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ORIGINAL ARTICLE

Desirability of outcome ranking (DOOR) for comparing diagnostic tools and early therapeutic choices in patients with suspected candidemia

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Abstract

Desirability of outcome ranking (DOOR) has been developed for assessing desirability of outcome in interventional studies. However, its possible use in observational studies of the diagnosis and early treatment of infectious diseases has not been explored so far, and it might introduce interesting features in specific scenarios. This was a post hoc analysis of a prospective observational study in intensive care unit patients with sepsis and at risk of candidemia. The probabilities that a randomly selected patient would have a more, less, and equally cost-effective early therapeutic choice following a BDG-based diagnostic strategy rather than the empirical administration of antifungals to all patients were calculated using DOOR methods. The probability of a more cost-effective therapeutic choice following the BDG-based rather than the empirical strategy was 67.81% (95% CI 67.32–68.30), whereas the probabilities of a less and equally cost-effective early therapeutic choice were 19.68% (95% CI 19.27–20.10) and 12.50% (95% CI 12.16–12.85), respectively. The application of DOOR methods to observational studies focused on diagnosis and early treatment is a novel field that could merit further investigation.

Keywords DOOR · Glucan · Candidemia · Diagnosis · Biomarker

Background

Desirability of outcome ranking (DOOR) is an innovative approach to compare different antibiotic therapies in randomized clinical trials [1]. It involves ranking of trial participants in terms of desirability of their overall outcome, considering both benefits and harms [1, 2].

While DOOR has been developed for assessing desirability of outcome in interventional studies, its possible use in observational studies focused on the diagnosis and early treatment

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of infectious diseases has not been explored so far, although it might introduce interesting features in specific scenarios.

For example, a suitable observational framework is the early diagnosis of candidemia (i.e., pending blood culture results) in patients with signs and symptoms of sepsis, defining the outcome as a composite endpoint of empirical antifungal choices and blood culture results, and assuming empirical antibacterials are universally administered. More in detail, outcomes could be arbitrarily ranked in terms of cost-effectiveness, from the most to the least desirable: (*i*) initiation or continuation of empirical antifungals followed by positive blood cultures for *Candida* (i.e., early antifungal in a patient with candidemia, in whom early antifungals might favorably impact survival; outcome coding = 4); (*ii*) non-initiation or discontinuation of empirical antifungals followed by negative blood cultures for *Candida* (i.e., avoidance of side effects and costs of antifungals in a patient without candidemia, in whom early antifungals have likely no effect on survival; outcome coding = 3); (*iii*) initiation or continuation of empirical antifungals followed by negative blood cultures for *Candida* (i.e., possible side effects and increased costs of antifungals in a patient without candidemia, in whom early antifungals have likely no effect on survival; outcome coding = 2); (*iv*) non-initiation or discontinuation of empirical antifungals followed by positive blood cultures for *Candida* (i.e., no early antifungal therapy in a patient with candidemia, in whom the lack of early antifungals might unfavorably impact survival; outcome coding = 1). In other words, DOOR principles might serve as a useful tool to compare different diagnostic strategies, with two important characteristics: (*i*) the inclusion of therapeutic considerations and (*ii*) the possibility of summarizing the comparison of different diagnostic strategies in a unique measure. Of note, this summary measure takes into account both sensitivity and specificity, and it allows to define which of the two matters the most (for example, in the proposed scenario, sensitivity will weigh more than specificity, since we consider early treatment of candidemia as the priority).

In the present post hoc analysis of a previously published prospective observational study in intensive care unit (ICU) patients with sepsis and at risk of candidemia [3], we used a DOOR approach to compare the desirability of outcome (i.e., cost-effectiveness of early therapeutic choices according to blood culture results available subsequently) of an early therapeutic strategy based on serum (1,3)-β-D-glucan (BDG) results vs. empirical antifungals for all subject at risk.

Materials and methods

Study design and setting

The original prospective study was conducted in an adult ICU ward at Policlinico Agostino Gemelli, a 1200-bed teaching hospital in Rome, Italy [3]. From January 2012 to June 2014, all consecutive critically ill patients fulfilling all the following criteria were included in the study: (*i*) length of stay in ICU of at least 96 h; (*ii*) clinical signs and/or symptoms of sepsis at the time of serum BDG testing; (*iii*) at least 3 points according to the Candida score prediction rule for invasive candidiasis [3, 4]. The complete flow chart of the patient inclusion process and the full characteristics of the study population are detailed elsewhere [3]. Briefly, 198 patients were included, and the use of a BDG-based antifungal therapy approach (initiating/continuing empirical antifungals if BDG ≥ 80 pg/mL and/or clinical suspicion of deep-seated candidiasis; non-initiating/discontinuing empirical antifungals if BDG < 80 pg/mL and no suspicion of deep-seated candidiasis) allowed to avoid unnecessary empirical antifungals in ~ 73% of potentially treatable patients and to early discontinue them in another ~ 20% [3].

