Critical Care

RESEARCH

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SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis

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BACKGROUND

The sequential organ failure assessment (SOFA) score was developed by an international group of experts to describe the time course of multiple organ dysfunction used **to predict mortality.**

[۱]. The function of **six organ** systems is **scored** from ۰ (no organ dysfunction) to ۴ (severe organ dysfunction), and the individual organ scores are **then summed** to a total score **between** ۰ **and** ۲۴.

The scores are calculated ۲۴ hours after admission to the **ICU** and every ۴۸ hours thereafter (the term **SEQUENTIAL ORGAN FAILURE**)

The SOFA score is an intrinsically **informative endpoint** because it can be used to evaluate the effects of treatment on organ dysfunction, a primary focus of intensive *care*.However it should be noted that Mortality may be substantially influenced by factors that are not captured by sofa score.

Sofa calculator in Adult

★ Brain: Glasgow coma score

۱۵ (۰ points)

۱۳ to ۱۴ (۱ point)

۱۰ to ۱۲ (۲ points)

۶ to ۹ (۳ points)

<۶ (۴ points)

★ Cardiovascular: Blood pressure

Hypotension absent (۰ points)

Mean arterial pressure <۷۰ mmHg (۱ point)

On dopamine ≤۵ mcg/kg/min or any dobutamine (۲ points)

On dopamine >۵ mcg/kg/min, epinephrine ≤۰,۱ mcg/kg/min or norepinephrine ≤۰,۱ mcg/kg/min (۳ points)

On dopamine >۱۵ mcg/kg/min or epinephrine >۰,۱ mcg/kg/min or norepinephrine >۰,۱ mcg/kg/min (۴ points)

Lung: Respiration

PaO٢/FiO٢ >۴۰۰ (۰ points)

PaO٢/FiO٢ ۳۰۱ to ۴۰۰ (۱ point)

PaO٢/FiO٢ ≤۳۰۰ (۲ points)

PaO٢/FiO٢ ۱۰۱ to ۲۰۰ with ventilatory support (۳ points)

PaO٢/FiO٢ ≤۱۰۰ with ventilatory support (۴ points

Liver: Bilirubin

<۱,۲ mg/dL (۲۰ mcmol/L) (۰ points)
۱,۲ to ۱,۹ mg/dL (۲۰ to ۳۲ mcmol/L) (۱ point)
۲ to ۵,۹ mg/dL (۳۳ to ۱۰۱ mcmol/L) (۲ points)
۶ to ۱۱,۹ mg/dL (۱۰۲ to ۲۰۴ mcmol/L) (۳ points)
>۱۲ mg/dL (>۲۰۴ mcmol/L) (۴ points)

Coagulation: Platelets

>۱۵۰ x۱۰۳/mm۳ (۰ points)
۱۰۱ to ۱۵۰ x۱۰۳/mm۳ (۱ point)
۵۱ to ۱۰۰ x۱۰۳/mm۳ (۲ points)
۲۱ to ۵۰ x۱۰۳/mm۳ (۳ points)
≤۲۰ x۱۰۳/mm۳ (۴ points)

Kidney: Renal function

Creatinine <۱,۲ mg/dL (۱۱۰ mcmol/L) (۰ points)
Creatinine ۱,۲ to ۱,۹ mg/dL (۱۱۰ to ۱۷۰ mcmol/L) (۱ point)
Creatinine ۲ to ۳,۴ mg/dL (۱۷۱ to ۲۹۹ mcmol/L) (۲ points)
Creatinine ۳,۵ to ۴,۹ mg/dL (۳۰۰ to ۴۴۰ mcmol/L) or urine output ۲۰۰ to ۵۰۰ mL/day (۳ points)
Creatinine >۵ mg/dL (۴۴۰ mcmol/L) or urine output <۲۰۰ mL/day (۴ points)

Sofa derivatives

Reporting **Fixed-day SOFA** allows readers to compare mean organ dysfunction in the trial arms, while **Delta SOFA** allows readers to compare the trajectory of organ dysfunction from baseline in the trial arms. Other SOFA derivatives include the **maximum** score during the ICU stay, the **mean** score during the ICU stay or the score at the day of **discharge** or **death.**

