LETTER TO THE EDITOR

In Light of the LANDI-SEP Trial: New Evidence or Double Jeopardy?

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Sir,

We read with interest the editorial published in the December issue of IJCCM in reference to our meta-analysis on clinical benefits and pitfalls of targeting a lower heart rate in septic shock published in the same issue.[1,2] At the outset we must thank Dr Gudivada for the excellent critical appraisal of our study.

While our article was under the peer review process, the results of the much anticipated LANDI-SEP trial was published.[3] We felt it worthwhile to investigate if including the results of this RCT would change the findings of study.

The LANDI-SEP trial was a large-scale multicentric RCT that investigated the benefit of a similar approach of heart rate lowering in patients with septic shock and persistent tachycardia. It was an open label study that compared a titrated infusion of landiolol in the intervention group to target a heart rate of 80–94 beats/minute vs usual care. The primary outcome of this study was a composite outcome of achievement and maintenance of target heart rate without an increase in vasopressor requirements. While a higher proportion of patients in the landiolol group achieved the primary outcome, there was no difference in secondary outcomes like 28 day mortality, or ICU length of stay.

The use of an approach of lowering of heart rate in septic shock did not translate into any benefit in 28-day mortality compared with the usual care, even after inclusion of LANDI-SEP study (RR: 0.82; 95% CI: 0.66–1.03; $p = 0.03$; $I^2 = 54\%$) (Fig. 1). The revised TSA curve after inclusion of the LANDI-SEP trial is represented in Figure 2. The pooled effect curve now lies within the conventional boundary of uncertainty. The TSA further corroborates our observation that as opposed to earlier studies that showed a trend toward mortality benefit with HR control, the recent studies appear to attenuate this signal.

We are reassured to report to the readers of this journal, that the findings of our meta-analysis remain robust even after including mortality data of LANDI-SEP trial. We would reinforce that the approach of targeted lowering of heart rate should not be done outside the ambit of well-designed RCTs given consistent lack of benefit. It remains to be explored if such a clinical approach of lowering heart rate is beneficial in patients with higher baseline rate or in specific subclusters of patients with septic shock.

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Study or subgroup	Heart rate control Events	Total	Standard care Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Morelli, 2013	38	77	62	77	18.3%	0.61 [0.48, 0.79]	2013
Xinqiang, 2015	6	24	15	24	6.4%	0.40 [0.19, 0.85]	2015
Wang, 2017	9	30	11	30	6.9%	0.82 [0.40, 1.68]	2017
Liu, 2019	31	50	34	50	17.1%	0.91 [0.68, 1.22]	2019
Kakihana, 2020	9	75	15	75	6.4%	0.60 [0.28, 1.29]	2020
Datta, 2021	18	30	22	30	14.6%	0.82 [0.57, 1.18]	2021
Michael, 2022	6	33	8	36	4.5%	0.82 [0.32, 2.11]	2022
Whitehouse, 2023	23	62	16	63	10.1%	1.46 [0.86, 2.49]	2023
Rehberg, 2024	43	98	39	98	15.7%	1.10 [0.79, 1.53]	2024
Total (95% CI)		**479**		**483**	**100.0%**	**0.82 [0.66, 1.03]**	
Total events	183		222				

Heterogeneity: Tau² = 0.06; Chi² = 17.38, df = 8 ($p = 0.03$); I² = 54%
Test for overall effect: Z = 1.70 ($p = 0.09$)

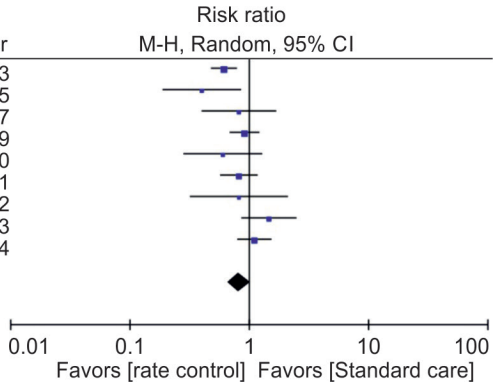

Fig. 1: A forest plot of 28-day mortality between rate control and standard care group after including LANDI-SEP study

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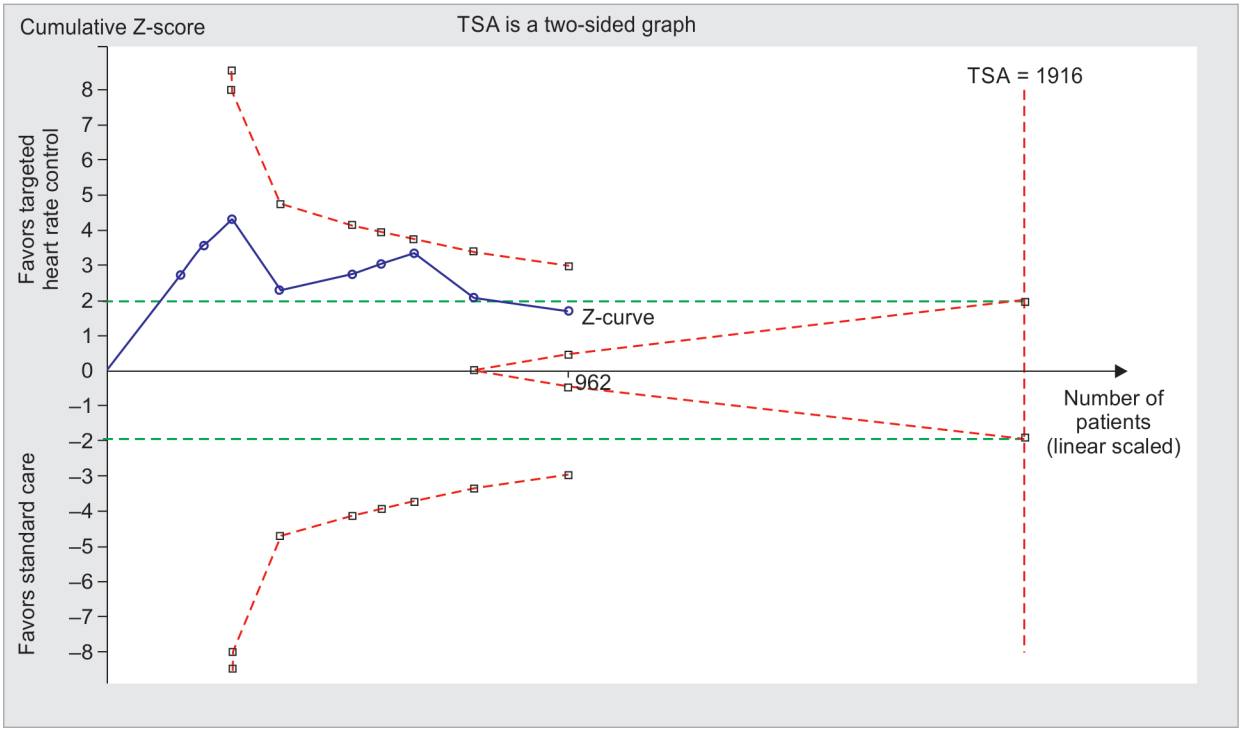

Fig. 2: Trial sequential analysis of 28-day mortality. The uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm and benefit, respectively. Horizontal lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary. The cumulative Z-curve represents the trial data. Pooled effect size with alpha-spending adjusted CI: RR = 0.82 (CI: 0.59–1.16), *p*-value = 0.0886. New diversity adjusted RIS = 1916

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