

More is exponentially less: marginal utility in critical care research

Mais é exponencialmente menos: utilidade marginal na pesquisa de cuidados intensivos

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ABSTRACT | BACKGROUND: Randomized clinical trials (RCT) in critical care mostly return negative results. The research community discusses strategies to improve RCTs design. **METHODS:** This paper presents a theoretical framework based on marginal utility to treat the problems of hypothesis generation and treatment effects valuation and presents recently published high-quality studies as instances where such a framework predicts irrelevant findings. **RESULTS:** Blindness to marginal utility, i.e., inobservance of the marginal utility of the proposed intervention, is common in critical care RCTs. **CONCLUSION:** Critical care RCTs are usually blind to marginal utility and are, therefore, prone to produce irrelevant findings.

KEYWORDS: Clinical trials. Critical care. Intensive care. Marginal utility. Cognitive bias.

RESUMO | FUNDAMENTO: Ensaios clínicos randomizados (ECRs) em cuidados intensivos, em sua maioria, retornam resultados negativos. A comunidade de pesquisa discute estratégias para melhorar o design dos ECRs. **MÉTODOS:** Este artigo apresenta uma estrutura teórica baseada na utilidade marginal para tratar os problemas de geração de hipóteses e avaliação de efeitos de tratamento, e apresenta estudos de alta qualidade recentemente publicados como instâncias em que tal estrutura prevê achados irrelevantes. **RESULTADOS:** A cegueira para a utilidade marginal, ou seja, a inobservância da utilidade marginal da intervenção proposta, é comum em ECRs de cuidados intensivos. **CONCLUSÃO:** ECRs de cuidados intensivos geralmente são cegos para a utilidade marginal e, portanto, são propensos a produzir achados irrelevantes.

PALAVRAS-CHAVE: Ensaios clínicos. Cuidados intensivos. Tratamento intensivo. Utilidade marginal. Viés cognitivo.

Introduction

It is notorious that randomized clinical trials (RCT) in critical care are prone to return negative results, especially if the study outcome is mortality. A bias towards treatment effects overestimation is considered a leading cause of negative trials. Prior estimates of treatment effect in recent RCTs commonly reached a 10% reduction in mortality, an estimate that proved optimistic when confronted with actual studies results and prior estimates provided by clinicians.^{1,2} Authors have even raised the hypothesis that most therapies for critical illness may be, in fact, inefficacious.^{3,4}

This article introduces a conceptual framework to discuss the plausibility of finding efficacious therapies in a multi-comorbidities, multi-intervention environment and then turns to medical literature to find instances where the framework applies. The main points of such a framework are now presented.

The additive paradigm

A clinical trial of streptomycin plus bed rest versus bed rest alone for the treatment of tuberculosis had a plausible potential for producing a 10% reduction in mortality.⁵ Now, let us examine a trial including patients with Acute Respiratory Distress Syndrome (ARDS) already receiving (1) oxygen, (2) positive pressure ventilation, (3) positive end-expiratory pressure (PEEP), (4) a high-PEEP, low tidal volume strategy, (5) vasopressors as necessary, (6) hemodialysis if indicated, (7) protocol-directed sedation, (8) early neuromuscular blockade, (9) a restrictive fluid strategy, (10) prone positioning if severely hypoxemic, (11) antibiotics as necessary, (12) respiratory care, (13) prophylactic measures for nosocomial infections, (14) prophylactic measures for venous thrombosis, (15) early mobilization, (16) nutritional support, and (17) glycemic control. The RCT protocol randomizes these patients to either receive or not receive a candidate therapy. Considering the combined effect of concurrent therapies on mortality, is there a remaining effect to be reaped? Can the addition of the 18th intervention cause a 10% decrease in mortality?

The *additive paradigm* is the assumption that each added therapy bears a significant effect and that

researchers should, therefore, test the efficacy of additional therapies.

Marginal Utility

We can borrow the concept of Marginal Utility from Economics to study the efficacy of adding new therapies.⁶ Utility refers to the benefit or satisfaction resulting from a unit of a good or service. Marginal utility is the benefit of an additional unit of the good or service. Consider the benefit of having a glass of water after three days in the desert. The second glass would also be very satisfactory. The marginal (residual) utility (benefit) of the 10th straight glass would be close to zero or even negative, causing more harm than good. The returns are incrementally smaller, *i.e.*, diminishing, as units of the good or service add. In the research, as well as in the clinical scenario, the marginal utility of every new therapy is expected to be incrementally smaller. In the limit, the effect becomes insignificant.

