



When data interpretation should not rely on the magnitude of P values: the example of ANDROMEDA SHOCK trial

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Comment on: Zampieri FG, Damiani LP, Bakker J, *et al.* Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels Among Patients with Septic Shock: A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. *Am J Respir Crit Care Med* 2020;201:423-9.

Submitted Dec 30, 2019. Accepted for publication Jan 08, 2020.

doi: 10.21037/atm.2020.01.49

View this article at: <http://dx.doi.org/10.21037/atm.2020.01.49>

Adequate treatment of patients with septic shock (SS) entails a reliable method to assess the circulatory requirements. A number of different indices have been tested to delineate the hemodynamic profile and to drive the treatment in patients with shock states. However, it is still an unresolved topic. Lactates represents one of the milestone to monitor the perfusion profile and drive hemodynamic resuscitation of patients in SS. High lactates, although are not a direct measure of tissue perfusion, are mainly considered a marker of tissue dysoxia shown to be associated with worst outcome in patients with sepsis and SS (1). However, although the “dysoxia/tissue hypoperfusion/anaerobic glycolysis” is the most commonly interpreted theory for lactates rise in SS, there are several other mechanisms leading to lactates hyper-production and accumulation. These mechanisms include the alteration of Na⁺/K⁺-ATPase activity enhanced by adrenergic stimuli (2), accelerated aerobic glycolysis induced by sepsis-associated inflammation, and the pyruvate accumulation due to mitochondrial pyruvate dehydrogenase reduction activity (3). Additionally, lactates kinetics could be influenced by many different factors (i.e., decreased production, dilution, oxidation, organ utilization as bioenergetic fuel) (4).

The skin is an accessible organ, mirroring the peripheral tissue perfusion through clinical non-invasive bedside

parameters, such as the skin temperatures gradient, capillary refill time (CRT, which is the measure of the time necessary for the skin to return to baseline color after applying a pressure on a soft tissue), and the extent of mottling. The underlying pathophysiology mechanisms inducing skin perfusion modification are not completely understood but seems to be driven by sympathetic neuroactivation inducing local vasoconstriction (5), local endothelial dysfunction (6), leukocyte adhesion and platelet activation (7). Hernandez *et al.* in the ANDROMEDA-SHOCK trial (8) compared CRT to lactate monitor peripheral perfusion for driving the resuscitation treatment in SS patients. Prolonged CRT was already shown to be associated with organ failure and volume responsiveness in patients with circulatory failure (9), as well as to be a predictive factor of 14-days mortality in SS patients after resuscitation (10). The authors showed that a peripheral perfusion-guided resuscitation strategy was associated with lower 28-day mortality when compared to lactate-guided resuscitation strategy (35% *vs.* 43%) in SS patients, even if the difference did not reach the statistical significance (P=0.06) based on the conventional P values threshold. Thus, Hernandez *et al.* concluded that the null hypothesis of their study (absence of difference between peripheral perfusion and lactate-targeted strategies) could not be rejected. Recently, Zampieri *et al.* (11) reported

a Bayesian reanalysis of this trial (8) demonstrating that peripheral perfusion-targeted resuscitation may result in lower mortality when compared to a lactated-targeted resuscitation strategy. We agree with the authors that this 8.5% absolute risk difference in the 28-day mortality observed in the ANDROMEDA-SHOCK trial remains clinically significant despite not yet statistically significant (11). Hernandez *et al.* stating that “among patients with SS, a resuscitation strategy targeting normalization of CRT, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality”, could be misleading for the readers who are at risk of labeling a study which such results as “negative”. Indeed, interpretation of clinical trials can be challenging when dichotomous rules for rejection of the null hypothesis are applied, especially when the P value is close to the arbitrary cutoff. Data analysts too often resort to binary decisions (e.g., whether to reject or accept the null hypothesis) in settings like the ANDROMEDA-SHOCK trial (8), where this may be misleading because the clinical relevance and the physiological plausibility overcome the statistical uncertainty. The question of interest in the testing framework concerns the relative likelihood of the null and alternative hypotheses given the experimental data, but P values are heavily dependent on sample size and even a large effect may not be found in a relatively small sample size. This is the reason because an effect can be relevant even if results are still not significant. In this context, a strict binary view of statistical inference is not useful and may promote the loss of important findings that do not claim the expected level of significance while provide fundamental insight shock pathophysiology. The Bayesian approach may be helpful in contextualizing statistics because can explicitly incorporate external information when interpreting the results of a study, including biological/clinical plausibility. It is important to note as the Bayesian approach differs in many ways from the frequentist approach (12,13): (I) starting with a prior opinion about probability distribution, and then using the posterior probability distribution on the basis of both the data and the prior distribution; (II) prior information is formally incorporated in the design; (III) parameters of interest are unknown random variables; (IV) population parameters are a distribution of values reflecting uncertainty; (V) large sample size are not required; (VI) a 95% credible interval represents the 95% probability that the true value of the unknown parameter is within the limits of the interval; (VII) the P value is defined as the probability of the (null) hypothesis.

Interestingly, Zampieri *et al.* performed their study by

using the R statistical computing environment (14). R, a free and open-source implementation of the S language, has become the lingua franca of the statistical computing (15), Zampieri *et al.* have made available the full R code used for their Bayesian reanalysis, making an important contribution to reproducible research (16).

Circulatory shock is a pathological situation associated with inadequate oxygen utilization by the cells and evidence of both clinical and biochemical tissue hypoperfusion. Currently available variables for the assessment of peripheral hypo-perfusion rely merely on macro-hemodynamics and established non-specific, clinical-biochemical signs. The evaluation of peripheral perfusion and its response to therapy with reliable and widely adoptable parameters has a potential to represent a more sensitive diagnostic and monitoring tool for the comprehensive assessment of cardio-vascular coupling at the bedside of patients in shock states (17). Arterial lactate may be due to the downstream consequences of yet established hypoperfusion with ongoing mitochondrial damage and the shift to anaerobic metabolism, whereas CRT allows a direct and pre-emptive evaluation of the adequacy of peripheral perfusion and its application in the perfusion-targeted resuscitation.

Bayesian analyses as either a primary or a complementary analysis should be considered to contextualized and improve clinical messages of adequately powered RCTs. In the specific case (11), it allowed to demonstrate that CRT driven treatment group was associated with lower mortality and faster resolution of organ dysfunction.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Glenn Hernández and Guo-wei Tu) for the series “Hemodynamic Monitoring in Critically Ill Patients” published in *Annals of Translational Medicine*. The article was reviewed by the Guest Editor Dr. Guo-wei Tu.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.01.49>). The series “Hemodynamic Monitoring in Critically Ill Patients” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Corradi F, Tavazzi G, Santori G, Forfori F. When data interpretation should not rely on the magnitude of P values: the example of ANDROMEDA SHOCK trial. *Ann Transl Med* 2020;8(12):802. doi: 10.21037/atm.2020.01.49