Quick sofa used at the bedside of any patient out of ICU { Respiratory Rate>۲۲ ,blood pressure<۱۰ ,deacresed Mental state}

The aim of this study was to quantify the relationship between SOFA and mortality in RCTs and to identify which SOFA derivative best reflects between-group mortality differences
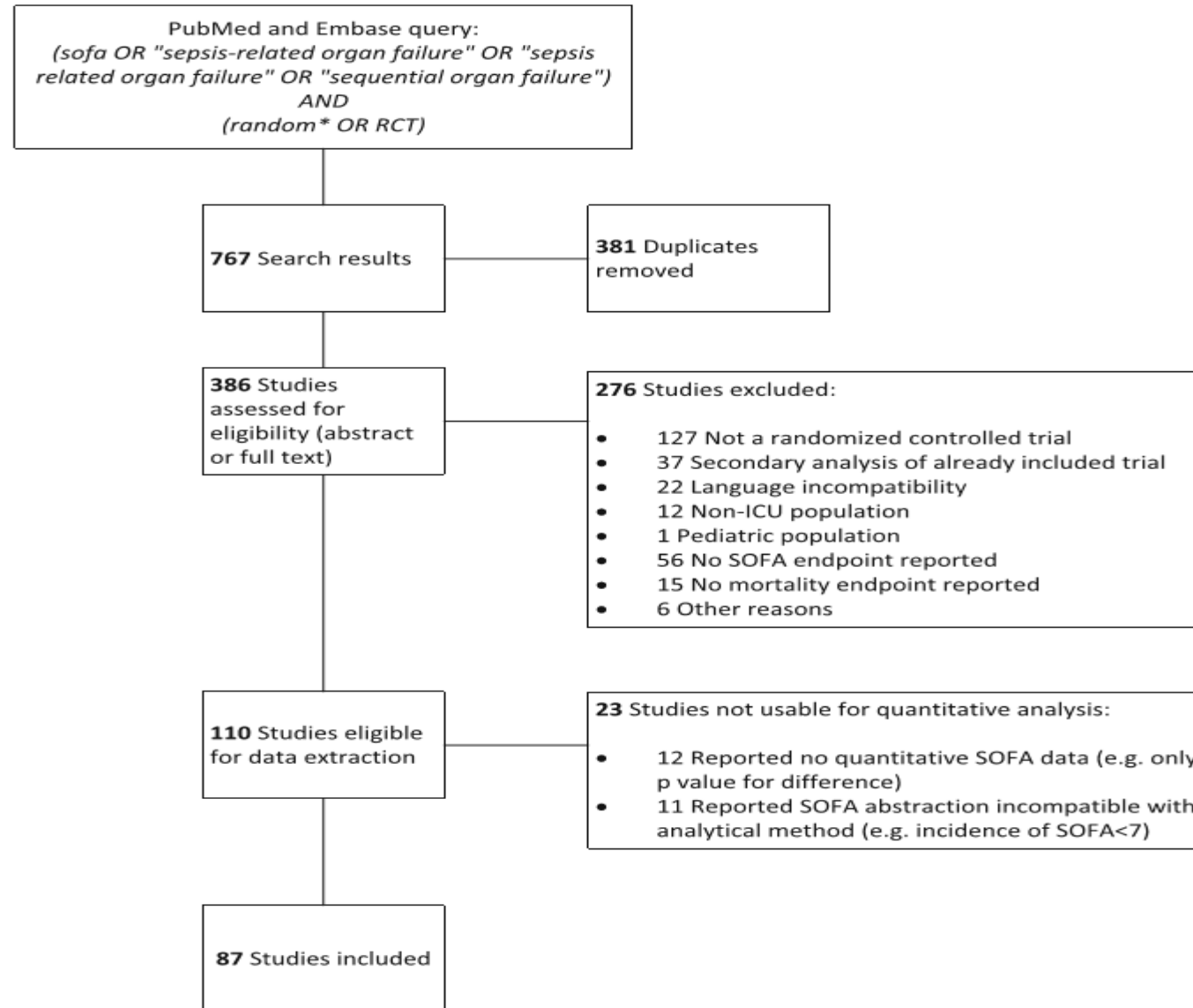
METHOD

