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Multilayered validation of graph attention autoencoder–derived drug repurposing candidates for COVID-19

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Research Article

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Multilayered validation of graph attention autoencoder–derived drug repurposing candidates for COVID-19

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Abstract

Background/Objectives: The COVID-19 pandemic highlighted the critical need for drug repurposing to rapidly identify therapeutic options. While computational graph-based approaches show promise, conventional single analytical methods often fail to capture the complex pathological mechanisms needed for clinical translation. We aimed to prioritize COVID-19 repurposing candidates by combining computational prediction with orthogonal validation.

Methods: We developed a Graph Attention Autoencoder (GATE) framework with multilayered validation integrating computational prediction, real-world data, and phenome analyses. Network-based embeddings identified candidates through latent-space similarity within biomedical knowledge graphs. Clinical relevance was assessed by disproportionality analysis (DPA) of an adverse event reporting system, and biological plausibility through gene expression and pathway profiling.

Results: Our GATE framework identified 17 drug candidates, including 13 already used or recognized in the context of COVID-19 or its symptoms, consistent with the model recovering known drug–disease associations. Four candidates with minimal prior COVID-19 associations were identified (cilastatin, megestrol, drotrecogin alfa, and ethacrynic acid). DPA prioritized two with significant inverse reporting associations for COVID-19-related adverse event terms: cilastatin (reporting odds ratio [ROR]: 0.19, 95% confidence interval [CI]: 0.09–0.43) and megestrol (ROR: 0.63, 95% CI: 0.42–0.94). Pathway profiling indicated that both drugs share molecular signatures with drugs investigated in COVID-19 clinical trials; gene expression analyses suggest cilastatin

may exert anti-viral and anti-inflammatory effects through DPEP1 inhibition.

Conclusions: By integrating GATE-based prediction, real-world evidence, and phenome-level pathway profiling, this study enabled multidimensional candidate validation that single analytical methods do not provide. Prioritizing clinically approved drugs with established safety profiles may facilitate accelerated clinical evaluation, and the analyses provide mechanistic working hypotheses to streamline preclinical validation. Although experimental confirmation remains essential, the framework offers a generalizable strategy for rapid candidate identification during pandemics and diseases with unmet therapeutic needs.

Keywords: drug repurposing; drug repositioning; COVID-19; SARS-CoV-2; graph attention autoencoder; knowledge graph; disproportionality analysis; real-world evidence; gene expression; hypothesis generation

1. Introduction

The spread of infectious diseases and the emergence of new pathologies have particularly increased the demand for treatments targeting rare diseases. The COVID-19 pandemic highlighted critical gaps in rapid therapeutic development, demonstrating the urgent need for drug repurposing strategies [1]. While traditional drug development requires over 10 years and billions of dollars and enormous time commitments [2-4], with approximately 10% of success rates in clinical development [5], drug repurposing offers accelerated timelines and higher success probabilities due to established safety and pharmacological profiles [6, 7]. Indeed, several computational approaches have successfully identified COVID-19 therapeutics, including baricitinib through network-based repositioning [8], validating the potential of systematic computational drug

discovery.

Computational drug repurposing leverages public databases and bioinformatics to propose novel therapeutic candidates [6]. Graph structure-based approaches – which model relationships between diseases, drugs, and genes as interconnected networks – have emerged as powerful tools for capturing this biological complexity. Ritonavir (a component of Paxlovid) and atorvastatin were successfully identified as potential COVID-19 treatments through network-derived relationship analysis, highlighting how graph-based representations can serve as powerful foundation for systematically uncovering repurposing opportunities [9].

In graph structure-based drug repurposing, it is common to convert graph nodes and edges into vector representations through embedding. Graph embedding methods have been applied to recommendation systems in web stores and other applications [10]. Building upon these foundations, Graph Neural Networks (GNNs), which employ neural networks for graph embedding, have been proposed [11] and have become widely used.

While various GNN methods exist, Graph Attention Networks (GATs) that utilize attention mechanisms have been widely adopted [12]. The attention mechanism is a technology used in Transformer Architecture, which forms the foundation of generative AI using large language models such as ChatGPT, and supports today's revolutionary AI evolution [13]. Recently, these GATs have increasingly been applied to drug repurposing research [14]. However, existing GNN approaches face critical limitations when confronting complex pathological mechanisms; moreover, predictions from any single computational method may be insufficient on their own and require complementary, orthogonal validation before they can guide therapeutic development.

In fact, COVID-19 pathogenesis involves complex, multifaceted mechanisms encompassing viral replication, host immune responses, and cellular metabolic

processes. Approximately 200 existing drugs may target SARS-CoV-2-associated pathways, spanning diverse targets from viral proteins (spike protein, papain-like protease (PLpro), 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and helicase [15]) and host cellular machinery (mTOR-PI3K pathway [16], autophagy [17], vesicular transport systems [18], and immune response [19]). This molecular complexity presents a fundamental challenge; single analytical approaches may be insufficient for adequate exploration of therapeutic candidates.

To address this challenge, we developed a comprehensive multilayered analytical framework that integrates a Graph Attention Autoencoder (GATE) with validation using real-world evidence and phenome data. Rather than relying on a single line of evidence, the framework triangulates each candidate across independent, heterogeneous data sources. This integrated strategy prioritized candidate drugs that have received little prior attention as COVID-19 therapeutics, such as cilastatin and megestrol, and generated actionable mechanistic hypotheses for therapeutic development.

2. Results

2.1. GATE-based identification of candidate drugs for COVID-19

To systematically identify and prioritize novel drug repurposing candidates, we developed a comprehensive multilayered analytical framework that complements single-method computational prediction with orthogonal validation. Our methodology consists of three integrated phases: (1) computational identification of candidate drugs through a graph attention autoencoder (GATE) utilizing attention mechanisms and data obtained from Open Targets [20], (2) assessment of potential clinical relevance using real-world evidence, and (3) molecular biological assessment for mechanism of action (MOA) hypothesis generation using phenome data (Figure 1). This multilayered

evaluation strategy integrates complementary lines of evidence, providing more actionable insights for therapeutic development than network-based prediction alone. To demonstrate the utility of this framework, we applied it to identify and prioritize novel drug repurposing candidates for COVID-19.

