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Validation of a High-Throughput Target Trial Emulation Platform for Drug Repurposing in Systemic Lupus

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Abstract

High-throughput target trial emulation (HT-TTE) using real-world data has been proposed as a scalable approach for drug repurposing, yet its operating characteristics remain insufficiently evaluated. Using systemic lupus erythematosus (SLE) as an application, this study assesses the sensitivity and specificity of an HT-TTE platform to identify repurposing candidates using the French nationwide healthcare database. The platform simultaneously evaluated hydroxychloroquine, the standard-of-care therapy for SLE, alongside 52 eligible topical or locally applied drugs (negative control drugs). Among more than 44,000 patients with mild-to-moderate SLE, HT-TTE blindly identified hydroxychloroquine as being associated with a reduced risk of lupus exacerbations with organ involvement, without prior specification of its expected effect. False-positive rates were quantified using negative control drugs, yielding high to very high specificity (88-98%), depending on comparator strategy. These findings provide empirical evidence that HT-TTE can support scalable screening for drug repurposing in large healthcare databases and underscore the importance of comparator choice.

Introduction

Real-world evidence derived from the analysis of large electronic healthcare databases is increasingly used to *test* hypotheses for drug repurposing (1). Among observational designs, target trial emulation (TTE) (2) has emerged as a commonly used framework for drug repurposing studies and has been applied, in combination with propensity score methods, to evaluate candidates, including sildenafil for Alzheimer's disease (DREAM study (3)). In parallel, the use of real-world data to *generate* repurposing hypotheses and contribute to drug discovery has been advocated for more than a decade (4) and has accelerated with the development of dedicated screening platforms (5) and the advancement of so-called **high-throughput** target trial emulation **(**HT-TTE) methods (6) (7). These approaches consist of running hundreds or thousands of TTEs simultaneously, either to assess the effects of all drugs used by patients with a target disease on a given outcome, or conversely to evaluate the effects of a single drug class, such as antihypertensives, across multiple outcomes (8). HT-TTE has also been proposed as a framework for the systematic evaluation of the large number of hypotheses generated at scale by artificial intelligence (AI)-based methods, including both mechanistic, molecular-level approaches and machine-learning models applied to real-world data (7) (9). By embedding causal inference principles within scalable analytic pipelines, HT-TTE aims to mitigate biases inherent to predominantly associative methods commonly used in modern observational research.

This paradigm is grounded in the observation that patients with comorbid conditions are routinely exposed to different medicinal products to treat each condition, thereby enabling cross-evaluation of treatment effects beyond their original indications. Consequently, most medicinal products (active ingredients) are used in large cohorts of patients with diverse clinical profiles and followed for extended periods – often spanning five to ten years – creating substantial opportunities for drug repurposing research in large electronic healthcare databases (9). Such approaches have been applied, for example, in Parkinson's disease research (10).

While the validity of the TTE design has been evaluated through the replication of several pivotal randomized controlled trials in the US FDA-sponsored RCT-DUPLICATE program (11), the validity of HT-TTE methods for identifying drug repurposing candidates has been poorly addressed to date. It cannot be assumed that highly standardized and semi-automated HT-TTE analyses – simultaneously evaluating hundreds of drugs – achieve the same validity as bespoke TTEs developed for comparative effectiveness studies conducted one drug at a time. Moreover, not all TTE replications in the RCT-DUPLICATE program were successful (12), further underscoring the need for careful validation.

In addition, HT-TTE-based repurposing research raises an important epistemological challenge related to the interpretation of results. When hundreds of associations are evaluated simultaneously, how confident can one be that previously unsuspected drug effects – by definition unknown prior to their observation – represent true signals rather than false positives? As with any screening methodology, HT-TTE approaches require internal positive controls (i.e., drugs with known effects on the outcome of interest) to demonstrate sensitivity and, ideally, negative controls to assess specificity and quantify the frequency of false-positive findings. To date, sensitivity and specificity have been only rarely addressed in the HT-TTE literature (8), and, to our knowledge, specificity has not been formally evaluated using negative controls, likely reflecting the inherent challenges of identifying appropriate negative controls in pharmacoepidemiological research (13).

The validation of large-scale generation of potential drug repurposing candidates in systemic lupus erythematosus (SLE) was conducted using the French national healthcare database (SNDS), which provides near-complete longitudinal follow-up of the population since 2010. SLE has previously been investigated in this database to evaluate the effects of standard-of-care therapy, including hydroxychloroquine (HCQ) (14). SLE represents a particularly relevant test case for drug repurposing, as patients are exposed to hundreds of therapeutic products for multiple comorbidities, while the effects of most of these drugs on SLE disease activity remain unknown.