The **review protocol** was prospectively registered (Prospero CRD۴۲۰۱۶۰۳۴۰۱۴). We performed a **literature search** (**up** to **May ۱, ۲۰۱۶**) for **RCTs** reporting both **SOFA** and **mortality,** and analyzed between-group differences in these outcomes. **Treatment** effects on **SOFA** and **mortality** were calculated as the between-group SOFA standardized difference and log **odds ratio** (OR), respectively. We used **random-effects meta-regression** to (۱) quantify the **linear relationship** between RCT treatment effects on mortality (logOR) and SOFA (i.e. responsiveness) and (۲) quantify residual heterogeneity (i.e.).

RESULTS ?

PubMed and Embase query:
(sofa OR "sepsis-related organ failure" OR "sepsis related organ failure" OR "sequential organ failure")
AND
(random* OR RCT)

767 Search results

381 Duplicates removed

386 Studies assessed for eligibility (abstract or full text)

276 Studies excluded:

- 127 Not a randomized controlled trial
- 37 Secondary analysis of already included trial
- 22 Language incompatibility
- 12 Non-ICU population
- 1 Pediatric population
- 56 No SOFA endpoint reported
- 15 No mortality endpoint reported
- 6 Other reasons

110 Studies eligible for data extraction

23 Studies not usable for quantitative analysis:

- 12 Reported no quantitative SOFA data (e.g. only p value for difference)
- 11 Reported SOFA abstraction incompatible with analytical method (e.g. incidence of SOFA<7)

87 Studies included

Fig. 1 Flowchart of the search strategy and included trials. *SOFA* sequential organ failure assessment, *RCT* randomized controlled trial

Table 1 Characteristics of included trials

Characteristic	Number of trials (% of 87 included) or median (IQR)
Trial population, *n* (%)	
Severe sepsis or septic shock	35 (40%)
Mixed ICU population	24 (28%)
Specific organ dysfunction	13 (15%)
Trauma	4 (5%)
Cardiac surgery	2 (2%)
Other	9 (10%)
Trial intervention, *n* (%)	
Drug	47 (54%)
Treatment bundle	12 (14%)
Device	10 (11%)
Nutrition	8 (9%)
Ventilation-related	4 (5%)
Other	6 (7%)
Jadad scale, median (IQR)	3 (2 − 3)
Jadad scale ≤1, *n* (%)	14 (16%)
Multicenter design, *n* (%)	40 (46%)
Sample size per trial, median (IQR)	64 (40 − 147)
Mean or median baseline SOFA score, median (IQR)	8.5 (7 − 10)
Mortality rate, median (IQR)	28% (19% − 36%)
Primary endpoint, *n* (%)	
SOFA score	19 (22%)
Mortality	14 (16%)
Other	36 (41%)
Not specified	18 (21%)

ICU intensive care unit, *IQR* interquartile range, *SOFA* sequential organ failure assessment

