Assessment of Drug Impact on Laboratory Test Results in Hospital Settings

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Patients experiencing adverse drug events (ADE) from polypharmaceutical regimens present a huge challenge to modern healthcare. While computational efforts may reduce the incidence of these ADEs, current strategies are typically non-generalizable for standard healthcare systems. To address this, we carried out a retrospective study aimed at developing a statistical approach to detect and quantify potential ADEs. The data foundation comprised of almost 2 million patients from two health regions in Denmark and their drug and laboratory data during the years 2011 to 2016. We developed a series of multistate Cox models to compute hazard ratios for changes in laboratory test results before and after drug exposure. By linking the results to data from a drug-drug interaction database, we found that the models showed potential for applications for medical safety agencies and improved efficiency for drug approval pipelines.

Keywords: adverse drug events, polypharmacy, electronic patient records, population-wide data

1. Introduction

1.1. *Electronic health record data to overcome health disparities in precision medicine*

Population-wide electronic health record (EHR) data present an important source to overcome health disparities in precision medicine. Adverse drug events (ADEs) describe known and yet unknown effects of a drug that may be due to undiscovered drug effects in specific population subgroups, or due to an unexpected interaction with one or more additional drugs. This is a particular area of interest within pharmacovigilance since most drugs are only clinically tested as monotherapies and additionally mostly on healthy men.[1,2]

As such, population-wide EHR data present an important source to identify potential ADEs among users of healthcare irrespective of e.g. co-morbidity burden and socioeconomic status. Models for detection of ADEs based on EHR data could overcome health disparities in precision medicine by identification of potential ADEs in real-world settings. Generally, only 10% of ADEs are reported and several studies have stated that up to 30% of ADE-related hospital admissions are preventable.[3–7] As the risk of ADE increases with the burden of polypharmacy, the phenomenon translates into an additional risk in multi-morbid patients. Therefore, methods for detection of ADEs are an integral aspect of overcoming health disparities in precision medicine.

Denmark's comprehensive laboratory, pharmaceutical, and disease registries represent a unique opportunity to explore associations between polypharmaceuticals, laboratory data and potential ADEs (pADEs).[8,9] To our knowledge, only one study, conducted in South Korea, has directly investigated ADE risk within drug-laboratory test pairs, but with the goal of identifying new signals for known ADR events.[10] We present a potential strategy for large-scale monitoring of drug effects when administered in combinations, which is of increasing interest in ageing, multi-morbid populations.[11–13]

2. Materials and Methods

2.1. *Data Availability and Sources*

Population-wide laboratory healthcare and pharmaceutical data from two of the five Danish healthcare regions (approximately 50% of the entire population) were collected and processed for this study. Data covered all in-patient, out-patient, and emergency room settings at public hospitals, in total 1,987,180 patients. As only 1% of healthcare costs originate from private hospitals in Denmark, these data were considered population-wide.[14] Due to Denmark's person identification system (initiated in 1968) we were able to completely link data records across hospitals and data sets, fully integrating the laboratory and pharmaceutical data for the study cohort.[15,16]

We defined the study period from 2011-10-28 to 2016-06-30 corresponding the period where all relevant hospital system data overlapped in an ideal manner. The cohort was further reduced, removing tourists and other short-term residents with unknown study exit dates and standing. It is important to note, that as of 2014 it was possible to legally change your person identification number to reflect a change in self-identified gender (restricted to a binary system of male/female), our data reflects the gender that was legally registered at the time of hospital interaction.

2.2. *Laboratory Healthcare Data*

The processed laboratory data applicable in this study consisted of 1,924,869 patients and 310,455,299 laboratory measurements. These data were systematically cleaned and conformed to a more centralized naming and coding system of which is thoroughly described in Muse et al.[17,18] In summary, typos and symbols (=, >, < etc.) were removed or corrected and naming systems were conformed and translated to English.[19–23] Typical test coding systems made use of the Nomenclature, Properties, and Units (NPU) classifications as is common in the Nordic countries. Failed or incomplete tests were removed from the data set.[19]

Tests were categorized as within range, normal (0), or out of range, abnormal (-1 or 1), based on the test result within national health authorities reference intervals that are calculated to be the 95% confidence interval for healthy patients. Tests were labelled as "-1" if the value was below the reference interval or "1" if they were above it, or otherwise abnormal for binary testing only (positive vs. negative). This labelling system was used throughout the study and in figures to distinguish an adverse change when the laboratory test in question was decreased (-1) or increased (1) in relation to the relevant reference interval. A unique laboratory test was defined as a unique analyte taken from a unique source: for example, B-LEUKOCYTES-1 indicates leukocytes taken from blood were abnormally low in relation to the given reference interval that may be age-dependent for some tests.