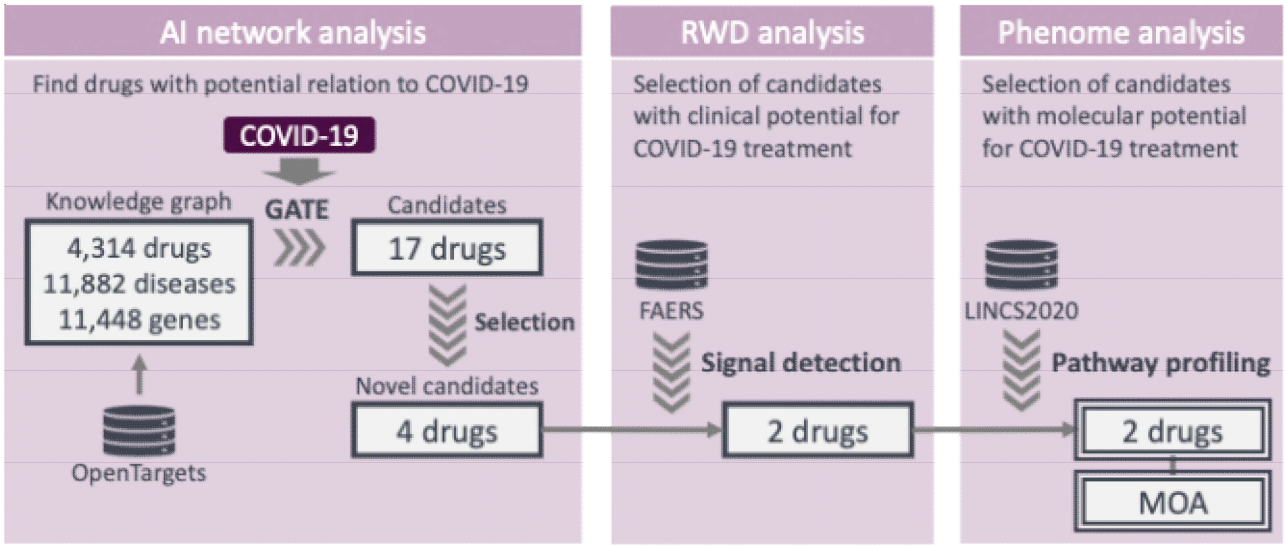

Figure 1. Workflow of analytical framework for COVID-19

AI network analysis using a graph attention autoencoder (GATE) selects candidate drugs for COVID-19, real-world data analysis (disproportionality signal detection) narrows them to drugs with inverse reporting signals for COVID-19-related AE terms, and phenome analysis (pathway profiling) evaluates their molecular plausibility and mechanisms of action.

Based on the latent space representation of GATE, we identified drug nodes showing high similarity to the COVID-19 node (Table 1). In interpreting the results, we considered different salt or derivative forms of the same compound (e.g., cilastatin and cilastatin sodium) as representing a single drug entity. Among the 17 drugs identified, 13 are already used in the clinical management of COVID-19 or its symptoms, or are otherwise recognized in the COVID-19 literature, consistent with the model recovering established, low-novelty drug–disease relationships. The remaining 4 drugs (cilastatin,

megestrol, drotrecogin alfa, ethacrynic acid) had minimal prior association with COVID-19, representing higher-novelty candidates that have received little prior attention as COVID-19 therapeutics. Notably, these candidate drugs and COVID-19 were not directly connected in the original knowledge graph (Figure 2, Figure S1-3), consistent with the embedding capturing latent associations that are not represented by direct edges.

159

160 **Table 1**. Top-ranked drug candidates based on embedding similarity to COVID-19 in the latent space learned by GATE model

ID	Name	Description	Cosine Similarity	OpenTargets Association Score	OpenTargets Rank of Score
CHEMBL1201057	**CILASTATIN SODIUM**	**Antibiotic, Dipeptidyl Peptidase I Inhibitor**	**0.86067**	**0.01**	**2672**
CHEMBL766	**CILASTATIN**	**Antibiotic, Dipeptidyl Peptidase I Inhibitor**	**0.86006**	**0.01**	**2672**
CHEMBL1201014	PREDNISOLONE SODIUM PHOSPHATE	Steroid Drug	0.85693	0.609	4
CHEMBL1201231	PREDNISOLONE PHOSPHORIC ACID	Steroid Drug	0.85526	0.609	4
CHEMBL679	EPINEPHRINE	Adrenergic Receptor Agonist	0.85111	0.372	169
CHEMBL2134724	IPRATROPIUM BROMIDE	Anticholinergic Drug, COPD and Bronchial Asthma Treatment	0.84696	0.076	737
CHEMBL1621597	IPRATROPIUM	Anticholinergic Drug, COPD and Bronchial Asthma Treatment	0.84621	0.076	737
CHEMBL1200689	NITRIC OXIDE	Nitric Oxide, Pulmonary Hypertension Treatment	0.84535	0.345	397
CHEMBL1201335	GLYCOPYRRONIUM	Anticholinergic Drug, COPD	0.84439	0.076	737
CHEMBL1437	NOREPINEPHRINE	Adrenergic Receptor Agonist	0.84266	0.372	169
CHEMBL1215	PHENYLEPHRINE	Adrenergic Receptor Agonist	0.84121	0.372	169
CHEMBL2108429	MEPOLIZUMAB	Anti-IL-5 Antibody	0.83772	0.068	799
CHEMBL1201139	**MEGESTROL ACETATE**	**Antineoplastic Drug, Contraceptive, Progesterone Receptor Agonist**	**0.83667**	**0.086**	**636**
CHEMBL1370	BUDESONIDE	Steroid Drug	0.83639	0.609	4
CHEMBL1364144	METHYLPREDNISOLONE ACETATE	Steroid Drug	0.83551	0.609	4
CHEMBL1201027	GLYCOPYRROLATE	Anticholinergic Drug	0.83493	0.076	737
CHEMBL2109065	**DROTRECOGIN ALFA (ACTIVATED)**	**Antithrombotic, Anti-inflammatory, Fibrinolysis-promoting Human Activated Protein C**	**0.83448**	**0.026**	**1339**
CHEMBL52440	DEXTROMETHORPHAN	Cough Suppressant and Expectorant (Medicon)	0.83335	0.365	334
CHEMBL1473	FLUTICASONE PROPIONATE	Steroid Drug	0.83256	0.609	4
CHEMBL3707243	GLYCOPYRRONIUM TOSYLATE	Anticholinergic Drug, Primary Axillary Hyperhidrosis Treatment	0.83239	0.076	737
CHEMBL456	**ETHACRYNIC ACID**	**Loop Diuretic Drug**	**0.83171**	**0.004**	**4822**

161 Drug candidates are ranked by cosine similarity scores in GATE latent space. Rows shown in bold indicate drugs not previously used

162 for COVID-19 treatment, representing candidates with minimal prior COVID-19 associations. The OpenTargets association scores

163 range from 0 to 1, with higher values indicating stronger relevance.

