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Ivan Lerner, Arnaud Serret-Larmande, Bastien Rance, Nicolas Garcelon, Anita Burgun, et al.. Mining electronic health records for drugs associated with 28-days mortality in COVID-19: a pharmacopoeia wide association study (PharmWAS). *JMIR Medical Informatics*, 2022, 10 (3), pp.e35190. 10.2196/35190 . hal-03792405v1

HAL Id: hal-03792405

<https://inria.hal.science/hal-03792405v1>

Submitted on 30 Mar 2022 (v1), last revised 30 Sep 2022 (v2)

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Submitted to: JMIR Medical Informatics
on: November 25, 2021

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Abstract

Background: Patients hospitalized for a given condition may be receiving other treatments for other contemporary conditions or comorbidities. The use of such observational clinical data for pharmacological hypothesis generation is appealing in the context of an emerging disease, but particularly challenging due to the presence of drug indication bias.

Objective: With this study, we aimed at developing a fully data-driven pipeline that would address this challenge, and assess its clinical relevance on patients with COVID-19. Therefore, we applied the so-called pharmacopoeia-wide association study, to analyze the associations between early - within 48h from admission - drug prescription and 28-day mortality in patients with COVID-19.

Methods: We performed a multicenter retrospective cohort study using electronic medical records from 16 University hospitals of the Greater Paris area. We included all adult patients hospitalized in conventional wards during the first three waves of COVID-19. We investigated the association between early - within 48h from admission - drug prescription and 28-days mortality. We implemented a fully data-driven procedure based on adaptive LASSO to determine drug specific adjustment sets. We systematically computed several measures of association including robust methods based on propensity scores to control indication bias, which allowed the report of automated diagnosis. We validated against an expert-knowledge based pipeline on three treatments of references for which experts agreed on the expected association with mortality.

Results: A total of 5,783 patients were included in the analysis. Median age at admission was 69.2 [IQR, 56.7 - 81.1] years old, and 3,390 (58.6%) of them were male. The performance of our automated pipeline was comparable or better for controlling bias than the expert-based adjustment set for three reference drugs: Dexamethasone, Phloroglucinol and Paracetamol. After correction for multiple testing, four drugs were associated with increased in-hospital mortality. Among these, Diazepam and Tramadol were the only ones not discarded by automated diagnostics.

Conclusions: Our innovative approach proved useful in rapidly generating pharmacological hypotheses in an outbreak setting, without requiring a priori knowledge of the disease. Our systematic analysis of early prescribed treatments from patients hospitalized for COVID-19 showed that Diazepam and Tramadol were associated with increased 28-days mortality. Whether these drugs could worsen COVID-19 needs to be further assessed.

(JMIR Preprints 25/11/2021:35190)

DOI: <https://doi.org/10.2196/preprints.35190>

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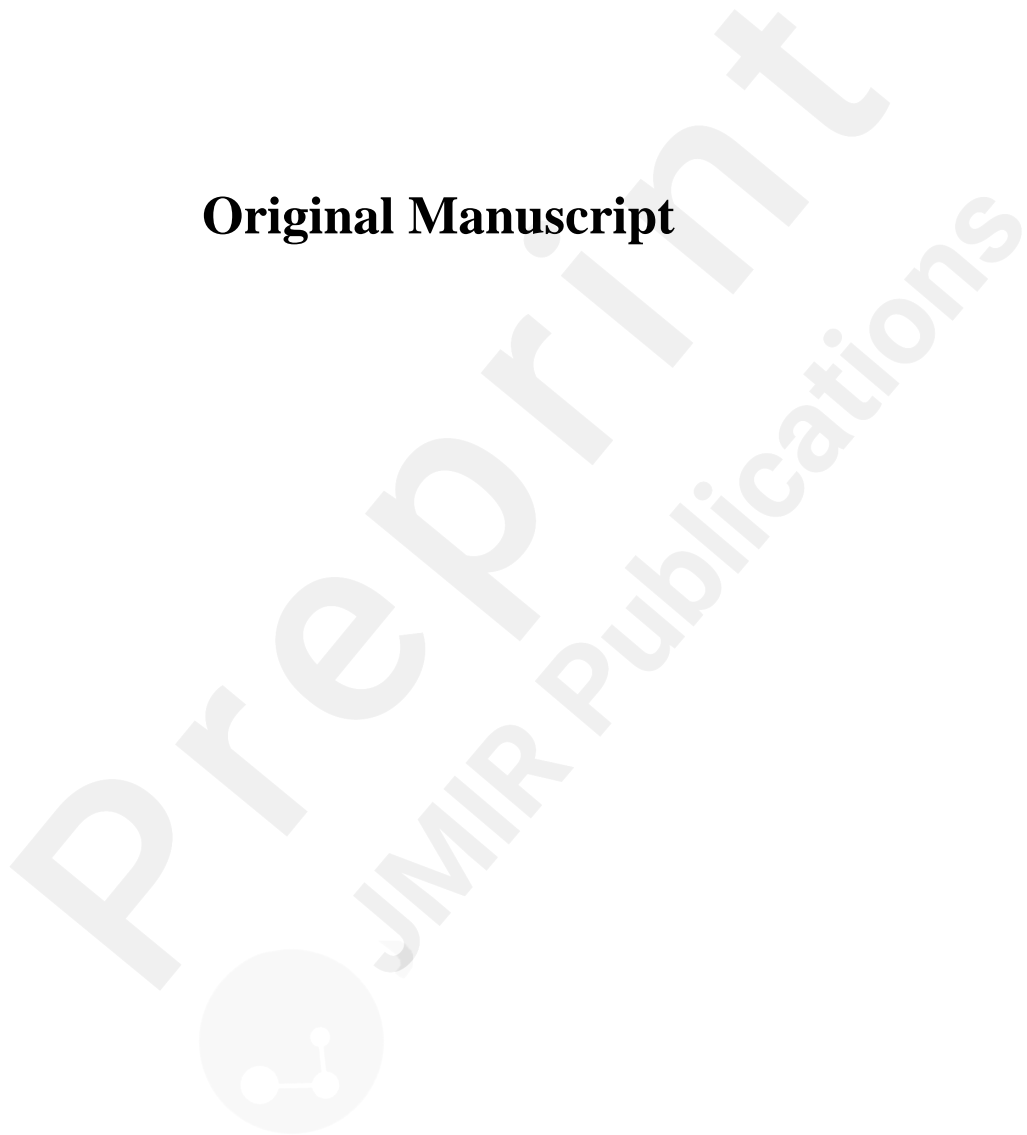
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Original Manuscript



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On behalf of AP-HP/Universities/Inserm COVID-19 research collaboration ; AP-HP COVID CDR Initiative and 'Entrepôt de Données de Santé' AP-HP consortium.

ABSTRACT

Background and objectives

Patients hospitalized for a given condition may be receiving other treatments for other contemporary conditions or comorbidities. The use of such observational clinical data for pharmacological hypothesis generation is appealing in the context of an emerging disease, but particularly challenging due to the presence of drug indication bias. With this study, our main objective was the development and validation of a fully data-driven pipeline that would address this challenge. Our secondary objective was to generate pharmacological hypotheses in patients with COVID-19 and demonstrate its clinical relevance.

Methods

We developed the pharmacopeia-wide association study (PharmWAS) pipeline inspired from PheWAS methodology, which systematically screens for associations between the whole pharmacopeia and a clinical phenotype. First, a fully data-driven procedure based on adaptive LASSO determines drug specific adjustment sets. Second, we compute several measures of association including robust methods based on propensity scores to control indication bias. Finally, we apply the Benjamini and Hochberg procedure of false discovery rate. We applied this method in a multicenter retrospective cohort study using electronic medical records from 16 University hospitals of the Greater Paris area. We included all adult patients between 18 and 95 years old hospitalized in conventional wards for COVID-19 between February 1, 2020 and June 15, 2021. We investigated the association between drug prescription within 48h from admission and 28-days mortality. We validated our data-driven pipeline against a knowledge-based pipeline on three treatments of reference, for which experts agreed on the expected association with mortality. We then demonstrate its clinical relevance by screening all drugs prescribed in more than 100 patients to generate pharmacological hypotheses.

Results

A total of 5,783 patients were included in the analysis. Median age at admission was 69.2 [IQR, 56.7 - 81.1] years old, and 3,390 (58.6%) of them were male. The performance of our automated pipeline was comparable or better for controlling bias than the knowledge-based adjustment set for three reference drugs: Dexamethasone, Phloroglucinol and Paracetamol. After correction for multiple testing, four drugs were associated with increased in-hospital mortality. Among these, Diazepam and Tramadol were the only ones not discarded by automated diagnostics, with adjusted odds-ratios of 2.51 [1.52-4.16] (q-value .1) and 1.94 [1.32-2.85] (q-value .02), respectively.

Conclusion

Our innovative approach proved useful in generating pharmacological hypotheses in an outbreak setting, without requiring a priori knowledge of the disease. Our systematic analysis of early prescribed treatments from patients hospitalized for COVID-19 showed that Diazepam and Tramadol were associated with increased 28-days mortality. Whether these drugs could worsen COVID-19 needs to be further assessed.

Introduction

COronaVirus Disease 2019 (COVID-19) has been a global threat for public health since its emergence in China in December 2019. On July 1, 2021, more than 182 million cases of COVID-19 have been reported world-wide, including more than 3.9 million deaths [1].

Multiple scientific questions have emerged over the course of the pandemic. Tremendous efforts towards finding adequate treatment options have been taken, to the point that as of August 18, 2021, 2,658 clinical trials were listed by the French Cochrane Centre [2]. To date, the most notable finding was that in the inflammatory phase of the disease, dexamethasone, a systemic glucocorticoid, showed a reduction in 28-day mortality among critical patients receiving respiratory support [3]. In addition, questions regularly arise regarding the safety profiles of known drugs (e.g. NSAIDs, ACE inhibitors) [4–6], or potential drug repurposing (e.g. ivermectin, fluvoxamine) [7,8]. These clinical trials are motivated by in vitro efficacy of molecules [8,9], by epidemiological observations, or both [7,10]. Furthermore, the understanding of COVID-19's physiopathology rapidly evolved. Hence, having understood the inflammatory component of severe cases and proven the benefit of Dexamethasone in severe COVID-19 patients, dozens of immunosuppressant molecules are being tested in clinical trials [2]. At the same time, high rates of venous thromboembolism in hospitalized patients were reported, 14.1% (95% CI, 11.6–16.9) compared to 2.8% to 5.6% before the pandemic [11–13], which led to multiple investigations on anticoagulant treatments.