2.3. *Pharmaceutical Data*

The pharmaceutical data were matched to the timeframe and patient IDs of the laboratory data. The pharmaceutical data used for this study is the first and last date of the confirmed administration of the drug and the respective Anatomical Therapeutic Chemical (ATC) group classification code. The data set only included drugs administered at the hospital (in-patient, out-patient, and emergency room data).[24,25] ATC codes are alpha-numeric codes used internationally as a tool for drug utilization monitoring and research. The codes are formula specific meaning that ATC codes may be the same for certain drugs, even though the route of administration differs. For example, the ATC code for the antibiotic drug moxifloxacin is J01MA14 irrespective of route of administration, e.g. orally or intravenously.[26]

ATC codes are seven characters long (representing the anatomical main group, therapeutic group, pharmacological subgroup, chemical subgroup, and chemical structure, respectively), but may in practice be registered with fewer characters. This study made use of the most specific codes available (i.e. preferably ATC codes containing seven characters) as to pinpoint possible relevant drug mechanisms. Dosing information was available, but not used or needed for the purpose of this study.

2.4. *Multistate Cox Model, Monotherapies*

The core model of the study was developed using a multistate approach Cox model.[27,28] In this model, the main hazard ratio (HR) calculation is defined as $\lambda_{12}/\lambda_{02}$, outlined in Figure 1.This risk can be intuitively understood as the increased risk of an event given an exposure, compared to those who never had the exposure (Figure 1). Here, we considered drug administrations and exposure and extrapolated from abnormal laboratory tests events. That is, the first position in the subscript indicates in the study whether the subject was exposed (0: "no"; 1: "yes").

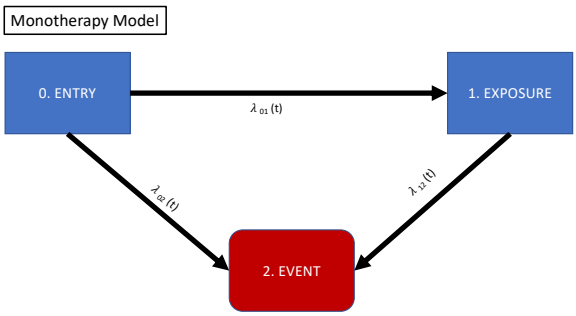

Figure 1: Schematic overview of potential pathways for each patient to take. The labeled paths exemplify the hazard at time t for a given individual. This study specifically examines the hazard ratio of $\lambda 12 / \lambda 02$ for any given time t. Different model state assumptions are clarified in Table 1.

The second position indicates if the event happened (2: "event) (Table 1). Two versions of the model were established: Model A based on abnormal tests followed by drug administration within a certain number of days, and Model B based on drug administration followed by a newly returned abnormal test (i.e., it was not documented as abnormal before the medication started) within a certain number of days, further detailed in Table 1. To capture the different types of pADEs that can develop within hours, days, weeks, or months, each model was created for different time frames: 24 hours, 48 hours, 72 hours, 7 days, 14 days, 30 days, 60 days, and 90 days.[29,30] Time was calculated from the first date of exposure; drug administration duration was therefore not included in these models.

In addition, only the earliest known administration of a drug within the time frame of the study was included. Similarly, only the first instance a patient had an abnormal test was retained. In Model A, the calculated HRs should follow typical diagnostic protocols. Model B included the inverse approach where single drugs can be investigated for their pADEs.

Table 1: Defined states for each model as outlined in figure 1

*x can be any of the defined time frames listed in Methods

State	Model A	Model B
0. Entry	Entering study with normal lab test and no drug administration	Entering study with normal lab test and no drug administration
1. Exposure	An abnormal lab test result	Being administered a drug
2. Event	Being administered a drug within x* days of exposure date	Receiving an abnormal lab test result within x* days of exposure date

2.5. *Monotherapy Model Parameters*

For the monotherapy multistate Cox model there are two required entries: time to exposure and time to event. Patients can have four paths, 1: never having the exposure or the event, 2: having the exposure but not the event, 3: having the exposure and the event, or 4: never having the exposure but having the event (Figure 1). The patients in the cohort were therefore always included in the model in question because they would always be categorized in one of these four paths. Times associated to each input was calculated as the patients age at the time, correcting for immortal time bias and accounting for age in the model. The HR outputs of these iterated models over the different time frames were corrected for multiple testing using the false discover rate (FDR) (full results for all models provided in supplemental Table 1). Models of all ATC codes and test combinations were run if at least 100 unique patients experienced both during the study window, removing drugs and laboratory tests that are least common, increasing the power of the study and relevance of the results.

2.6. *Multistate Cox Model, Polypharmaceutical Therapies*

The same core multistate Cox model approach was used to study pADE in the context of polypharmacy, here modelled by simultaneous administration of two different drugs. Figure 2 shows a schematic outline for the polypharmaceutical model where patients experiencing monotherapies and polypharmacy can be accounted for in the same design.