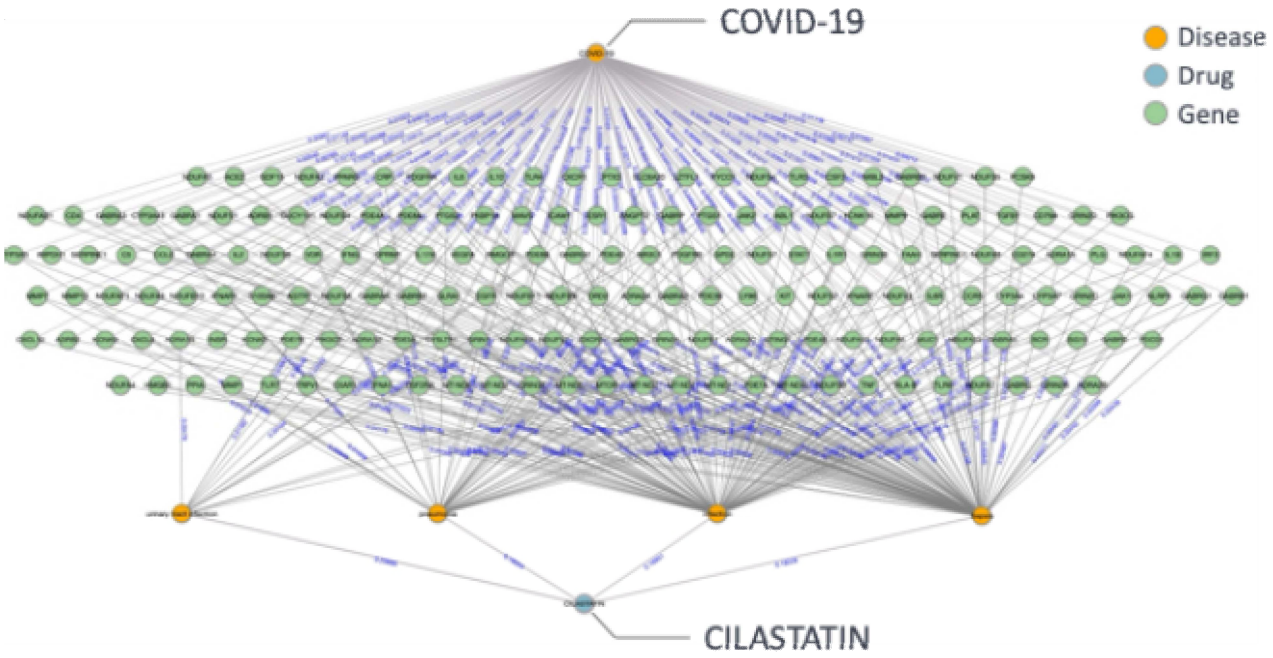

Figure 2. Subnetwork connecting COVID-19 and cilastatin in multimodal knowledge graph

Subnetwork extracted from a multimodal knowledge graph consisting of drugs, diseases, and genes. Nodes are colored by type: orange for diseases, blue for drugs, and green for genes.

To further evaluate the findings, we investigated the association scores between COVID-19 and the target genes of each candidate drug using the Open Targets Platform, an integrated drug discovery database. Association scores are comprehensive relatedness indicators based on literature information, genetic evidence, experimental data, and other sources. This analysis revealed that all four candidate drugs showed low association scores with COVID-19 (Table 1), suggesting that these drugs would not be visible through existing knowledge bases. In particular, our top candidate, cilastatin, had an association score of 0.01, which is markedly lower than scores (0.068–0.609) of drugs that are known to have effects on COVID-19.

2.2. Disproportionality analysis of candidate drugs in FAERS

We further analyzed the four drugs identified by the GATE approach using real-world adverse event (AE) data from the FDA Adverse Event Reporting System (FAERS) to examine potential associations with COVID-19-related AE terms by disproportionality analysis (DPA). In this DPA, the reporting odds ratio (ROR) and its 95% confidence interval (CI) quantify whether COVID-19-related AE terms are reported disproportionately more or less often for a given drug relative to all other drugs in the database; an ROR < 1 indicates an inverse reporting association, and a 95% CI upper limit < 1 indicates that this association is statistically significant at the reporting level. Both cilastatin and megestrol showed significant inverse reporting associations for COVID-19-related AE terms, with RORs of 0.19 (95% CI: 0.09–0.43) and 0.63 (95% CI: 0.42–0.94), respectively (Figure 3).

A

Drug	ROR	95%CI
cilastatin	0.19	0.09-0.43
megestrol	0.63	0.42-0.94
drotrecogin alfa	NA	NA
ethacrynic acid	NA	NA

NA: Not calculable due to small sample size

B

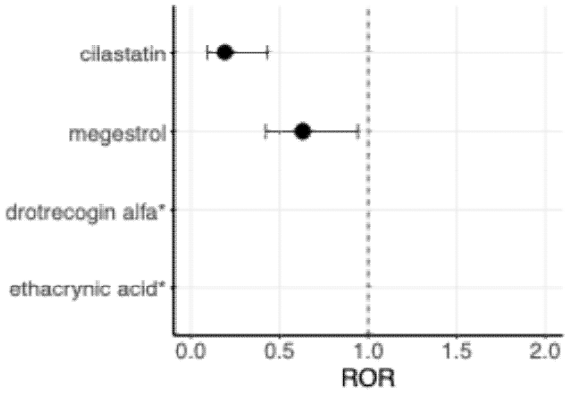

Figure 3. DPA of repurposing candidate drugs and coronavirus infections

(A) Reporting odds ratios (ROR) and 95% confidence intervals (CI) for candidate drugs through GATE-based analysis. "NA" indicates values that could not be calculated due to insufficient sample size. (B) Forest plot visualizing RORs for the same set of drugs. The horizontal bars represent 95% CIs. RORs for drotrecogin alfa and ethacrynic acid were not calculable and are indicated with asterisks (*).

