Propensity Scores

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Outlines

- Background/Motivation
- What is propensity score?
- Applications of propensity score
- How to analyze treatment effect using propensity score?
- Propensity score matching
- How to analyze matched pair data?
- Example of BMT study using propensity score
- Conclusions

Motivation

- **In medical studies physicians and patients often want to know the treatment effect:**
- **Example:** A cohort study comparing survival outcome of diffuse large B cell lymphoma patients underwent HLA-identical sibling allogeneic transplantation versus autologous transplantation (Lazarus et al., *BBMT*, 2010)
- **This is a retrospective cohort study:**
- Auto HCT often uses PB (peripheral blood) and
- HLA-identical sibling HCT often uses BM (bone marrow) and for high risk patients;

  Allo HCT patient needs to have a HLA-matched sibling donor available
- This **treatment selection bias** will introduce conclusion bias:

  ➔ **Estimate treatment effect will be biased**
- **Without adjustment we may comparing apples to oranges.**

Motivation

- **Randomized clinical trial is the gold standard method for analyzing treatment effect**
- **BUT, Randomized clinical trial cannot be done for all studies:**
  - Infeasible or unethical to assign patients to different treatment
  - In stem cell transplant study, not all patients are having HLA-identical sibling donor available
  - Cost and time related issues

- **Researches need to analyze treatment effect for observational cohort study using data from non-randomized clinical trial:**
  - want to show the difference in outcome is attributable to difference in treatment, not due to patient selection bias

Purpose of Propensity Score

- **Propensity score approach has been proposed to mimic the clinical trial**
- Propensity score approach can be used to **produce unbiased comparison of treatment effect** under some nonrandomized conditions
- Propensity score approach has been wildly adapted recently:

-- Publications in Pub Med with phrase of “propensity score”:

1983 – 1997: 0 – 10/year

1998 – 2002: 11 – 50/year

2003 – 2004: 51 – 100/year

2005 – 2006: 150 – 170/year

2007: 250/year

Treatment Causal Effect

- $R^{(A)}$: response if subject receives treatment

  A=1 (case: treated) or 0 (control)

- The **TRUE treatment causal effect** is:

$$E\{R^{(1)}\} - E\{R^{(0)}\} \qquad (1)$$

- But, the "observed" expected difference in response is

$$E\{R^{(1)} | A=1\} - E\{R^{(0)} | A=0\} \qquad (2)$$

  for a randomly selected treated subject (A=1) compare to a randomly selected control subject (A=0)

- For an observational study,

$$(1) \neq (2)$$

  since subjects are not randomly assigned to treatments

Randomized Clinical Trial

- In a randomized clinical trial, treatment assignment ***A*** and response $(R^{(1)}, R^{(0)})$ are conditionally **independent** give covariates (risk factors) ***Z***
- Under this conditional independent assumption, one can show that

(1) = (2)

- **Randomized clinical trial leads to an unbiased estimate for the treatment causal effect**

What is Propensity Score?

- **Propensity score is the probability of receiving treatment (*A*=1) given covariates *Z*,**

$$\pi(Z) = P(A=1 \mid Z)$$

Assuming $0 < \pi(Z) < 1$

- Note: **There is a positive probability, $\pi(Z) > 0$, even he/she received a ``NO" treatment (*A*=0)**.
- Rosenbaum and Robin (1983, *Biometrika*) showed that **conditioning on the propensity score allows for unbiased estimation of treatment effect**
- **Balancing propensity score mimics a randomized clinical trial**

Propensity Score Estimation

- **True propensity score is unknown: It needs to be estimated**
- **Logistic regression modeling is typically used to estimate the unknown propensity score:** based on a set of covariates which determent the treatment assignment
- Propensity score ranges from 0 to 1
- Propensity score estimation only depends on known covariates (such as patient characteristics), **it is independent of OUTCOMES**

Use of Propensity Score

- Rosenbaum and Rubin suggested **three common methods to estimate treatment effect using propensity score:**

1. **Stratification (sub-classification)**
2. **Matching**
3. **Covariate adjustment (treating propensity score as a covariate)**

Propensity Score Matching

- **The most common implementation of propensity score matching is pair matching, where pairs of treated (A=1) and untreated (A=0) subjects with similar propensity scores are formed**
- Similar propensity score is often defined as within a constant of standard deviation of the propensity score
- For example, 0.5 or 1 of standard deviation. Then,

