RESEARCH QUESTION

SARS-CoV-2 continues to mutate rampantly and remains a global health crisis.

Three emergency-use antivirals were authorized ***(Paxlovid, Molnupiravir, Remdesivir)***

- Still investigational
- Limited clinical knowledge
- Post-marketing safety concerns
- **Drug-drug interactions (DDIs)**

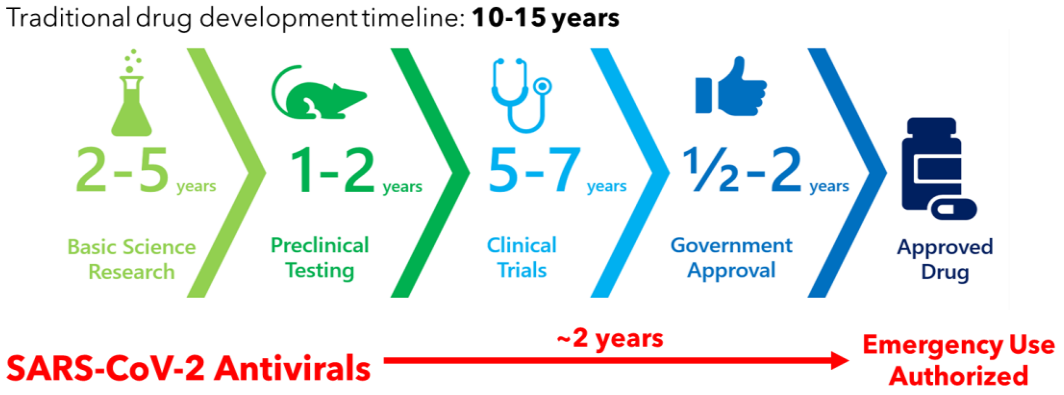


Fig1. *Traditional v. SARS-CoV-2 drug development timeline.*

Patients at high risk for SARS-CoV-2 illness are also at high risk for DDIs

Existing DDI tools:

- Rely on complete clinical trials
- Disregard emergency-use-authorized and developing drugs
- Ignore interaction severity
- **Not comprehensive, transparent, or adaptable**

Image: Harvard Graduate School of Arts and Sciences

AIM: To increase safe and effective SARS-CoV-2 treatment by developing a machine-learning algorithm to predict undiscovered DDIs.

