Is donor age and/or sex associated with in-hospital mortality? The Hamilton Data

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Disclosures

- MCTR receives infrastructure program funding from CBS & Health Canada
- Study was funded by a priority program grant from CBS & Health Canada
- I am not a biostatistician!

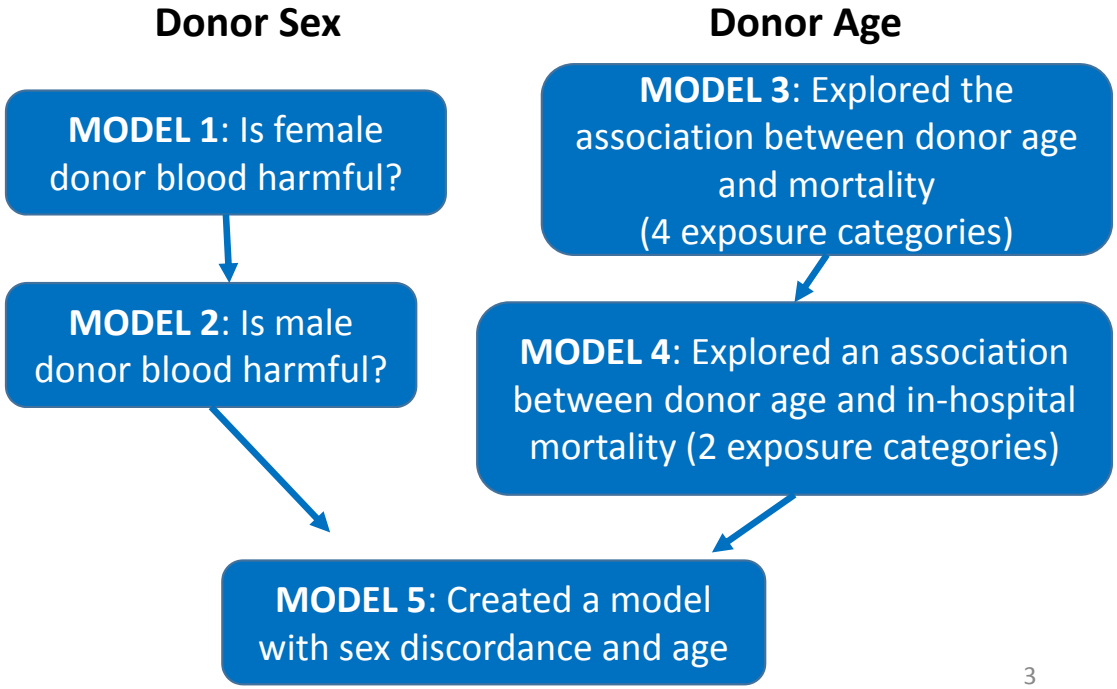
- NOTE: Actual results (except for descriptive summaries) have been deleted as they are currently unpublished

Objective

To use Hamilton data (2008-2014) to determine if there is an association between donor age and donor sex and in-hospital mortality in transfused adults admitted to hospital