1. Randomly select one matched control among all possible matched controls *OR*
2. Select one matched control with smallest difference in propensity score

How to Analyze Propensity Score Matched Pair Data

- To estimate the treatment effect, propensity score matching is often used **to reduce or eliminate** the effect of treatment selection bias
- A systematic **review of medical literature** between 1996 and 2003 by Austin (*Int. J. of Biostat*., 2009) found that **majority of studies did not account for the matched nature**
- Similar findings were observed in cardiovascular surgery literature and general cardiology literature

How to Analyze Propensity Score Matched Pair Data

- **Question: How to analyze matched pair data?**

  Do we need to count for the matching?
- Matched subjects are, on average, more similar in baseline covariates than two randomly selected treated and untreated subjects

  ➔ **propensity score matched sample are not from independent observations**
- Austin's simulation study showed that **adjusted matched-pair analysis will be needed to have correct nominal level of type I error**

HTC Study Using Propensity Score Matched-Pair Analysis

- For illustration purpose, we consider a **CIBMTR** (Center for International Blood and Marrow Transplant Research) study
- The CIBMTR is comprised of clinical and basic scientists share data on their blood and bone marrow transplant patients with CIBMTR Data Collection Center and Statistical Center located at the **Medical College of Wisconsin**
- The CIBMTR is a repository of information about results of transplants at more than **500 transplant centers worldwide**

HCT Study

- CIBMTR study compared outcomes of HLA-identical sibling allogeneic versus autologous transplantation for **diffuse large B-cell lymphoma (DLBCL)**
- 916 adults DLBCL patients (age: 18-60) underwent **1st Auto HCT (N=837)** or **myeloablative (MA) HLA-id sibling Allo HCT (N=79)** between 1995 and 2003
- Patients were reported to the CIBMTR by 156 centers in 17 different countries
- **This is a retrospective study (not a randomized clinical trial study)**

HCT Study

- **Key risk factors are imbalanced between cohorts:**

	Auto	Allo	P
Disease Stage III/IV	27%/39%	8%/62%	0.003
B Symptoms at DX	46%	58%	0.04
Ext Dis Involvement	57%	70%	0.02
Marrow Involvement	17%	42%	<0.001
Chemo Resistant Disease	15%	42%	<0.001
Graft Score: BM	9%	37%	<0.001
DX to TX, median, M	13(2-287)	11(2-156)	0.03

➔ **Allogeneic HCT for high risk patients**

HCT Study

- **ALLO HCT often uses BM for HIGH RISK patients**
- **Risk factors are imbalanced:**

  ➔ Directly estimate treatment effect will be biased

- **CIBMTR study performed a matched pair comparison** of the ALLO HCT group with a subset of closely matched AUTO HCT patients selected based on propensity score matching

HCT Study

- **Propensity score was calculated based on a fitting a logistic-regression model** with key risk factors of:

AGE	*SEX*
Karnofsky performance score	*B symptoms at DX*
Disease stage at diagnosis	*Extranodal disease at DX*
Marrow Involvement at DX	*# of prior-chemo*
Sensitivity to chemo	*Time from DX to TX*
Graft source	*Year of TX*

- **Propensity Score: Median (range; SD)**

-- **Combined Sample (N=893):** 0.042 (0.002 – 0.895; 0.123)

-- **Case (ALLO: N=79):** 0.236 (0.008 – 0.895; 0.239)

-- **Control (AUTO: N=814):** 0.039 (0.002 – 0.624; 0.086)

HCT Study

- **Propensity Score (PS) Matching:**

1. For each ALLO HCT patient (Case). Any AUTO HCT patient (Control) with a difference in propensity score of less than SD=0.123 was considered as a potential matched control. A matched control with smallest difference in PS was selected
2. Matching procedure (Step 1) was performed for each case
3. Matching Step 1 and 2 were repeated 4 times for possible 1 to 4 matching