However, two questions can be raised in the context of an emergent disease: (1) Are there pharmacological hypotheses that were not explored due to an incomplete physiological understanding of the disease? and (2) how can we better prioritize hypotheses to improve clinical research efficiency?

This context motivated the development of a systematic and data-driven approach which could guide clinical and epidemiological research by mining routinely collected data from electronic health records (EHRs) without the necessity of *a priori* knowledge. For that purpose, we took inspiration from the phenome wide association study (PheWAS) model [14–17] to derive its drug counterpart, the pharmacopeia wide association study (PharmWAS). This methodology analyzes in a hypothesis-free approach the association of the whole set of drug exposure with the phenotypes of a given population, similarly to a phenome wide association study which analyzes the association of the whole set of phenotypes with genetic variants. The idea of PharmWAS has gained popularity in recent years under different names and was implemented under different designs [17–20]. The PharmWAS methodology was first described by Ryan & al in 2013 [17], using a self-controlled case approach to detect adverse events. A methodology based on Cox survival models was applied by Patel & al. to discover drugs associated with cancer risk [18].

The principal challenge of a PharmWAS is to control the treatment specific indication bias for multiple treatments. For that purpose, we developed a two-step pipeline motivated by the literature on *causal variable selection* [21–23] that we empirically validated using reference drugs. This pipeline had to be fully data-driven in order to scale to a large number of drugs. Our implementation combined a multivariate regression adjustment model, and two propensity score based methods: PS weighting and matching [24–27]. Each method represented different trade-offs between precision of the estimation and robustness to confounding. The rationale was not to report exact treatment effects, which would require domain expert knowledge supporting strong assumptions for a large set of drugs, and necessitate the strict respect of causal inference assumptions: no unmeasured confounders (exchangeability), every patient having a non zero probability of being treated or not (positivity), and well specified models [26]. Instead, our goal was to generate pharmacological hypotheses, and we assumed that the combination of these models would reduce false positive findings caused by indication bias.

Our main objective was to develop and validate a fully data-driven pipeline addressing these challenges. Our secondary objective was to generate pharmacological hypotheses, whether to highlight potential candidates for COVID-19 treatment or prevention, or drugs worsening condition of patients with COVID-19. To that end, we screened for associations between all drugs prescribed in the first 48 hours after admission and 28-days mortality in adults hospitalized for COVID-19 in a conventional ward.

Materials and methods

Study design and data sources

We performed a multicentric retrospective study using the EDS-COVID database, developed upon the Assistance Publique - Hôpitaux de Paris (AP-HP) clinical data warehouse (CDW), regrouping data from 39 different sites in the greater-Paris area [28]. We used four types of data in this study: (i) medico-administrative data, including diagnosis codes recorded using the International Classification of Diseases, 10th edition (ICD-10), (ii) laboratory results from admission, (iii) physiological measurements (e.g., blood pressure) at admission and (iv) all medical text reports associated with inpatient stays.

Population

Selection of the study population was performed according to the following criteria: (1) first admission with an ICD code of U07.1 (COVID-19), (2) age at admission between 18 and 95 year-old, (3) hospitalization in a conventional ward for at least 48 hours, (4) hospitalization in an AP-HP site uploading drug information to the CDW and (5) exclusion of patients who initiated palliative therapy within 48 hours (Figure 1). Study timeframe spanned from February 1, 2020 to June 15, 2021.

Drug exposure and clinical endpoint definition

We extracted the patient's drug exposure status from the clinical data warehouse corresponding to the first 48 hours after the patient was admitted for COVID-19. A code from the anatomical therapeutic chemical (ATC) classification [29] was assigned to patients with at least one corresponding drug regardless of the dose. We restricted the analysis to ATC codes level 5 that were present for a minimum of 100 patients. In the following sections, we use the term *drugs* to refer to these codes. The outcome was defined as all-cause 28-day mortality, with patients discharged alive before 28 days assumed to be alive at 28 days.

Adjustment covariates definition

First, we included the ICD-10 codes from the current inpatient stay, restricted to chronic diseases. These codes were then grouped into broader categories using the first 3-characters and first 2-characters of the ICD-10 system [16]. Secondly, we considered all laboratory results and physiological measurements. For covariates measured in at least 10% of patients, we kept only the first observation within 48 hours after admission. For covariates measured in at least 5% of patients, we kept indicator variables of the measure (1 if measured 0 if not measured). Body mass index (BMI) was extracted from clinical reports using regular expressions. Finally, we added some feature engineered variables, accounting for the study period by using quintiles of the time since study initiation, and quintiles of the number of measurements by source (e.g. number of lab results). All continuous variables were winsorized at 2nd and 98th percentiles to account for outliers.

Pharmacopeia wide association study pipeline

The core principle is to test for the association between each drug exposure and the outcome, controlling for covariates given an adjustment set. This analysis is repeated n times per outcome, with n being the number of drug exposure. The results of the n tests (p-values) obtained from this process are subsequently corrected to take into account the multiple testing.

In the first step of the pipeline, we determine adjustment sets for every drug exposure, given the set of all possible pre-treatment covariates. Using an adaptive LASSO procedure [30], we keep covariates associated with each drug from the subset of covariates associated with the outcome, after cross-validation of the model's deviance. We include for each continuous covariate three possible forms: square root transformation, log-transformation and discretization in quintiles.

In the second step, we compute the conditional odds-ratio (OR) between the drug and the outcome in a multivariate logistic regression model, given the selected covariates. In addition, we produce two supplementary measures of association based on propensity scores (PS) as secondary analyses. Namely, the marginal OR on the matched population, and the marginal OR on the inverse probability weighted (IPW) population restricted to the "empirical equipoise region" (EER, i.e. after trimming) [27]. The EER is defined to approximate the region of *clinical equipoise*, among which uncertainty among treatment options is strong

enough, so that prescribers' preference drives the prescription instead of only patients' characteristics [27]. PS models were fitted using multivariate logistic regression. The matching procedure was implemented with a case-control ratio of 1:4 and a caliper of 0.2 standard deviation of the logit of the propensity score [31]. With IPW, the cohort is resampled by weighting each individual i with a weight that is based on its estimated stabilized PS π_i (preference score) [27]. Stabilized PS or preference scores are PS corrected for prevalence (logit of the preference score equals the logit of the PS minus the logit of the drug prevalence). Treated individuals are then weighted by $1/\pi_i$, and controls are weighted by $1/(1-\pi_i)$. Patients with stabilized PS outside the "empirical equipoise region", i.e. the stabilized PS interval [0.3 - 0.7], are discarded [27]. Finally, both PS based methods allow the generation of automated diagnostics to assess the validity of the estimates. First, the residual imbalance in covariates, which we report as the fraction of balanced covariates (FBC), i.e. covariates with absolute standardized mean difference (ASMD) between treatment groups below 0.1 [32]. Second, the fraction of exposed population (FEP) remaining after applying the caliper in the matched subset or within the EER in the trimmed subset.

Alpha risk inflation caused by multiple testing was addressed following the Benjamini and Hochberg procedure of false discovery rate ($Q=0.05$), and p-values for the OR were corrected accordingly [33].

Validation with treatments of reference

We compared the data-driven determination of adjustment sets with a knowledge-based approach on 3 treatments of reference. First, Dexamethasone, for which we expect a beneficial effect on 28-days mortality, and which we assume is subject to strong indication bias. Second and third, drugs of reference with expected null effect, with high prevalence (Paracetamol) and low prevalence (Phloroglucinol). We studied the association of these treatments of reference with 28-day mortality on the overall population and in age-based subgroups, patients < 70 or ≥ 70 years old. Indeed, age is the most important prognosis factor in COVID-19, and Dexamethasone beneficial effect is heterogeneous across age subgroups [3].

We compared the association after adjusting on the data-driven adjustment set. For the knowledge-based approach. We used a set of known prognosis factors extracted from Medline articles, including: age, gender, number of comorbidities, platelets blood count, prothrombin ratio, creatinin, blood urea nitrogen, C-Reactive Protein (CRP), mean arterial pressure, systolic arterial pressure, peripheral capillary oxygen saturation [34–37].

Missing data management strategy

Missing data management followed a two-step strategy targeting 2 different missing data mechanisms. In the first step, we excluded patients with a number of observations lower than the 2nd percentile for drugs, laboratory tests, or physiological measurements. A comparison of baseline characteristics between patients included in the analysis and patients excluded for missing data was performed to detect a possible selection bias. In a second step, we performed multiple imputation with chained equations (MICE) [38]. MICE was performed using 5 imputed datasets and the predictive mean matching strategy was chosen, using all adjustment covariates (i.e., not including drugs). The adjustment set selection was adapted to the setting of multiple imputed datasets by selecting variables that appeared in at least half of the imputed datasets. OR were pooled according to Rubin's rule after log-transformation.

Beside these missing-data handling strategies, we also report a measure of data missingness specific to each model, the fraction of missing information (FMI), which is considered moderately large above 0.3 and high above 0.5 [39].

Implementation

The analyses were performed using R Statistical Software version 3.5.1. [40]. The following packages were combined in custom functions to provide a reproducible and configurable pipeline: MICE [41], glmnet [42], MatchIt [43], PSWeight [44]. Code will be made available online for transparency at [45].

Ethics

This study was approved by the Institutional Review Board of the AP-HP CDW under the reference CSE-20-

18-COVID19. All patients admitted to the AP-HP are informed of the possible reuse of their EHRs for research purposes according to the European General Data Protection Regulation and have the right to opt out of participating, in agreement with the Commission Nationale de l'Informatique et des Libertés (regulatory decision DE-2018-155).