Reductio ad absurdum

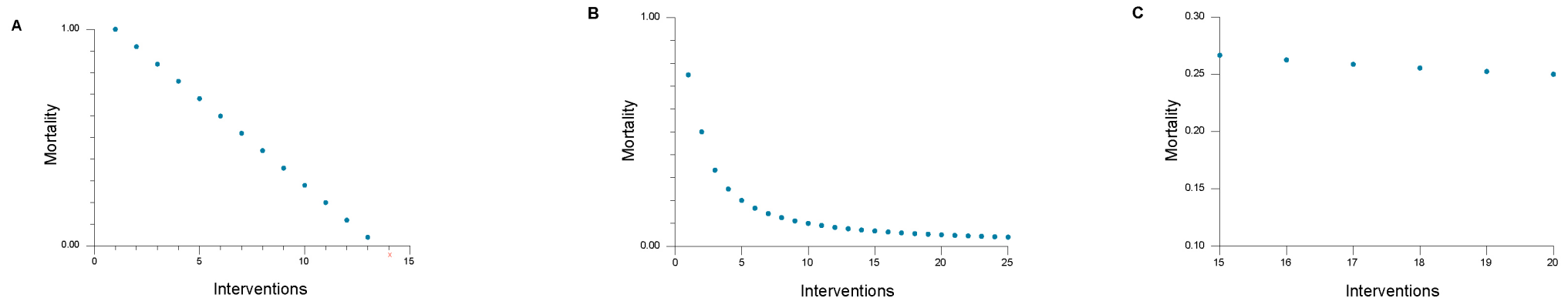
The idea above is graphically demonstrated in Figure 1. Consider a graph with a y-axis representing mortality (or another outcome) and an x-axis designating the number of therapies. Let the axes cross at $x=0$ and $y=0$. Under the additive paradigm, the addition of therapies translates into a simple equation $[y = e_1 + e_2 + e_3 + \dots + e_i]$ where "y" stands for the net clinical effect, "e" is the effect for each therapy already present in both the intervention and control groups, and "ei" the assumed effect size of the intervention under study. *Reductio ad absurdum*⁷, the additive paradigm eventually reaches absurd consequences such as less than 0% mortality as treatments keep adding (Figure 1, A).

To avoid overestimation, an estimate of the treatment effect of additional interventions should observe that as the number of interventions increases, marginal utility shrinks. Hence, the marginal utility of the 18th intervention sits between the marginal utility of the 17th intervention and zero. The same applies whenever other intervention stacks up. The process fits best as an exponential function with any exponent below one and above zero, e.g. $[y = i^{0.45}]$, where "i" stands for the number of therapies (Figure 1, B).

The Edge of Irrelevance

The corollary, as the marginal utility compresses, the effect signal becomes too small to be captured by an RCT. This boundary is The Edge of Irrelevance. Beyond the edge of irrelevance, RCTs of a new therapy for a given critical care syndrome monotonously return negative results due to decreasing marginal utility. The continuous stream of critical care RCTs showing non-significant effects is the consequence of a flattened marginal utility curve (Figure 1, C).

Figure 1. Additional treatments effect on mortality



- A. Failing to consider marginal utility. The estimate absurdly implies there is always a significant amount of mortality reduction to be added by the new therapy, eventually leading to zero or less-than-zero mortality as interventions add.
- B. Taking marginal utility into account. A few interventions dominate the treatment effect. The marginal (residual) utility (benefit) of any additional therapy lies between the cumulative effect of current interventions and zero.
- C. Beyond the edge of irrelevance. The treatment effects are so compressed that they go undetected by clinical trials. The edge of irrelevance is the limit of the additive paradigm.

The three types of marginal utility

Any assumption of efficacy built upon the additive paradigm is likely to be wrong.

Marginal treatment is a therapy that adds to current therapies and is prone to produce marginal returns, as exemplified above in the hypothetical ARDS trial. Marginal intensity is present when adding more units of a treatment yields diminishing returns.

Finally, comorbidities do not concur equally with the outcome. The relative contribution of each concurrent condition to the outcome may also be framed in terms of marginal utility. Utility, in this case, is measured as the contribution of each associated disease or physiologic derangement to the outcome. Marginal causes are the associated conditions that contribute marginally to the disease process, thus, providing only marginal opportunities for improving the net clinical result.

Depending on the nature of the candidate therapy, the hypothetical ARDS trial could be a case of marginal treatment (e.g., adding an alveolar recruitment maneuver), marginal intensity (e.g., applying lower or higher levels of inspired oxygen, PEEP, tidal volume, hours in prone position, etc.) or marginal cause (e.g., blocking a metabolic pathway not dominantly related to the outcome).