BACKGROUND

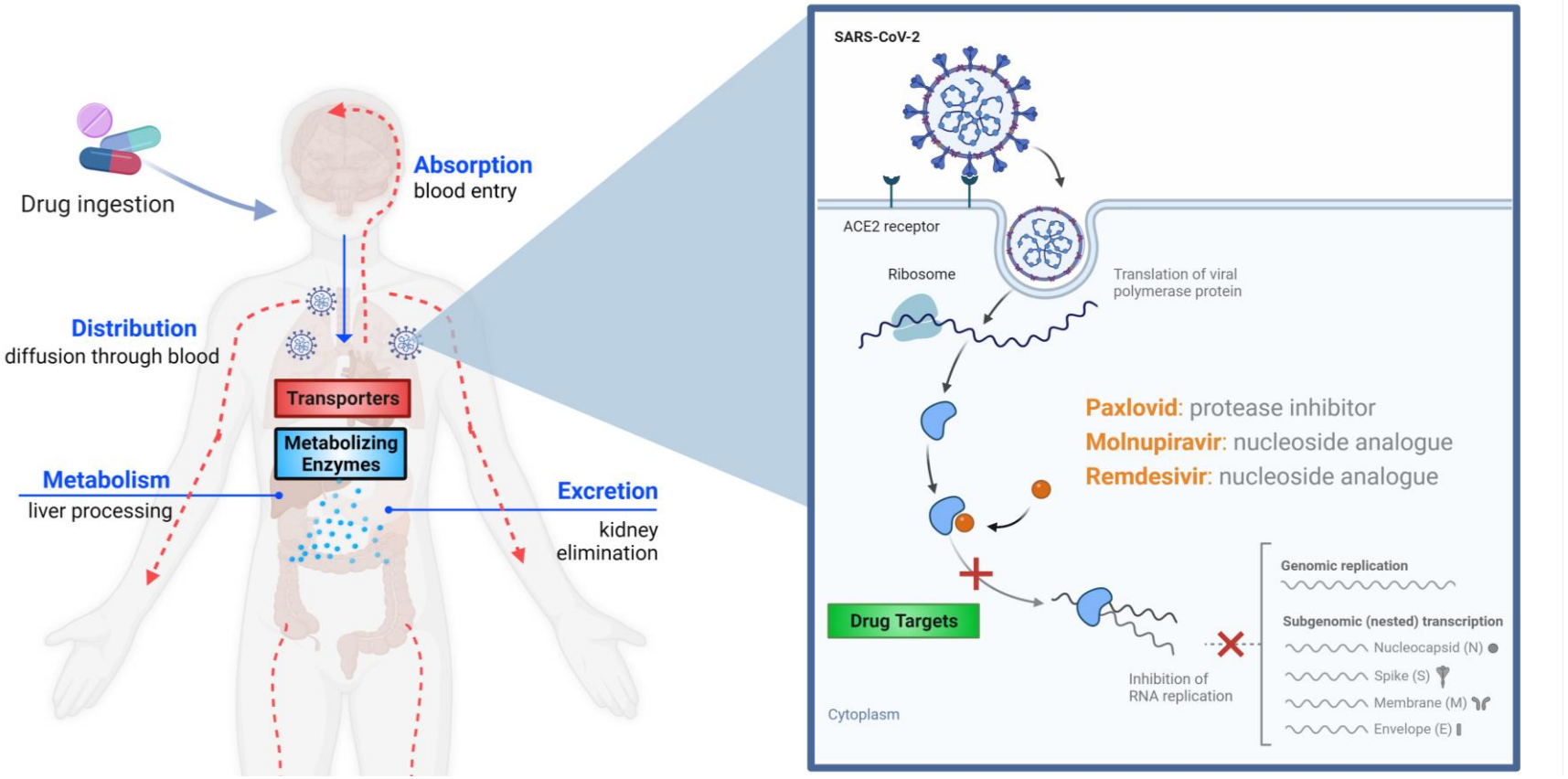


Fig2. *Antiviral drug pharmacologic pathways.*

- DDIs are alterations of drug's pharmacologic profile during co-medications.
- Mediators of DDIs
  - ❖ Metabolic enzymes and transporter proteins during movement of drugs into, through, and out of the body
  - ❖ Drug specific target(s) during drug action
- Risks of DDIs: adverse drug reactions (ADRs)
  - ❖ Severity levels: mild, moderate, severe, and lethal
- With the **complexity and unique pharmacologic aspects of each drug, it's challenging to prevent** immediate and long-term adverse effects, unexpected outcomes, and mortalities from DDIs.