Results

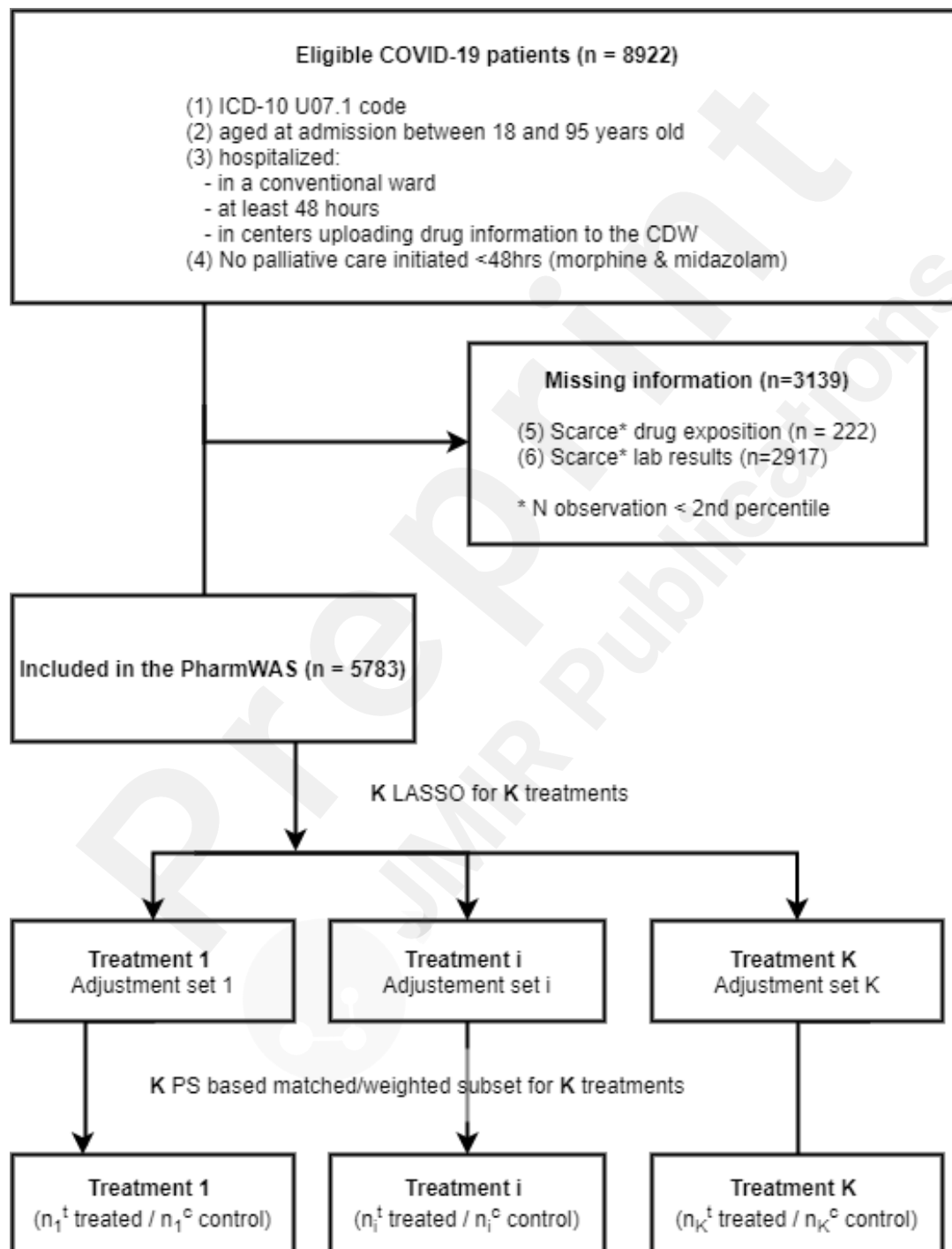


Figure 1. Flowchart and PharmWAS pipeline

Population characteristics

Sixteen out of 39 different hospitals were retained for the study based on the availability of drug exposure

information from computerized physician order entries. In these 16 hospitals, we found a total of 8,922 eligible patients, of which 3,139 (35%) were excluded because of insufficient information regarding drug exposure, lab tests, or physiological measurements (see Figure 1). Included and excluded patients were comparable for age (median age 69.18 (56.68, 81.06) versus 70.90 (55.79, 83.84) years old, respectively) and number of comorbidities (2,731 (47.22%) versus 1,591 (50.68%) patients with at least 3 comorbidities), but were more often male (59% versus 51%) (Table S1).

	Total (N=5783)
Age at diagnostic, years	
Median (Q1, Q3)	69.2 (56.7, 81.1)
Age group at diagnostic, years	
18-39	322 (5.6%)
40-49	538 (9.3%)
50-59	948 (16.4%)
60-69	1184 (20.5%)
70-79	1241 (21.5%)
80+	1550 (26.8%)
Gender, Male	3390 (58.6%)
Deaths	933 (16.1%)
Follow-up, days	
Median (Q1, Q3)	8.8 (5.2, 14.9)
28 days mortality	635 (11%)
Centre	
GH A.CHENEVIER-H.MONDOR	965 (16.7%)
HOPITAL SAINT ANTOINE	887 (15.3%)
HOPITAL TENON	849 (14.7%)
Other	3082 (53.3%)
Time period	
Febr. to Jul. 2020	2187 (37.8%)
Aug. to Nov. 2020	1197 (20.7%)
Dec. 2020 to Jun. 2021	2399 (41.5%)
Hypertension	2065 (35.7%)
Severe protein-energy malnutrition	655 (11.3%)
Chronic kidney disease	554 (9.6%)
Light or moderate protein-energy malnutrition	509 (8.8%)
Atrial fibrillation and flutter	458 (7.9%)
Dyslipidemia	357 (6.2%)
Ischemic chronic heart disease	356 (6.2%)
Deficiency in vitamin D	339 (5.9%)
Presence of cardiac and vascular implants and grafts	306 (5.3%)
Hypothyroidism, unspecified	288 (5%)
BMI	26.5 (23.4, 30.3)
Pulsations (/min)	89 (78, 102)
Diastolic arterial pressure (mmHg)	76 (66, 85)
Systolic arterial pressure (mmHg)	131 (117, 146)
Respiratory rate (/min)	24 (20, 28)
Peripheral capillary oxygen saturation (%)	95 (92, 97)
Body temperature (° celsius)	37.4 (36.8, 38.2)
Hemoglobin (g/dL)	13.10 (11.80, 14.30)
White Blood Cell Count (10⁹/L)	6.38 (4.79, 8.51)

Creatinin ($\mu\text{mol/L}$)	80 (65, 105.50)
Blood urea nitrogen (mmol/L)	6.40 (4.60, 9.50)
C-Reactive Protein (mg/L)	69.80 (32.50, 122.20)
Oxygen blood saturation (%)	95 (92.70, 97)
Fibrinogen (g/L)	5.80 (4.85, 6.82)
Bicarbonate (mmol/L)	25 (22, 27.60)

Table 1: Baseline characteristics of the population

A total of 5,783 patients were included in the analysis with median age at admission 69.2 [IQR, 56.7 - 81.1] years old, 3,390 (58.6%) of them were male (Table 1). Patients were admitted from 16 hospitals with 3 hospitals representing 47.7% of patients. Frequent comorbidities included hypertension (35.7%), chronic kidney disease (9.6%), atrial fibrillation or flutter (7.9%), dyslipidemia (6.2%) and ischemic chronic heart disease (6.2%) (Table 1).

Validation with treatment of references

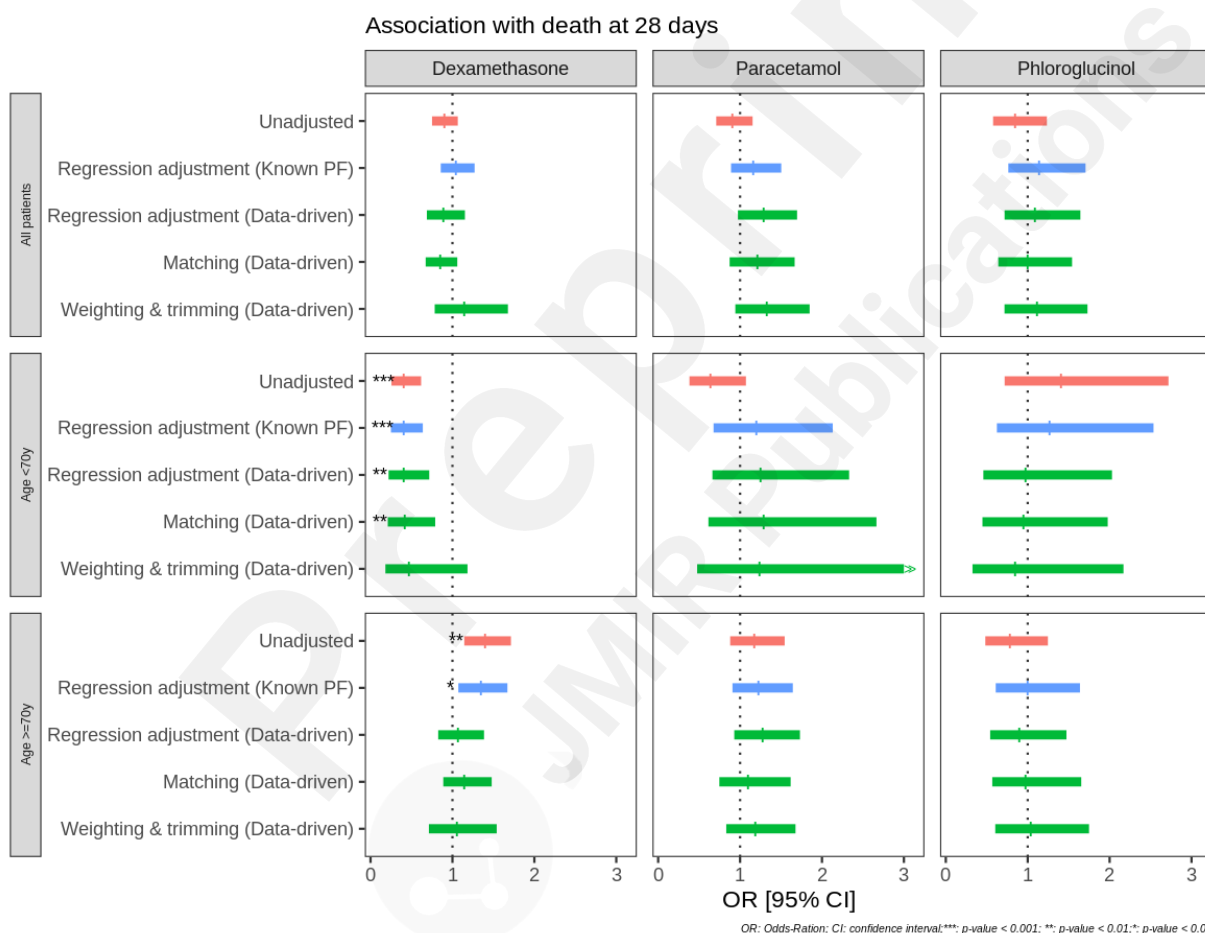


Figure 2. Treatment of reference for validating data-driven adjustment sets selection

Association between 28-days mortality and early exposure to treatment was measured as odds-ratio for 3 treatments of reference: (1) dexamethasone with expected beneficial effect on 28-days mortality, and (2) treatments with expected null effect, with high prevalence (Paracetamol) or low prevalence (Phloroglucinol). We compare two pretreatment covariate sets: ‘Known PF’ using prognostic factors from the literature (blue) and ‘Data-driven’ for a model selection procedure based on adaptive LASSO (green) targeting confusion factors. Odds-ratio were computed by logistic regression on the overall dataset (red), matched or weighted and trimmed subpopulations based on propensity scores.

