PRACTICUM AND CULMINATING EXPERIENCE FOR EPIDEMIOLOGY - MPH

Outcomes and Trends in Primary Graft Dysfunction Following Heart Transplant from DCD versus DBD donors: An Analysis of the Scientific Registry of Transplant Recipients

Laura Aguilar Franco MD

2025 MPH candidate

October 31, 2024

Agenda

Background and Public Health Relevance

- Primary graft dysfunction (PGD) results in poor post-transplant outcomes. It’s the leading cause of patient death in the first 30 days after a heart transplant.
- Although the ISHLT consensus developed a classification system, Heart transplant centers continues refining the PGD definition
- Several single-center studies show the incidence of PGD varies from 2.3 percent to 28.2 percent
- There is a great concern for PGD into clinical applications outside of the research realm from DCD donors, that there could be increased risks for PGD from these donors, especially in centers that are just learning the DCD process, however there is limited data nowadays that have shown an association to this.
- As DCD transplants expand the donor pool, it is crucial to understand how these differences affect patient outcomes.

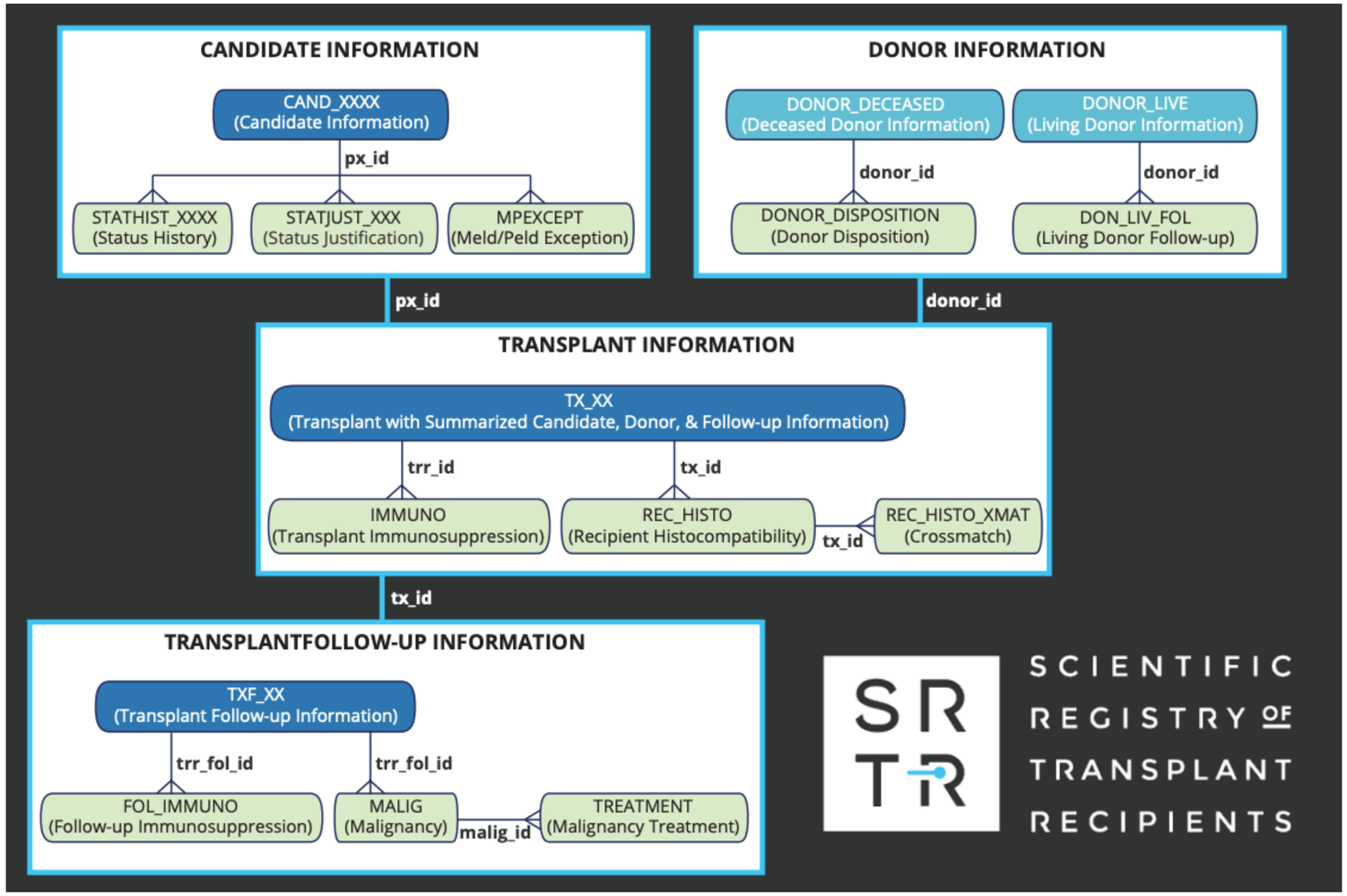
Brief overview of the proposed project

This project aims to compare the incidence, severity, temporal trends comparisons and clinical outcomes of primary graft dysfunction (PGD) in heart transplant recipients who received hearts from donation after circulatory death (DCD) versus donation after brain death (DBD). Using data from the Scientific Registry of Transplant Recipients (SRTR), we will conduct a retrospective cohort analysis to examine differences in early post-transplant survival, graft function, and clinical recovery.

About the data base