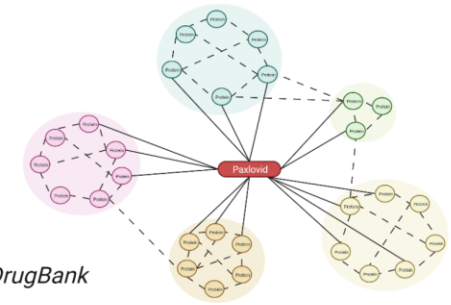
METHODS

Fig2. *Flowchart of methodology.*

All 13,117 FDA-approved Drugs

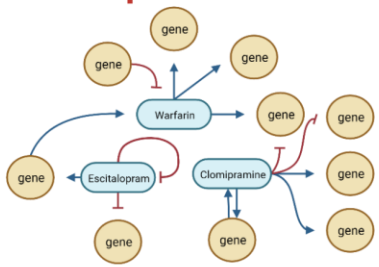
Mechanism-based DDIs

Drug Targets



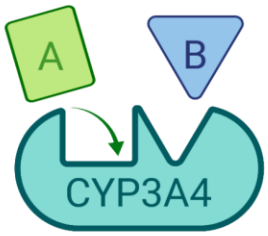
DrugBank

Transporter Proteins



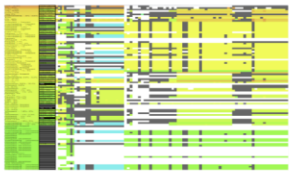
Carrier or transporter proteins involved in distribution

Metabolizing Enzymes



Inhibited/induced or involved in metabolism

Adverse drug reactions



- ADRs on package inserts
- ADRs extracted from published literature
- Frequency of side effects
- Classification of drugs and side effects

SIDER

Natural Language Processing

Severity correlations

- Standardized medical terminology to facilitate drug regulatory information
- Hierarchical structure of clinical syndromes
- Serious ADRS (i.e., sudden death, disability, congenital anomaly)

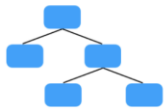
FDA, MedDRA

Jaccard Index $R_{(d_i,d_j)} = \frac{|d_i \cap d_j|}{|d_i| + |d_i| - |d_i \cap d_j|}$

Machine Learning Algorithms

Feature Set Generation

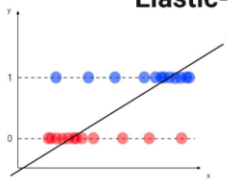
Extreme gradient boosting (XGBoost)



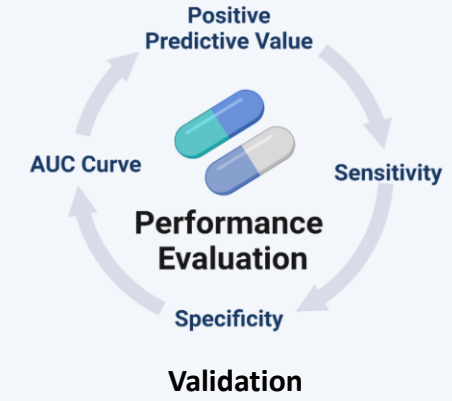
$$f(x) \approx f(a) + f'(a)(x-a) + \frac{1}{2}f''(a)(x-a)^2$$

$$\mathcal{L}^{(t)} \simeq \sum_{i=1}^{n}[l(y_i, \hat{y}^{(t-1)}) + g_i f_t(\mathbf{x}_i) + \frac{1}{2}h_i f_t^2(\mathbf{x}_i)] + \Omega(f_t)$$

Elastic-net logistic regression (GLMnet)



$$\frac{\sum_{i=1}^{n}(y_i - x_i^J\hat{\beta})^2}{2n} + \lambda\left(\frac{1-\alpha}{2}\sum_{j=1}^{m}\hat{\beta}_j^2 + \alpha\sum_{j=1}^{m}|\hat{\beta}_j|\right)$$