In this work, we evaluate the feasibility and validity of using internal positive and negative controls within the RE-MEDs semi-automated HT-TTE platform for drug repurposing. We further assess the suitability of topical drugs as negative control drugs (NCDs), given their minimal systemic bioavailability and the low likelihood that they influence the risk of lupus exacerbations with organ involvement, the outcome of interest. For operational purposes, the term “drug” refers to active ingredients, irrespective of formulation, route of administration, or combination.

Results

A total of 52,937 patients with SLE were identified in the SNDS between 2010 and 2020. Of these, 791 incident cases were excluded because diagnosis occurred less than one year before the end of the study period (2020), and 7,195 patients were excluded because advanced disease was identified within their first year of observation. The remaining 44,951 patients, classified as having mild-to-moderate SLE, constituted the study population (Figure 1). Among these, 16,363 were incident cases diagnosed after

2010, while 28,588 were prevalent cases who already met the criteria for mild-to-moderate SLE in 2010, the first year of the study period.

Patients in the eligible study population of mild-to-moderate SLE were predominantly female (87.1%) with a mean age of 45.3 years at cohort entry (SD: 15.8) (Table 1). Over the period between SLE cohort entry and exit, 88.7% received a synthetic antimalarial drug –almost exclusively HCQ–and 89.5% received a systemic corticosteroid (corresponding to eight products from Anatomical Therapeutic Chemical [ATC] subclass H02AB).

Table 1 shows that nearly all patients (98.1%) received at least one of the 150 topical or locally applied drugs considered as potential candidates for negative control drugs at any time after entry into the SLE cohort (distribution by product presented Supplementary Table 1), with dermatologic formulations being the most frequently used (94.1% of patients exposed at least once). Among these 150 products, 62 (41.3%) had at least 2,200 eligible treatment sequences (ETS), defined as first incident use during the study period, which was the minimum number required to achieve adequate statistical power for assessing associations between individual drugs and lupus exacerbations with organ involvement. Collectively, all other products used by the study population spanned nearly the entire range of other reimbursed drugs listed in the French compendium, covering a wide variety of formulations and dosages. These comprised 1,052 drugs, including 27 non-steroidal anti-inflammatory drugs (NSAIDs; ATC M01A), 29 analgesics (ATC N02), 83 antineoplastics (ATC L01), 13 immunostimulants (ATC L03), 36 immunosuppressants (ATC L04A) and 864 miscellaneous products.

Among immunosuppressants, methotrexate was the most commonly used, with 22% of patients exposed. During follow-up, 12% of patients received at least one of the six products prescribed for severe SLE, resulting in censoring of follow-up (Supplementary Table 2); among these, azathioprine was the most frequently used (4%).

A total of 16,301 eligible hydroxychloroquine (HCQ) treatment sequences (ETS), defined as first initiation during the study period, were identified within the study population. For each HCQ ETS, potential comparator ETS were sought among patients initiating alternative treatments at the same calendar time. Matching on high-dimensional propensity score (hdPS) and index date (i.e., treatment initiation) resulted in 8,957 HCQ ETS (56%) matched to a comparator defined as “any other drug”, corresponding to a randomly selected treatment initiation for any drug other than HCQ and used as a proxy for placebo. In contrast, only 1,907 (12%) could be matched to an ETS for a drug within the same ATC level 2 category, which served as an active comparator and comprised chloroquine and other antiparasitic drugs.

Of the 62 topical or locally administered products that met the minimum of 2,200 ETS with balanced covariates required for the HT-TTE analysis, a match could be found for 52 products. These were thus considered as NCDs. Supplementary Tables 3a and 3b present the characteristics of the included ETS for HCQ and by NCD, for the comparators “any other drug” and ATC level 2, respectively. Overall, matched ETS were highly similar in terms of sex distribution, age, and prior history of SLE exacerbations with organ involvement. Very few covariates included in the hdPS were meaningfully unbalanced.

Figure 2, as well as Supplementary tables 4a and 4b, present the results of the HT-TTE intent-to-treat (ITT) analysis evaluating the association between HCQ and the risk of SLE exacerbation with organ involvement relative to respectively, “any other drug” comparator and “same ATC level 2” comparator. HCQ was associated with a lower risk of serious SLE exacerbation compared with the ‘any other drug’ comparator (adjusted hazard ratio [aHR]=0.61, 95% CI 0.52 - 0.72). No statistically significant difference in hazard was observed when HCQ was compared with drugs in the same ATC level 2 category (aHR=0.80, 95% CI 0.52 - 1.22), although this analysis was limited by suboptimal sample size (1,907 ETS versus the required minimum of 2,200). In the supplementary while-on-treatment analysis for HCQ, the aHR was 0.63 (95% CI: 0.55 - 0.72) against the “any other drug” comparator and 0.90 (95% CI: 0.64 - 1.27) against the ATC level 2 comparator.