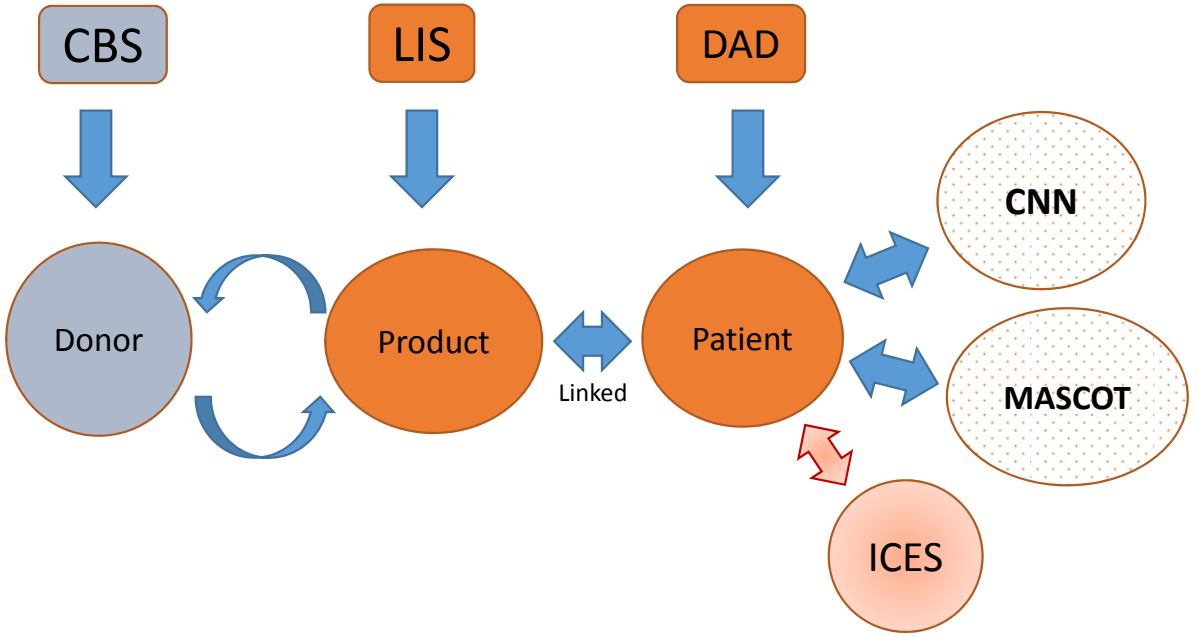
Approach

- Progressive Model Approach (started with specific question(s) and results from the analysis lead to subsequent questions).



The Data Source

- TRUST (**TR**ansfusion **R**egistry for **U**tilization, **S**urveillance and **T**racking)
- 2002 – present
- Demographic and clinical data on all in-patients within Hamilton Hospitals
- Transfusion/product data (total inventory)
- Laboratory test results (in- and outpatients)
- Linked with other data sources



CNN – Canadian Neonatal Network
MASCOT – Pharmacy Radiology orders & Physician Roster
ICES – Institute for Clinical Evaluative Sciences
CBS – Canadian Blood Services
LIS – Laboratory Information System
DAD – Discharge Abstract Database

Design -All Models

Design: Retrospective cohort exploratory study of linked data

Analysis: Cox regression models controlling for fixed and time dependent variables.

Covariates

- Age
- Sex
- ABO group
- Intervention (CCI codes, categorized as YES/NO)
- Whole Blood Processing (B1/B2) –Exposure to B2 vs exclusive exposure to B1 (binary YES/NO)*
- Fresh Blood (≤ 7 days vs exclusively older YES/NO)*

Stratification Variables

- Cumulative # RBCs transfused
- Hb level groups (categorized by quartiles)
- Creatinine level groups (categorized by quartiles)
- Exposed to non ABO-identical RBCs (binary Yes/No)*
- Platelets (binary Yes/No)*
- Plasma (binary Yes/No)*
- Most responsible diagnosis – ICD10 (21 groups)
- Fiscal year admission

*Once the variable switched on (yes response) it stayed on for the duration of follow-up.