Data in the SRTR database are largely collected directly by the **Organ Procurement and Transplantation Network (OPTN).** These data are supplemented by data from the **Centers for Medicare & Medicaid Services (CMS)** and the **National Technical Information Service's** (NTIS) Death Master File.

Data sets are released quarterly (March, June, September, and December of each year)



Candidate files:

- Status history
- Status justification

Donor files:

- Donor disposition
- Living donor follow-up information

Transplant

- Summarized candidate information
- Summarized donor information
- Summarized follow-up information
- Transplant immunosuppression
- Recipient histocompatibility
- Cross-match information

Transplant follow-up information.

- Follow-up patient status
- Immunosuppression
- Malignancy
- Malignancy treatment information.

PGD Data Elements

Transplant hospitals will be required to collect and report data on all heart recipients at 24 and 72 hours (+/- 4 hours) after patient's arrival to ICU

Data Element	Values and/or Ranges
Primary Graft Dysfunction	Yes or no
Left Ventricular Dysfunction	Yes or no
Right Ventricular Dysfunction	Yes or no
Left Ventricular Ejection Fraction	Percentage
Right Atrial Pressure (RAP)	mm Hg
Pulmonary Capillary Wedge Pressure (PCWP)	mm Hg
Pulmonary Artery Systolic Pressure / Pulmonary Artery Diastolic Pressure	mm Hg
Cardiac Output	Liters / minute
Support Device	Yes or no
If Yes	Right, left, or biventricular
Type of Device	Device name(s)
Inotrope support	Drug(s) and range dosages
Nitric Oxide following transplant	Yes or no
Flolan following transplant	Yes or no

PGD UNOS definition:
Refers to graft dysfunction occurring immediately after transplant, requiring greater than typical medical support, or mechanical support. PGD is graft dysfunction not attributable to hyperacute rejection, acute rejection, antibody mediated rejection, surgical implant issues, or acute infarction.

