Assessing The External Validity Of Drotrecogin Alfa (Activated) Clinical Trials In An Observational Study Using Propensity Score Matching To Reduce Recruitment Bias

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Rationale

Severe sepsis affects ~15% of patients admitted in Intensive Care Units (ICUs) and is associated with important mortality rates (one month mortality ~35%) and high treatment costs (27-35 k€).[1,2]

Drotrecogin alfa (activated) (DA) has been shown to reduce mortality and was adopted in Europe for treatment of adult patients with severe sepsis and multiple organ failure (MOF). In this indication, DA has an OR of 28-day mortality of 0.70 (p=0.004, $IC_{95\%}$=[0.54–0.91]). The associated RR is of 0.78.[3]

DA's acquisition cost is estimated to be of ~8 k€ per treated patient.[4]

Table 1: 28-day mortality among PROWESS patients with MOF[3]

	Died	Survived	Total
Died	216 (33.91%)	421	637
Survived	168 (26.50%)	466	634
Total	384	887	1271

The French ministry of health funded in 2002 a research project aiming at the estimation of the treatment's impact on ICUs: the PREMISS study. The study's main objective was to estimate the observational costs of DA's introduction..

Methods

Study Design

The study protocol was elaborated with two professional associations: the SFAR (French Society of Anaesthesia and Intensive Care) and the SRLF (French Speaking Reanimation Society).

The study followed a quasi-experimental, multicenter, pre/post design: *Before* DA's market introduction, a control group was recruited; the intervention group was included *After* DA's market authorisation. Data was collected using the Internet.

Sample Size

At a bilateral significance level of 5%, with a power of 80% and with equal sample sizes in control and treatment groups:

- 340 patients per group are needed to identify a difference of €7'700 in mean treatment *costs*;
- 600 patients per group are needed to identify a difference of 7.4% in 28-day *mortality*.

Recruitment bias

Accounting for recruitment bias

The comparability of the control and treatment groups was measured using *standardised differences* d:

$$d = \frac{(x_{Ctl} - x_{Trt})}{\sqrt{\frac{(s^2_{Ctl} + s^2_{Trt})}{2}}}$$

Were x_{Ctl} and x_{Trt} are the means of the control and treatment groups, and s^2 their estimated variances.

Propensity Score matching

The Propensity Score (PS) is defined as the conditional probability of belonging to the treatment group given the baseline characteristics and summarises all initial covariates in a single scalar:

PS = P(Treatment | Initial characteristics)

The PS was estimated using logistic regression. Missing initial characteristics were handled using multiple imputation techniques. Treatment patients were matched to controls on the basis of their PS using an optimal matching algorithm.

Results

Crude Analysis

Included patients

1096 patients were retained for the analysis, less than the number needed to identify a difference in mortality:

- Control group: 509 patients;
- Treatment group: 587 patients.

Drotrecogin alfa administration

Only 51% of the patients conformed to DA's indications of use (24 µg/kg/h, during 96h except in the cases of premature death, occurrence of an adverse effect or a treatment contraindication).

Recruitment biases

There is evidence of recruitment bias as many baseline characteristics showed signs of imbalance (d > 10%).

Table 2: Examples of unbalanced covariates in the study

	Control	Treatme nt	d
Age (mean)	63.9	58.1	36.2%
Respiratory failure	87.9%	95.7%	-28.7%
McCabe=3	9.0%	3.6%	22.4%
Neurological failure	53.9%	45.5%	16.7%
Haematological failure	18.9%	24.0%	-12.5%
Renal failure	87.8%	91.0%	-10.3%

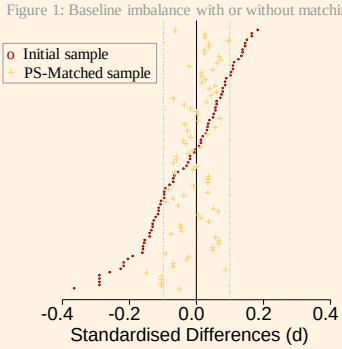
PS-Matched Analysis

Matched patients

The optimal matching procedure rejected 23% of the initial sample patients. The PS-matched sample keeps 840 patients, 420 per group.

Recruitment bias reduction

Figure 1: Baseline imbalance with or without matching



PS-Matching succeeds in reducing baseline imbalance between the groups: d<10% for all covariates, except for the patients aged ≥ 80 years (d=15.0%) and for respiratory failure (d=10.5%).

Clinical Outcomes (Matched Sample)

Bleeding events

Bleeding events (all severities) occurred in 13.6% of the control and 21.7% of the treated patients (p=0.002).

The average number of bleeding events was of 0.18 and 0.28 in the control and treatment groups respectively (p=0.021). In a multivariate confirmatory analysis, it was best described by a negative binomial model and DA's effect remained significant (p=0.024).

28-day mortality

The PREMISS sample size is too small to detect a significant difference in mortality.

Table 3: 28-day mortality in the PREMISS study

	Died	Survived	Total
Control	155 (37.35%)	260	415
DA	140 (34.06%)	271	411
Total	295	531	826

28-day status was unknown for 14 patients.

In the PS-matched sample, DA has an OR of 28-day mortality of 0.87 (p=0.345, $IC_{95\%}$=[0.64-1.17]).

A random intercept model (estimated to take the clustering of patients among the participating ICUs into account) leads to similar estimates.

Discussion

PREMISS was an observational study aiming at providing more information about DA's impact in "real life" practice. It was not designed to make further inferences about DA's clinical *efficacy*, already assessed in a randomised clinical trial. The choice of a less constraining study design allowed us to collect information about the daily practice patterns of care – and therefore to explore the treatment's *effectiveness*.

However, non-randomised studies are more prone to biases which need to be addressed in the analysis. We tried to reduce recruitment bias using an increasingly popular device in epidemiology: the propensity score. The PS allows to mimic a randomised trial by reducing baseline imbalance between the groups to be compared. Still, only the measured variables can be taken into account and unmeasured variables can act as confusing factors.

Conclusion

While the main objective of the PREMISS study was to estimate DA's economic impact, it still brings valuable information at the clinical level.

- The presence of recruitment bias is interesting on its own. The intensive care practitioners did not include every patient meeting the treatment's indications of use: for example, the patients in the treatment group were younger and had less co-morbidities.
- There is evidence of variability in the way DA is prescribed: half of the patients did not receive the treatment at the recommended posology.
- We lack the power to infer about DA's effectiveness. Yet, the observed tendencies in the PREMISS study are convergent with the randomised clinical trial results.

Based on prior randomised clinical trials and taking explicitly the presence of recruitment bias into account, PREMISS illustrates the benefits of post-hoc observational studies.

References

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