BLACK – fixed variables

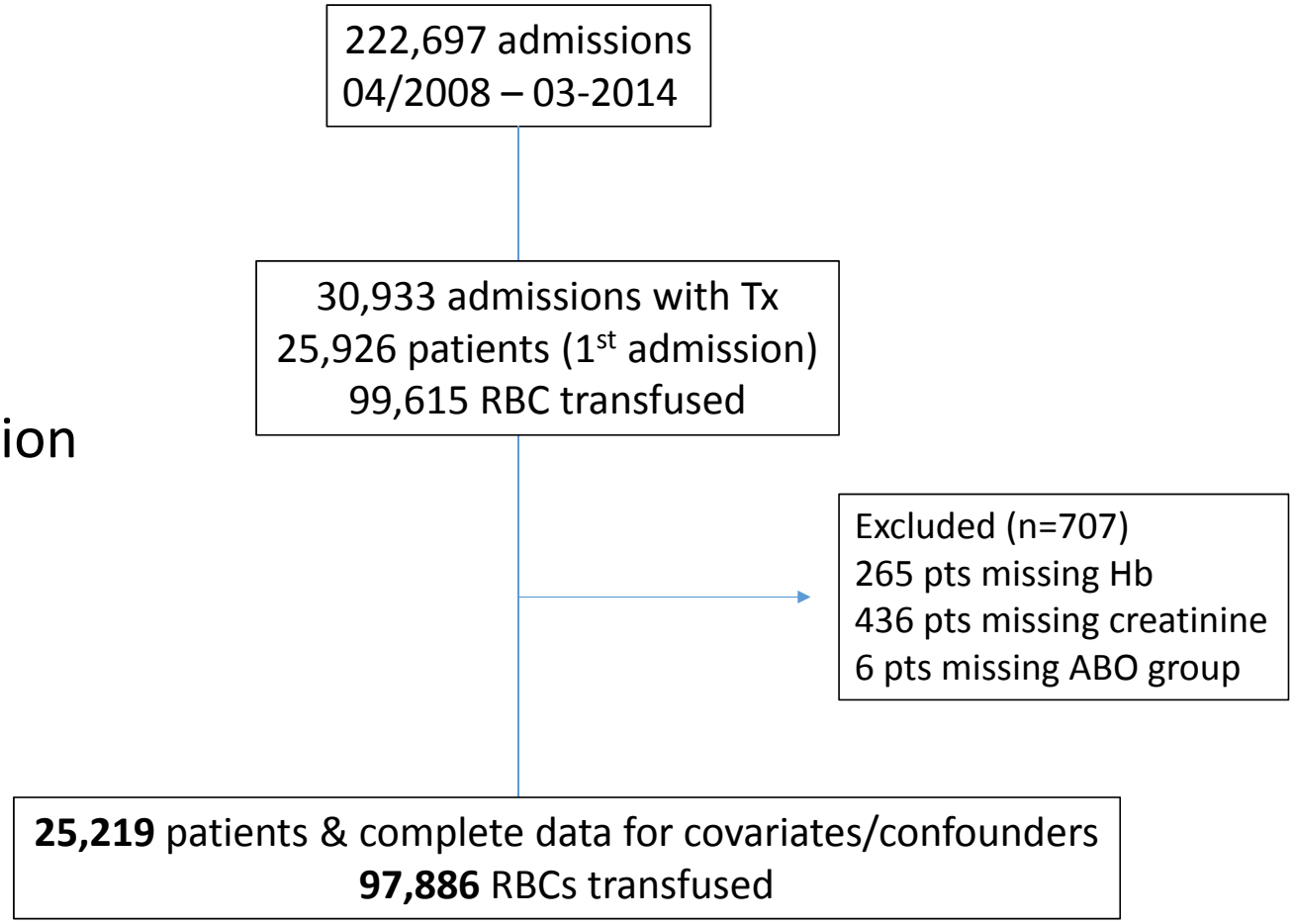
RED – time dependent change over time

Population

- Adults
- In-patients
- Received one or more allogeneic RBC transfusion (2008-2014)
- 1st hospital admission

Outcome

- In-hospital mortality



Patient Demographics

Characteristic		Overall n=25,219
Female, n (%)		12821 (50.8)
Age (y)	mean/SD median (IQR)	67.6/15.8 70 (59,79)
Any Intervention, n (%)		18092(71.7)
Blood group, n (%)		
A		10141(40.2)
AB		1086(4.3)
B		2899(11.5)
O		11093(44.0)
Hemoglobin (g/L) at first transfusion	mean/SD median (IQR)	78.5/12.8 77 (71,84)
Creatinine (µmol/L) at first transfusion:	mean/SD median (IQR)	111.7/107.2 81 (61,118)
Duration of hospital stay (d):	mean/SD median (IQR)	18.1/24.8 11 (7,20)
Most Responsible Diagnosis, n (%) *		
Diseases of the circulatory system		7261(28.8)
Neoplasms		3933(15.6)
Injury, poisoning and certain other consequences of external causes		3878(15.4)
Diseases of the digestive system		2636(10.5)