PGD Data Elements

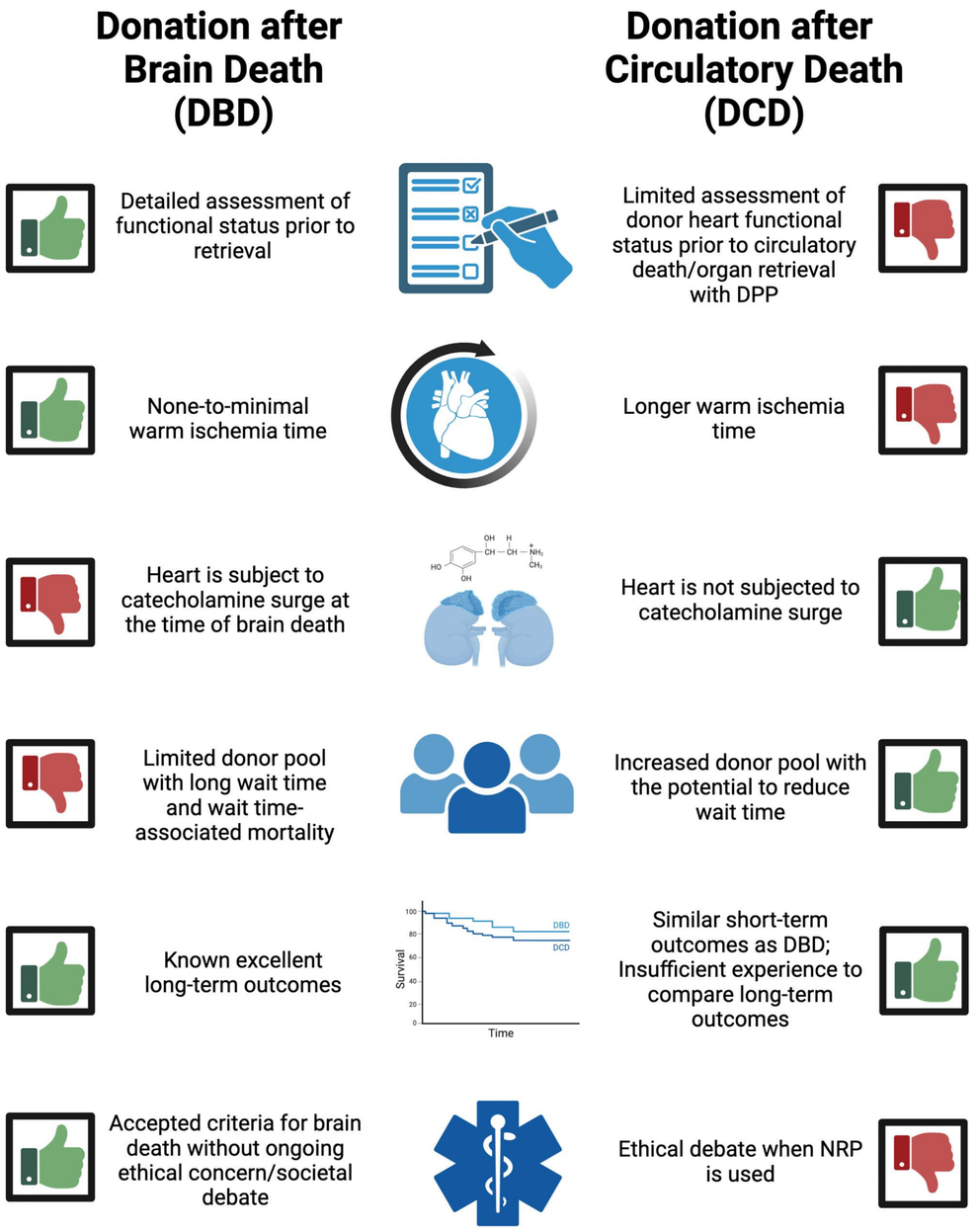
Inotrope	Dose (mcg/kg/min)
Epinephrine	• None • >0 – ≤ 0.05 • >0.05 – ≤ 1.0 • >1
Milrinone	• None • >0 – ≤ 0.3 • >0.3 – ≤ 0.5 • >0.5
Dobutamine	• None • >0 – ≤ 3 • >3 – ≤ 7.5 • >7.5
Dopamine	• None • >0 – ≤ 3 • >3 – ≤ 7.5

Vasopressors	Dose (mcg/kg/min)	Dose (mcg/min)
Levo (Norepinephrine – Levophed)	• None • >0 – ≤ 0.05 • >0.05 – ≤ 0.1 • >0.1	• None • <5 • 5 – < 12 • ≥12
Vaso (Vasopressin – Pitressin)	--	• None • >0 – <0.05 • 0.05 – <0.08 • ≥0.08
Neo (Phenylephrine – Neosynephrine)	--	• None • >0 – < 100 • 100 – <200 • ≥200