Among the 52 NCDs, false-positive associations were observed for four, which were significantly associated with a lower rate of SLE exacerbation with organ involvement compared to their “any other drug” comparators (Figure 2), corresponding to a specificity of 92.3% (Table 2). When using ATC level 2 comparators, only one NCD was significantly associated with a lower rate of exacerbations, yielding a specificity of 98.1%. Across both comparator strategies, a single NCD was consistently and incorrectly associated with a lower hazard of exacerbations, corresponding to an overall specificity of 98.1%.

Discussion

This study demonstrates that an HT–TTE approach, applied to nearly all patients diagnosed with mild-to-moderate SLE in a nationwide healthcare database was able to blindly identify hydroxychloroquine (HCQ) as being associated with a reduced risk of exacerbations with organ involvement, without encoding HCQ as a positive control. By simultaneously evaluating a large set of negative control drugs the approach exhibited low to very low rates of false positives, thus yielding high to very high specificity, depending on the comparator strategy employed, whether using placebo-proxy comparators, active-comparators, or both. Nevertheless, several limitations should be noted and are discussed below.

Previous studies have shown that TTE methods can retrieve known drug effects. In particular, Shahn et al. *(8)* demonstrated that their method successfully identified the effects of antihypertensive treatments on the prevention of cardiovascular outcomes using large electronic healthcare databases. Taken together, their findings and those of the present study suggest that HT-TTE approaches can detect true drug effects when applied at scale to real-world data. However, only one positive control drug could be evaluated in the present work, as hydroxychloroquine was the only treatment recommended and supported by randomized controlled trials for the prevention of exacerbations in mild-to-moderate SLE during the study period. Other drugs with similar indications, such as belimumab, were introduced later and were insufficiently used by the study population to serve as reliable positive controls. A comprehensive evaluation of the sensitivity of HT-TTE methods will require multiple validation studies across diverse drug-outcome pairs. One plausible explanation for the successful identification of the expected association between hydroxychloroquine and SLE exacerbations with organ involvement in the present study is the use of highly specific, “hard” outcome definitions restricted to hospitalizations with

documented organ involvement (e.g., lupus nephritis, myocarditis, pericarditis, SLE-related pulmonary involvement, or seizures). Such definitions are likely to have reduced outcome misclassification, thereby limiting bias toward the null. A trade-off of this approach is that these outcomes are relatively rare and require very large databases to achieve adequate statistical power – conditions met by the SNDS – but also restrict the number of drugs that can be meaningfully evaluated.

To our knowledge, this study is the first to report quantitative estimates of false-positive rates within a HT-TTE framework, thereby providing an empirical assessment of the specificity of the method. Specificity was high (88– 92%) when "any other drug" was used as a comparator, higher when drugs from the same ATC level 2 category were used (92 – 98%), and very high (96-98%) when drugs were required to be falsely positive across both comparator strategies. These findings suggest that topical and locally applied drugs may represent suitable candidates for negative control drugs in HT-TTE analyses.

However, the use of ATC level 2 comparators may be suboptimal for screening-oriented repurposing research, as this strategy can include drugs with pharmacological activity similar to that of the index drug, thereby reducing sensitivity. This limitation is illustrated by the HCQ analysis, in which the ATC level 2 comparator group included chloroquine, resulting in a hazard ratio estimate closer to the null. Despite this limitation, many HT-TTE repurposing studies have relied on ATC-based comparators in combination with randomly selected drug comparators (5) (6) (7) and have further required candidate drugs to demonstrate statistically significant associations in both comparator settings. Such stringent criteria may partly explain why some studies have identified only a limited number of repurposing candidates.

One of the central challenges of TTE approaches is achieving adequate balance between comparison groups with respect to confounding variables. This challenge may be amplified in HT-TTE settings, where large numbers of drugs are evaluated simultaneously (7). Conversely, HT-TTE applications focused on drug repurposing may be less susceptible to confounding by indication, as the effects of interest typically involve non-intended outcomes rather than the conditions for which the drugs were prescribed.

To address confounding, previous HT-TTE studies have relied on a range of strategies, including propensity scores with stabilized weights (5), inverse probability of treatment weighting (IPTW) (10) (8) (7), and machine-learning or AI-based approaches designed to further reduce residual confounding (6) (7), sometimes in combination with causal diagrams such as directed acyclic graphs (DAGs) (7). However, it remains unclear to what extent these increasingly complex approaches improve causal inference, as formal evaluations of sensitivity and specificity have generally not been reported in HT-TTE studies.

In conclusion, this study provides empirical evidence that high-throughput target trial emulation (HT-TTE) can achieve high specificity when applied to drug repurposing research using large electronic healthcare databases. By leveraging internal positive and negative control drugs, the approach successfully and blindly identified a known effective therapy while quantifying false-positive signals across alternative comparator strategies. These findings support the use of HT-TTE as a scalable, semi-automated

screening framework for prioritizing repurposing candidates, while underscoring the importance of careful comparator selection. Further validation across multiple diseases, drug classes, and outcomes will be essential to fully characterize the operating characteristics of HT-TTE and to define its role alongside other real-world data-driven approaches in drug discovery.