*Only 4 categories of 21 total shown – frequencies of all other categories <15%

Donor/Product Characteristics

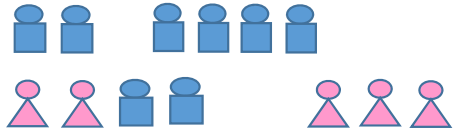
		RBC units N=99,578
Donor Sex	Female	43,518 (43.7%)
	Male	56,060 (56.3%)
Donor Age	mean/SD	42.8 /14.6;
	median (q1,q3)	45 (30,54)
Donor Age Group (years)		
	17-19	6,964 (7.0%)
	20-29	17,482 (17.6%)
	30-39	13,733 (13.8%)
	40-49	22,679 (22.8%)
	50-59	26,132 (26.2%)
	60-69	11,777 (11.8%)
	≥70	811 (0.8%)
Pack type	B1	52,463 (52.7%)
	B2	46,888 (47.1%)
	Other	227 (0.2%)
Age categories	Female donor age ≤45	23,229 (23.3%)
	Female donor age >45	20,289 (20.4%)
	Male donor age ≤45	26,728 (26.8%)
	Male donor age >45	29,332 (29.5%)

MODEL 1: Donor Sex- Is FEMALE blood harmful?

Categorized Exposure (mutually exclusive groups)

REFERENCE: Exposure to exclusively **MALE** blood

Comparison: Exposure to **FEMALE** blood ± **MALE** Blood



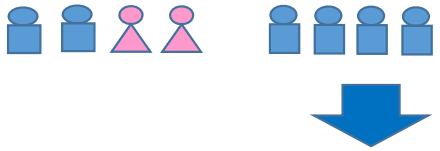
RESULTS

	Is FEMALE blood harmful? Reference Exclusive male RBC Exposure
Female Recipients exposed to female blood	Unpublished data at this time
Male Recipients exposed to female blood	Unpublished data at this time

MODEL 2: Donor Sex- Is MALE blood harmful?

Categorizing Exposure (mutually exclusive groups)

REFERENCE: Exposure to exclusively FE**MALE** blood 

Comparison: Exposure to **MALE** blood ± FEMALE Blood 

	Is FEMALE blood harmful? Reference Exclusive male RBC Exposure	**Is MALE blood harmful?** Reference Exclusive female RBC Exposure
Female Recipients exposed to female blood exposed to male blood		
Male Recipients exposed to female blood exposed to male blood		
Recipient sex*exposure to female donor RBCs Recipient sex*exposure to male donor RBCs		

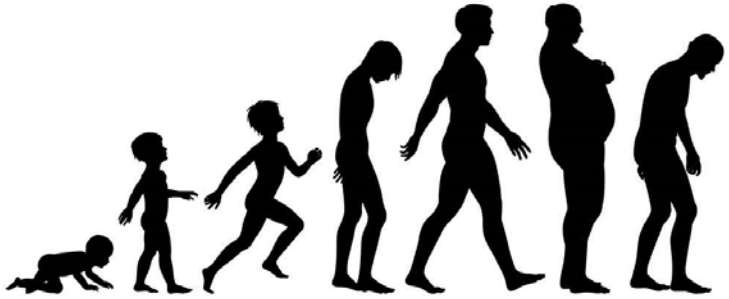
Unpublished data at this time

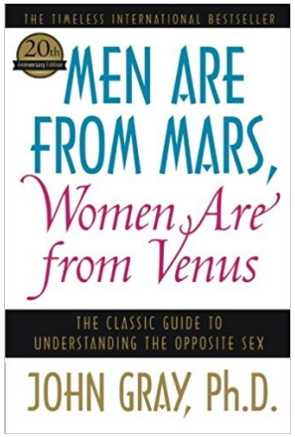
MODEL 4: Donor Age – (exposure defined by 2 groups)

