the corticosteroid and placebo groups was 38.1% and 34.8%, respectively	Adequate, un-blinded, analysis by intention to treat, all patients completed the study

Continued

Table 1 Continued

Author, country of origin, year of publication [reference number]	Characteristics of the included patients	Interventions	Observed and predicted hospital mortality	Adequate, blinding, analysis by intention to treat, % of subjects completed the study
Mussack and colleagues, Germany, 2005 [19]	Septic shock. Mean APACHE II of the corticosteroid and placebo groups was 25 and 28, respectively	Hydrocortisone loading i.v. 100 mg followed by infusion of 0.18 mg kg <sup>-1</sup> h <sup>-1</sup> and dose reduced to 0.08 mg kg <sup>-1</sup> h <sup>-1</sup> after vasopressor was weaned and remained at that dose for a total of 6 days and dose of corticosteroid was weaned by 24 mg day <sup>-1</sup> steps when the underlying infection was successfully treated or serum sodium concentrations >155 mM litre <sup>-1</sup> (n=12) or placebo (n=12)	Observed mortality of the corticosteroid and placebo groups was 3 (25%) and 5 (41.7%), respectively. Predicted mortality of the corticosteroid and placebo groups was 56.1% and 66.5%, respectively	Unclear, un-blinded, analysis by intention to treat, all patients completed the study
Confalonieri and colleagues, Italy, 2005 [20]	Severe community-acquired pneumonia. Mean APACHE II of the corticosteroid and placebo groups was 17.2 and 18.2, respectively	Hydrocortisone loading 200 mg followed by infusion 10 mg h <sup>-1</sup> for 7 days (n=23) or placebo (n=23)	Observed mortality of the corticosteroid and placebo groups was 0 (0%) and 7 (30.4%), respectively. Predicted mortality of the corticosteroid and placebo groups was 28.5% and 31.5%, respectively	Adequate, double-blinded, analysis not by intention to treat, 4.2% did not complete the study
Yildiz and colleagues, Turkey, 2002 [21]	Sepsis. Mean APACHE II of the corticosteroid and placebo groups was 15.4 and 17.9, respectively	Prednisolone 5 mg i.v. in the morning and 2.5 mg in the afternoon for a total 10 days (n=20) or placebo (n=20)	Observed 28 day mortality of the corticosteroid and placebo groups was 8 (40%) and 12 (60%), respectively. Predicted mortality of the corticosteroid and placebo groups was 22.9% and 31.5%, respectively	Adequate, double-blinded, analysis by intention to treat, all completed the study
Briegel and colleagues, Germany, 1999 [22]	Hyperdynamic septic shock. Mean APACHE II of the corticosteroid and placebo groups was 26 and 27, respectively	Hydrocortisone loading 100 mg followed by infusion 0.18 mg kg <sup>-1</sup> h <sup>-1</sup> until cessation of vasopressor then 0.08 mg kg <sup>-1</sup> h <sup>-1</sup> for 6 days and dose of corticosteroid was weaned by 24 mg day <sup>-1</sup> steps when the underlying infection was successfully treated or serum sodium concentrations >155 mM (n=20) or placebo (n=20)	Observed ICU mortality of the corticosteroid and placebo groups was 4 (20%) and 6 (30%), respectively. Predicted mortality of the corticosteroid and placebo groups was 59.7% and 63.1%, respectively	Adequate, un-blinded, analysis by intention to treat, all completed the study

groups, although this was not statistically significant ( $P=0.17$ ) (Fig. 5).

The L'Abbé plot showed that the distribution of the trials was almost parallel to the line of equality, suggesting that interactions between effectiveness of corticosteroids and severity of illness were not apparent (Fig. 6). The pooled calibration plot also did not suggest an increased effectiveness of corticosteroids for patients who were at high predicted risk of mortality. The observed mortality rates of the placebo groups from three positive RCTs were, however, higher than those predicted by the severity of illness reported in the studies (Fig. 7).<sup>3 18 21</sup> After excluding

these three studies in the meta-analysis, there was a reduction in the point estimate of the benefit of corticosteroids on mortality of patients with severe sepsis or pneumonia (OR 0.97, 95% CI: 0.71–1.33,  $P=0.87$  by a fixed-effect model,  $P=0.59$  by a random-effects model;  $I^2=16.4%$ ) (Fig. 8), and the relationship between severity of illness and effectiveness of corticosteroid was less apparent (Fig. 9).