Without adjustment, Dexamethasone was associated with decreased 28-days mortality in patients under 70 years old (OR 0.40 [95% CI, 0.26-0.62], p-value <.001), and with increased 28-days mortality in patients over 70 years old (OR 1.40 [1.14-1.71], p-value <.001).

Adjusting using the ‘Known PF’ adjustment set and the ‘Data-driven’ adjustments sets yielded close results except for Dexamethasone in patients over 70 years old. In the latter subgroup, only the ‘Data-driven’

adjustment set yielded no association of Dexamethasone with increased 28-days mortality (Figure 2). On the matched subset for Dexamethasone in patients under 70 years, 54.6% of exposed patients found matches, the association with mortality was strong (OR 0.41 [0.21-0.79], p-value .008), but the fraction of balanced covariates (FBC) was only 35%. On the weighted & trimmed subset, the fraction of exposed population (FEP) that fell in the “empirical equipoise region” (EER) was only 23.1%, the association with mortality was no longer significant (OR 0.46 [0.18-1.18], p-value .1), but 100% of covariates were balanced. The fraction of missing information was low and never exceeded 0.2. The FEP was lower than 50% for Dexamethasone in all subgroups.

Pharmacopeia wide association with 28-days mortality

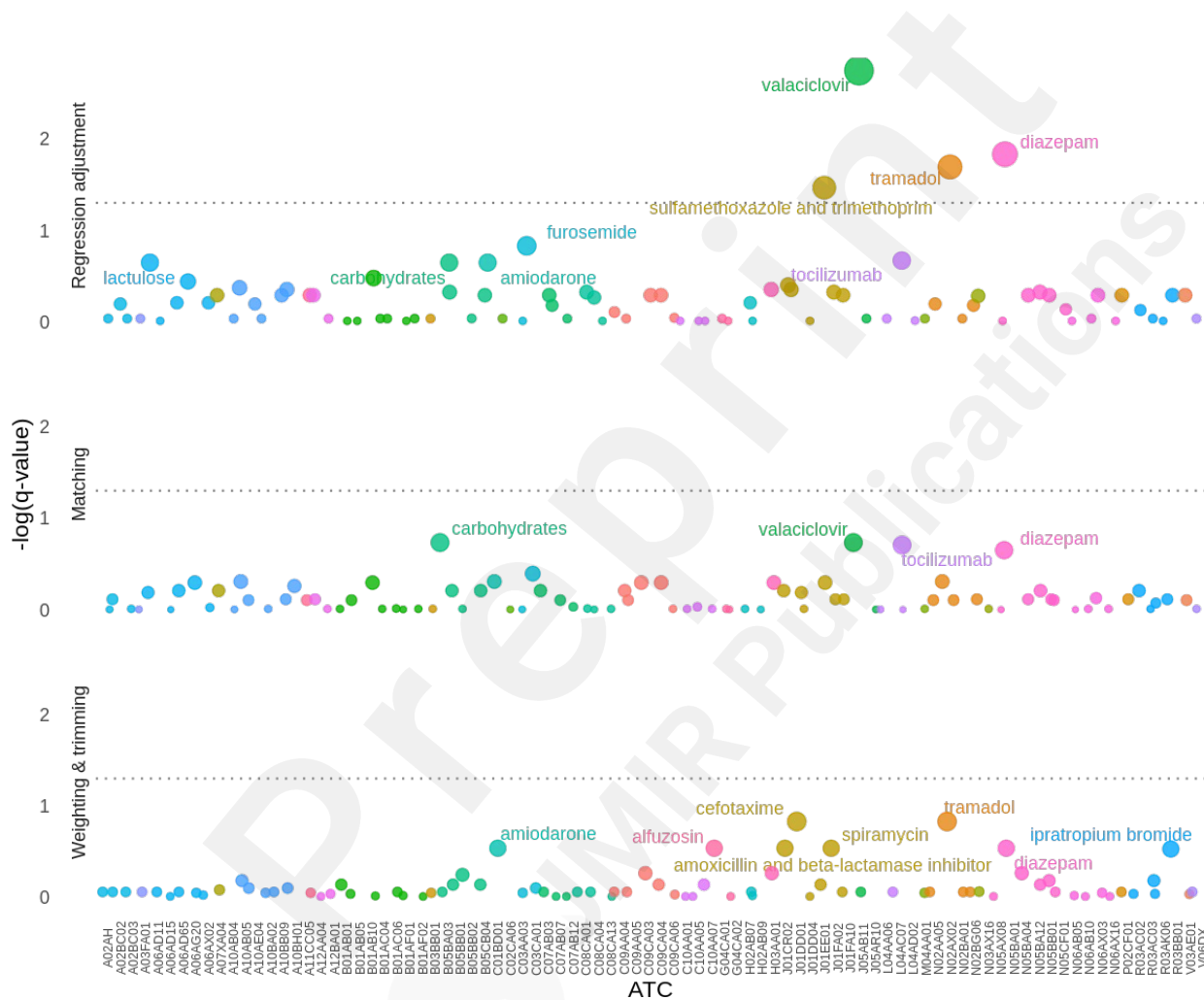


Figure 3. Pharmacopeia-wide association with 28-days mortality

Each dot represents the FDR corrected p-value (q-value), on a negative log-scale (y-axis) of a drug (ATC code), on the x-axis. An ATC code is attributed if the drug is prescribed in the first 48 hours of COVID-19 admission in conventional wards. The colour indicates the pharmacological subgroup (ATC level 2). The top panel reports q-value from the primary analysis, using a multivariate logistic regression model, the dotted line indicates a 5% false discovery rate. The middle and bottom panels report secondary analyses using matching and inverse probability weighting methods, respectively. Dot sizes are inversely proportional to q-values.

Primary analysis

We identified a total of 87 different drugs (ATC 5th level codes, e.g., B01AF01 rivaroxaban) administered within the first 48hrs and present in at least 100 patient records (Figure 3). Detailed results are given in Figure 4 for drugs with a p-value < .15. After correction for multiple hypothesis testing, none were associated with a reduced in-hospital mortality, and 4 remained associated with increased in-hospital mortality on the overall population after adjustment: sulfamethoxazole-trimethoprim, valaciclovir, tramadol and diazepam (Table 2).

Analyses on matched subpopulations found consistent results, with a good fraction of covariate balance (between 98% and 100% of covariates with absolute standardized mean difference (ASMD) below 0.1) except for Diazepam (89%). Analyses on weighted subpopulations were not consistent and found a small FEP for sulfamethoxazole-trimethoprim and valaciclovir.

	Treated Vs Controls (N. events / N. exposed)	OR [95%CI]	q-value	FBC (%)	FEP (%)	FMI
sulfamethoxazole and trimethoprim						
Regression adjustment	(31 / 161) vs (604 / 5622)	2.22 [1.36-3.64]	.03		100	<0.01
Matching	(31 / 160) vs (63 / 518)	1.65 [0.98-2.78]		99	99.3	0.03
Weighting & trimming	(8 / 51) vs (172 / 1790)	1.86 [0.74-4.68]		91	32.1	0.02
valaciclovir						
Regression adjustment	(24 / 107) vs (611 / 5676)	3.21 [1.88-5.48]	.002		100	0.01
Matching	(24 / 107) vs (41 / 404)	2.54 [1.38-4.67]		98	99.4	0.08
Weighting & trimming	(6 / 35) vs (210 / 2136)	1.64 [0.49-5.51]		71	32.5	0.16
tramadol						
Regression adjustment	(40 / 302) vs (595 / 5481)	1.94 [1.32-2.85]	.02		100	<0.01
Matching	(40 / 301) vs (108 / 1191)	1.55 [1.03-2.34]		100	99.7	0.08
Weighting & trimming	(31 / 223) vs (362 / 4002)	1.85 [1.22-2.79]		100	74	0.02
diazepam						
Regression adjustment	(24 / 120) vs (611 / 5663)	2.51 [1.52-4.16]	.01		100	<0.01
Matching	(23 / 116) vs (47 / 448)	2.09 [1.19-3.66]		89	96.7	0.06
Weighting & trimming	(15 / 89) vs (483 / 4925)	1.92 [1.08-3.41]		100	74.3	0.01

Table 2. Treatment associated with 28-days mortality at 5% false discovery rate

Treatment associated with 28-days mortality after regression adjustment at 5% false discovery rate. FMI: fraction of missing information; FEP: fraction of exposed population; FBC: fraction of balanced covariates; q-value:FDR corrected p-value