RESULTS 1

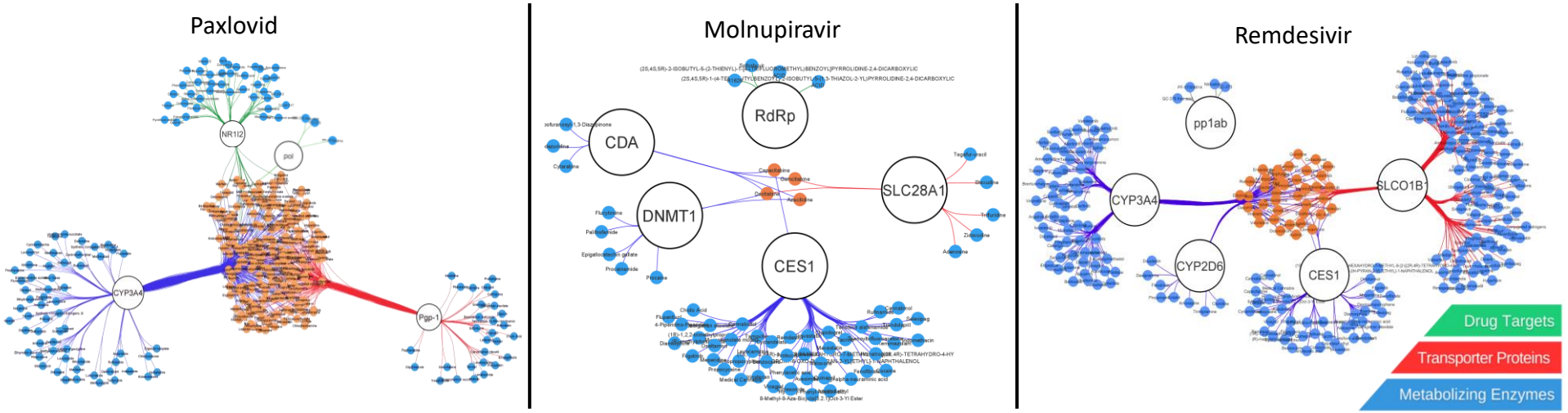


Fig3. *Predicted DDI networks through pharmacologic pathways.*

Large white circles represents a drug's major DDI networks. The edges are categorized by color: drug targets (green), transporter proteins (red), and metabolizing enzyme (blue). Each small blue node represents a concomitant drug that shares the same pathway or cellular process. The center orange nodes include the drugs that have multiple similarities, meaning that they could incite greater interaction severity.

Table1. *Summary of predicted DDI frequencies.*

	Predicted DDIs		
Drugs	**Total**	**Existing**	**New**
Paxlovid	865	639	226
Molnupiravir	76	0	76
Remdesivir	421	368	53

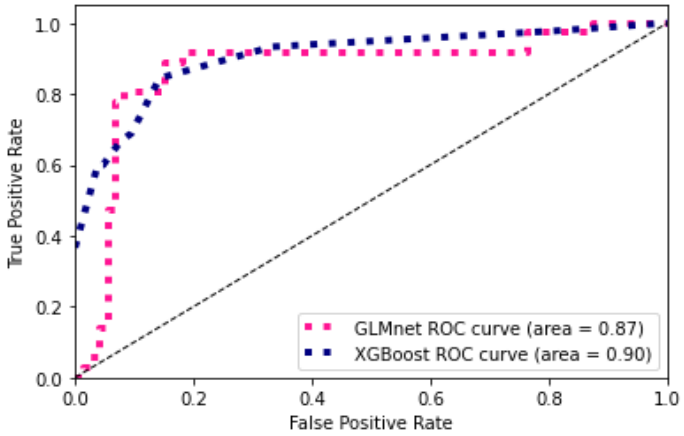


Fig4. *Machine learning receiver operating characteristic.*

Model performance, measured by Receiver Operating Characteristic curve AUC

- GLMnet: 0.87 (95% CI: 0.86-0.87)
- XGBoost 0.90 (95% CI: 0.89-0.91)

