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Simulating In-Silico Clinical Research Using Diverse Real-World Data

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Introduction/Hypothesis

- Using Real-World-Data (RWD), develop in-silico models for rapidly identifying repurposed drugs that can lower the risk of death due to Sars-CoV-2 infection

- Risk of death due to COVID-19 is predominantly due to hyperactive host inflammatory responses resulting from infection

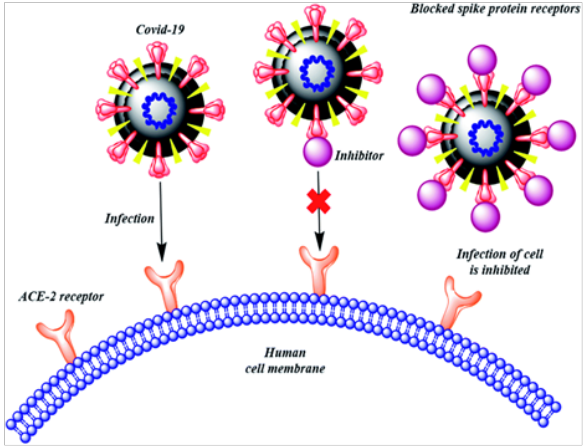
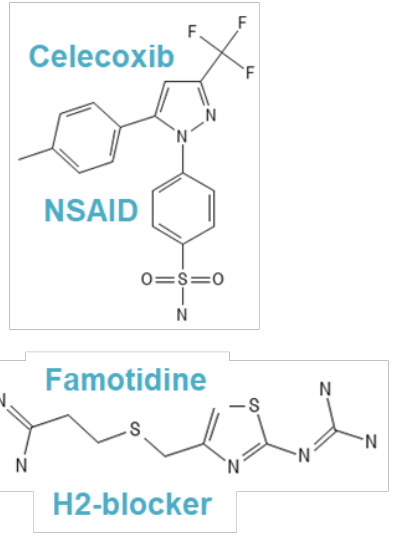


Fig 2 from https://doi.org/10.1039/D0RA04795C



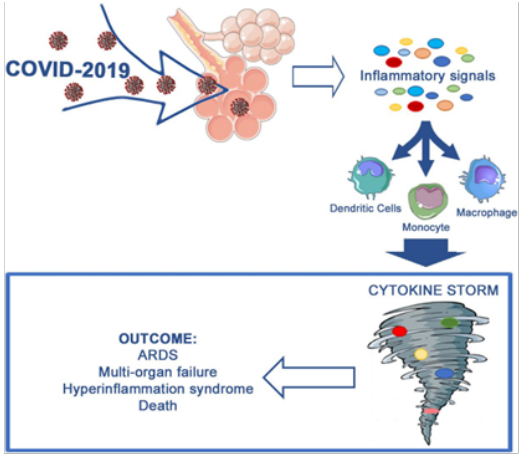


Fig1 from https://doi.org/10.3389/fimmu.2020.02132

COVID-19 Real-World-Data Sources

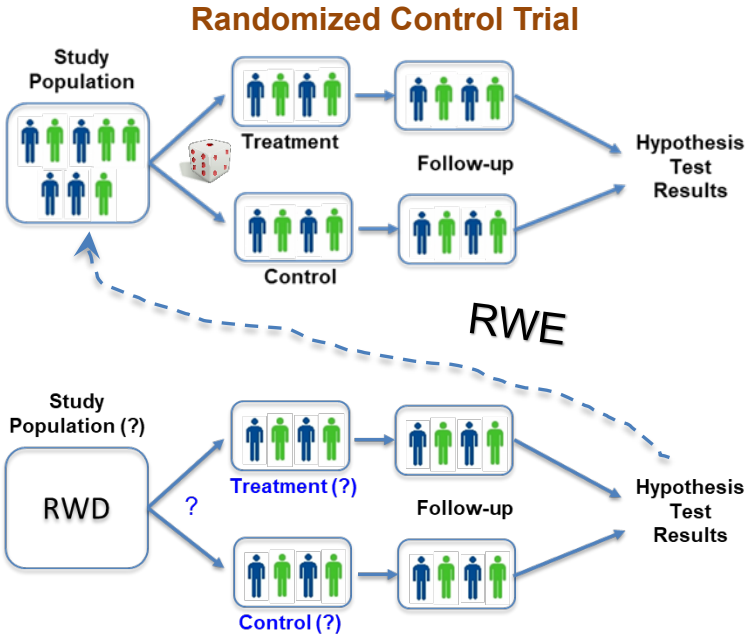
- Two appropriate RWD sources were chosen to model the causal effect of Celecoxib/Famotidine in COVID-19 patients