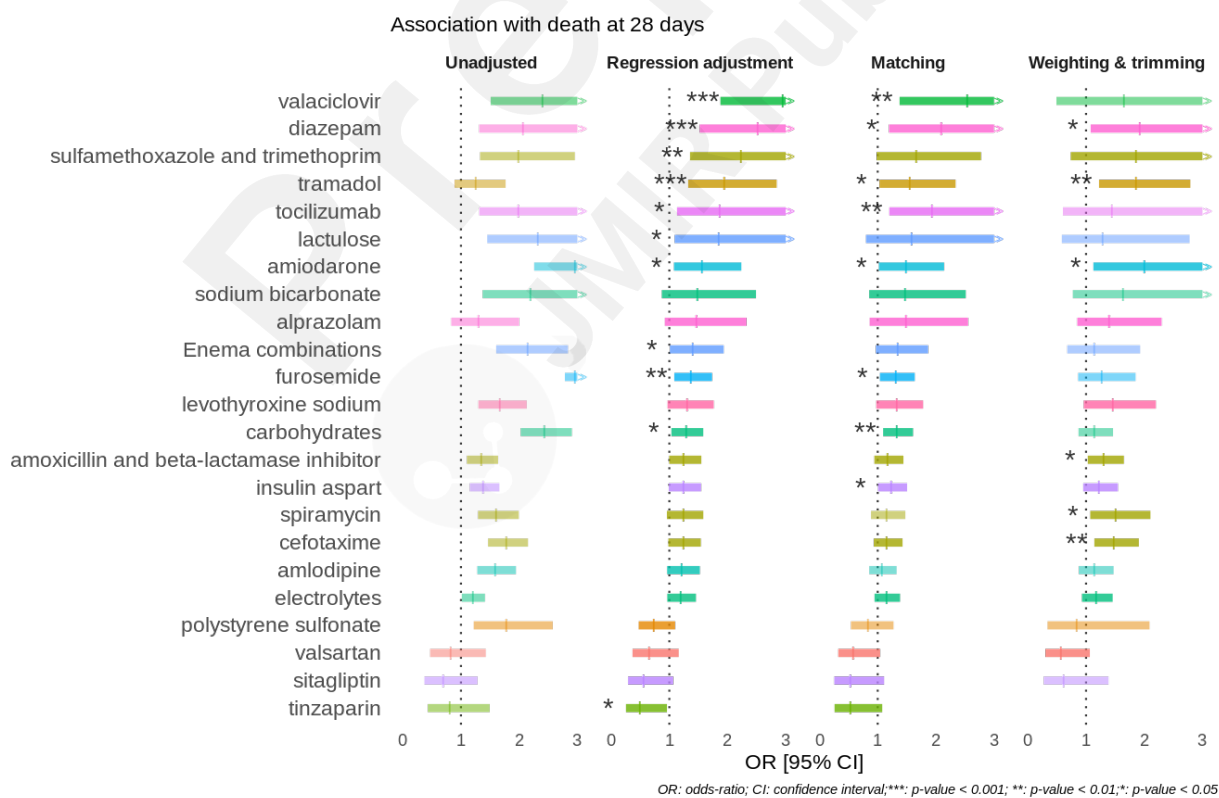


Figure 4. Increased and decreased mortality for the top drugs

Association is reported as odds-ratio between treatment exposition and 28-days mortality in different settings: without adjustment, after adjusting, on matched and weighted subpopulations based on treatment specific propensity scores. p-values are indicated without

multiple hypothesis testing correction. Treatments are ordered from top to bottom by decreasing adjusted OR. Drugs at the top tend to be associated with increased mortality, drugs at the bottom with decreased mortality. Colors correspond to ATC level 2. Only drugs with $p\text{-value} < .15$ are reported.

Secondary analysis

We highlight here the results on the weighted and trimmed population where patients are more comparable (Figure 4). Interestingly, two ARB come up in the top five treatments with an $OR < 1$, with treatments ordered by p -values (Table 3). We explored further this hypothesis and found that in a weighted and trimmed analysis, ARB with a high-affinity for angiotensin-receptor 1 (dissociation constant $K_d \geq 6$: telmisartan, valsartan, losartan) tended to be associated with decreased 28-days mortality compared to ARB with a lower affinity ($K_d < 6$: irbesartan, candesartan, olmesartan), OR 0.56 [0.34-0.91].

Treatment	Treated Vs Controls (N. events / N. exposed)	OR [95%CI]	FBC (%)	FEP (%)	FMI
sitagliptin	(7 / 100) vs (426 / 4023)	0.61 [0.27-1.39]	100	71.7	0.01
valsartan	(11 / 132) vs (562 / 4567)	0.57 [0.30-1.06]	100	87.1	0.01
irbesartan	(32 / 277) vs (538 / 4527)	0.77 [0.52-1.13]	100	91.4	0.01
rosuvastatin	(12 / 131) vs (399 / 3214)	0.64 [0.35-1.19]	100	60	0.01
alfuzosin	(6 / 100) vs (182 / 1875)	0.34 [0.13-0.84]	100	39.3	0.03

Table 3. Top 5 treatments with $OR < 1$ in the weighted & trimmed population

Top five treatments with $OR < 1$ in the weighted & trimmed population, ordered by p -value. None were significantly associated with mortality after false discovery rate correction in the primary analysis. FMI: fraction of missing information; FEP: fraction of exposed population; FBC: fraction of balanced covariates

Discussion

We systematically assessed the association of early in-hospital treatments with 28-day mortality in a large multicenter retrospective case study of 5,783 patients with COVID-19, using an innovative PheWAS-like approach. We showed empirical evidence that our fully data-driven pipeline was comparable or better than a knowledge-based approach to adjust for confounding on three drugs of reference. We showed in this practical implementation for COVID-19 how such a pipeline can be used to mine EHR pharmacopoeia and generate pharmacological hypotheses in an exploratory fashion. Indeed, out of 87 treatments prescribed in the first 48 hours, 4 were associated with increased 28-days mortality after adjustment on confounding factors and multiple testing correction, and none were associated with an increased mortality. Among those, only Diazepam and Tramadol had consistent results in secondary analyses more robust to confounding. In addition, secondary analyses suggested that high-affinity ARB were associated with a reduced COVID-19 28-day mortality, suggesting they may be beneficial in patients with COVID-19.

Validation with drugs of reference

We tested our adjustment methods on treatments for which effect on 28 day-mortality is documented (protective effect for dexamethasone) or unlikely to be different from null (absence of effect for paracetamol and phloroglucinol). Subgroup analysis of the RECOVERY trial suggests that patients under 70 year old only benefited from Dexamethasone, with RR 0.64 [0.53–0.78] versus 1.03 [0.84–1.25] between 70 and 80 years old and 0.89 [0.75–1.05] after 80 years old [3]. Our automated pipeline finds overall consistent results between the 'Data-driven' and the 'Known PF' adjustment set for the three drugs of reference. The differences observed for the dexamethasone effect on the >70 age group could be explained by missing or misspecified confounding factors in the 'Known PF' adjustment set compared to the 'Data-driven' (see Table S2). Overall, these results provide empirical evidence that the automated determination of adjustment sets on these 3 drugs yielded valid adjustment sets, sufficient for controlling indication biases.

Pharmacopoeia wide association with 28-days mortality

Interestingly, diazepam, an anxiolytic benzodiazepine was found to be associated with a detrimental effect on in-hospital mortality in our study. This result might not be COVID-19 specific as benzodiazepines have shown a dose response association with mortality in patients with very severe chronic obstructive pulmonary disease [46]. We also found that tramadol, a weak opioid, was associated with an increased 28-day mortality.

Noteworthy both benzodiazepines and tramadol may have adverse respiratory effects such as respiratory depression, which, although not specific to COVID-19, could be detrimental in patients with severe COVID-19 pneumonitis [47]. In addition, our automated pipeline allowed us to generate a pharmacological hypothesis consistent with results from a clinical trial. Indeed, an open RCT showed that death by day 30 was reduced in patients undergoing Telmisartan (control 22.54%, 16/71; Telmisartan 4.29%, 3/70 participants; $p = 0.0023$) hospitalized for COVID-19 [48]. However, other studies did not find an association with ARB and COVID-19 mortality and further studies are needed to assess this finding and investigate potential mechanisms [49].

Limits and strengths

This retrospective study methodology is based on reusing routinely collected clinical data across 16 hospitals of the greater Paris area. Unexpectedly, from an initial set of 8922 COVID-19 patient records, only 5783 patient records (65% of the whole set) ended up following all inclusion criterias. However, this is not intrinsically linked to our method but rather to the relative lack of maturity of the hospital's information systems, particularly concerning drug prescription. Indeed, at the beginning of the pandemic, computerized physician order entry was not available in all hospitals and units or not linked to the clinical data-warehouse. While this study follows most of the guidelines provided by Kohane et al. such as multidisciplinary approach, code transparency and robustness against variability across hospitals, this result stresses out that data completeness in EHR remains an open question [50]. We can hypothesize that the pandemic will have a boosting effect on the maturation of the information system of hospitals. Regarding confusion adjustment, we could have used more flexible models to fit PS, such as random forest, and use double robust estimators which are less sensible to model misspecification [26]. However, we found that the most important factors for accurate measures of treatment association with mortality were the choice of adjustment sets, and the use of trimming. Moreover, we decided to restrict to methods that would easily scale to large sets of exposures. Globally, our results are dependent, as in all complex analysis of real-life data, on choices in the preprocessing and modelling of the data. These dependencies can be subtle and lead to changes in amplitude or direction of the measured associations, sometimes framed as “vibration of effect” [51]. Our rationale was to decide these questions based on theoretical grounds (or simulation studies), to leverage treatment of references if not possible (e.g. data-driven versus knowledge-based), and finally to report multiple analyses if uncertainty remains among which method is more relevant (e.g. matching or inverse probability weighting).

Large-scale association studies such as this work are known to require a large amount of data to reveal significant associations. Therefore, it may be difficult to obtain sufficient statistical power. To get around this difficulty, it is possible to run the association test using aggregated data to an upper level in the ATC.

Regarding clinical significance, COVID-19 is a biphasic disease, with the viral replication period and then an inflammatory state, and patients may not be hospitalized at the same time of the disease. This may have led to heterogeneity in the condition of the patients and complicated the interpretation of the results. Furthermore, there is a potential risk of selection bias since we dropped 35% of COVID-19 admissions due to data missingness. However, excluded patients were comparable in terms of age and number of comorbidities to the patients included in this study (Table S1), which is in favor of the generalizability of the obtained results. In addition, we cannot rule out that some confounding factors remain unobserved. Secondary analyses based on EER allowed to partially address this issue, since sample size remained large enough in this setting to include a broad number of potential confoundings, and that we analyzed a rather homogeneous population by excluding patients admitted to ICUs in the first 48 hours.

The main strength of our study lies in its external validity: it used data collected across 16 different hospitals of the greater Paris area, and included a large number of patients with COVID-19. These characteristics make it likely to capture the variability of populations and disease management in real-life settings. Similarly, we addressed treatment specific indication biases in a fully data-driven fashion, which we validated empirically on drugs of reference. This methodology based on a hypothesis-free exploration of COVID-19-related EHRs is easily exportable to other settings. Population trimming based on stabilized PS allowed to restrict the analysis to comparable patients, which cannot be done by a simple outcome oriented regression adjustment. Finally, it allows to generate a measure of covariates balancing, which turns out to be a critical diagnostic for studying a large array of drug-outcome associations.