Methods

Overview

A semi-automated high-throughput target trial emulation (HT-TTE) approach was used, standardizing each stage of the emulation process. This included transformation of raw data into analysis-ready metadata, identification of eligible disease populations and subpopulations, construction of drug exposure sequences, selection of comparator groups, and covariate balancing through high-dimensional propensity score (hdPS) matching.

In this validation study, two comparator strategies were applied for each drug investigated, consistent with previous HT-TTE research (5) (6) (10) (8) (7): (i) comparison with “any other drug,” serving as a proxy for a placebo control, and (ii) comparison with drugs within the same Anatomical Therapeutic Chemical (ATC) level 2 category (15), serving as a proxy for an active comparator. Follow-up was implemented under both intention-to-treat (ITT) and while-on-treatment analytical frameworks, as in previous work.

This study was designed to evaluate the sensitivity and specificity of the HT-TTE method for the automated identification of potential drug repurposing candidates, using systemic lupus erythematosus (SLE) as an application. All analyses were conducted using the RE-MEDs semi-automated HT-TTE platform.

Drug effects assessed

For this validation study, the effects of 150 topical and locally applied drugs – each initiated by at least 2,200 patients with mild-to-moderate SLE – were evaluated alongside the standard therapy hydroxychloroquine (HCQ) for their association with SLE exacerbations with organ involvement. The working hypothesis was that the high-throughput process would correctly identify HCQ as being associated with a reduced risk of lupus exacerbations – consistent with its established role in SLE management – while the topical and locally applied drugs, which have minimal systemic bioavailability, would show no association with exacerbation risk.

High-throughput target trial emulation process

The HT-TTE process followed a structure similar to that of previously published platforms (5) and relied on a set of semi-automated, highly standardized components:

(a) Application of a common analytical model to an electronic health database, automatically transforming raw source data into analysis-ready metadata suitable for pharmacoepidemiologic

research.

(b) Identification of disease populations and subpopulations corresponding to predefined indication groups.

(c) Characterization of exposure to all drugs used over several years using data-driven parameters and disease-specific drug-disease relationships. This step included automated identification of treatment and non-treatment sequences, specification of at-risk and immortal-time windows, and semi-automated classification of use patterns (first use, new use, repeat use, continuous use, and unique use).

(d) Selection of potential comparators for each evaluated drug within predefined time-windows. Two comparator strategies were applied: (i) 'any other drugs', randomly selected and used as a proxy for a placebo comparator, and (ii) drugs within the same Anatomical Therapeutic Chemical (ATC) level 2 category as the evaluated drug, considered potentially active comparators.

(e) Balancing of treatment arms using statistical techniques including matching on high-dimensional propensity scores (hdPS). Drug-comparator pairs that failed to meet predefined balance criteria were excluded from further analysis.

(f) Handling of intercurrent events occurring during follow-up (e.g., outcome occurrence, treatment switching, death) using predefined strategies aligned with ICH E9(R1) estimand framework (16). The causal contrasts of interest included a treatment policy estimand corresponding to an intention-to-treat (ITT) effect and an on-treatment estimand corresponding to a while-on-treatment (WoT) effect, each defined by distinct follow-up and censoring rules.

(g) Estimation of associations between drug exposure and SLE exacerbations with organ involvement using Cox proportional hazard models.

The specific parameter settings applied to each component in this validation study are described in detail below.

Data source

The common analytical model was applied to data from the French National Health Data System(i.e., *Système National des Données de Santé* (SNDS)), which captures healthcare claims for more than 99% of French residents (approximately 67 million individuals) and is linked to the national hospital discharge database. The SNDS provides comprehensive longitudinal data, including demographic characteristics, reimbursed outpatient dispensings, inpatient diagnoses and procedures, and vital status. A key strength of this system is the continuous insurance coverage of all residents from birth or immigration to death or emigration, enabling the identification of incident disease populations. For this study, data covering the period from January 1, 2010, to December 31, 2020, were used.

Study population for the validation study

Patients with SLE were identified using algorithms previously developed and published by the same research group (14). These algorithms combine International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes recorded in hospital discharge data, SLE-specific treatments, and long-term chronic condition status *(Affectation de Longue Durée* (ALD)*)* for SLE – a designation applied to conditions requiring prolonged and costly care under specific reimbursement rules. The full list of codes and the identification algorithm are provided in Supplementary Table 5 . Patients entered the SLE cohort on the date at which they first met any criterion of the identification algorithm. Individuals who met the criteria during the first year of the study period were assigned a cohort entry date of January 1st, 2010.

The target population consisted of patients who entered the SLE cohort with mild or moderate disease. Patients with evidence of advanced disease during the first year of observation (i.e., 2010) were excluded. Advanced disease was defined by the presence at cohort entry of any of the following criteria: (i) chronic kidney disease; (ii) a procedure code for dialysis; (iii) dispensing of any medication used for advanced SLE; or (iv) two or more hospitalizations for acute nephritis. Code list for these criteria is shown in Supplementary Table 6.