To examine whether the observed inverse associations were specific to each drug, we conducted DPA for drugs in the same class as each candidate drug or for drugs that are often co-administered with the candidate drug. Cilastatin is often co-administered with imipenem, a ß-lactamase inhibitor. DPA for ß-lactamase inhibitors showed ROR values around 1.0, and the remarkable inverse associations observed with cilastatin were not observed (Figure S4). Megestrol is a progesterone receptor agonist. Progesterone preparations classified as progesterone receptor agonists showed RORs around 0.5 with 95% CI upper limit less than 1, indicating inverse association trends similar to megestrol (Figure S5).

Note that drotrecogin alfa and ethacrynic acid could not be evaluated using this DPA due to insufficient co-occurrence reports with COVID-19-related AEs in the FAERS database during the analysis period.

2.3. Pathway-profile concordance with known COVID-19 candidates (LINCS 2020)

To further explore these findings at the phenome level, we conducted correlation analysis using pathway profiling with the Library of Integrated Network-Based Cellular Signatures (LINCS) 2020 for cilastatin and megestrol, the two drugs that showed statistically significant inverse associations in DPA. LINCS 2020 is the successor database to the Connectivity Map (CMAP), an established platform for comparing phenomic signatures of any given drug with those associated with specific diseases or disease therapeutics [21]. For each drug, we explored compounds with correlated pathway profiles from 17,170 compounds (241,597 profiles) using Fisher's exact test.

The compounds showing the strongest correlations with cilastatin (Table 2) included artesunate and sirolimus, which are drugs that have undergone clinical trials for COVID-19. The analysis also revealed ipidacrine, ursolic acid, wortmannin, and thapsigargin, which have been reported in the literature as COVID-19 therapeutic candidates.

227

228 **Table 2.** Top-ranked compounds positively correlated with the pathway profile of cilastatin

PertID	Name	MOA	Cell	Conc	Time	Adj. P-value	COVID-19 relation
BRD-K79759031	artesunate		HT29	10uM	6h	4.4E-42	10 clinical studies
BRD-K66896231	ipidacrine	Acetylcholinesterase inhibitor	HT29	10uM	6h	1.0E-40	1 report
BRD-K60067222	BRD-K60067222		PC3	10uM	24h	8.7E-40	
BRD-K68185022	ursolic-acid	11-beta hydroxysteroid dehydrogenase inhibitor	PC3	70uM	24h	4.2E-39	4 reports
BRD-A19037878	BRD-A19037878		K562	2.5uM	24h	8.0E-39	
BRD-A75409952	wortmannin	PI3K inhibitor	PC3	10uM	6h	2.6E-38	2 reports
BRD-K81855038	roxatidine		HT29	10uM	6h	4.9E-38	
BRD-A79768653	sirolimus	MTOR inhibitor	PC3	3.33uM	24h	1.5E-37	9 clinical studies
BRD-K69023402	thapsigargin	ATPase inhibitor	JURKAT	0.37uM	24h	1.5E-37	3 reports
BRD-K56032964	AP-26113		HT29	0.37uM	24h	1.6E-37	

229 The "COVID-19 relation" column indicates whether each compound has been previously associated with COVID-19 through

230 publications or clinical trials. Details of the corresponding reports and studies are provided in Supporting Information 1 and 2.

Similarly, the compounds showing the strongest correlations with megestrol (Table 3) included tianeptine, fedratinib (TG-101348), AZD-6482 and vorinostat. Tianeptine and fedratinib (TG-101348) have undergone clinical trials for COVID-19. AZD-6482 and vorinostat have been reported as COVID-19 therapeutic candidates.

Table 3. Top-ranked compounds positively correlated with the pathway profile of megestrol

PertID	Name	MOA	Cell	Conc	Time	Adj. P-value	COVID-19 relation
BRD-K37142460	MI-2		OCILY3	10uM	24h	1.3E-08	
BRD-A81370665	BI-D1870	Ribosomal protein inhibitor	HBL1	10uM	24h	1.3E-08	
BRD-K01436366	XMD-1150	Leucine rich repeat kinase inhibitor	BJAB	10uM	24h	3.4E-08	
BRD-K36363294	I-BET-151		HIMG002	2.5uM	24h	3.4E-08	
BRD-A53077924	tianeptine	Selective serotonin reuptake enhancer	HIMG001	15uM	24h	4.1E-08	1 clinical study
BRD-K12502280	TG-101348	FLT3 inhibitor	OCILY3	10uM	4h	2.5E-07	1 clinical study
BRD-K58772419	AZD-6482	PI3K inhibitor	MCF7	1.11uM	24h	3.0E-07	1 report
BRD-K12502280	TG-101348	FLT3 inhibitor	TMD8	2.5uM	4h	5.7E-07	1 clinical study
BRD-K81418486	vorinostat	HDAC inhibitor	JURKAT	10uM	24h	5.7E-07	3 reports
BRD-K54606188	BRD-K54606188		TMD8	0.66uM	4h	1.9E-06	

The "COVID-19 relation" column indicates whether each compound has been previously associated with COVID-19 through publications or clinical trials. Details of the corresponding reports and studies are provided in Supporting Information 1 and 2.

2.4. Pathway alterations following cilastatin treatment

In the LINCS 2020 data, cilastatin treatment significantly decreased the expression of 42 pathways in the HT29 cell line (Table S2). Enrichment Map analysis revealed that gene sets related to splicing, ribosome, mitochondria, telomere, and ubiquitin pathways were altered (Figure 4).