Excellent predictive accuracy

RESULTS 2

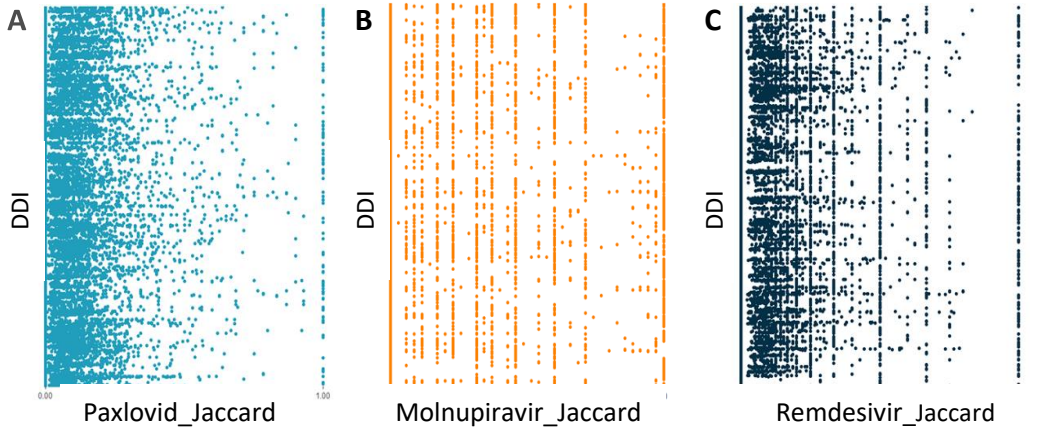


Fig5. *Jaccard index scatterplot of interaction severity.*

(A) **Paxlovid**: 865 total, 226 new, 44 life-threatening; (B) **Molnupiravir**: 76 new, 15 life-threatening; (C) **Remdesivir**: 421 total, 53 new, 17 life-threatening; (D) Interaction categorization into nonsevere, severe, and life threatening

Table2. *Validation of DDIs Prediction in independent FAERS datasets.*

Concomitant Drug	Indication	Severity	Cases (FAERS)	Adverse drug reactions (FAERS)	Recommendation
Simvastatin	Hyperlipidemi	0.959	11	Loss of consciousness, cardio-respiratory arrest, acute pancreatitis, syncope, death	Contraindicated: risks outweigh the potential benefits, use alternative COVID agent.
Tacrolimus	Immuno-suppressant	0.943	98	acute kidney injury, pulmonary embolism, nephropathy toxicity, tremor, multiple organ dysfunction syndrome	Contraindicated: risks outweigh the potential benefits, use alternative COVID agent.
Colchicine	Gout	0.865	1	Gout, Fatigue, Weight Decreased, Hypertension, Diabetes Mellitus, Nephropathy	Contraindicated: risks outweigh the potential benefits, use alternative COVID agent.
Cyclosporine	Organ transplantation	0.837	5	Renal impairment, hypercalcemia, metabolic acidosis	Do not coadminister due to risk of serious toxicity, hold and restart 2 days after completing Paxlovid.
Ramipril	Hypertension	0.812	5	Syncope, loss of consciousness, vertigo, fall	Do not coadminister due to risk of serious toxicity, hold and restart 2 days after completing Paxlovid.
Amlodipine	Hypertension	0.648	6	Blood pressure decreased, muscle twitching, rhabdomyolysis, palpitations, dizziness, urticaria	Potential interaction, therapy modification required.
Digoxin	Heart failure	0.536	2	Acute kidney injury	Potential interaction, therapy modification required.
Dexamethasone	Inflammation	0.455	5	Syncope, Dermatitis Allergic, Rash, Palpitations	Potential interaction, therapy modification required.
Warfarin	Anticoagulant	0.295	5	Eyelid bleeding, INR increased	Potential interaction, therapy modification required.
Ceftriaxone	Bacterial infection	0.037	0	None	No clinically relevant interactions.
Aspirin	Analgesic	0.028	0	None	No clinically relevant interactions.

CONCLUSIONS

Summary

- Created novel framework to **optimize SARS-CoV-2 treatment**
- **Predicts undiscovered DDIs** based on underlying biochemical mechanisms
- Covers 13,000+ drugs to **easily adapt to other fields**
- May **accelerate** clinical trials and new **drug development**

Future Directions

- Software for easy **implementation in clinical settings** and streamline drug prescriptions
- Personalized medicine (PGx) with patient genotypes that could also affect DDIs

All figures are self-created unless otherwise stated.