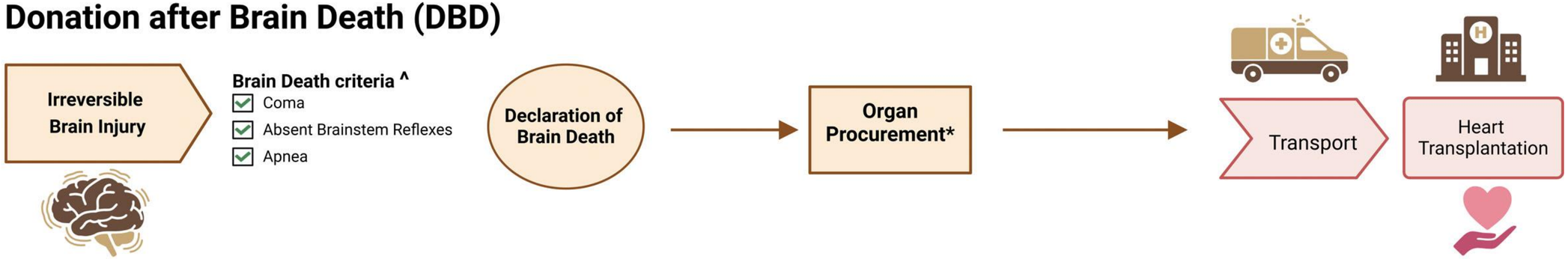
Aims and hypothesis

The pathophysiology of PGD remains incompletely understood, particularly in relation to the differences between DCD and DBD recipients. We hypothesize that variations in ischemic stress during organ recovery and preservation in DCD versus DBD transplants result in distinct mechanisms of PGD onset, progression, clinical course, and recovery.

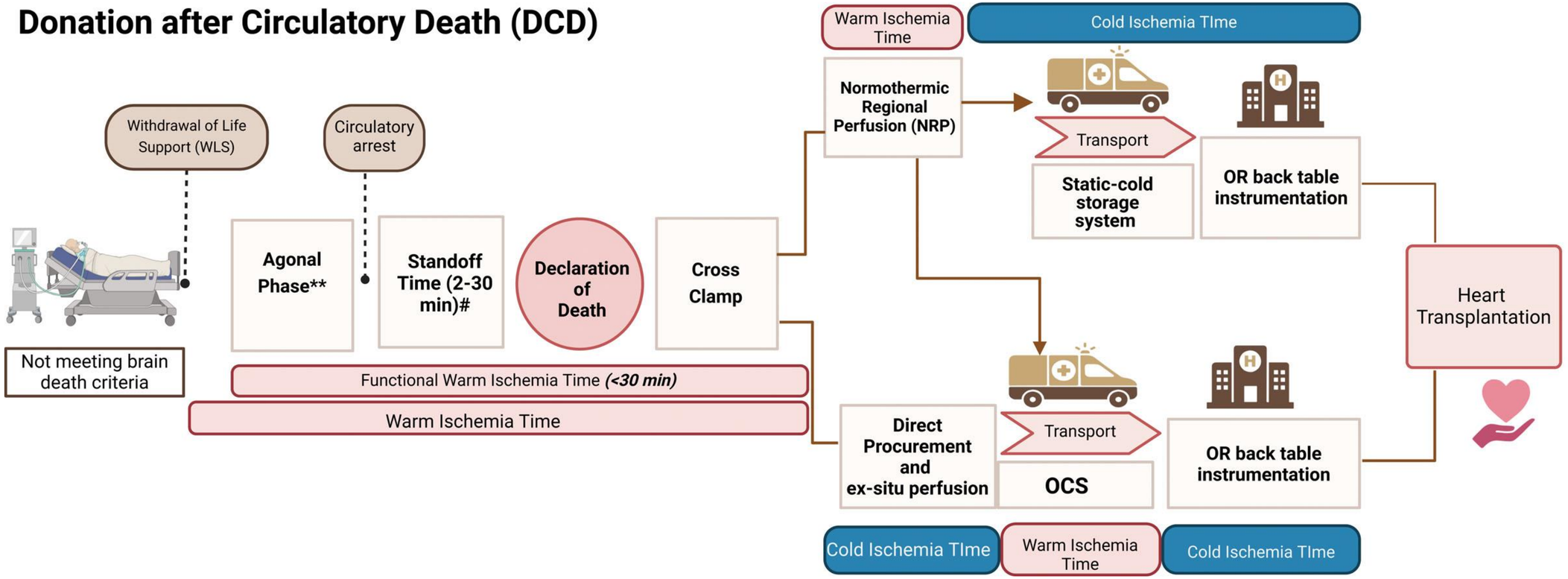
The primary aim of this study is to compare the incidence, temporal trends, clinical outcomes, and survival rates of PGD between DCD and DBD heart transplant recipients, providing a deeper understanding of their differential recovery patterns and guiding future transplant protocols.