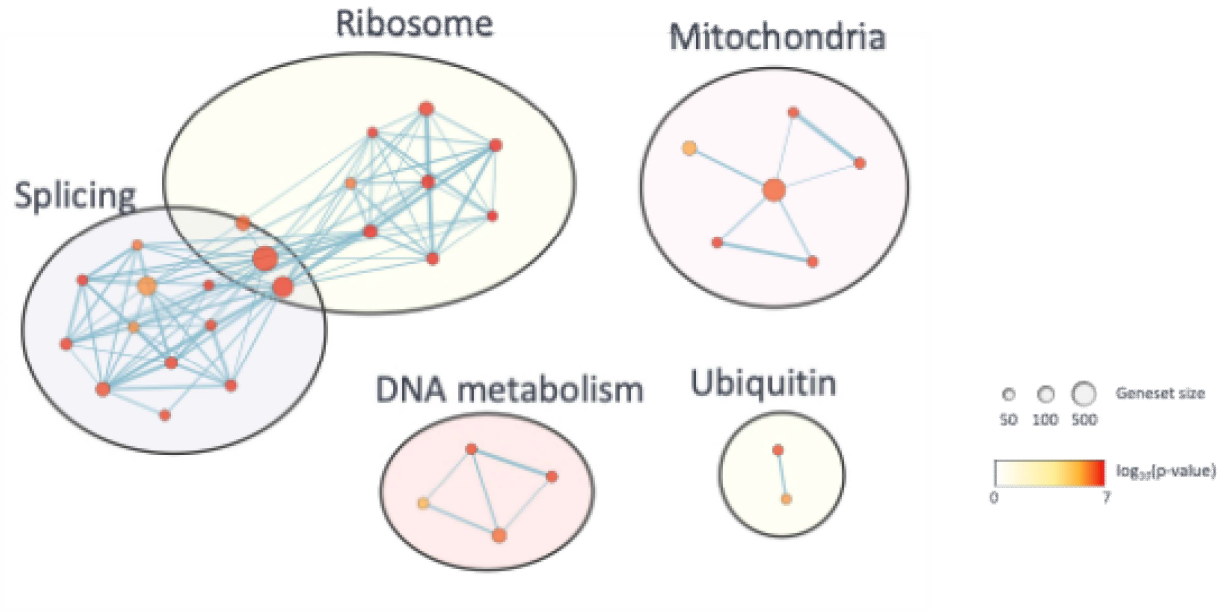

Figure 4. Enrichment map of down-regulated pathways following cilastatin treatment This network visualizes gene ontology (GO) biological process terms significantly down-regulated by cilastatin treatment. Each node represents a gene set corresponding to a GO term, with node size proportional to the number of genes in the set and node color reflecting statistical significance ($\log_{10}$-transformed p-value). Edges indicate gene overlap between gene sets. Functionally related clusters are annotated.

3. Discussion

3.1. Recovery of latent drug–disease associations by the GATE approach

To assess whether these candidates had been overlooked in prior repurposing efforts, we examined whether the four drugs had been reported as COVID-19 repurposing

candidates—and, where reported, investigated in depth—in existing studies. Cilastatin was reported as one of 78 candidates for SARS-CoV-2 3CLpro inhibition through docking simulation approaches, but detailed validation was not performed [22]. Megestrol was proposed as one of 34 COVID-19 therapeutic candidates through network-based approaches, though detailed investigation was not conducted [23]. Drotrecogin alfa had no existing reports; to our knowledge, this is the first report of this drug as a COVID-19 candidate. Ethacrynic acid was reported as a promising candidate for SARS-CoV-2 main protease (Mpro) inhibition through docking simulation approaches, with experimental validation also performed [24].

Although some candidate drugs identified by the GATE approach have been previously reported by other computational methods, those studies provided only preliminary identification without comprehensive evaluation of therapeutic potential. Notably, three of the four candidates (cilastatin, drotrecogin alfa, and ethacrynic acid) were not identified by the conventional network-based approaches we surveyed. This suggests that GATE may identify complex associations that remain undetected by conventional network analysis, exemplified by drotrecogin alfa.

These results suggest that the GATE approach is complementary to existing methods and has the potential to efficiently discover novel relationships between drug–disease pairs. Furthermore, the identification of candidates such as ethacrynic acid, for which experimental validation has been conducted, provides additional support for the plausibility of the prioritized candidates. However, these remain computational predictions that require experimental validation.

3.2. Potential clinical relevance of candidate drugs from FAERS disproportionality analysis

For cilastatin, COVID-19-related AE terms were reported approximately 5-fold less frequently among cilastatin reports than among non-cilastatin reports, and for megestrol approximately 40% less frequently. Although these disproportionality signals

are hypothesis-generating and cannot by themselves establish a causal effect, the inverse association for cilastatin was among the largest observed in this analysis, suggesting that both drugs may have potential worth investigating as COVID-19 repurposing candidates.

The ß-lactamase inhibitor comparison suggests that the inverse reporting association observed for cilastatin is not explained by co-reported ß-lactamase inhibitors and may be relatively specific to cilastatin at the reporting level. For megestrol, the progesterone receptor agonist comparison suggests that the observed inverse reporting association reflects a pharmacological class effect mediated through progesterone receptors rather than a signal specific to megestrol. However, more detailed analysis is needed to clearly distinguish the influence of class effects.

The inverse reporting association observed for cilastatin is consistent with previously proposed mechanisms by which this drug might reduce SARS-CoV-2 viral replication and modulate the cytokine response observed in severe COVID-19 [25]. Based on these findings, cilastatin warrants further investigation as a potential therapeutic candidate for COVID-19.

Regarding megestrol, no literature has reported direct associations with COVID-19. However, progesterone, a drug in the same class that showed a significant inverse reporting association with COVID-19-related AE terms in our DPA, has anti-inflammatory properties, suggesting potential as a COVID-19 treatment [26-28]. Clinical studies on COVID-19 treatment using progesterone have been conducted (NCT04365127, NCT04865029) and in the NCT04865029 trial, progesterone administration in moderate to severe COVID-19 patients resulted in significant improvement in clinical status (a score of 1.5 points, corresponding to a 3-day reduction in oxygen supplementation and 2.5-day reduction in hospitalization duration) [29]. Given the observed class effect of progesterone receptor agonists and the clinical

evidence supporting progesterone, megestrol merits evaluation to determine whether it shows similar effects in confirmatory studies.