discussion
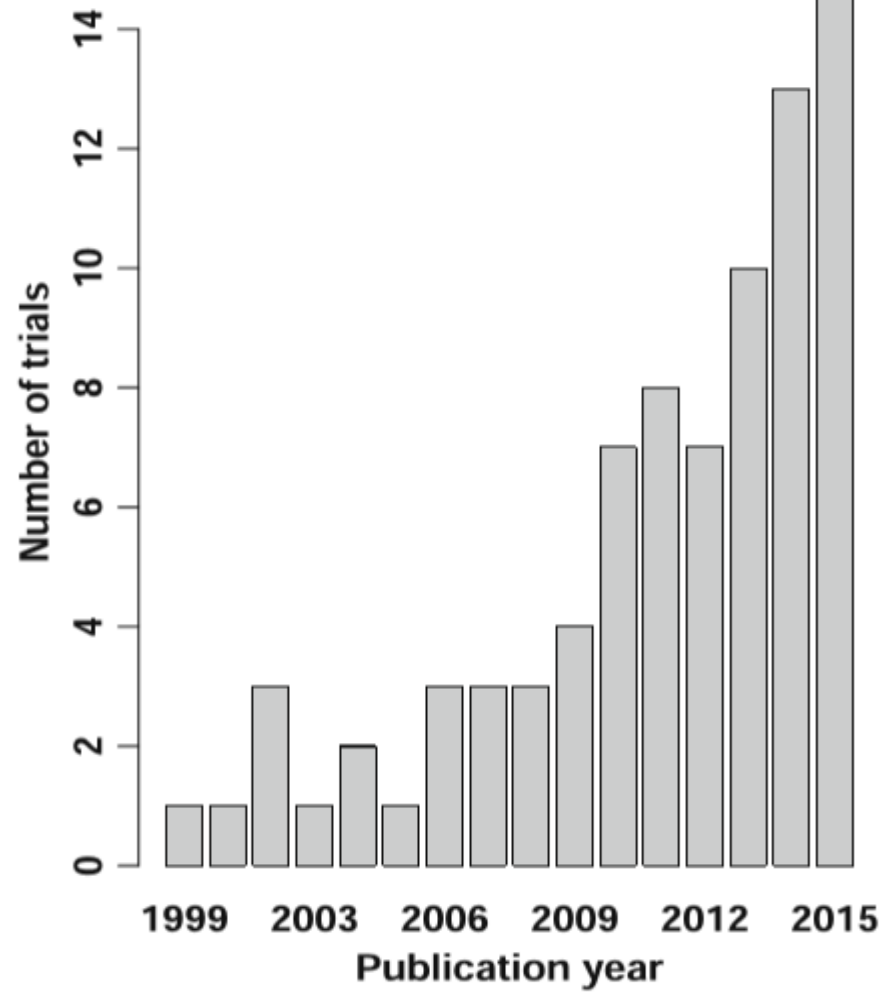
Fig. 2 Included trials by publication year

Table 2 SOFA derivatives used as endpoints

SOFA derivative	Description	Included RCTs
Fixed-day SOFA	SOFA score on a fixed day after randomization	58[a]
Early fixed-day SOFA	SOFA score on days 2, 3, 4 or 5 after randomization	55[a]
Late fixed-day SOFA	SOFA score on days 7, 10 or 14 after randomization	32[a]
Delta SOFA	Trajectory of SOFA score from baseline	25
Delta fixed-day SOFA	SOFA score on a fixed day after randomization minus baseline SOFA score	18
Delta maximum SOFA	Maximum SOFA score during ICU stay minus baseline SOFA score	7
Other SOFA derivatives		
Maximum SOFA	Maximum SOFA score during ICU stay	9
Mean SOFA	Mean SOFA score during ICU stay	3
Discharge SOFA	SOFA score at ICU discharge or death	3

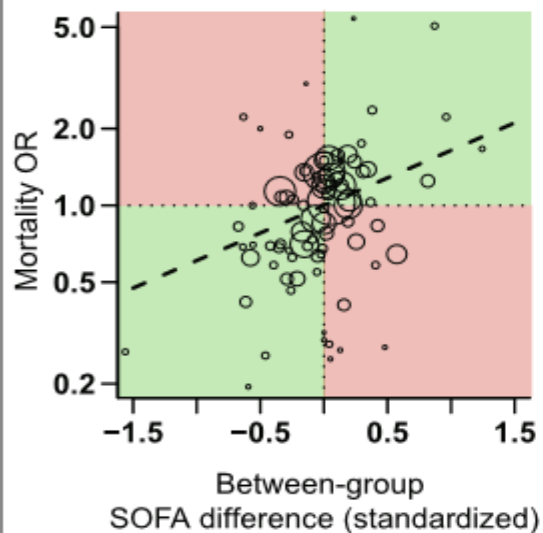[a]Twenty-nine trials reported both early and late SOFA scores. *SOFA* sequential organ failure assessment

a. Any SOFA endpoint vs. mortality

Number of RCTs: 87
Patients per trial: 64 (IQR 40–146)