Donation after Brain Death (DBD)



Donation after Circulatory Death (DCD)



Design and population

Analytical study, Retrospective cohort study

Primary exposure(s)
DCD vs DBD

Primary outcome(s)
Clinical outcomes
- Incidence of PGD
- Need of Mechanical circulatory device, days
- Length of stay in ICU
- Early survival (30 days)
- 1 year Survival

Secondary Outcomes:
- Center-level trends in PGD incidence by DCD/DBD donor type, with a focus on DCD transplant volume and time-related changes.

Analytical plan – Predictive Model and Validation for the temporal trends analysis

The prediction model for primary graft dysfunction (PGD) will be developed using SRTR data from September 2023 onward, as this period includes directly measured PGD. Internal validation will be performed within the 2023 dataset using cross-validation to rigorously assess model performance. Model discrimination will be evaluated with the area under the receiver operating characteristic curve (AUROC), and calibration will be assessed using calibration plots to ensure model predictions align with observed outcomes.

Retrospective Application of the Prediction Model

Once validated, the model will be retrospectively applied to heart transplant cases from **2019 to 2022** to estimate PGD incidence. Predicted PGD incidence will be calculated at the **patient level for each year, then aggregated by transplant center volume and donor type (DCD vs. DBD). Centers will be stratified into tertiles based on annual DCD transplant volume** (low, medium, high) to investigate potential differences in PGD incidence related to center experience with DCD procedures. This stratification will allow us to examine temporal trends and assess potential risks associated with the learning curve in centers adopting DCD transplantation practices.

Analytical plan – Model Training and Validation for the temporal trends analysis

Statistical Analysis for Temporal Trends

Temporal trends in predicted PGD incidence will be analyzed using linear regression, with adjustments for clustering by center.

An interaction term **between year and center volume** will be included to assess whether the impact of time on PGD rates varies by DCD transplant volume. (? Sub-stratify analysis)

Sensitivity analyses will compare predicted PGD rates in high- versus low-volume DCD centers, adjusting for potential confounders such as recipient and donor characteristics. **This approach will allow for a better understanding of the relationship between DCD experience and PGD risk over time, taking into account center-specific and temporal factors.**

Analytical plan – For Primary outcomes

The study will include heart transplant recipients recorded in the **SRTR database over a one-year period (September 2023–2024) with the potential for expanding the cohort to include transplants back to 2019 if the PGD prediction model demonstrates high accuracy.** The primary exposure of interest is donor type, comparing patients who received hearts from donation after circulatory death (DCD) with those from donation after brain death (DBD).

Descriptive Analysis

Descriptive statistics will be reported for all baseline characteristics of heart transplant recipients, stratified by donor type (DCD vs. DBD).

Incidence of PGD by Donor Type

To determine the association between donor type and the incidence of PGD, logistic regression models will be used with DCD as the exposure variable, **adjusting for relevant covariates such as recipient age, donor age, comorbidities, cold ischemia time, and other baseline characteristics**. Results will be presented as adjusted odds ratios with 95% confidence intervals.

Analytical plan – For Primary outcomes

Comparative Outcomes in Patients with PGD
Need for Mechanical Circulatory Device (MCD): Logistic regression will be used to assess the association between donor type (DCD vs. DBD) and the need for MCD, adjusting for recipient and procedural factors. If available, the duration of MCD support (in days) will be analyzed using Poisson regression or negative binomial regression, depending on data distribution.

Length of Stay in ICU: The length of ICU stay, measured in days, will be analyzed using linear regression if normally distributed or using Poisson/negative binomial regression for skewed data.

Early (30-Day) Survival: A Cox proportional hazards model will be used to estimate the hazard ratio for 30-day mortality in DCD versus DBD recipients with PGD, adjusting for relevant clinical and demographic covariates.

One-Year Survival: One-year survival will also be analyzed using Cox proportional hazards modeling, with survival curves generated using the Kaplan-Meier method to visually compare survival probabilities over time by donor type among patients with PGD.

Analytical plan – For Primary outcomes

Sensitivity Analysis

Sensitivity analyses will be conducted to assess the robustness of the findings:

If retrospective application of the PGD prediction model to data from 2019 to 2022 is feasible, analyses will be repeated using this expanded dataset to confirm consistency in the observed associations.