Our systematic hypothesis-free approach constitutes a promising tool that can be rapidly used in the setting of emergent diseases to generate potential drug candidates. Still, these drug candidates need to be further assessed from a pharmacological point of view before being tested in clinical trials. Further developments will

include time dependency of treatments, covariates and outcome in a more flexible way, not restricted to landmark analysis (28-days mortality) and window type restriction of exposition. In addition, including information from NLP extraction workflow would largely enrich such a pipeline [50,52].

CONCLUSION

Our innovative approach proved useful in rapidly generating pharmacological hypotheses in an outbreak setting, without requiring *a priori* knowledge of the disease. Our systematic analysis of early prescribed treatments from patients hospitalized for COVID-19 showed that Diazepam and Tramadol were associated with increased 28-days mortality. Whether these drugs could worsen COVID-19 needs to be further assessed.



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Declarations

Authors' contributions

IL contributed to conceptualization; data curation; formal analysis; methodology; software; and writing - original draft. ASL contributed to methodology and writing - reviewing & editing. LC contributed to conceptualization; formal analysis; and writing - reviewing & editing. BR contributed to validation; and writing - reviewing & editing. NG contributed to validation; and writing - reviewing & editing. AB contributed to project administration; resources; supervision; validation; and writing - reviewing & editing. AN contributed to conceptualization; data curation; formal analysis; software; resources; supervision; validation; writing - original draft; and writing - reviewing & editing.

List of abbreviations

AP-HP: Assistance publique - Hôpitaux de Paris

COVID-19: COronaVirus Disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PharmWAS: pharmacopeia-wide association study

ICD-10: International Classification of Diseases, 10th edition

CDW: clinical data warehouse

OMOP CDM: Observational Medical Outcomes Partnership's common data model

ATC: anatomical therapeutic chemical

Declarations of interests

The authors declare no conflicting interests.

Acknowledgements

The authors thank the EDS APHP COVID consortium integrating the APHP Health Data Warehouse team as well as all the APHP staff and volunteers who contributed to the implementation of the EDS-COVID database and the operating solutions for this database.

Data and code

The aggregated results data will be published online, along with code generating it, at <https://gitlab.com/lerner.ivan/pharmwas>.

Funding

This work was supported by state funding from The French National Research Agency (ANR) under the "Investissements d'Avenir" program (Reference: ANR-10-IAHU-01).

