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Editorial

Look at the Fragility Index of Randomized Controlled Trials

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Two groundbreaking trials, the EOLIA trial and the PARAMEDIC II trial, were just published in the 2018 in New England Journal of Medicine. Those trials added new knowledge to the current literature about extracorporeal membrane oxygenation (ECMO) and out of hospital cardiac arrest (OHCA) since they reached a statistical significance. However, we looked at those trials from the point of view of the fragility index (FI), an intuitive measure of the robustness of randomized controlled trials (RCTs) recently introduced in critical care medicine.

The EOLIA study

Acute respiratory distress syndrome (ARDS) is one of the main causes of mortality in critically ill patients [1]. The use of extracorporeal technology in the management of ARDS has been improved in the past decade [2]. Recently, we read with great interest the paper by Combes et al (EOLIA trial) showing, in patients with acute respiratory distress syndrome (ARDS), a 60-day mortality of 35% in extracorporeal membrane oxygenation (ECMO) group and of 46% in control group (p = 0.09) with a crossover to ECMO of 35 patients [3]. According to this, the authors concluded that there was no significant benefit of early ECMO over conventional strategy in ARDS [3]. On the contrary, the most recent trial about the use of ECMO in ARDS, the CESAR trial, reported a significant improvement in 6-month survival in patients transferred to a specialist center for ECMO treatment compared with conventional strategies [4].

According to FI, the studies with larger FI have more robust findings compared with the studies with poor FI [5,6]. Since low fragility index in critical care trials reinforced the finding that the robustness of evidence available to clinical decision makers in this setting is limited and perhaps more limited than previously appreciated, we calculated the FI by using a two-by-two contingency table and p-value produced by Fisher exact test for the EOLIA and CESAR trials [3-5].

We found that the FIs of the study by Combes., *et al.* and Peek., *et al.* were equal to zero, even considering all the possible combination of patient groups for the study by Combes., *et al.* (Table 1). Gattinoni., *et al.* in their editorial asked if these studies on ECMO in ARDS may change the clinical practice or ECMO use [7]. We agree with Gattinoni., *et al.* that statistics in an operational tool [7], indeed we urged the critical care physicians to not trust p value but to look at the FI of randomized controlled trials to change their clinical practice.

	ECMO group (124)	**Control Group (125)**	**FI (p)**
Mortality at 60 days	44	57	0 (0.122)
	ECMO group (124)	No ECMO crossover (90)	FI (p)
Mortality at 60 days	44	37	0 (0,476)
	ECMO group + crossover (159)	No ECMO crossover (90)	FI (p)
Mortality at 60 days	64	37	0 (0.0894)
	ECMO group + crossover (159)	Crossover group (35)	FI (p)
Mortality at 60 days	64	20	0 (0.089)
	Crossover group (35)	No ECMO crossover (90)	FI (p)
Mortality at 60 days	20	37	0 (0.115)
	ECMO group (90)	Control group (90)	
CESAR trial 180-day mortality	33	44	0 (0.132)

Table 1: *Fragility index (FI) for studies by Combes., et al. [3] and Peek., et al [4].*

The PARAMEDIC II study

The paper by Perkins found a significant higher rate of 30-day survival in epinephrine group compared with placebo group by using epinephrine in out-of-hospital cardiac arrest (OHCA) [8]. This survival rate was very small and associated with no improvement in functional recovery [9].

The FI indicated how many patients would be required to convert a trial from being statistically significant to not significant ($p \geq 0.05$) [5]. Using a two-by-two contingency table and p-value produced by Fisher exact test, we calculated the FI for the RCT by Perkins., *et al* [8,10]. We found a FI of 6. This means that if we add 6 patients to the control group, the primary outcome of the study by Perkins., *et al.* will lose its statistical significance. According to this, we must ponder whether the epinephrine use during resuscitation for OHCA is really effective for improving 30-days survival.

Conclusions

We strongly recommend to evaluate the RCTs with the FI since the challenge is that not robust studies may guide the medical decisions in clinical practice.

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