- Created mutually exclusive groups
- Used donor age of 45 years as the cut-point
- Two categories
  - REFERENCE – Exclusive exposure to donors > 45 yoa (safest, older)
  - Comparison – exposure to donors ≤ 45 yoa (younger, most risky?) ± older donors
  - Interaction (recipient sex*donor age) p=0.25
    - No difference between males and females recipients
  - MODEL without interaction

Concluding Remarks

- Its complicated!
- Models can show associations but not causation
- Causation can “only” been demonstrated using a RCT design
- If associations are real – we need to understand the biology
- Men are from Mars, Women are from Venus!
- Advantage of aging – your blood may be safer!





Acknowledgements

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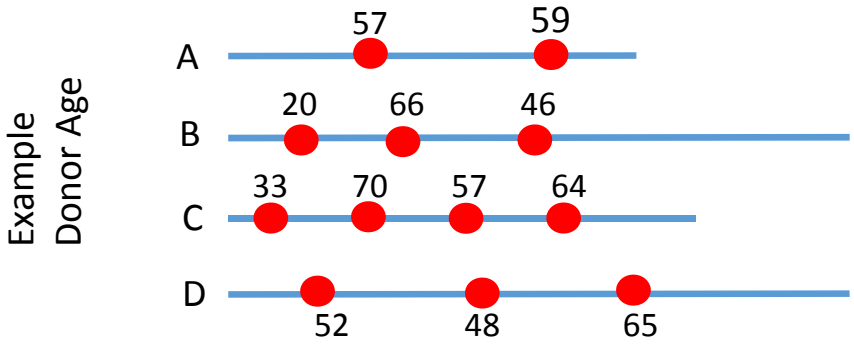
Categorizing Donor Exposures

Question – how should exposure be categorized?

Its complicated!



Mean	Median	Oldest	Youngest	Exposure to Donors <40
58	58	59	57	No
44	46	66	20	Yes
55	60.5	70	33	No
55	52	65	48	No

Defined Exclusive Categories

Donor age quartiles used in Model 3

Q1	17-30
Q2	31-45
Q3	46-54
Q4	≥55

Quartiles Youngest donor age exposure	Exposure Group 1	Exposure Group 2	Exposure Group 3	Exposure Reference Group (RR 1)
17-30 years	X			
31-45 years	±	X		
46-54 years	±	±	X	
≥55 years (REF) RR 1	±	±	±	X
Donor (Example)	B	C	D	A

Interpretation Donor Age – Ottawa Analysis?

Explored the impact on mortality of the number of units transfused (continuous variable) by age category

Age in Years	HR
17-19	1.08*
20-29	1.06*
30-39	1.01
40-49	REFERENCE
50-59	1.01
60-69	1.01
≥ 70	0.96