## Discussion

We have described the use of L'Abbé and pooled calibration plots to assess potential interactions between treatment

effect and severity of illness. We found no apparent relationship between severity of illness and effectiveness of corticosteroids on mortality of patients with sepsis, severe sepsis, or pneumonia in the published RCTs.

The use of corticosteroids for patients with sepsis, severe sepsis, or pneumonia remains controversial.<sup>3-5</sup> Using two graphic assessment methods, this descriptive study did not show an apparent relationship between severity of illness and benefits of corticosteroids. Our findings are consistent with the results of an experimental study in which the survival benefit of hydrocortisone was not dependent on severity of illness.<sup>23</sup> However, the pooled calibration plot did suggest that a higher than expected mortality occurred in three studies and, in all of these three studies, corticosteroids were associated with a survival benefit.<sup>3 18 21</sup> A higher than expected mortality in the placebo group suggests variations in quality and practice of standard care

between different study centres or practice misalignments in RCTs.<sup>24 25</sup> The Food and Drug Administration (FDA) in the USA has a strong requirement on whether a drug has a consistent effect across different centres in a multicentre study, and uses 'treatment-centre' interaction as a surrogate marker of the quality of the trial and generalizability of treatment effect.<sup>26</sup> Furthermore, recent evidence suggests that benefits associated with an intervention under investigation can be due to increased harm in the control group from practice misalignments between trial protocol and characteristics of subjects in the control group.<sup>25</sup> Regardless of the mechanisms for the higher than expected mortality rates of the placebo groups of these three trials,<sup>3 18 21</sup> our results raise questions about the external validity of these studies. This is similar to the situation surrounding the controversial trial on tight blood glucose control for critically ill patients.<sup>10</sup> Perhaps, the standardized mortality ratio (observed/