3.3. Phenome-level plausibility from pathway profiling

These phenome-level correlations suggest that both cilastatin and megestrol may have potential as COVID-19 therapeutic candidates. The correlation with established COVID-19 therapeutic candidates supported the plausibility of cilastatin as a candidate worth further investigation.

3.4. Hypothesized mechanisms of action of cilastatin

To provide mechanistic insights that could guide future preclinical studies, we sought to elucidate the underlying biological mechanisms based on pathway profiling data. We argued that because pathway-level information represents a functional layer closer to biological responses than individual genes, a detailed analysis of the LINCS 2020 data can facilitate hypothesis generation regarding mechanisms of action.

Based on the pathway alterations following cilastatin treatment (Figure 4), we constructed a mechanistic hypothesis for how cilastatin might intervene in the pathophysiological processes of COVID-19 induced by SARS-CoV-2 infection (Figure 5).

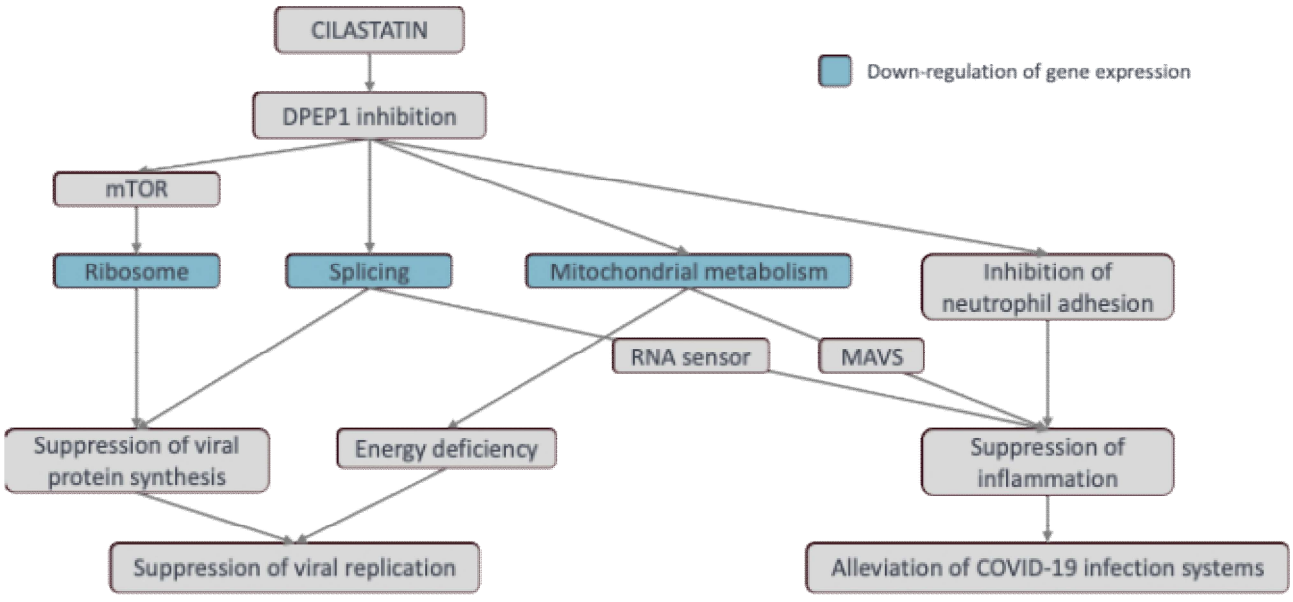

Figure 5. Hypothesized mechanisms of action of cilastatin in COVID-19

This schematic illustrates potential therapeutic mechanisms by which cilastatin may

alleviate COVID-19 pathology, inferred from pathway-level gene expression changes. Cilastatin-mediated inhibition of DPEP1 is proposed to influence multiple downstream biological processes, including ribosome biogenesis, RNA splicing, and mitochondrial metabolism. These changes converge on antiviral and anti-inflammatory outcomes such as suppression of viral replication and inflammation. Pathways shaded in blue indicate those with down-regulated gene expression following cilastatin treatment.

Cilastatin is clinically used as a dipeptidase-1 (DPEP1) inhibitor in combination with imipenem to prevent renal degradation of the antibiotic by DPEP1. Beyond this established role in antibiotic protection, our analysis of LINCS 2020 data indicated that cilastatin modulates multiple cellular pathways related to splicing, ribosomal function, and mitochondrial processes in cells. DPEP1, in addition to its primary function of dipeptide hydrolysis in the kidney, also functions as a neutrophil adhesion receptor on vascular endothelial cells and is known to promote neutrophil recruitment during inflammation [30]. DPEP1 may restrict host ribosomes utilized by SARS-CoV-2 by controlling the PI3K/Akt/mTOR pathway [31], which regulates cellular protein synthesis and metabolism [32]. This may suppress viral replication through a mechanism similar to that of mTOR inhibitors such as sirolimus (rapamycin) [33].

Of particular interest, it is known that the nonstructural protein 16 (NSP16) of SARS-CoV-2 binds to U1/U2 snRNA and interferes with the host splicing mechanism [34]. Suppression of splicing-related pathways may function as a cellular stress response that limits host gene expression and potentially suppresses viral replication by restricting protein synthesis. Moreover, splicing abnormalities may activate antiviral responses via RIG-I-like receptors [35].

Beyond the splicing mechanism, cilastatin also affects mitochondrial pathways. Decreased expression of mitochondria-related genes suggests changes in cellular

metabolic activity and immune signaling. These changes are expected to achieve balanced immune regulation by limiting energy available for viral replication while maintaining type I interferon responses through mitochondrial antiviral signaling protein (MAVS) [36].

3.5. Study limitations

While our multilayered computational approach successfully identified several promising therapeutic candidates and generated mechanistic hypotheses, there are several important limitations that must be addressed.

