Title: Cytokine Levels In Sepsis and TNFα Association with Mortality but not Sepsis Severity or Infection Source: a Systematic Review and Meta-analysis. Omar Samara, MD Candidate in the School of Medicine, Amal A. Gharamti, Anthony Monzon, Lilian Vargas Barahona, Sias Scherger, Kristen DeSanto, Daniel B. Chastain, Stefan Sillau, Carlos Franco-Paredes, Andrés F. Henao-Martínez, Department of Infectious Disease, university of Colorado, Denver, CO, Leland Shapiro

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 TNFα 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)α. 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 TNFα levels, 25 showed interleukin (IL)-1β levels, and 6 presented interferon (IFN)γ levels. The pooled estimate mean TNFα 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-1β, and IFNγ 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 TNFα concentrations are associated with increased 28-day mortality (P=0.001). In a subgroup analysis, TNFα 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 TNFα levels.

Conclusion:

We estimate levels of TNFα, IL-1β, and IFNγ in human sepsis and show TNFα elevations associated with sepsis mortality. TNFα 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.

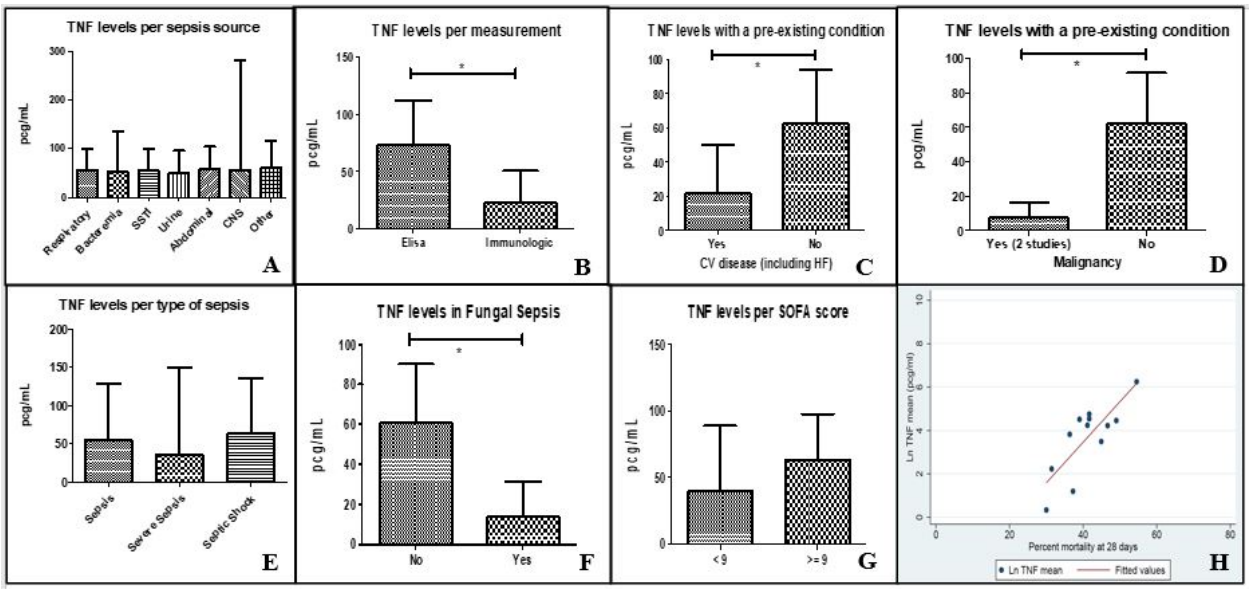

Figure 1: A: TNFα levels according to sepsis source. B: TNFa levels according to measurement technique. C: TNFα levels according to presence or absence of cardiovascular disease. D: TNFα levels according to presence or absence of malignancy. E: TNFα levels according to sepsis severity. F: TNFα levels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