Responsiveness:
Slope = 0.49 (95%CI 0.17; 0.82)
p = 0.006

Heterogeneity of relation between SOFA and mortality:
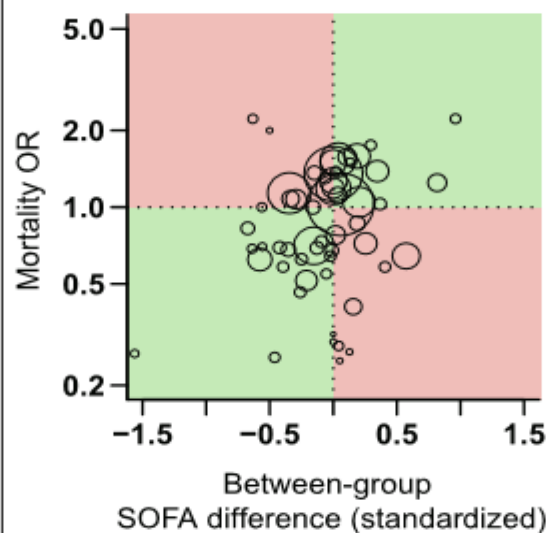I^2 = 5%

Mortality effect explained by SOFA:
R^2 = 9%

b. Fixed-day SOFA endpoint vs. mortality

Number of RCTs: 58
Patients per trial: 60 (IQR 39–148)

Responsiveness:
Slope = 0.35 (95%CI -0.04; 0.75)
p = 0.081

Heterogeneity of relation between SOFA and mortality:
I^2 = 12%

Mortality effect explained by SOFA:
R^2 = 3%

c. Delta SOFA endpoint vs. mortality

Number of RCTs: 25
Patients per trial: 64 (IQR 32–143)

Responsiveness:
Slope = 0.70 (95%CI 0.26; 1.14)
p = 0.004

Heterogeneity of relation between SOFA and mortality:
I^2 = 0%

Mortality effect explained by SOFA:
R^2 = 32%

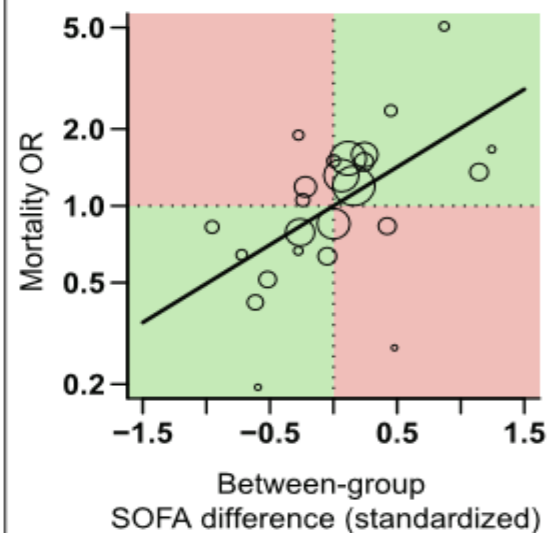# Strengths and weaknesses of this study

— Omit some researches (during search title ,abstract,….&not in English)

— used aggregated study-level data rather than individual patient data

— The included trials did not test similar interventions but rather represented a common biological pathway of multiple organ dysfunction as a determinant of ICU-related mortality

— Statistical heterogeneity in the relationship between SOFA score and mortality therefore seemed inevitable, and we have modeled this explicitly by using mixed-model regression.

Among the analyzed RCTs, there was considerable heterogeneity in the reported mortality measures (e.g. ۲۸-day, hospital or ICU) and the SOFA endpoints.

Conclusion

In this systematic analysis, ٨٧ RCTs were included

study level data aggregated in this systematic review,

Delta fixed-day SOFA appears to be **most** responsively and consistently associated with mortality

Fixed-day SOFA was the most frequently reported outcome measure

Maximum SOFA showed **excellent** responsiveness and consistency, but was used in too **few** trials for sufficient statistical power.

We **recommend** that researchers planning to use SOFA as a trial endpoint should use **Delta SOFA** in preference to Fixed-day SOFA, choose an **appropriate timeframe**, describe **how discharged** and **deceased** patients are scored and evaluate the within-trial association between the SOFA endpoint and mortality.