Limitations of the GATE approach: The predictive performance of our knowledge graph-based method heavily depends on the comprehensiveness and quality of the base knowledge graph being used. In biomedical knowledge graphs, data bias tends to occur based on research progress and attention levels, with particularly insufficient information regarding rare diseases and drugs in early development stages. This deficiency may limit the discovery of novel drug-disease associations and reduce predictability. Therefore, developing comprehensive knowledge graphs that systematically incorporate data on rare diseases and emerging therapeutics will be essential for improving comprehensiveness and reducing bias in future studies.

Limitations of real-world data analysis: Since FAERS is a spontaneous AE reporting system, it inherently contains problems such as reporting bias, underreporting, and selective reporting. A critical limitation emerged from our analysis of drotrecogin alfa and ethacrynic acid, which revealed that the method cannot analyze drugs with insufficient data in the database. This particularly affects newer drugs that lack extensive real-world usage data, limiting our ability to detect potential associations. Conversely, this suggests that classical, widely used drugs may have higher detection sensitivity due to larger volumes of available data. Furthermore, inferring causal relationships from observed associations remains challenging, and the influence of confounding factors cannot be completely eliminated.

Limitations of phenome analysis: The LINCS database used is primarily based on drug responses in cancer cell lines, which exhibit different characteristics from alveolar epithelial cells, vascular endothelial cells, and immune cells, which are important in COVID-19 pathogenesis. Additionally, drug responses under the inflammatory environment in patients during SARS-CoV-2 infection may differ significantly from normal cell culture conditions. Furthermore, it is difficult to capture host-virus interactions and other complex biological processes that can only be detected in in vivo conditions using cell line-based phenome data. While extensive animal data have been accumulated and could potentially be curated and integrated into such databases, comprehensive incorporation remains challenging due to species differences in drug target molecules, including variations in binding site homology and pharmacological responses between species.

Need for experimental validation: This study primarily focused on computational predictions and analysis of existing databases to systematically identify therapeutic candidates and elucidate potential mechanisms. While this approach provided valuable insights into drug repurposing opportunities for COVID-19 treatment, future studies should include direct validation using SARS-CoV-2-infected models and/or clinical evaluation.

4. Materials and Methods

4.1. Graph attention autoencoder (GATE)

4.1.1. Knowledge graph construction

We constructed a heterogeneous knowledge graph comprising three node types — disease, drug, and gene (target) — with data primarily obtained from Open Targets (version 24.06) [20], which aggregates target–disease association data from multiple public sources. Four edge types were defined: (i) "Molecular interactions" (target–target),

(ii) "Associations — direct (overall score)" (target–disease), (iii) "Drug — mechanism of action" (drug–target), and (iv) "Drug — indications" (drug–disease). The resulting knowledge graph comprised 11,882 disease, 4,314 drug, and 11,448 gene nodes connected by 341,911 edges.

Initial node attribute vectors were generated by our proprietary LLM-based feature-engineering pipeline, which produces an embedding vector reflecting the characteristics of each node.

4.1.2. Model architecture and training

Node embeddings were learned with a graph attention autoencoder (GATE) implemented in Python using the Spektral library (v1.3.1) [37] with the TensorFlow 2.15.0/Keras backend. The encoder applied a single graph attention layer (GATConv) with 8 attention heads (concatenated; 256 channels per head) and an exponential linear unit (ELU) activation, with L2 regularization (2.5×10^{-4}) applied to the kernel, attention-kernel, and bias weights. The decoder reconstructed the input node features through two fully connected layers (256 units with ReLU activation, followed by a linear layer matching the input feature dimension). The adjacency matrix was normalized using the standard GATConv preprocessing. The model was trained as a feature-reconstruction autoencoder by minimizing the mean squared error between the input and reconstructed node features (plus the L2 penalty), using the Adam optimizer (learning rate 1×10^{-3}) in full-graph mode for approximately 4×10^{4} epochs, without dropout; a fixed random seed was set.

4.1.3. Candidate identification

From the trained model, an attention-based latent node representation was used to rank all nodes by their cosine similarity to the COVID-19 node, with higher cosine similarity indicating greater proximity in the latent space. Drug nodes that fell within the top 500 of all ranked nodes were retained as candidates; different salt or derivative forms of the same compound (e.g., cilastatin and cilastatin sodium) were treated as a single drug

entity.

4.2. Disproportionality analysis with spontaneous reporting systems

We utilized a spontaneous adverse event (AE) reporting database constructed by U.S. Food and Drug Administration (FDA). The FDA Adverse Event Reporting System (FAERS) contains reports of spontaneous AEs reported by consumers, pharmaceutical companies, and medical professionals worldwide. FAERS consists of seven datasets: DEMO (patient demographic and administrative information), DRUG (drug information), REAC (AEs), INDI (indications for the use of reported drugs), THER (start and end dates for the reported drugs), OUTC (outcomes for the event) and RPSR (sources for the event). The present study used FAERS data from January 2020 through March 2022, representing 3,617,885 reports. This data was obtained through JAPIC-AERS (Japan Pharmaceutical Information Center (JAPIC), Tokyo, Japan), a commercially processed FAERS database.

AEs in the FAERS database are coded using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs). COVID-19-related AE terms were defined as the preferred terms grouped under the MedDRA High Level Term (HLT) "Coronavirus infections" (code 10084510); the complete list of these 17 preferred terms is provided in Table S1, and this set is referred to as "coronavirus infections" in the figures.

AE risk was evaluated by calculating the reporting odds ratio (ROR) and corresponding 95% confidence intervals (CI). The ROR and 95% CI were defined as follows: $ROR = (a/c) / (b/d)$; $95\%\ CI = \exp[\ln(ROR) \pm 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}]$, where a, b, c and d refer to the number of individuals in the FAERS database divided into: (a) those who received the drug of interest (e.g., cilastatin) and had COVID-19-related AE terms reported; (b) those who received the drug of interest without COVID-19-related AE terms; (c) those who did not receive the drug of interest and had COVID-19-related AE terms reported; and (d) those who did not receive the drug of interest and did not have COVID-19-related

AE terms. If the upper limit of the 95% CI was < 1, a significant inverse association was assumed between use of the drug of interest and the reporting of COVID-19-related AE terms.