- Hospital data*
  - Patients (aged 18 years or older)
  - in/out-patients with documented COVID-19 diagnosis from 6/1/2020 – 1/31/2021

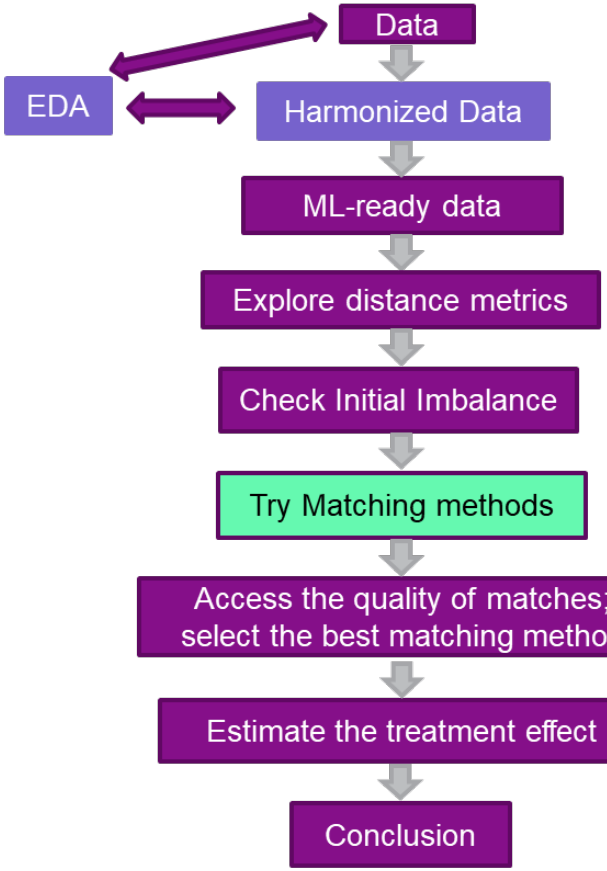
- Pharmacy data*
  - 120-day lookback from each patient's earliest hospital visit with a COVID-19 diagnosis

* IQVIA Hospital Charge Data Master; IQVIA Longitudinal Prescription database (LRx)

Causal Treatment Effect Modeling



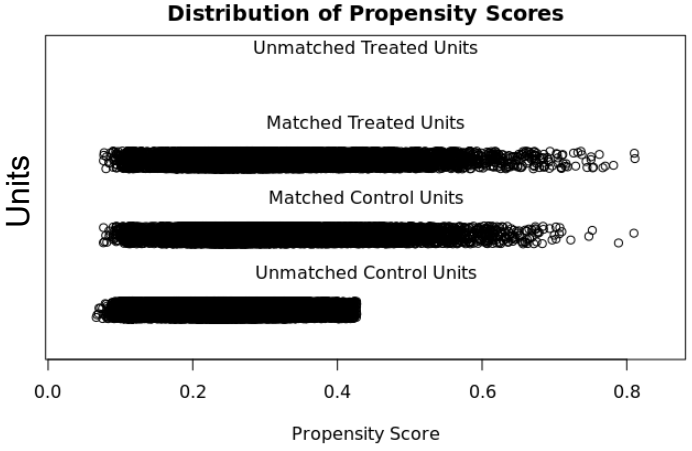
Areas of focus	Solution
Identify study population, randomization, and removing confounding	Inclusion-exclusion, matching, and DAG