* Lower limit of CI >1

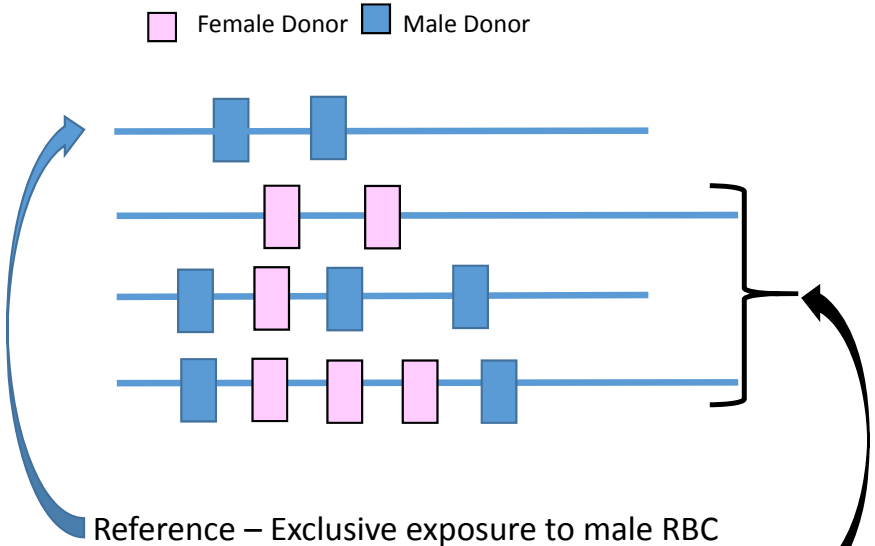
Interpretation:
For one additional RBC unit transfused from a donor age 17-19 years of age there is an 8% increased risk of death compared to reference (40-49 year old donors)

What does this mean clinically?

Question – how should exposure be categorized?

Hamilton Approach – Make Mutually Exclusive Categories

Donor Sex (2 categories)



Reference – Exclusive exposure to male RBC

Comparison Group – exposure to female RBCs

- Exclusively female or male and female

Donor Age

- Based on the Ottawa results and the similar trend seen with Hamilton data we selected 45 years of age as the cutpoint
- Defined mutually exclusive groups

  REFERENCE: > 45 years (exclusively)

  Comparison: ≤ 45 years ± older donors

Having mutually exclusive groups makes the comparison clear.

Analysis

What is the best approach?

What is the optimal approach for analysis?

Answer – time dependent Cox regression model

Rationale

Exposure changes over time

Some patient variables change over time

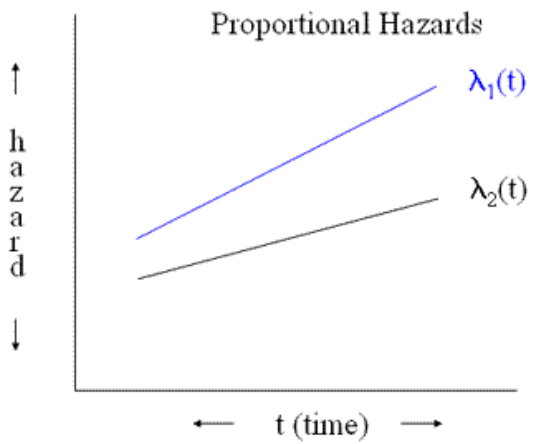
"Prospective analysis" of retrospective data – as new information becomes available over the patients course it is added into the model

Always comparing patients with similar characteristics

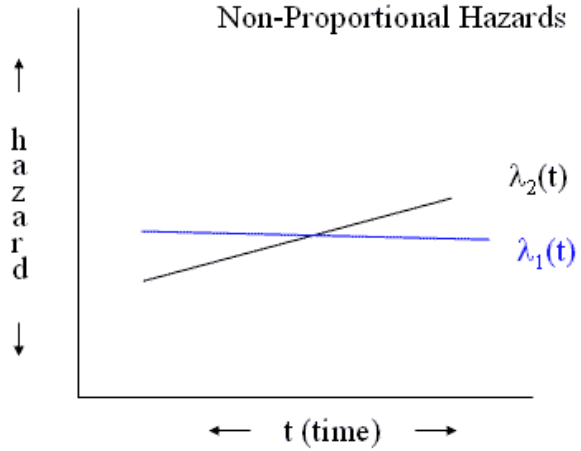
Proportional hazards assumption needs to be met for the model to be valid

- When a variable does not meet the PH assumption it can be used as a stratification variable

Graph Demonstrating Proportional Hazards



$\lambda_1(t)/\lambda_2(t)$ is constant, regardless of time



$\lambda_1(t)/\lambda_2(t)$ is a function of time