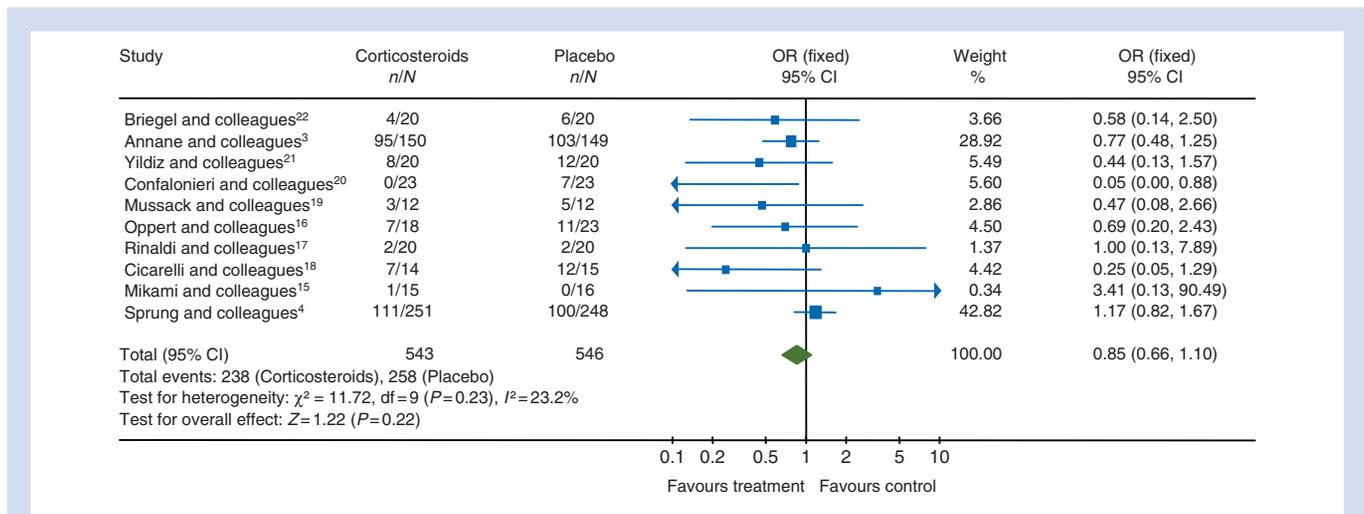


Fig 4 Forest plot showing the effect of corticosteroids on mortality of subjects with sepsis, severe sepsis, or pneumonia when all included trials were considered.

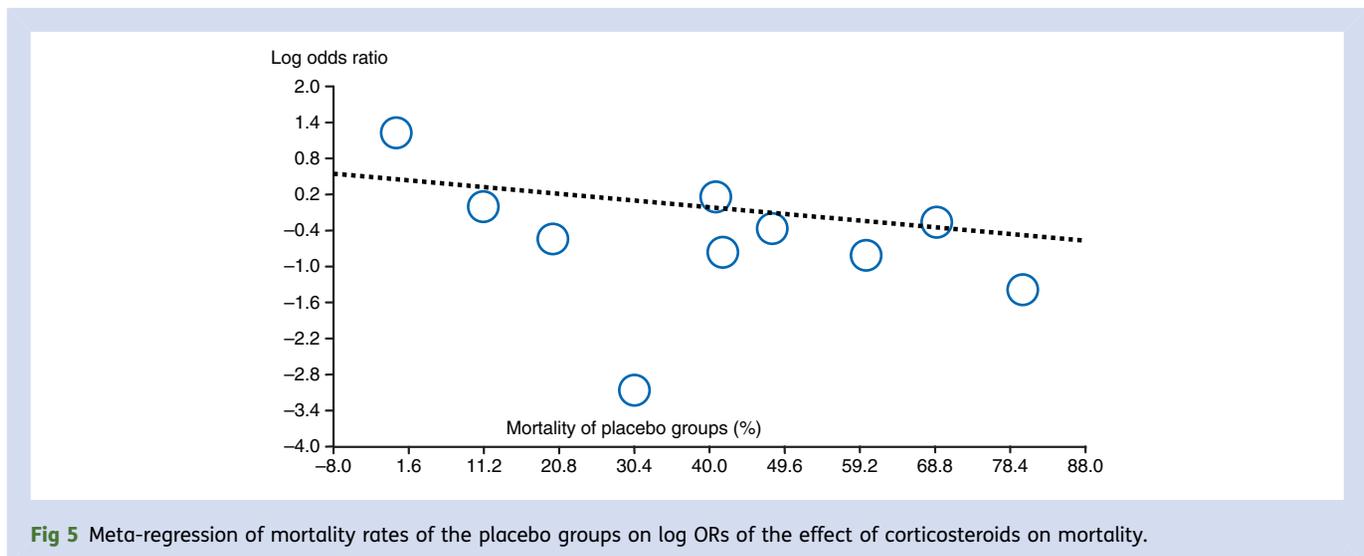
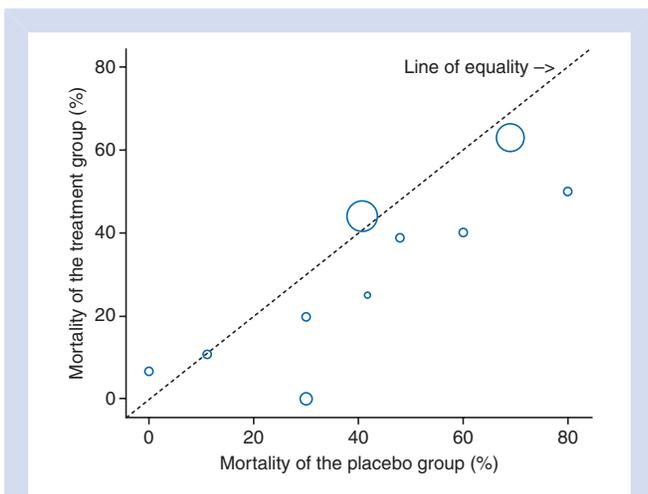
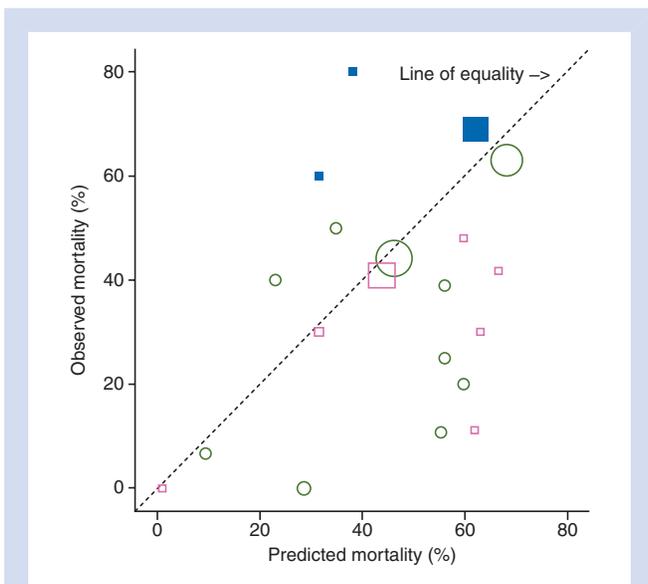