Distribution of the relative size of marginal efficacy of therapies

Being all the interventions subject to a power law, it is expected that only a few will provide the bulk of clinical effects, e.g., any mechanical ventilation for ARDS, whereas the majority will fall on the long tail of marginal, irrelevant interventions (Fig 1.B). The distribution may be roughly represented by popular power law distribution rules such as the Pareto Principle (80% of effects come from 20% of causes).

Dominance

The interventions that currently provide the best part of treatment results are the dominant interventions. These must be challenged if the researcher aims to reach a real breakthrough in critical care. The dominant interventions are always targeted at the dominant causes, the conditions that explain most of the outcome incidence. Dominant causes/interventions are, therefore, central to the disease/intervention process, whereas marginal interventions or causes lie peripherally. A better understanding of pathophysiology in critical care syndromes may provide insight into tailoring an intervention capable

of defying the current pairs of dominant causes and interventions. Moreover, the researcher and the clinician should observe that dominance changes as patients survive through the course of critical illness.

Harm is not subjected to diminishing returns

As different interventions add, the probability of having a harmful interaction increases indefinitely. Hence, there is a point where the potential harm of adding an intervention exceeds the potential benefits.

Cognitive bias

Despite the best research efforts, the relentless decades-long stride of negative trials in critical care suggests a biased approach to the estimation of effects sizes. *Blindness to Marginal Utility*, i.e., failing to consider the marginal utility of the proposed intervention, is a cognitive bias that leads to treatment effects overestimating. Finally, it is important to emphasize that it applies to any outcome, not only mortality.

Methods and Results

Critical care research articles recently published in two high-quality medical journals were searched to find 20 illustrative examples of Blindness to Marginal Utility.⁸⁻²⁷ This does not intend to be a systematic review or comprehensive list but rather to provide different instances of the interpretation of marginality. Results are displayed in Table 1.

Table 1. Representative instances of trials testing marginal effects (to be continued)

Authors	Scenario	Dominant Cause	Dominant Intervention	Hypothesis	Case	Comment
Dankiewicz et al., NEJM 2021 ⁸	Post-cardiac arrest care	Anoxic encephalopathy, myocardial dysfunction, the cause that immediately led to the cardiac arrest	Supportive care, specific care targeting the leading cause of the cardiac arrest	Inducing lower body temperature early after the cardiac arrest reduces mortality in six months	Marginal Cause	Tests the effect on mortality of treating a condition (normothermia) that is marginal to the causal pathway to death.
Schjørring et al., NEJM 2021 ⁹	Mechanically ventilated patients	Hypoxemic ventilatory failure	Supplemental oxygen, mechanical ventilation.	A lower target for partial pressure of arterial oxygen (PaO ₂) yields lower mortality.	Marginal Intensity	Supplemental oxygen is a dominant therapy targeted at a dominant cause of death (hypoxia). The trial tests the marginal utility of additional oxygen.
Hughes et al., NEJM 2021 ¹⁰	Mechanically ventilated sepsis patients	Dysregulated immune response to an infection, ventilatory failure.	Antibiotics, mechanical ventilation	Propofol or dexmedetomidine differently affect arousability, immunity, and inflammation; therefore could affect outcomes differently.	Marginal Treatment	The trial studies the marginal effect of the two sedatives in patients at the same degree of sedation. Targets some inflammatory pathways in the overwhelmingly complex immune response observed in septic patients.
Olsen et al., NEJM 2020 ¹¹	Mechanically ventilated patients	Ventilatory failure	Mechanical ventilation	Light sedation with daily interruption is associated with higher mortality, as compared to no sedation.	Marginal Treatment	Tests for the presence of a marginal harmful effect of light sedation.

Table 1. Representative instances of trials testing marginal effects (continuation)

Authors	Scenario	Dominant Cause	Dominant Intervention	Hypothesis	Case	Comment
Shehaby et al, NEJM 2019 ¹²	Mechanically ventilated patients that required sedation	Ventilatory failure	Mechanical ventilation	Sedation with dexmedetomidine lowers mortality as compared to sedation with other agents.	Marginal Treatment	At the same sedation levels, individual effects of sedatives are marginal to the disease process.
The PETAL investigators, NEJM 2019 ¹³	Acute Respiratory Distress Syndrome on a high PEEP strategy	Hypoxemic ventilatory failure	Mechanical ventilation	Adding neuromuscular blockade decreases mortality	Marginal Treatment	The prototypical marginal intervention
Arabi et al., NEJM 2019 ¹⁴	Thromboprophylaxis in critical care	Poorly described. Immobilization, pro-coagulant estases.	Mobilization, prophylactic anticoagulants	The addition of intermittent pneumatic compression to pharmacologic thromboprophylaxis results in a lower incidence of deep vein thrombosis or other outcomes such as pulmonary thromboembolism and death.	Marginal Treatment, and also a Marginal Cause for the mortality outcome	Explores the marginal effect of an additional intervention for the prophylaxis of a pre-clinical outcome, assuming a mechanistic link with relevant clinical outcomes.