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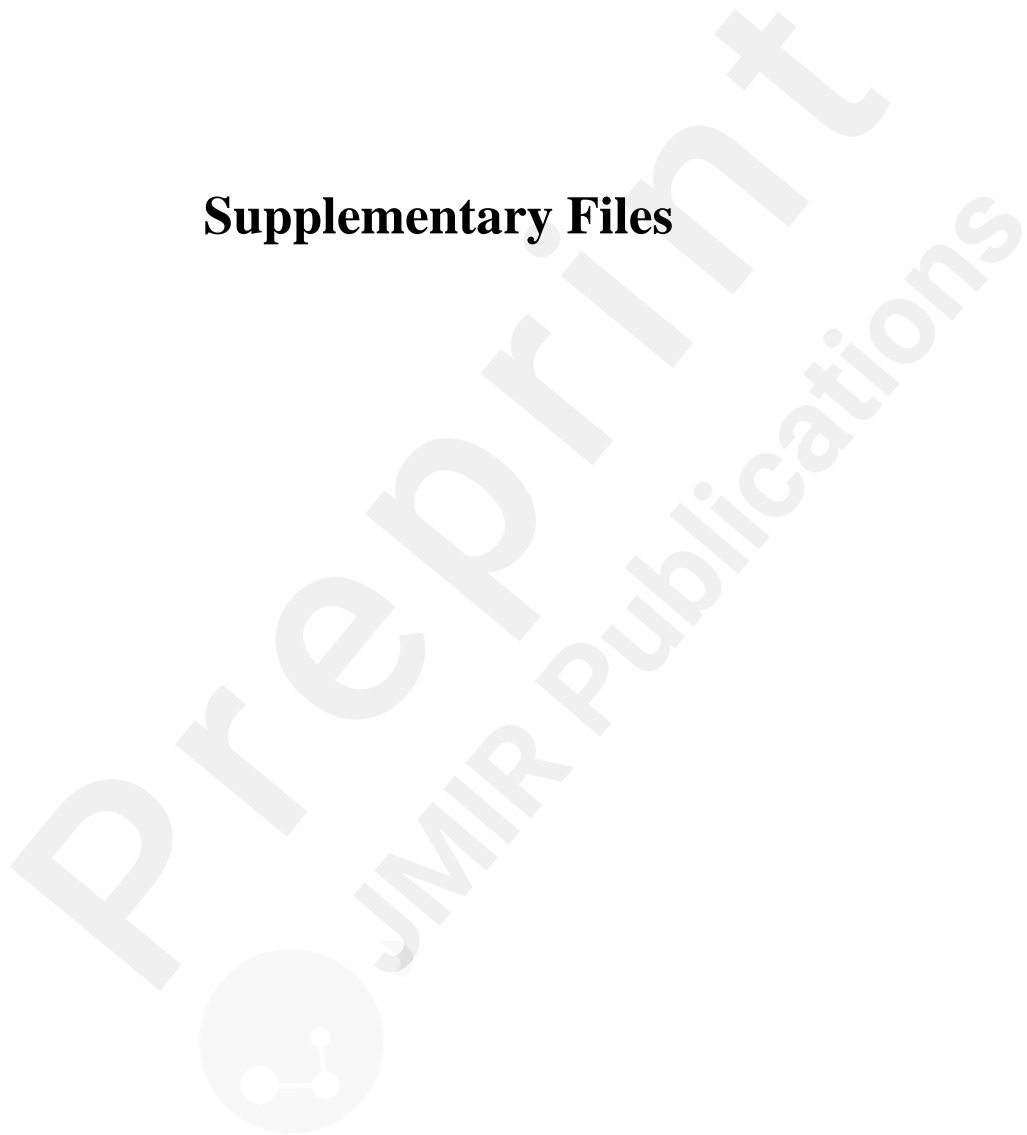
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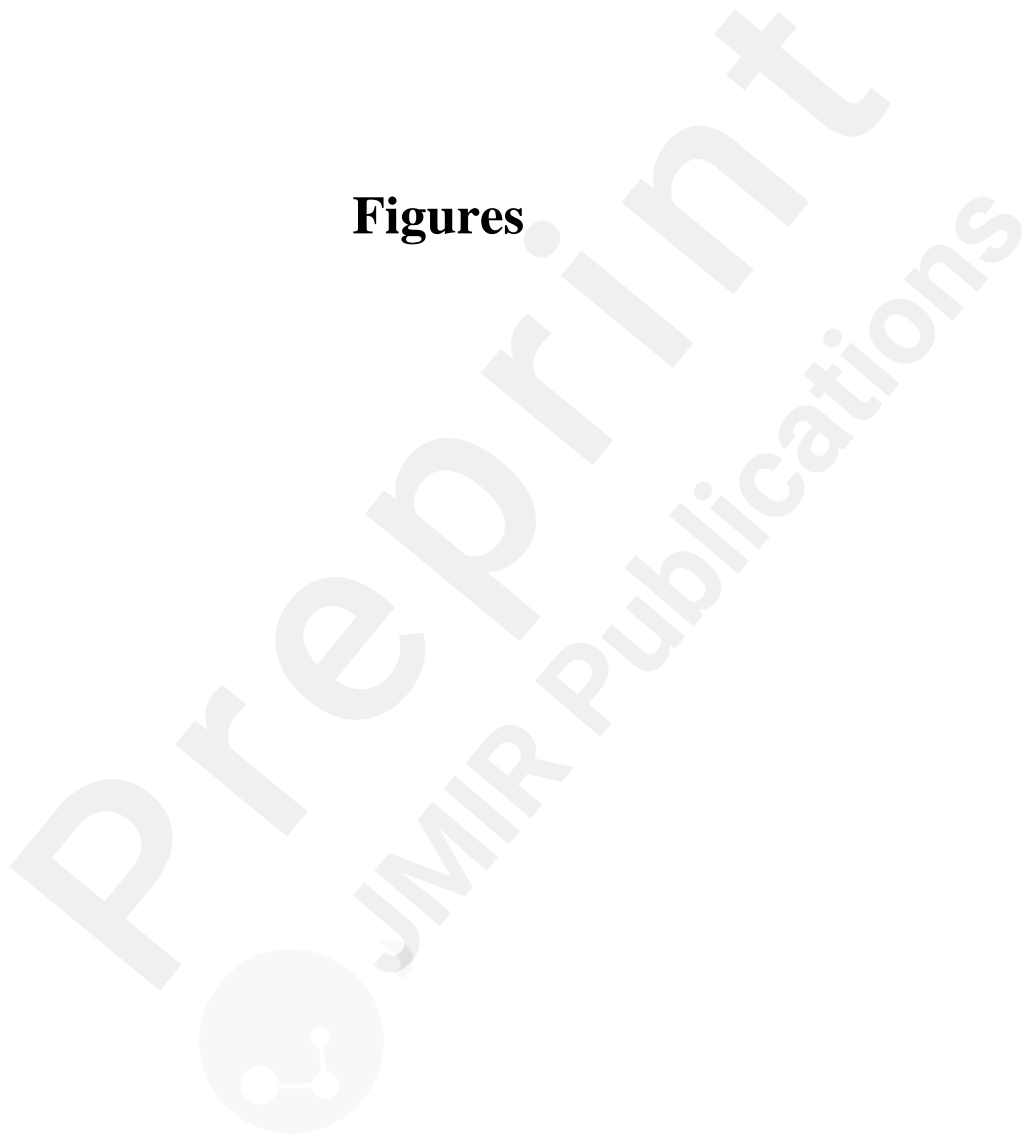
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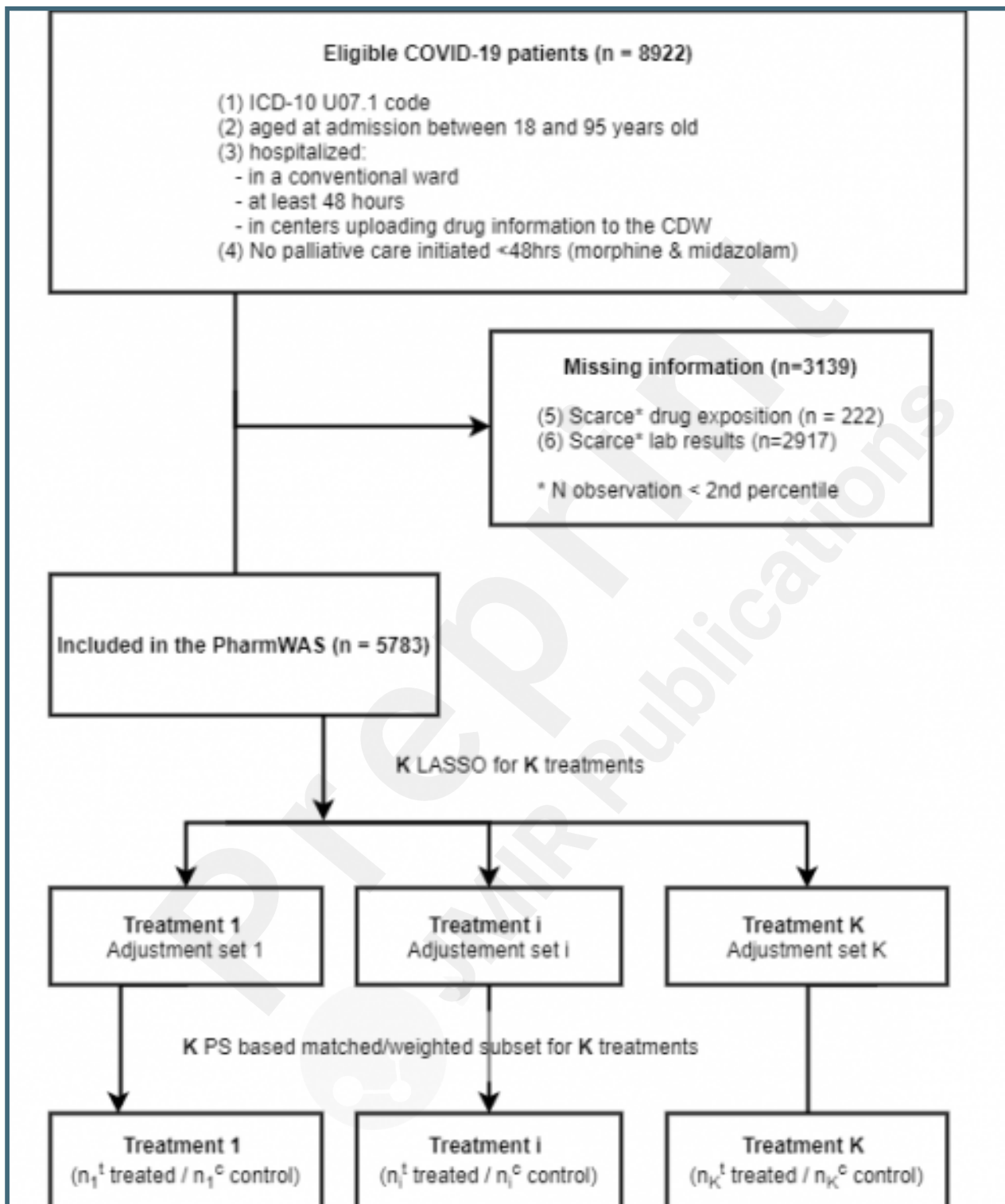
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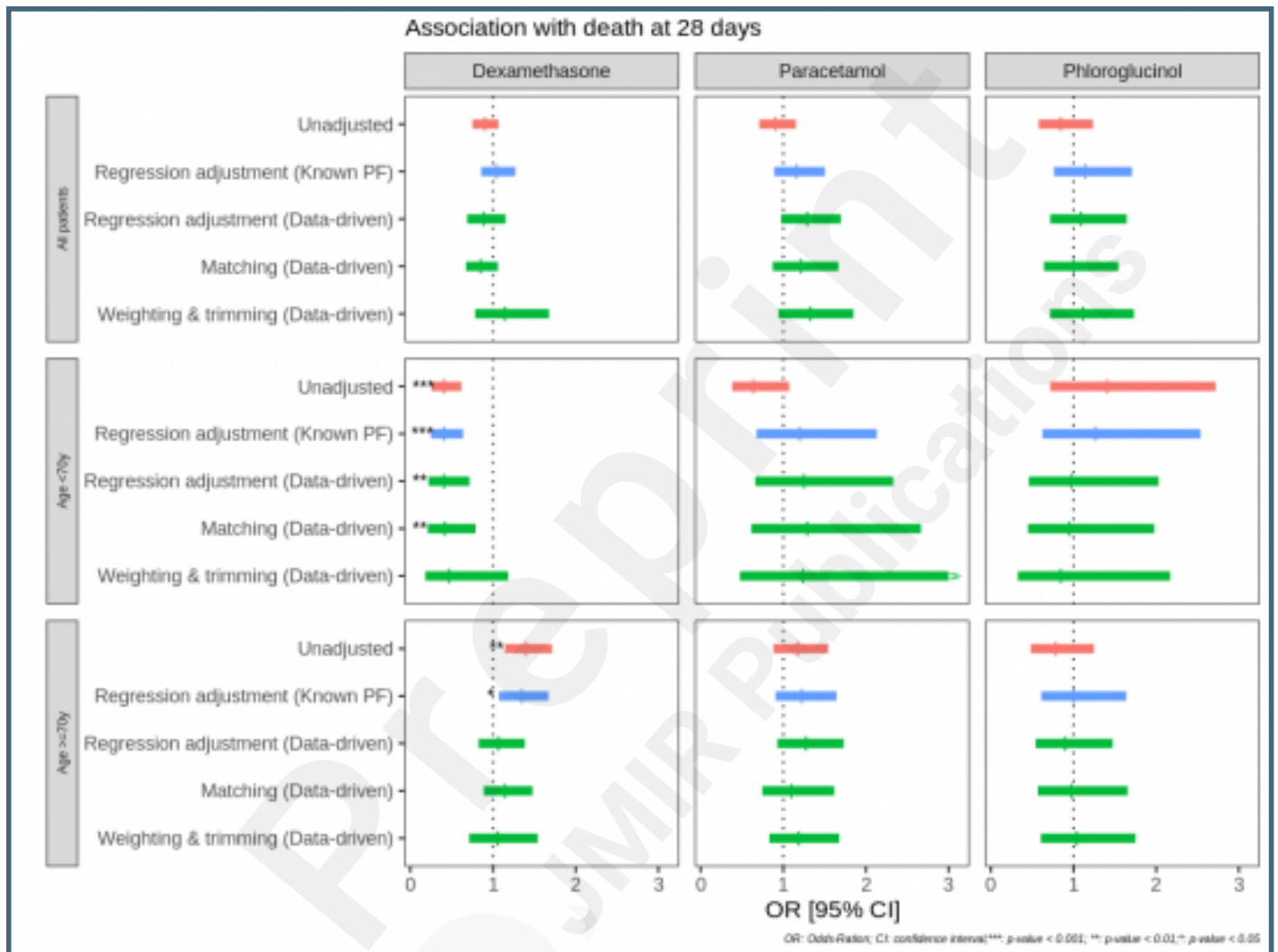
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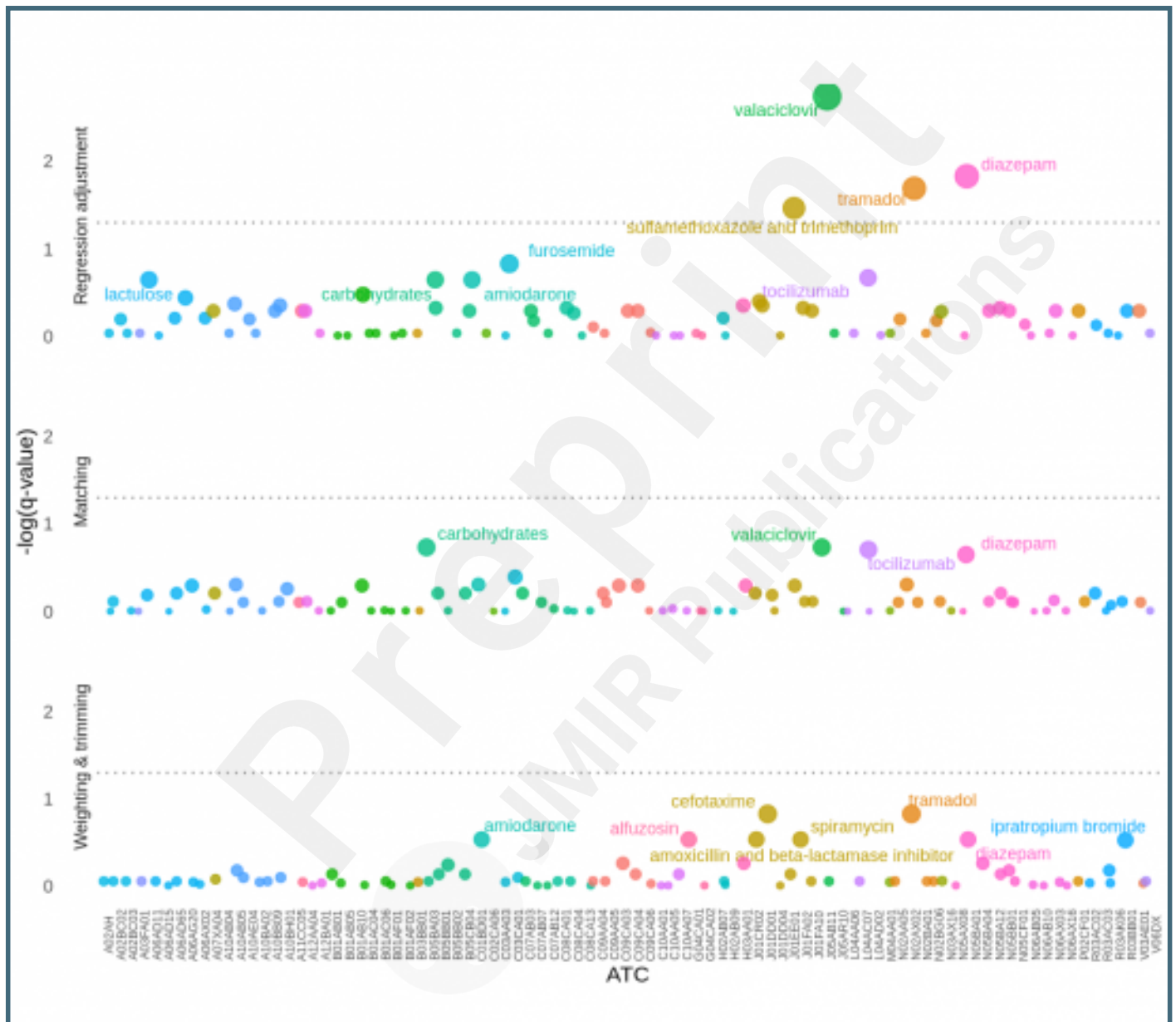
Flowchart and PharmWAS pipeline.