Eligible treatment sequences

All drug-use sequences were identified automatically. An eligible treatment sequence (ETS) was defined as the first dispensing of any drug that was preceded by at least 360 days without use of the same drug; this washout period was chosen to align with multiples of 30 days. The index date corresponded to the date of initiation of the first ETS during the study period. To ensure that exposure followed an established diagnosis of SLE, ETS were required to begin at least 360 days after entry into the SLE cohort.

Because the SNDS does not record prescribed treatment duration or the number of units dispensed, single dispensing events were assigned a default exposure duration of 60 days to account for suboptimal adherence. For treatments with repeated dispensings, exposure duration was inferred from successive dispensing dates, with overlapping intervals accounted for; the 60-day duration was applied to the final dispensing.

Eligible treatment sequences were identified for all distinct active ingredients among patients with SLE. For the purposes of this validation study, ETS corresponding to hydroxychloroquine (HCQ) and to topical or locally applied drugs were retained as exposures of interest.

Comparators

A single, shared pool of eligible treatment sequences (ETS) was constructed and served as the comparator sampling base for all drug evaluations. This pool comprised ETS corresponding to the first new use of any drug used in the study population. Comparator ETS were randomly sampled from this common pool for each drug-specific analysis according to the following predefined rules: for a given exposure ETS, the comparator was selected by sampling an ETS from the shared pool matched on

calendar date and excluding ETS corresponding to the drug under evaluation. Because patients could contribute ETS for multiple products, only one ETS per patient was randomly selected for inclusion in the comparator pool to avoid over-representation of patients with higher comorbidity burden. Patients exposed to the study drug were eligible to contribute ETS to the comparator pool only during the period preceding initiation of the study drug.

ETS corresponding to HCQ, topical or locally applied drugs, and randomly selected ETS for other drugs were collectively referred to as the “assigned ETS”.

For each ETS of a drug under evaluation, two comparative treatment strategies were applied, consistent with previously published HT-TTE frameworks (17). First, a “placebo-proxy” comparator was used by randomly sampling an ETS from the shared comparator pool, excluding ETS corresponding to the drug under evaluation. Second, a proxy “active comparator” was defined as an ETS corresponding to initiation of a drug within the same ATC level 2 category as the study drug, reflecting a similar therapeutic indication. For this latter comparison, the sampling base was restricted to the subset of the shared comparator pool comprising ETS for drugs within the same ATC level 2 category as the study drug.

Hospitalized acute exacerbations and organ involvement

The outcome was the occurrence of acute SLE exacerbations with organ involvement, consistent with the clinical progression of SLE. It was defined as a composite endpoint including hospitalization for acute nephritis, myocarditis, pericarditis, endocarditis, pneumonia, hematologic disorders, or seizures (codes listed in Supplementary Table 7). These events were defined *a priori* by clinical experts and retained because their coding specificity within the SNDS was expected to be high. To avoid misclassifying early diagnostic hospitalizations as exacerbations, events had to occur more than 360 days after SLE cohort entry, as early hospitalizations often correspond to diagnostic work-up and cannot be distinguished from disease activity in claims data.

Balancing

High-dimensional propensity scores (hdPS) were automatically estimated for all assigned ETS using the full set of data available in the SNDS. Covariates were drawn from ten predefined data dimensions (Supplementary Table 8), covering demographic characteristics, diagnostic history, medication history, and healthcare utilization. Automated covariate selection and score estimation followed high-throughput procedures adapted from established hdPS pipelines (18). For each dimension, up to 200 candidate covariates were initially considered; from these, up to 300 covariates across all dimensions that were associated with both the study drug ETS-comparator contrast and the composite outcome were retained for inclusion in the multivariate logistic regression model.

A 1:1 greedy matching algorithm was applied to both the index date (± 90 days) and the hdPS using a caliper of 0.2 standard deviations of the logit of the PS. For each study drug ETS, the comparator ETS

with the closest hdPS was selected from the “any drug” comparator pool and one was selected from the “same ATC level 2” comparator pool.

Balance was evaluated using standardized mean differences (SMDs) for all covariates included in the hdPS. ETS pairs were excluded if more than 1% of covariates exhibited a SMD greater than 10%. Topical or locally applied drugs with satisfactory covariate balance and adequate sample size (see below) in both comparator settings were retained for the specificity analysis as negative control drugs (NCDs).

Follow-up

Eligible ETS cohorts were followed for 180 days after the index date for the intent-to-treat (ITT) strategy, whereby outcomes were assessed regardless of subsequent treatment changes, discontinuation, or switching.