Fig 5 Meta-regression of mortality rates of the placebo groups on log ORs of the effect of corticosteroids on mortality.



**Fig 6** The L'Abbé plot suggests that there is no apparent relationship between the treatment effect of corticosteroids and severity of illness measured by mortality rates of the placebo groups. The size of the symbol is proportional to the size of the trial.



**Fig 7** The pooled calibration plot suggests that the observed mortality rates of the placebo groups in three studies and the observed mortality rates of the treatment groups in two studies were higher than predicted. Circles represent the treatment group and squares represent the placebo group of the included studies. Symbol size is proportional to the sample size of the studies. The excessive mortality rates of the placebo groups of three positive studies are highlighted in blue.

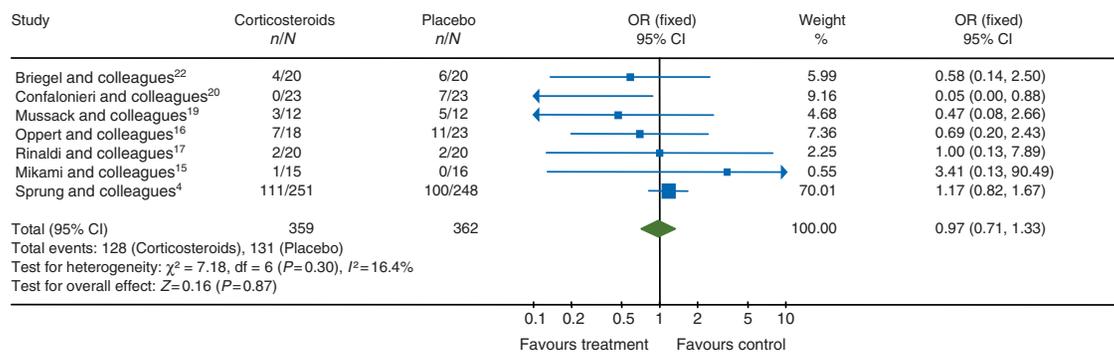
predicted mortality) of the placebo group of a trial can be considered as a surrogate marker of the quality or external validity of the trial and as one criterion in selecting RCTs for meta-analysis or excluding trials in the sensitivity analysis of a meta-analysis.