Table 1. Representative instances of trials testing marginal effects (continuation)

Authors	Scenario	Dominant Cause	Dominant Intervention	Hypothesis	Case	Comment
François et al., NEJM 2019 ¹⁵	Post-cardiac arrest care	Anoxic encephalopathy, myocardial dysfunction, the cause that immediately led to the cardiac arrest.	Supportive care, specific care targeting the leading cause of the cardiac arrest.	Prophylactic antibiotics reduce early-onset pneumonia and, therefore, death.	Marginal Cause	Early-onset pneumonia is a marginal cause of death.
Krag et al., NEJM 2018 ¹⁶	Prevention of stress ulcers in critical care patients	Concurrent causes: mucosal atrophy, acidic luminal environment, poor gastric perfusion	Unknown. Better supportive care and earlier enteral nutrition also appear to play a role in stress ulcer prevention	Pantoprazole reduces mortality	Marginal Treatment of a Marginal Cause	Explores the marginal effect of an additional intervention for the prophylaxis of stress ulcers, wrongly assuming a dominant mechanistic link with mortality
The TARGET investigators, NEJM 2018 ¹⁷	Mechanically ventilated patients	Ventilatory failure	Mechanical ventilation	Higher caloric intake reduces mortality	Marginal Cause	The treatment does not target the dominant cause
Sevransky et al., JAMA 2021 ¹⁸	Sepsis and cardiovascular or ventilatory failure	Dysregulated immune response to an infection	Antibiotics, supportive care	Vitamin C, thiamine, and hydrocortisone reduce mortality	Marginal Cause	C vitamin, thiamine, or hydrocortisone deficits are marginal causes of death.
Johnstone et al., JAMA 2021 ¹⁹	Mechanically ventilated patients predictably at risk for incident ventilator-associated pneumonia (VAP).	Microaspiration due to the presence of the endotracheal tube is associated with oral, and pharyngeal colonization	VAP prevention bundles	Treating dysbiosis with probiotics reduces VAP incidence	Marginal Cause	Misses the dominant cause.

Table 1. Representative instances of trials testing marginal effects (continuation)

Authors	Scenario	Dominant Cause	Dominant Intervention	Hypothesis	Case	Comment
The RELAX Collaborative Group, JAMA 2020 ²⁰	Mechanically ventilated patients	Ventilatory failure	Mechanical ventilation	Lower PEEP is non-inferior to higher PEEP in non-ARDS patients	Marginal Intensity	Tests the marginal effects of PEEP levels
The PEPTIC Investigators, JAMA 2020 ²¹	Prevention of stress ulcers in mechanically ventilated patients	Concurrent causes: mucosal atrophy, acidic luminal environment, poor gastric perfusion	Unknown. Better supportive care and earlier enteral nutrition also appear to play a role in stress ulcer prevention	Proton-pump inhibitors and histamine-2 receptor blockers associate with different mortality rates	Marginal Treatments of a Marginal Cause	Both therapies aim to reduce acidity in the gastric lumen, a marginal driver of a marginal cause of mortality.
Lamontagne et al., JAMA 2020 ²²	Elderly patients with vasodilatory hypotension	Reduced blood flow in vasoconstriction vascular beds due to vasopressors	Standard mean arterial pressure (MAP) targets	A lower MAP target reduces mortality due to less vasopressors use	Marginal Intensity	Tests the marginal effects of vasopressors dosages
Laterre et al., JAMA 2019 ²³	Septic shock patients on norepinephrine	Hypotension	Vasopressor	Adding another vasopressor reduces ventilator- and vasopressor-free days	Marginal Treatment	Once the patient is on norepinephrine, the second vasopressor effect is marginal.
the PROBESE Collaborative Group, JAMA 2019 ²⁴	Obese patients undergoing surgery	Need for short-term mechanical ventilation during surgery	Conventional mechanical ventilation	The addition of alveolar recruitment and higher PEEP is associated with fewer pulmonary complications	Marginal Treatment (alveolar recruitment) and Marginal Intensity (PEEP levels)	Exemplifies the dynamics of marginal utility by adding two marginal interventions

Table 1. Representative instances of trials testing marginal effects (conclusion)