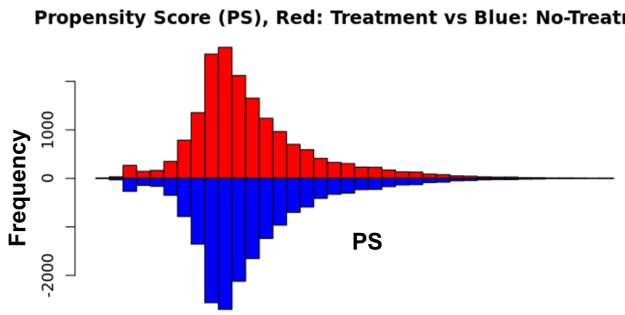


RWD: Real-World-Data
RWE: Real-World-Evidence
EDA: Exploratory Data Analysis
ML: Machine-Learning
DAG: Directed Acyclic Graph

Results

$$\text{Propensity Score(PS)} = \pi_i = P(\text{Trtmnt} = 1|X_i) \text{ (for a person i)}$$

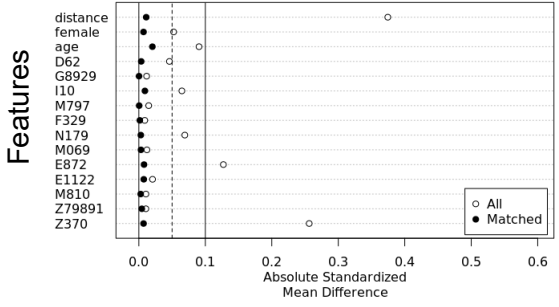


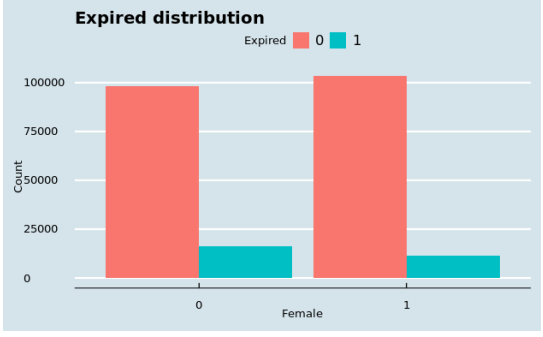


Results shown for Famotidine;
Celecoxib results are similar

$$\text{SMD} = \left(\frac{\bar{x}_{treatment} - \bar{x}_{\text{control}}}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}} \right)$$

Estimating Balancing
(few features are displayed)





Findings

In both treatment options, among the discordant pairs, we see that there is a bigger number where the treated is the person who died, so this suggests that the treated group is at higher risk.

Paired-Outcome Observations

Control \ Treatment	$Y^0=0$	$Y^0=1$
$Y^1=0$	a	c
$Y^1=1$	b	d

$H_0: p_b = p_c$; $H_A: p_b \neq p_c$

p = proportion; α: 0.05; 2-sided

Exact McNemar Test

	Celecoxib				Famotidine			
Run	N	OR	CI (95%)	P-value	N	OR	CI (95%)	P-value
1	1013	2.3870	1.5498, 3.7573	3.276e-05	17916	2.400	2.2254, 2.5898	< 2.2e-16
2	999	4.5882	2.6903, 8.2730	1.642e-10	17892	2.5143	2.3304, 2.7145	< 2.2e-16
3	1019	2.0000	1.3148, 3.0927	8.200e-04	17622	2.5978	2.4045, 2.8085	< 2.2e-16
4	1026	2.3636	1.5545, 3.6669	2.326e-05	17897	2.4851	2.3029, 2.6833	< 2.2e-16
5	1046	2.4838	1.6175, 3.9002	1.115e-05	17916	2.5967	2.4056, 2.8050	< 2.2e-16

R libraries

tableone
matching
ipw
survey
tidyverse
Matchit
sandwich

Conclusions

- We have created a procedure to emulate an in-silico randomized control trial for estimating the causal treatment effects
- Our matched case-control study results for both Celecoxib and Famotidine show OR > 1 indicating that the exposure is associated with higher odds of death for COVID-19 patients
- This procedure can help shorten drug development, review and approval timelines, eliminate bias in data and adequate representation of trial population
- The RWE Methods pipeline can be expanded to add additional methods for new use cases like drug safety, and sequencing

OR: Odds Ratio; **MSM**: Marginal Structural Model; **IPTW**: Inverse Probability Treatment Weighting

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Thank you!

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