Although the use of L'Abbé plots in meta-analysis has been well described in the literature,<sup>12 13</sup> the use of a

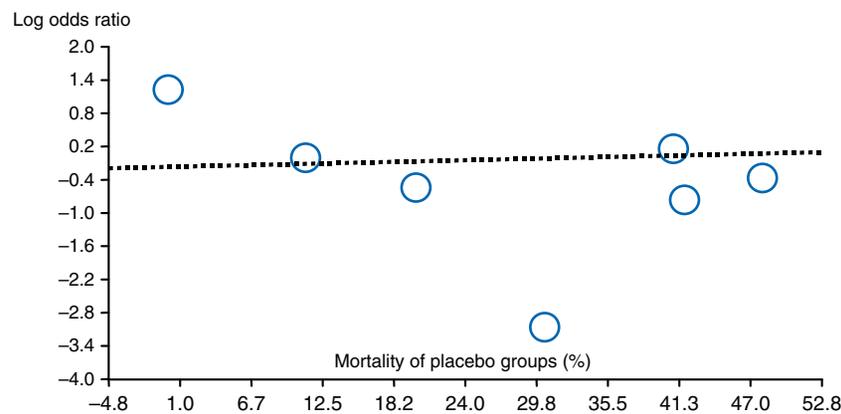
pooled calibration curve to assess the relationship between severity of illness and effectiveness of an intervention in an RCT or meta-analysis has not been described. There are potential advantages of using a calibration curve to assess interactions between severity of illness and effectiveness of an intervention under investigation. First, the relationships between the full spectrum of severity of illness and the effectiveness of the intervention are assessed at the same time. This is particularly important if the intervention under investigation might be harmful for patients with mild disease, but the intervention is potentially beneficial for patients at extreme risk of mortality, as in the situation for activated protein C in severe sepsis. Secondly, a calibration plot will assess whether the observed mortality rates of the placebo groups are compatible or consistent with the severity of illness as predicted by a well-validated predictive model. This is particularly important when an intervention under investigation shows a positive result, because external validity of the effectiveness of the intervention will be doubtful if the mortality rate of the placebo group is unexpectedly high. A forest subgroup plot describing treatment effects of different subgroups will not give an indication whether the mortality rates of the placebo groups are excessive or higher than predicted. Thirdly, the interactions between severity of illness and effectiveness of the intervention can be statistically tested by  $\chi^2$  statistics, similar to using the Hosmer-Lemeshow statistics to assess the calibration of a prognostic model. The slope and intercept of the calibration curves of the treatment and placebo groups can also be calculated to assess whether they are sufficiently different across the full spectrum of severity of illness of the patients, if a significant number of patients are included in the trial.<sup>27</sup>

There are limitations in using a calibration plot to assess the relationship between severity of illness and effectiveness of an intervention under investigation either in an RCT or meta-analysis. First, this graphic assessment is feasible only if a well-validated predictive model, such as APACHE or SAPS II, is available to assess the severity of illness of patients under investigation. Secondly, a calibration plot is useful only if the subjects recruited in an RCT or trials of a meta-analysis have a reasonable spread in their severity of illness; trials specifically focused on patients with either extreme of severity of illness will not be suitable. Finally, the number of subjects recruited in a single RCT (or the total number of RCTs in a meta-analysis) has to be reasonably large before a calibration curve can be used in order to reduce the risk of a type II error.

In summary, we describe the use of L'Abbé and calibration plots as a graphical means to assess potential interactions between effectiveness of an intervention and severity of illness. We found no apparent relationship between severity of illness and effectiveness of corticosteroids on mortality of patients with sepsis, severe sepsis, or pneumonia. Further assessment on the utility of a calibration plot in evaluating interactions between severity of illness and effectiveness of an intervention in a large RCT is needed.



**Fig 8** Forest plot showing the effect of corticosteroids on mortality of patients with sepsis, severe sepsis, or pneumonia after excluding the three trials with excessive deaths in the placebo groups.



**Fig 9** Meta-regression of mortality rates of the placebo groups on log ORs of the effect of corticosteroids on mortality after excluding the three studies with higher than expected mortality in the placebo groups.

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## Conflict of interest

None declared.

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