Definitions

In the present post hoc analysis, the two diagnostic/therapeutic strategies to be compared through a DOOR approach were defined as follows: (*i*) a BDG-based strategy as in the original study (initiation/continuation of antifungals if BDG ≥ 80 pg/mL; non-initiation/discontinuation of antifungals if BDG < 80 pg/mL) and (*ii*) a hypothetical empirical strategy (initiation/continuation of antifungals in all the patients included in the study, based on their high baseline risk [Candida score ≥ 3]). Patients with suspicion of deep-seated candidiasis ($n = 12$) were excluded from the present analysis, since they would have initiated/continued early antifungals independent of the strategy used and BDG results.

Statistical analysis

The probabilities that a randomly selected patient would have a more, less, or equally cost-effective early therapeutic choice if assigned to the BDG-based rather than to the empirical strategy were calculated using DOOR methods. Briefly, all patients were considered both as cases (BDG-based strategy) and controls (empirical strategy). Then, the number of controls with lower, higher, and equal DOOR in terms of cost-effectiveness (in this study, equivalent to the number of controls with lower, higher, and equal outcome coding, respectively) was calculated for each patient, added up, and divided for the total number of pairwise comparisons, to obtain the above-mentioned probabilities. The normally distributed 95% confidence intervals (CI) were calculated for each probability.

In this study, we hypothesized the absence of effects due to the non-independence of cases and controls in some pairwise comparisons (i.e., when a patient was at the same time the case and his/her control), since any possible individual propensity to display low or high BDG values (independent of

candidemia) would have affected the therapeutic choice only in cases (BDG-based strategy) and not in controls (empirical strategy). To verify this hypothesis, we also conducted 100,000 simulations with random assignment. In each simulation, we assigned 50% of patients to the BDG-based strategy (cases) and 50% to the empirical strategy (controls). We kept the population prevalence of candidemia (26%) fixed and equal in cases and controls in each simulation, to avoid changes in prevalence that could have influenced the measured probabilities.

In each simulation, we computed the probabilities of a more, less, and equally cost-effective early therapeutic choice if a patient is assigned to the BDG-based rather than to the empirical strategy, with the same methods described above. Then, the mean probabilities of a more, less, and equally cost-effective therapeutic choice, with their mean 95% CI added with the standard error of the respective mean, were calculated from all 100,000 simulations.

All the analyses were performed using R Statistical Software version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 186 patients were included in the present analysis (see Fig. 1). As shown in Table 1 and in supplementary material (Table S1, reporting all calculated values), the probability of a more cost-effective therapeutic choice by using the BDG-based rather than the empirical strategy was 67.81% (95% CI 67.32–68.30), whereas the probabilities of a less and equally cost-effective early therapeutic choice were 19.68% (95% CI 19.27–20.10) and 12.50% (95% CI 12.16–12.85), respectively.

The mean probabilities obtained from the 100,000 simulations were in line with the probabilities obtained when all patients were considered both as cases and controls, thereby testifying to the absence of any relevant effect due to the non-independence of some comparisons, and confirming the minimization of random confounding. More in detail, the mean probabilities of a more, less, and equally cost-effective early therapeutic choice from the 100,000 simulations were 67.76% (95% CI 66.65–68.88), 19.72% (95% CI 18.83–20.60), and 12.52% (95% CI 11.69–13.34), respectively. An example of results from a single simulation is reported in Table S2.

Discussion

In the present study, we explored the possibility of applying DOOR methods to observational studies on diagnostic procedures and early therapeutic choices in infectious diseases. Specifically, we observed a higher probability of a more cost-effective early therapeutic choice (67.81%) by using a BDG-based strategy rather than universal empirical antifungals in a cohort of ICU patients with sepsis and high risk of candidemia. Nonetheless, a couple of potential limitations should be considered before either generalizing our results or widening the use of DOOR methods to other studies focused on diagnosis and early treatment.