- **Matching Result:**

-- **1 – 4 matching = 49 pairs; 1 – 3 matching = 2 pairs**

-- **2 – 3 matching = 12 pairs; 1 – 1 matching = 6 pairs**

-- 10 case cannot find any matched control

HCT Study

- **Analyzing matched time-to-event data:**
- **Variable:**

  allo=1 for ALLO HCT; =0 for AUTO HCT

  intxsurv=time from TX to death or end of FU (month)

  dead=1 for died; =0 for alive

  ipair: index of matched pair

1. Stratified Cox model (SAS Code):
   proc phreg; model intxsurv*dead(0)=allo; strata ipair;
2. Marginal Cox model (SAS Code):

   proc phreg covs(aggregate);

   model intxsurv*dead(0)=allo; id=ipair;

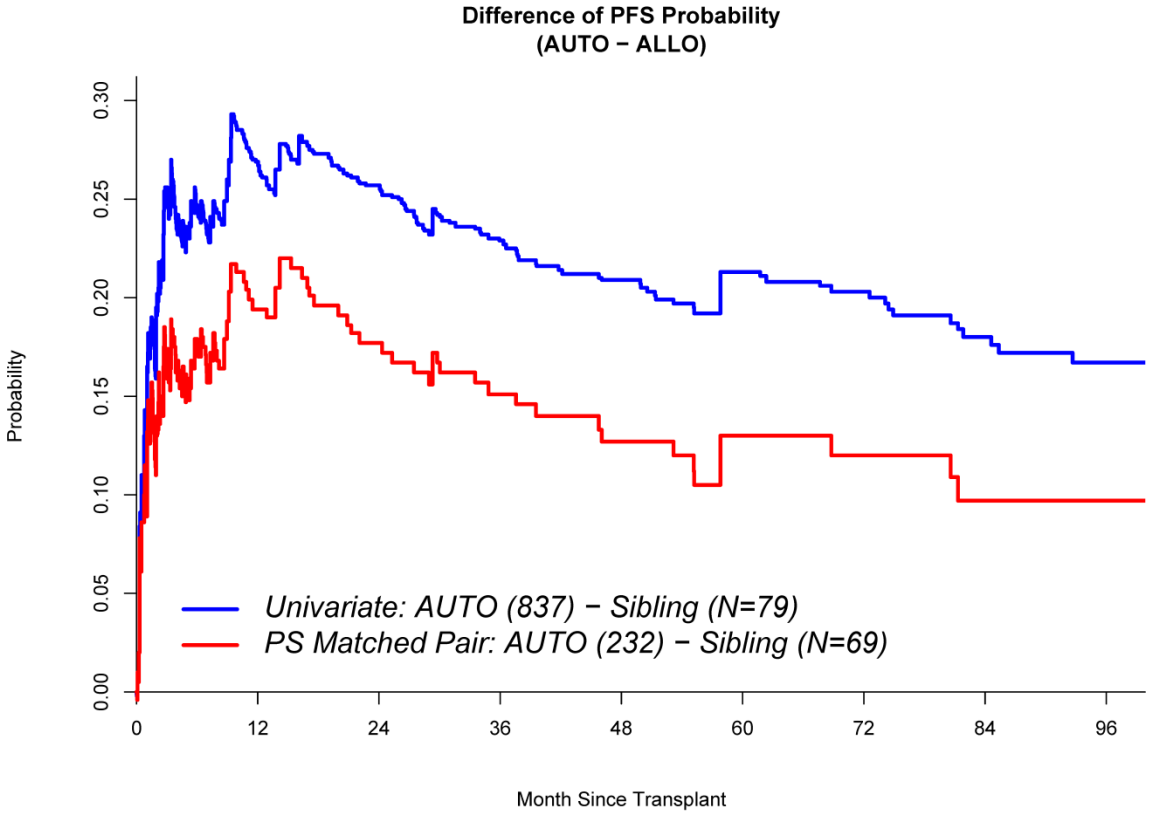
HCT Study

- **Summary of outcomes from matched pair comparison:**

	RR (95% CI)	P
Treatment Failure (1 – PFS)		
Allo vs Auto (overall)	1.95 (1.34 – 2.83)	0.0005
Within first 2 months after HCT	2.04 (1.38 – 3.01)	0.0003
Beyond first 2 months after HCT	1.19 (0.32 – 4.40)	0.7948
Mortality (1 – Survival)		
Allo vs Auto (overall)	2.38 (1.68 – 3.53)	<0.0001
Within first 2 months after HCT	2.77 (1.81 – 4.25)	<0.0001
Beyond first 2 months after HCT	1.05 (0.38 – 2.93)	0.9232

