

**Title: Cytokine Levels In Sepsis and TNF $\alpha$  Association with Mortality but not Sepsis Severity or Infection Source: a Systematic Review and Meta-analysis.** Omar Samara, MD  
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## **Introduction:**

Sepsis is a global health problem associated with significant morbidity and mortality and is attributed to elevated cytokine levels. However, anti-cytokine therapies have failed to lower sepsis mortality in clinical trials. Quantifying cytokine levels in sepsis is required to establish their role in pathogenesis. This systematic review and meta-analysis characterizes levels of key cytokines in the circulation of sepsis patients and relates TNF $\alpha$  levels to mortality and patient characteristics.

## **Methods:**

Medline, Embase, Cochrane Library, and Web of Science Core Collection databases were searched from 1946 to May 2020 for studies in English disclosing cytokine levels in sepsis. Keywords included sepsis, septic shock, purpura fulminans, and tumor necrosis factor (TNF) $\alpha$ . The primary clinical outcome evaluated was 28-day mortality. Data analyses were performed using a random-effects model to estimate pooled odds ratios (OR) and 95% confidence intervals (CI). This systematic review is registered in PROSPERO under number CRD42020179800.

## **Results:**

A total of 3656 records were identified. After exclusions, 109 studies were included in the meta-analysis. Among studies in sepsis patients, 72 disclosed TNF $\alpha$  levels, 25 showed interleukin (IL)-1 $\beta$  levels, and 6 presented interferon (IFN) $\gamma$  levels. The pooled estimate mean TNF $\alpha$  level in sepsis patients was 58.4 pg/ml (95% CI, 39.8-85.8 pg/ml;  $I^2 = 99.4\%$ ). Pooled estimate means for IL-1 $\beta$ , and IFN $\gamma$  levels in sepsis patients were 21.8 pg/ml (95% CI, 12.6-37.8 pg/ml;  $I^2 = 99.8\%$ ) and 63.3 pg/ml (95% CI, 19.4-206.6 pg/ml;  $I^2 = 99.7\%$ ), respectively. Elevated TNF $\alpha$  concentrations are associated with increased 28-day mortality ( $P=0.001$ ). In a subgroup analysis, TNF $\alpha$  levels did not relate to sepsis source, sepsis severity, or sequential organ failure assessment (SOFA) score (figure 1). In a metaregression: age, percentage of females and mortality at 28 days associated with TNF $\alpha$  levels.

## **Conclusion:**

We estimate levels of TNF $\alpha$ , IL-1 $\beta$ , and IFN $\gamma$  in human sepsis and show TNF $\alpha$  elevations associated with sepsis mortality. TNF $\alpha$  concentrations did not correlate with sepsis severity. We believe the concept that elevated cytokines cause sepsis should be revisited in the context of these data.

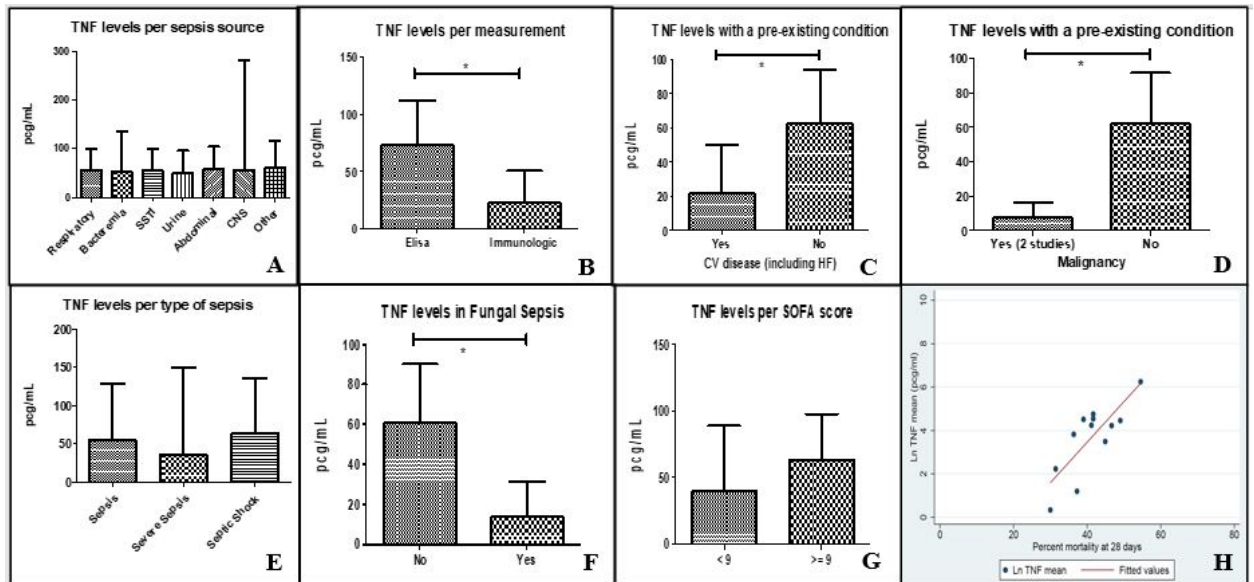


Figure 1: A:  $\text{TNF}\alpha$  levels according to sepsis source. B:  $\text{TNF}\alpha$  levels according to measurement technique. C:  $\text{TNF}\alpha$  levels according to presence or absence of cardiovascular disease. D:  $\text{TNF}\alpha$  levels according to presence or absence of malignancy. E:  $\text{TNF}\alpha$  levels according to sepsis severity. F:  $\text{TNF}\alpha$  levels in fungal compared to other causes of sepsis. G:  $\text{TNF}\alpha$  levels according to SOFA score. H:  $\text{TNF}\alpha$  levels and mortality at 28 days.