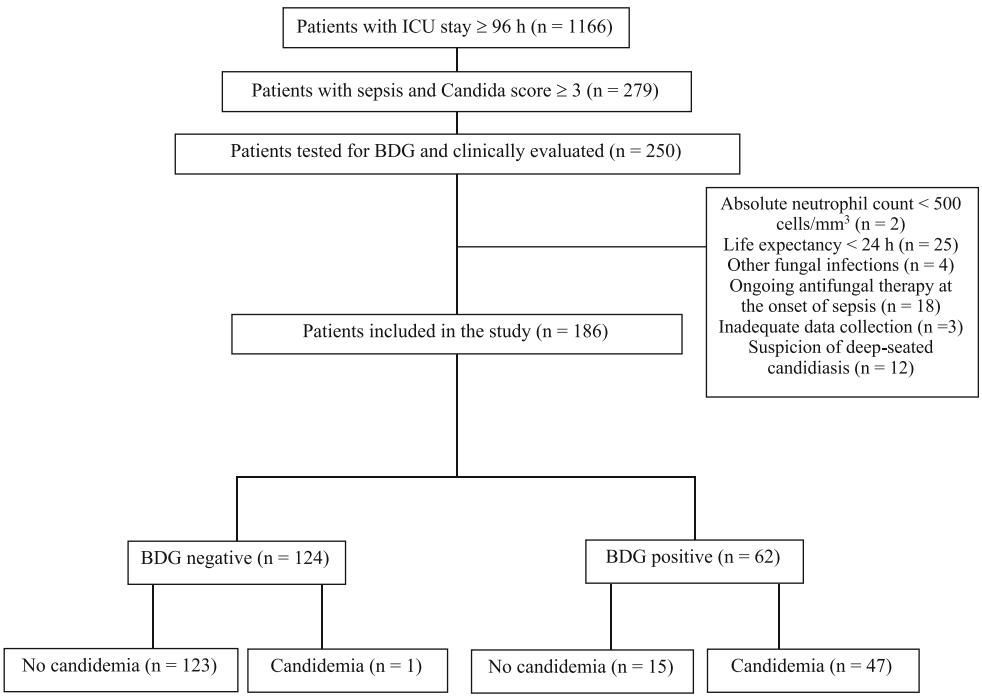

Fig. 1 Flow chart of the patient inclusion process

Table 1 Calculation of the probabilities of more, less, and equally cost-effective early therapeutic choices by using a BDG-based diagnostic strategy rather than empirical antifungals for all subjects

Patient	Group*	Condition	Outcome coding**	No. of pairwise comparisons	No. of controls with a lower DOOR[a]	No. of controls with a higher DOOR[b]	No. of controls with equal DOOR[c]
1	Case	Candidemia	4	186	138	0	48
2	Case	Candidemia	4	186	138	0	48
3	Case	Candidemia	1	186	0	186	0
4	Case	Candidemia	4	186	138	0	48
[…]	[…]	[…]	[…]	[…]	[…]	[…]	[…]
47	Case	Candidemia	4	186	138	0	48
48	Case	Candidemia	4	186	138	0	48
49	Case	No candidemia	2	186	0	48	138
50	Case	No candidemia	3	186	138	48	0
[…]	[…]	[…]	[…]	[…]	[…]	[…]	[…]
185	Case	No candidemia	3	186	138	48	0
186	Case	No candidemia	3	186	138	48	0
				Sum = 34,596	Sum = 23,460	Sum = 6810	Sum = 4326

DOOR, desirability of outcome ranking; *BDG*, (1,3)-β-D-glucan; *ICU*, intensive care unit; *CI*: confidence intervals

*Each case (BDG-based strategy) was also considered as a control (empirical strategy). The full list of cases and controls is provided as supplementary Table S1

**Outcome coding, from the most to the least desirable in terms of cost-effectiveness: (4) initiation or continuation of empirical antifungals followed by positive blood cultures for *Candida*; (3) non-initiation or discontinuation of empirical antifungals followed by negative blood cultures for *Candida*; (2) initiation or continuation of empirical antifungals followed by negative blood cultures for *Candida*; (1) non-initiation or discontinuation of empirical antifungals followed by positive blood cultures for *Candida*

[a] The probability of a more cost-effective early therapeutic choice for a randomly selected patient from the BDG group compared with the empirical group is the number of pairwise comparisons in which the case has a higher DOOR than the control (23,460), divided by the total number of possible pairwise comparisons (34,596) = 67.81% (95% CI 67.32–68.30)

[b] The probability of a less cost-effective early therapeutic choice for a randomly selected patient from the BDG group compared with the empirical group is the number of pairwise comparisons in which the case has a lower DOOR than the control (6810), divided by the total number of possible pairwise comparisons (34,596) = 19.68% (95% CI 19.27–20.10)

[c] The probability of an equally cost-effective early therapeutic choice for a randomly selected patient from the BDG group compared with the empirical group is the number of pairwise comparisons in which the case and the control have equal DOOR (4326), divided by the total number of possible pairwise comparisons (34,596) = 12.50% (95% CI 12.16–12.85)

First, DOOR is a new methodology subjected to several flaws pending standardization [5]. For example, as observed by Phillips and colleagues in the setting of RCT [6], results can be influenced by the arbitrariness in the number of categories and in the outcome definition, thus possibly allowing for some manipulation in absence of standardization a priori [6]. Second, the measured probability might be influenced by the prevalence of the targeted disease (in this case candidemia), and any result should thus be extrapolated cautiously to settings with appreciable differences in the baseline risk. It should also be reminded that the measured outcome here just reflects the desirability of early therapeutic choices (in terms of ranked and not purely quantitative cost-effectiveness) according to subsequently available blood culture results, and should thus not be confounded with desirability in terms of actual patients' outcomes, which need proper investigational studies to be assessed. Finally, this was a post hoc analysis of a previous study where absence of candidemia was defined by clinicians according to absence of fungi in blood cultures, and it thus suffers from the same possible categorization weaknesses of the original work [3]. However, our major aim was to explore potential pros and cons of applying DOOR principles to observational studies on diagnosis and early therapeutic choices, and not to draw definite conclusions on the role of BDG or add to our previous findings.

In conclusion, the application of DOOR methods to observational studies focused on diagnosis and early treatment is a novel field that could merit further investigation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Not required because of the post hoc nature of the analyses. A waiver of informed consent was obtained in the original study.

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