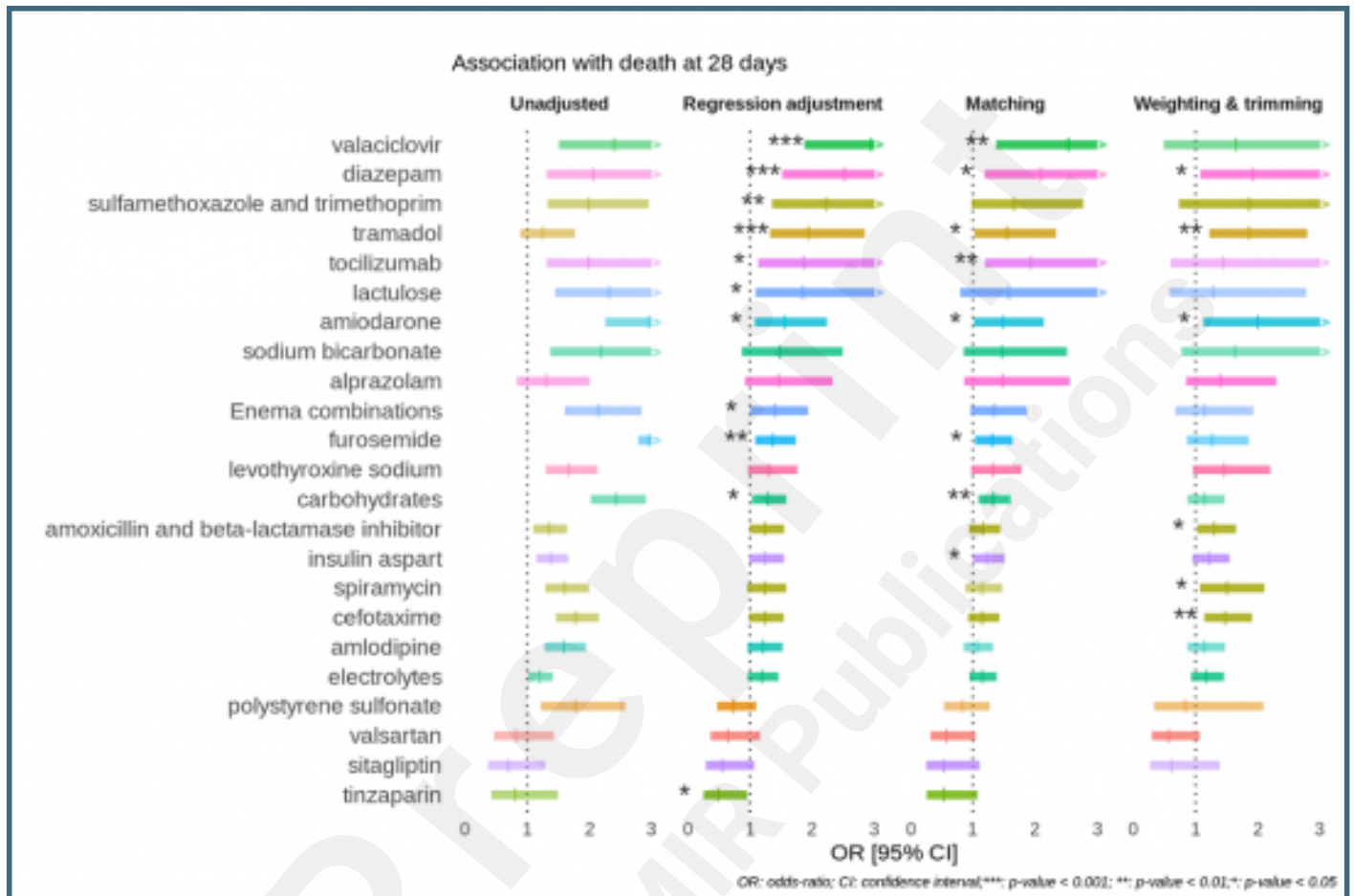
Treatment of reference for validating data-driven adjustment sets selection Association between 28-days mortality and early exposure to treatment was measured as odds-ratio for 3 treatments of reference: (1) dexamethasone with expected beneficial effect on 28-days mortality, and (2) treatments with expected null effect, with high prevalence (Paracetamol) or low prevalence (Phloroglucinol). We compare two pretreatment covariate sets: ‘Known PF’ using prognostic factors from the literature (blue) and ‘Data-driven’ for a model selection procedure based on adaptive LASSO (green) targeting confusion factors. Odds-ratio were computed by logistic regression on the overall dataset (red), matched or weighted and trimmed subpopulations based on propensity scores.



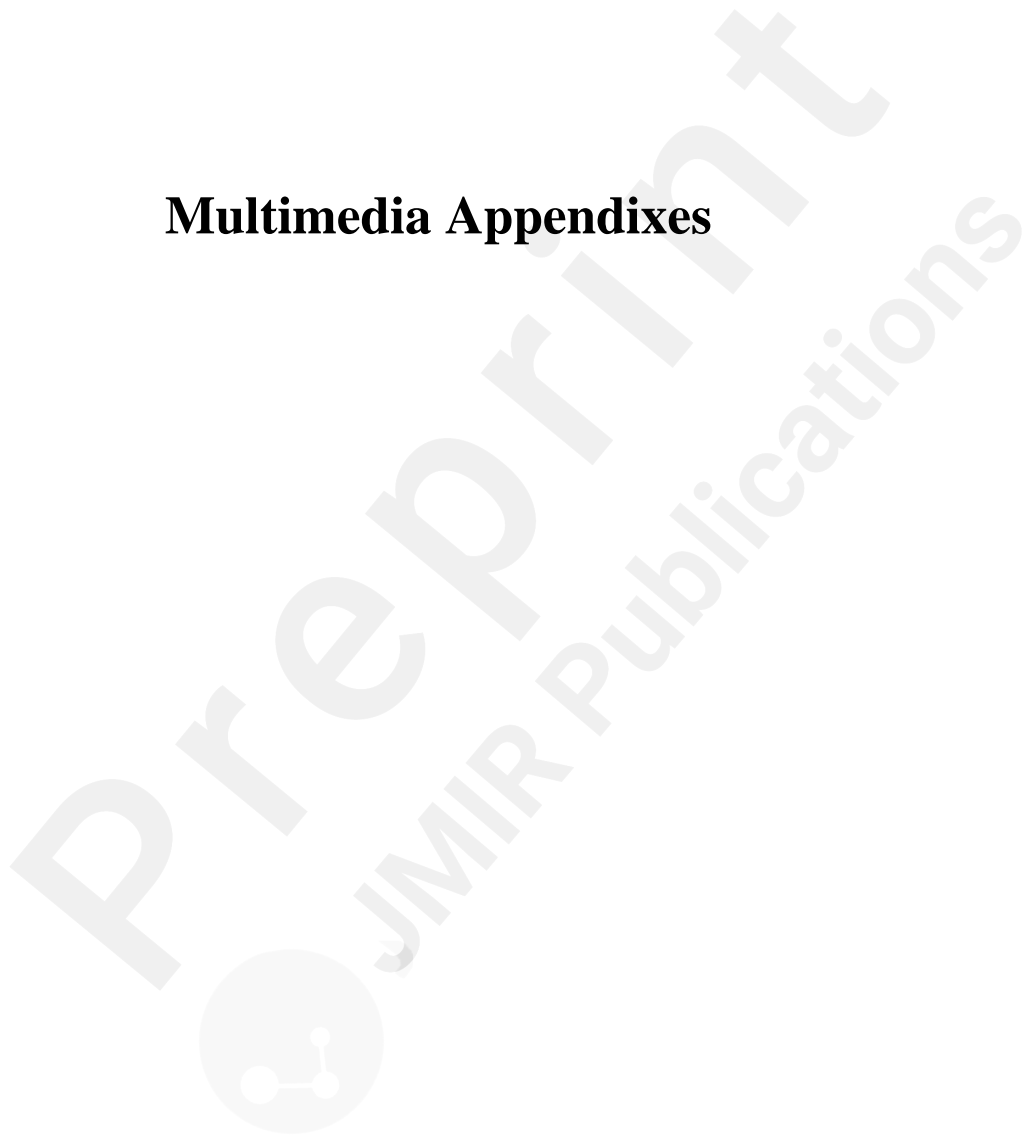
Pharmacoepia-wide association with 28-days mortality Each dot represents the FDR corrected p-value (q-value), on a negative log-scale (y-axis) of a drug (ATC code), on the x-axis. An ATC code is attributed if the drug is prescribed in the first 48 hours of COVID-19 admission in conventional wards. The colour indicates the pharmacological subgroup (ATC level 2). The top panel reports q-value from the primary analysis, using a multivariate logistic regression model, the dotted line indicates a 5% false discovery rate. The middle and bottom panels report secondary analyses using matching and inverse probability weighting methods, respectively. Dot sizes are inversely proportional to q-values.



Increased and decreased mortality for the top drugs Association is reported as odds-ratio between treatment exposition and 28-days mortality in different settings: without adjustment, after adjusting, on matched and weighted subpopulations based on treatment specific propensity scores. p-values are indicated without multiple hypothesis testing correction. Treatments are ordered from top to bottom by decreasing adjusted OR. Drugs at the top tend to be associated with increased mortality, drugs at the bottom with decreased mortality. Colors correspond to ATC level 2. Only drugs with p-value < .15 are reported.



Multimedia Appendixes



Supplementary materials.

URL: <http://asset.jmir.pub/assets/7dec0f7dc4279f1603acfa01797323a7.docx>