An additional while-on-treatment (WoT) analysis was conducted for HCQ-ETS, in which follow-up was restricted to the estimated duration of HCQ exposure based on dispensing dates; comparator ETS were assigned the same follow-up duration. An WoT analysis was not performed for topical or locally applied drugs because these products are often stockpiled and used on demand, making exposure duration difficult to ascertain reliably.

Follow-up was censored at the earliest occurrence of any of the following: (i) criteria indicating advanced disease (identical to those used as exclusion criteria at SLE cohort entry), (ii) occurrence of the composite outcome, (iii) end of registration in the SNDS, or (iv) death. In the WoT analysis of HCQ, comparator follow-up was additionally censored at the time of an HCQ dispensing (referred to as cross-censoring) in the comparator group (19).

Statistical Analysis

Outcome rates were estimated as the number of composite events per 100 person-years of follow-up. Adjusted hazard ratios (aHRs) for exacerbations with organ involvement were estimated using Cox proportional hazards models under both the ITT framework (for all drugs studied, including HCQ and NCDs) and the WoT framework for HCQ. Covariates included exposure to NSAIDs and corticosteroids (except methylprednisolone, which is frequently prescribed following the occurrence of the outcome) in the 180 days prior to index date. Models were applied irrespective of the matched pairs generated during balancing (“de-matched” analysis). False positives in the negative control analysis were prespecified as statistically significant protective associations (aHR<1 with $p<0.05$), consistent with the screening objective of identifying potentially beneficial drug repurposing candidates. Additionally, the threshold for statistical significance was set at $p< 0.1$ (one-sided) to enable identification of borderline significant associations.

Based on an expected outcome rate of 3.5 per 100 person-years, derived from the comparator group, 1,100 person-years of cumulative follow-up per arm were required to detect a relative risk of 0.5 with

80% power and 95% confidence. This requirement corresponded to retaining only drug pairs with at least 2,200 ETS per arm since the ITT analysis was for 180 days of follow-up.

All analyses were performed using the RE-MEDs real-world evidence high-throughput platform developed by the authors.

Declarations

Ethics approval and data governance

This study was conducted using anonymized data from the French National Health Data System (*Système National des Données de Santé*, SNDS), in accordance with French data protection regulations. The study was approved by the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*, CNIL) and the CESRESS institutional review board (approval number: DR-2021-058). In accordance with French law governing the secondary use of anonymized health data for research in the public interest, informed consent was not required.

Data availability

Data cannot be extracted from the SNDS portal and thus cannot be provided upon request. However, access to the SNDS data is free and can be granted upon application to the French Health Data Hub at https:// https://www.health-data-hub.fr/

Code availability

The code is not publicly available since the RE-MEDs analytical pipeline is proprietary. However, it can be made available for peer review.

Author contributions

L.A. proposed the initial idea.Y.M. was the chief investigator. All authors contributed to the design and implementation of the RE-MEDs HT-TTE platform, and the statistical analyses.Y.H. processed and analyzed the SNDS data. All authors contributed to the development of the manuscript and interpretation of results. Y.H. had access to the raw data of the SNDS.

Competing interests

The authors declare no competing interests.

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Tables

Table 1: Sociodemographic characteristics of the overall study population and stratified by study drug use

Values are shown as mean (SD) or *n* (%). The table reports age and sex for the overall study population of patients with mild-to-moderate systemic lupus erythematosus (SLE), as well as the proportion of users, proportion of female patients, and mean age (SD) among patients who used at least once during follow-up hydroxychloroquine, chloroquine, corticosteroids, and topical or locally applied drugs, stratified by indication.

	N Patients (%)*	Female n (%)#	Mean Age (years) [SD]¶ at Index Date
Study Population (Mild to Moderate SLE[1])	44,951	39,153 (87.1%)	45.3 [15.8]
Study Drugs at least once			
• Hydroxychloroquine	39,894 (88.7%)	34,892 (87.5%)	44.47 [15.46]
• Chloroquine	2,938 (6.5%)	2,495 (84.9%)	43.29 [14.08]
• Corticosteroids	40,209 (89.5%)	35,406 (88.1%)	45.08 [15.59]
• Topical drugs or locally applied drugs	44,108 (98.1%)	38,493 (87.3%)	45.35 [15.72]
• Dermatologic	42,305 (94.1%)	36,956 (87.4%)	45.38 [15.69]
• Ophthalmologic	34,820 (77.5%)	30,930 (88.8%)	46.29 [15.73]
• Muscle & joints	30,146 (67.1%)	26,651 (88.4%)	46.69 [15.28]
• Gynecologic	16,309 (36.3%)	16,294 (99.9%)	39.44 [12.51]
• Nasal	16,127 (35.9%)	14,474 (89.8%)	44.49 [14.99]

Abbrevations: SLE, systemic lupus erythematosus; SD, standard deviation

(*) Column percentages of the study population

(#) Row percentages

Table 2 Specificity analysis of false-positive associations among negative control drugs for lupus exacerbations with organ involvement

False-positive associations were defined as statistically significant protective associations. Borderline significance was defined using a one-sided test with p<0.10.

