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NPMODS: A sepsis phenotype that provides the “R” and “O” of PIRO Staging

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We appreciate the comments about our manuscript¹ from Baldanzi and Delgado² as well as the editorial by Workman and Larsen.³ Both groups of authors highlight excellent points with which we agree. First, these authors highlight that our manuscript does not offer definitive proof that new or progressive multiple organ dysfunction syndrome (NPMODS) satisfies all criteria for and has been proven to be a surrogate outcome measure for mortality. We agree that for NPMODS to be proven to be an appropriate surrogate for mortality as defined by Prentice, Fleming, and DeMets^{4,5} data are required that demonstrate that reduction or reversal of NPMODS decreases mortality. While this relationship is likely true, to our knowledge, no definitive causative evidence has been reported. Our data do indicate a nearly two-fold higher mortality in patients developing NPMODS regardless of presence or absence of MODS on the first day of sepsis recognition. We feel that this independent correlation between NPMODS and mortality provides further support for a causal relationship between NPMODS and death.

Secondly, as Baldanzi and Delgado suggest, we also concur that understanding which organ system dysfunction persists beyond seven days from sepsis onset would help define the

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characteristics of longer-term morbidities. Unfortunately, because the SPROUT data set was limited to only seven days of data collection about organ dysfunction, we were not able to address this important concern in this study.

Lastly, as both the letter and the editorial indicate, NPMODS by definition occurs after initial presentation and reflects progression of severity of illness that may be affected by therapies occurring after the first day. However, we believe that the independent association of NPMODS with higher mortality and morbidity suggests that NPMODS could be a potential measure of treatment effectiveness. A subsequent hypothesis would be that more effective therapy or therapies would decrease NPMODS. Moreover, because NPMODS most commonly occurs within first 4 days from sepsis recognition, it may represent a more efficient measure of successful treatment both at the bedside and in the conduct of clinical trials.

In essence, as Baldanzi, Delgado, Workman, and Larsen discuss, definitions of sepsis must now incorporate the building body of literature about biomarkers, genotypes, disease-specific characteristics, and patient response over time with and without therapy. Clinicians, researchers, and administrators alike would benefit from a defined mechanism of stratifying morbidity and mortality risk for patients suffering from sepsis. Just as the American Joint Committee on Cancer utilizes a staging system⁶ to define cancer severity, identify best treatment regimens, develop common language, and create clinical trial enrollment criteria, one conceptual framework recommended for a sepsis “staging system” is the PIRO model: **P**redisposition; **I**nfection / **I**nsult; **R**esponse; **O**rgan injury.⁷ NPMODS fulfills the “R” and “O” variables in the PIRO model. The inclusion of organ dysfunction in the “Sepsis-3” definitions⁸ highlights the importance of incorporating life-threatening organ dysfunction in sepsis nomenclature and understanding. We would propose that NPMODS be a further distinguishing feature of “R” and “O” separate from single or presenting organ dysfunction. Certainly, as Workman and Larsen highlight, the growth in understanding the genomic expression of sepsis may allow earlier identification of those with highest risk for NPMODS, morbidity, and mortality. Patient genotype and changes in biomarkers from baseline to illness to convalescence would fulfill the “P” and “R” variables of the PIRO model. Within the PIRO model that would incorporate understanding of the impact of I-Infection / Insult to genomic predisposition and subsequent host response and organ dysfunction, NPMODS indeed fulfills the Merriam-Webster definition of phenotype as “the observable properties of an organism produced by the interaction between genotype and environment.”

Abbreviations

NPMODS	new or progressive multiple organ dysfunction syndrome
SPROUT	Sepsis Prevalence, Outcomes, and Therapy
PIRO	Predisposition, Insult/Infection, Response, Organ dysfunction

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