Mallat *Critical Care* (2017) 21:101
DOI 10.1186/s13054-017-1685-2

Critical Care

LETTER Open Access

Understanding the null hypothesis (H_0) in non-inferiority trials

Jihad Mallat[1,2,3]

See related research by Zhou et al., http://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1617-1

I read with great interest the article by Zhou et al. [1] aiming to test whether a lactate-decreasing resuscitation protocol (lactate strategy), compared with central venous oxygen saturation-oriented resuscitation therapy ($ScvO_2$ strategy), would decrease mortality among septic shock patients.

It is not clear why the authors performed a non-inferiority trial (NIT) whereas the primary objective of the study was to establish whether the lactate strategy was "superior" to the $ScvO_2$ strategy [1]. Even though evidence of superiority can be claimed from NITs, there are several fundamental differences between superiority trials and NITs [2]. Whereas superiority trials aim to determine whether a new intervention is superior to the best available one, NITs seek to demonstrate that the new intervention is no worse than the comparator by more than a prespecified, small amount. This amount is known as the non-inferiority margin, or delta (Δ). The null hypothesis (H_0) of superiority trials asserts that there is no true difference between the interventions, and the alternative hypothesis (H_1) states that there is a difference between the interventions. A type I error is the error of rejecting H_0 when it is actually true. A type II error is a failure to reject H_0 when in fact H_1 is true. NITs, by contrast, have a H_0 that the new intervention is inferior or worse than the old by more than – Δ (it is inferior). The H_1 to be proven is that the new intervention is inferior to the standard intervention by less than – Δ (it is not inferior; Fig. 1) [2]. Thus, the definitions of type I and type II errors are reversed for NIT.

In this study, the authors claimed the superiority of the lactate strategy over the $ScvO_2$ strategy because the lactate group had a significantly lower mortality compared with the $ScvO_2$ group (18.3 versus 27.9%, $P = 0.033$). However, the P value that is calculated in NITs is special and is called the P value for non-inferiority, which differs from the P value for superiority [3]. The finding that P value of the difference in mortality was 0.033 means only that H_1 is accepted and the lactate strategy is not inferior to the $ScvO_2$ strategy. To be able to claim superiority, the 95% confidence interval of the mortality difference, which is not provided in this study, should exclude zero (Fig. 1).

Moreover, the non-inferiority margin in this study was 15% [1]. However, the authors did not provide any justification as to why they chose 15 rather than 10% as used in a previous trial [4].

Correspondence: mallatjihad@gmail.com
[1]Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, Lens cedex, France
[2]Intensive Care Unit, Centre Hospitalier d'Arras, Arras, France
Full list of author information is available at the end of the article

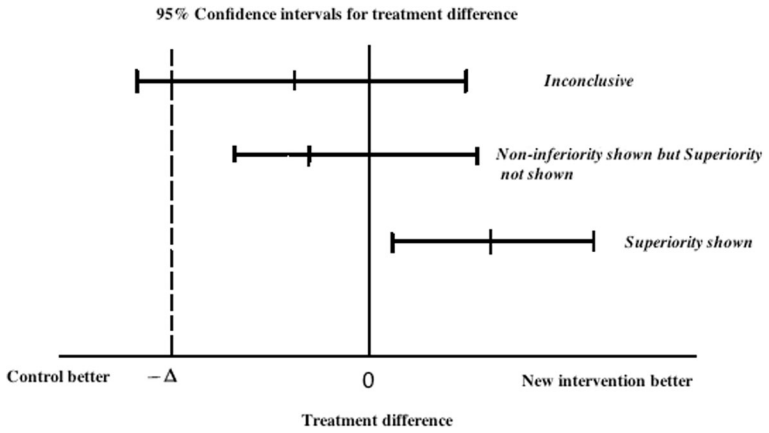

Fig. 1 Different possible scenarios of the results of a non-inferiority clinical trial. Δ is the non-inferiority margin

Abbreviations
NIT: Non-inferiority trial; $ScvO_2$: Central venous oxygen saturation

Acknowledgements
Not applicable.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Authors' contributions
JM drafted, read, and approved the final manuscript.

Competing interests
The author declares that he has no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Publisher's Note

Author details
[1]Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, Lens cedex, France. [2]Intensive Care Unit, Centre Hospitalier d'Arras, Arras, France. [3]Centre Hospitalier du Dr. Schaffner, Service de Réanimation polyvalente, 99 route de La Bassée, 62307 Lens cedex, France.

Published online: 06 May 2017

References

1. Zhou X, Liu D, Su L, Yao B, Long Y, Wang X, Chai W, Cui N, Wang H, Rui X. Use of stepwise lactate kinetics-oriented hemodynamic therapy could improve the clinical outcomes of patients with sepsis-associated hyperlactatemia. Crit Care. 2017;21(1):33.
2. D'Agostino Sr RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. Stat Med. 2003;22(2):169–86.
3. Ferreira-González I. Basis for the interpretation of noninferiority studies: considering the ROCKET–AF, RE-LY, and ARISTOTLE Studies. Rev Esp Cardiol (Engl Ed). 2014;67(6):432–5.
4. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate kinetics vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303(8):739–46.