Additional subgroup analyses will be performed, stratifying by factors such as transplant center volume, recipient comorbidity score, and ischemia time?, to investigate potential effect modification.

Missing Data

Missing data will be addressed by using multiple imputation if data are missing at random, or by complete-case analysis if missingness is minimal.

Questions for the team

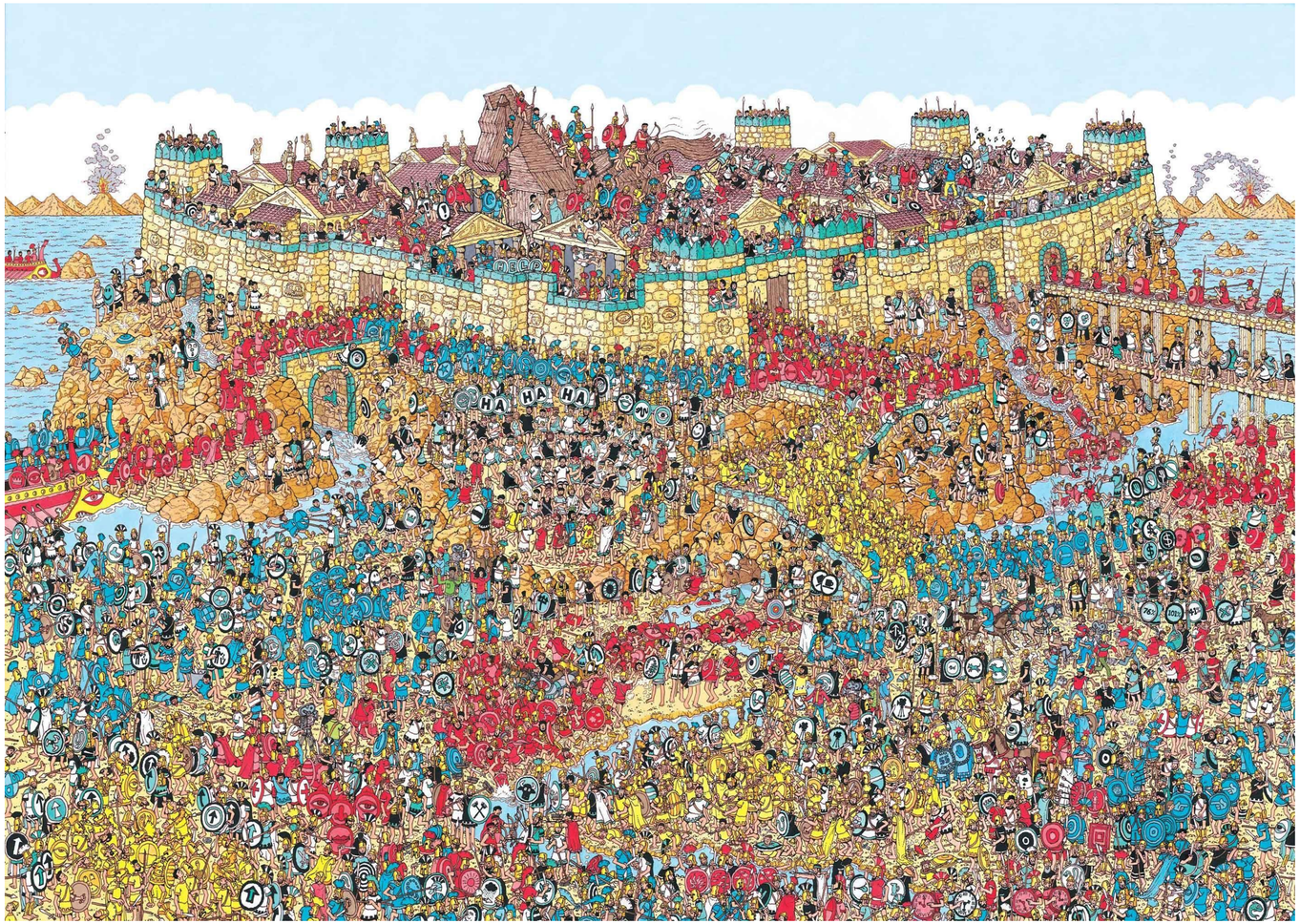
- Opinion of the temporal trend analysis and the validation of a prediction model