Authors	Scenario	Dominant Cause	Dominant Intervention	Hypothesis	Case	Comment
Vincent et al., JAMA 2019 ²⁵	Sepsis-associated coagulopathy	Dysregulated immune response to an infection associated with coagulopathy	Antibiotics, supportive care	Recombinant human soluble thrombomodulin reduces mortality.	Marginal Treatment	Acts on one out of an unknown number of dysregulated pathways in sepsis.
Azoulay et al., JAMA 2018 ²⁶	immunocompromised patients with acute hypoxemic respiratory failure	Hypoxia	Supplemental oxygen	Oxygen delivered non-invasively on a high-flow device is associated with lower mortality	Marginal Intensity	Tested for the marginal effect of oxygen therapy at different levels
the PREVENT Investigators, JAMA 2018 ²⁷	Mechanically ventilated patients without ARDS	Ventilatory failure	Mechanical ventilation	A ventilation strategy with lower tidal volume improves mortality	Marginal Intensity	Tests the marginal utility of tidal volumes keeping the same minute ventilation.

Discussion

The main result is that blindness to marginal utility is frequently found in critical care RCTs and that marginal effect sizes are common.

In the last years, the critical care community witnessed notable advances in the design and size (power) of clinical trials. Methodologically robust trials planned and performed by highly skilled researchers now avoid false-positive results caused by systematic and aleatory errors. The improvement in RCTs design enabled the realization that the proposed interventions are mostly inefficacious.

The research community acknowledges the challenge and has put forward suggestions to improve clinical trial design and find statistically significant effects. These suggestions span from improving patient selection and sample size calculations to a flexible trial design and targeting outcomes other than mortality.²⁸ However, "delta inflation", an optimistic mortality estimate in the intervention group combined or not with overestimated mortality in the control group, is common and suffices to explain the lack of positive results.²⁹ Although practical concerns on trial costs, size, and feasibility may lead to delta inflation, blindness to marginal utility is likely to be the root cause of delta inflation in many trials.

Clinical trials of ARDS and sepsis, both poorly defined syndromes, usually fail because of the teleological "find a patient for a treatment" approach of current diagnostic criteria. These definitions lack specific mechanistic reasoning but rather offer a triage tool for selecting patients for a generic treatment strategy (e.g., antibiotics in the first hour). Therefore, such disease models will not single out a targetable pathophysiological hallmark, *i.e.*, a dominant cause that is not observable at the bedside.

Current ARDS definitions do not go further than pointing to hypoxemia as the sole treatable condition.³⁰ Hence, hypoxemic ventilatory failure is currently the dominant cause of mortality and as a

consequence, RCTs of added therapies to improve ventilatory support are subjected to marginal utility as trials of marginal treatments or marginal intensity of treatments. These RCTs and those on marginal causes (e.g., a metabolic pathway) will predictably land beyond the edge of irrelevance until a stronger disease model emerges. Not surprisingly, an ARDS drug trials overhaul was called, highlighting that the dominant cause of death may differ among patients.³¹ Regarding sepsis, current definitions do not indicate a targetable condition other than a presumed infection.³² Indeed, the very word "sepsis" does not add meaning to "complicated infection". Thus, the dominant pair of infection/antibiotics will last until a new pathophysiological model sets a new dominance. The sepsis research pipeline has stalled with the realization that better development of appropriate targets in pre-clinical research is needed.³³ Such a model shall come from a better understanding of the basic molecular mechanisms of the multiple phenotypes.³⁴

Furthermore, due to the distribution of marginal efficacy of therapies, it is expected that a comprehensive model that points to several causes but fails to identify a dominant cause is also doomed to be unsuccessful. Take the dominant pairs coronary thrombosis/thrombolysis and H. pylori infection/eradication in comparison to the hypothesis that using insulin to achieve tight glycemic control reduces mortality in the critically ill by (1) avoiding cellular glucose overload, which in turn promotes free radicals formation, and ultimately leads to apoptosis; (2) avoiding hyperglycemia-associated impaired immune response, regarding macrophages; (3) reducing susceptibility to nosocomial infections; (4) amelioration of dyslipidemia; (5) anabolic effects on muscle; and (6) promoting vasodilation.³⁵ The corollary is that if one can not identify a single straightforward reason why an intervention should work, the odds are that the intervention will not work.

In conclusion, blindness to marginal utility results in poor research hypotheses. Recent studies have shown the irrelevance of such hypothesis.

Conflicts of interest

No financial, legal or political conflicts involving third parties (government, corporations and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to grants and funding, advisory board participation, study design, preparation of manuscript, statistical analysis, etc.).

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