	Vs. Any drug		**Vs. Drugs of same ATC Level 2**		**Both**	
	Rightly classified	Wrongly classified	Rightly classified	Wrongly classified	Rightly classified	Wrongly classified
Significant results						
Negative Control Drugs	48	4	51	1	51	1
Specificity	**92.3%**		**98.1%**		**98.1%**	
Including borderline significant results*						
Negative Control Drugs N	46	6	48	4	50	2
Specificity	**88.4%**		**92.3%**		**96.2%**	

**p<0.1, one-sided*

Figures

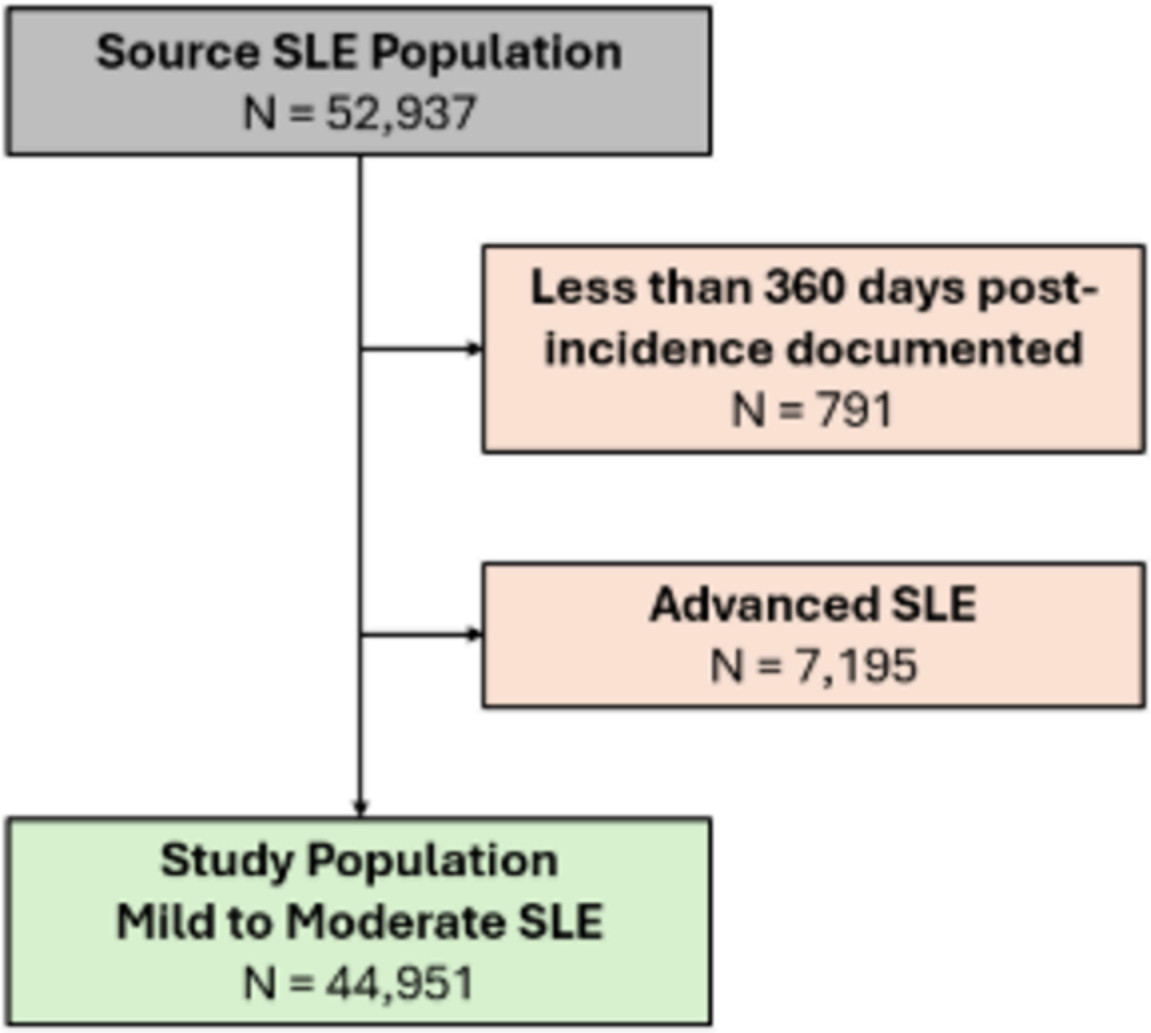


Figure 1

Flow chart of study population identification and selection

Figure 1 Legend: The figure depicts the identification of patients with systemic lupus erythematosus (SLE) in the French National Health Data System (SNDS), application of inclusion and exclusion criteria, and derivation of the final study population used in the validation analyses.