- Potential confounders and effect modifiers

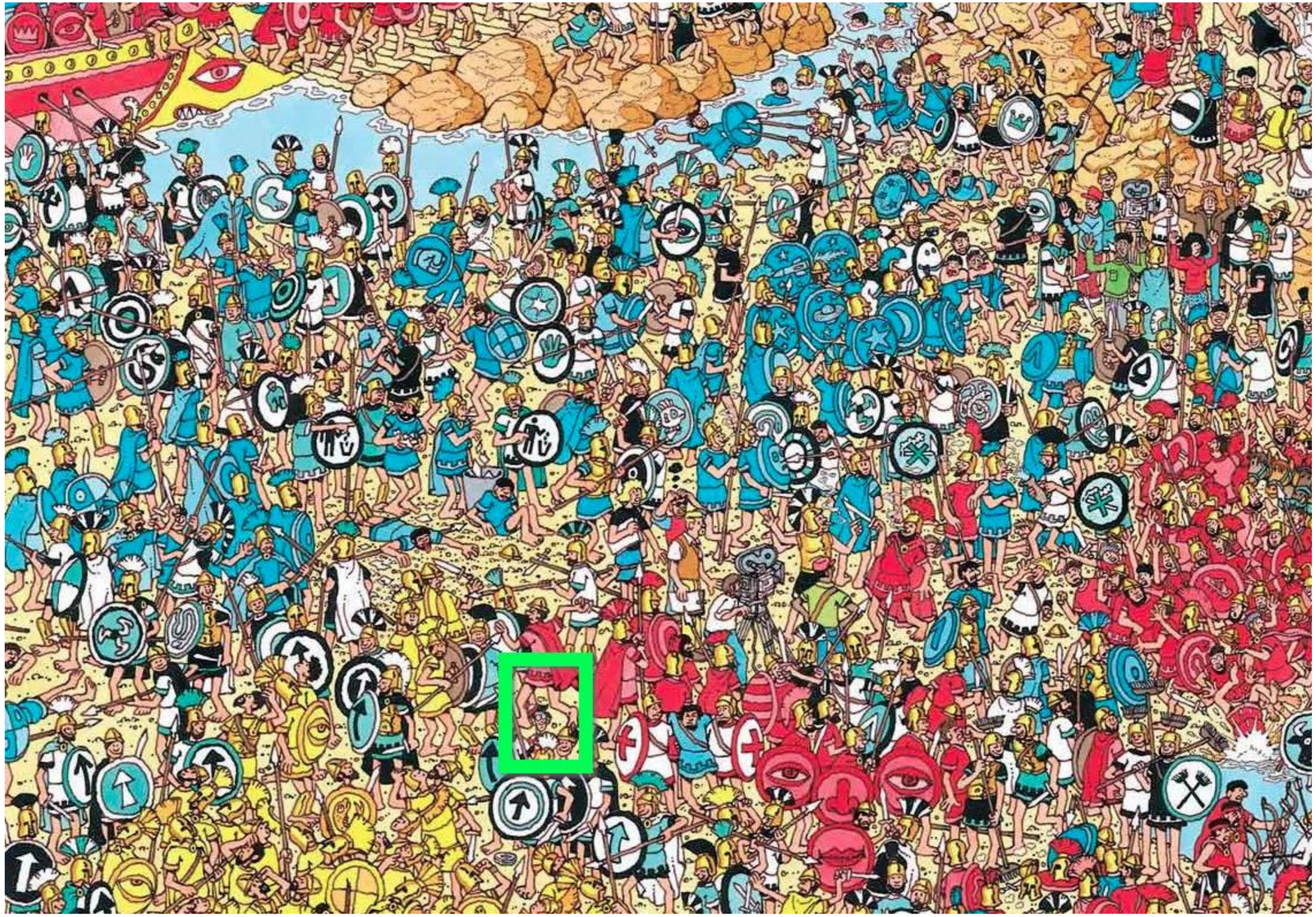
- Question for the team about severity

- Overall feedback

- Next steps to update the data



“The more searching we do, the more meaning we’ll find. Everywhere we search a Waldo is waiting to be found” -D.



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