HCT Study

- Over Estimate AUTO Treatment Effect without Adjusting the Imbalance of Key Risk Factors between Cohorts:



HCT Study

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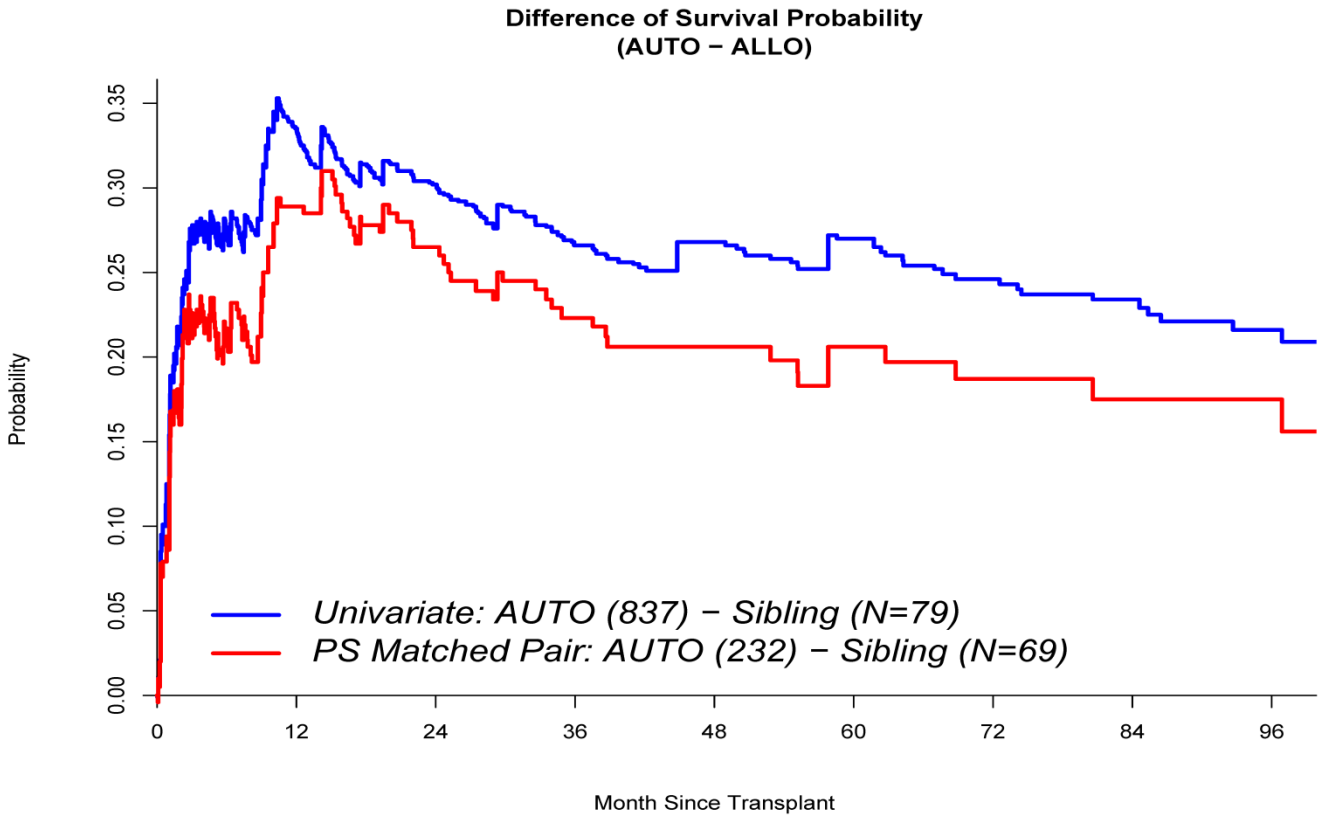

Conclusions

- **Benefits:**
  - Useful and unbiased method to analyzing treatment effect
  - Easy to adjusting a large number of risk factors
  - Useful matched design for saving time and money
  - Independent of outcomes
- **Limitations:**
  - Only adjust observed risk factors (Randomized clinical trial balance all risk factors (observed & unobserved))
  - Bias still may occur (To obtain unbiased inference using propensity score needs some assumptions/conditions. These assumptions/conditions may not hold)

References

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Questions?