Abbreviation: SLE, systemic lupus erythomatosus

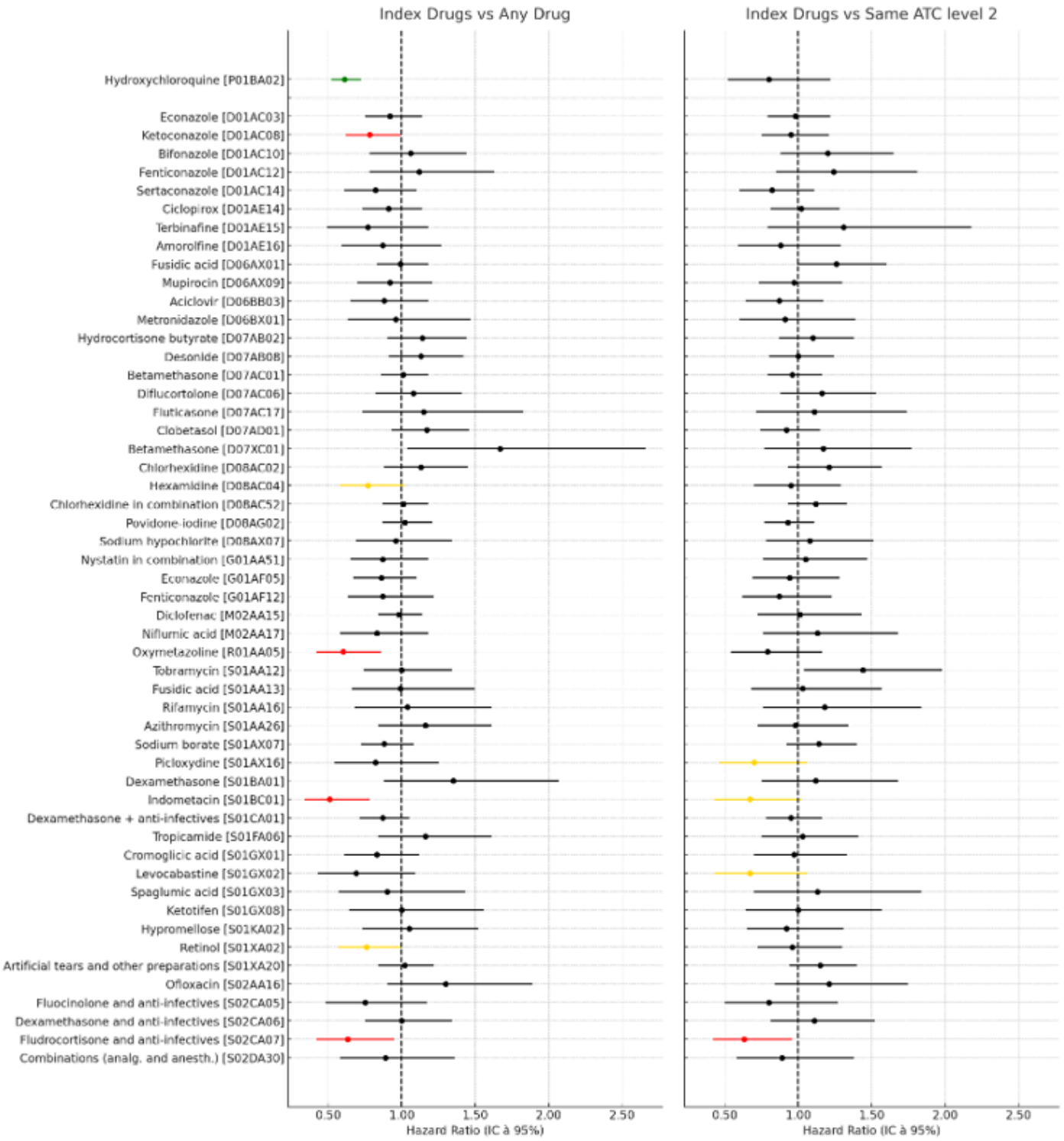


Figure 2

Association between exposure to the positive control (hydroxychloroquine [HCQ]) and 52 negative control drugs and lupus exacerbation in high-throughput target trial emulations.

Figure 2 Legend: Panel A presents adjusted hazard ratios (aHRs) for HCQ and all negative control drugs compared with any drugs, whereas Panel B presents aHRs for HCQ and all negative control drugs

compared with drugs within the same ATC Level 2 category. Hazard ratios were estimated using Cox proportional hazard models matched on high-dimensional propensity scores (hdPS) and included, as covariates, exposure to NSAIDs and corticosteroids (except methylprednisolone) in the 180 days prior to index date. Estimates are shown with 95% confidence intervals. Results highlighted in green represent true positives, those in red indicate false positives, and those in yellow denote borderline false positives ($p<0.10$, one-sided)

Abbrevation: ATC, Anatomical Therapeutic Chemical

Supplementary Files

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