4.3. Pathway profiling

To explore potential therapeutic agents at the phenome level, we conducted analyses using pathway alteration profiles following drug treatment. We utilized gene expression profile data from the Expanded CMAP LINCS Resource 2020 [21], which contains transcriptome data generated from cell lines treated with various compounds. To mitigate noise inherent in high-throughput methodologies, we employed a quality control process based on gene expression distribution across replicate samples, retaining only high-confidence data; for each perturbation condition, approximately three replicate samples were aggregated into a single expression profile. Plate-to-plate normalization was performed to eliminate assay bias. Furthermore, we applied distribution analysis to determine gene expression alteration levels, selecting only profiles with gene alterations at a Q-value threshold of < 0.20. Gene Set Enrichment Analysis (GSEA) [38, 39] was conducted on the filtered profiles to identify significantly altered pathways for each profile, using a false discovery rate (FDR) cutoff of < 0.20, with up- and down-regulated pathways considered separately. For the GSEA analysis, we utilized ontology gene sets (C5) [40] from the Molecular Signatures Database (MSigDB) [41, 42]. Correlations between pathway profiles were evaluated using Fisher's exact test to identify compounds with similar phenotypic effects. Statistical analysis was implemented in C and Ruby, ensuring computational efficiency for large-scale comparisons. Multiple testing correction was applied at the profile level using the Benjamini-Hochberg method, with an FDR threshold of 0.20 to determine statistical significance. These relatively lenient thresholds were chosen given the exploratory, hypothesis-generating nature of the analysis. Pathway enrichment visualization was performed using Enrichment Map (v3.4.0) [43], a plugin for Cytoscape software (Version

3.10.1) [44]. Significantly enriched pathways with FDR < 0.20 were included in the analysis. The pathway network was constructed with each node representing an enriched gene set, and edges connecting pathways with shared genes, where the edge weight corresponds to the overlap coefficient between the gene sets. To improve interpretability of the resulting network, we utilized the AutoAnnotate plugin (v1.5.1) [45] to cluster and label groups of functionally related pathways based on their shared gene content. Clusters were manually reviewed and annotated to ensure biological relevance.

5. Conclusions

In this study, we systematically evaluated the applicability of existing drugs for COVID-19 treatment using the GATE-based latent space analysis with real-world evidence and phenome-level validation. We identified two candidate drugs for further investigation: cilastatin and megestrol, both clinically approved medications with established safety profiles, which may be amenable to accelerated clinical evaluation.

Our multilayered validation approach achieved confident candidate drug selection by comprehensively assessing clinical and molecular biological plausibility. Integration of these heterogeneous data sources – static knowledge graphs, real-world clinical observations, and dynamic gene expression data – enabled multi-dimensional insights difficult to obtain with a single analytical method. Real-world data analysis indicated potential clinical relevance at the reporting level, while phenome data analysis supported molecular biological validity and mechanistic hypotheses for both drugs.

This integrated framework offers a practical approach to computational drug discovery that bridges the gap between in silico prediction and clinical translation. This multimodal methodology has applications for rapid candidate identification during pandemics and for diseases and conditions with limited therapeutic options. Future

developments in large language models (LLMs) and agentic AI may further strengthen this multilayered framework, including by improving knowledge-graph comprehensiveness.

Future research should focus on in vivo validation and clinical trials of these repurposed drug candidates. It should also explore the applicability of this methodology to other diseases and establish selection criteria for optimal computational methods based on data scale and intended use.

Supplementary Materials: The following supporting information can be downloaded: SupplementalTables.pdf, containing Table S1 (the preferred terms grouped under the MedDRA HLT "Coronavirus infections") and Table S2 (significantly down-regulated gene sets in cilastatin-treated HT29 cells (LINCS 2020)); SupplementalFigures.pdf, containing Figure S1 (subnetwork connecting COVID-19 and megestrol), Figure S2 (subnetwork connecting COVID-19 and drotrecogin alfa), Figure S3 (subnetwork connecting COVID-19 and ethacrynic acid), Figure S4 (DPA of ß-lactamase inhibitors and coronavirus infections), and Figure S5 (DPA of progestins and related drug classes and coronavirus infections); SupportingInformation1_COVID-19_clinicaltrials.xlsx, providing details of the clinical studies corresponding to the "COVID-19 relation" column in Tables 2 and 3; and SupportingInformation2_COVID-19_reports.docx, providing details of the reports corresponding to the "COVID-19 relation" column in Tables 2 and 3.

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Institutional Review Board Statement: Not applicable. This study used only secondary, de-identified data and did not involve human participants, animals, or human tissue; institutional review board approval was therefore not required. All research was conducted in accordance with ICMJE, MEXT, and JSPS ethical guidelines.

Informed Consent Statement: Not applicable. This study did not involve human participants.

Data Availability Statement: Publicly available datasets were analyzed in this study. These data can be found at: the Open Targets Platform (https://platform.opentargets.org/downloads), the CMAP LINCS 2020 collection on the CLUE platform (https://clue.io/data/CMap2020#LINCS2020), and the MSigDB C5 collection (https://www.gsea-msigdb.org/gsea/msigdb/). Spontaneous adverse event data were obtained from JAPIC-AERS, a commercially licensed database derived from the FDA Adverse Event Reporting System (FAERS); although the underlying FAERS data are publicly available from the FDA, the JAPIC-AERS data used in this study are

subject to licensing and commercial restrictions and are not publicly available. Derived data supporting the findings of this study are provided within the article and its Supplementary Materials where possible. The node features used to initialize the model were generated by a proprietary LLM-based feature-engineering pipeline; full public release is not possible owing to commercial and intellectual-property considerations associated with this proprietary embedding-generation methodology, although these node features may be made available to editors and reviewers for verification during peer review.

Code Availability: The code for this work was developed for and is proprietary to GEXVal Inc. and may be made available to editors and reviewers for scrutiny during peer review; full public release is not possible owing to commercial and intellectual-property considerations.

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Conflicts of Interest: J.K.-S. is the founder and representative director of GEXVal Inc. Y.N. is an employee of GEXVal Inc. S.T., K.Y. and K.H. are external consultants providing scientific and technical advice under service agreements with GEXVal Inc. for

this academic study. The algorithms and methodologies reported in this study will be utilized by GEXVal Inc. for internal research and development activities and external collaborations. All authors have reviewed and approved this statement.

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