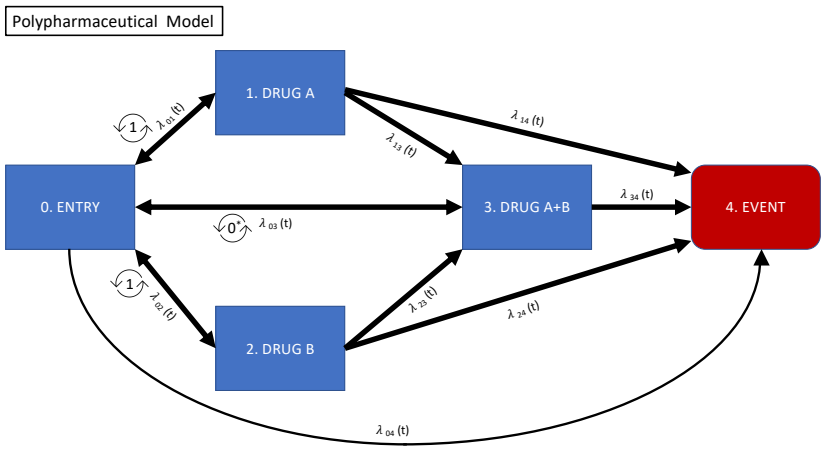

Figure 2: Schematic diagram of the polypharmaceutical model. All patients begin the study at state 0. The double-sided arrows indicate that a patient can move back to state 0 one time, the single sided arrows indicate a uni-directional path for patients. The event/exit indicates that the study window is over either with a patient incurring an adverse outcome, or the study window ending. Further details of each possible path are found in supplemental table 2. * Symbol indicates the patient can only move to state 4 after moving back to 0 (i.e. monotherapy exposures not considered after concomitant administration).

Again, this model only considered the first time an abnormal test was recorded for each patient. This means that the model only "counts" an abnormal test after concomitant therapy if the patient in question had no previous record of that abnormal test occurring. Drug pairs studied included only those listed in the Danish Drug-Drug Interaction (DDI) database (maintained by the Danish Medicines Agency) due to computational feasibility limitations (it would require ~6 months to compute all possible iterations).[25,31] Data from this database is then used to analyze results from this model. Other conditions for this model can be related to time frames. Drugs administered

sequentially were considered in the model if the two drugs were administered within six hours of each other (from last administration of the first drug). This is done under the assumption that the pharmacokinetic (PK) profile of a given drug will remain in the patients' blood stream for at least several hours and therefore has an interaction with the second drug in question.[32] Given the complexity of the system, the polypharmaceutical model only examined possible ADEs after 24 hours after co-administration time (i.e., when the second drug was administered).

2.7. *Polypharmaceutical Model Parameters*

As the case for the monotherapy model, there are several paths a patient can take in the multistate model. To adjust for potential immortal time bias, each patient record was broken into several records that account for a patient's movement between states as outlined in Figure 2. As exemplified there, every patient enters at state 0 and can move to state 1, 2, or 3. In this model, patients can also move back to state 0 from state 1 or 2 if no ADE was detected, and then move back into any state again. This event can only happen once per patient to consider if the patient in question did not experience a monotherapy induced ADE. From any of the states, the given patient can move to state 4, i.e., the exit state as this indicates an ADE occurred (or end of study) and the patient "exits" the study window. Patients' ages for each pathway were recorded for all patients and used as inputs to the Coxph model; this approach therefore integrates age into the model directly.[28] Because of the complexity of this approach, patients can have their record broken up into up to five entries in preprocessing steps. All possible pathways are summarized in supplemental table 2. Models of all possible ATC code pairs and test combinations were run if at least 5 unique patients experienced both during the study window, as per research approval guidelines (see data approval section). The HR outputs of these iterated models were corrected for multiple testing using FDR (processed results of reported models provided in supplemental table 3). All analyses were performed in R version 4.0.0 with the "The Coxph package" as the main resource.[33]

2.8. *Correlations between Laboratory Tests and Polypharmaceutical Drug Dosage Changes*

To substantiate the results of our multistate Cox models, we compared our findings with the results of a recent study published by Rodríguez et al.[24] In brief, in a data set of 77,494 potential drug pairs, Rodríguez et al. identified 694 drug pairs where drug dosage changes are more likely to happen during co-administration, compared to when they were administered as a monotherapy. Moreover, these 694 drug pairs had not previously been reported in 15 different drug-drug interaction databases. We assessed the overlap of drug pairs identified in the present study and the drug pairs identified by Rodríguez et al.

3. Results

A total of 1,634,655 patients were included in the model for all interactions of 462 medications and 323 possible biochemical outcomes at the 90-day time frame, decreasing for the other time frames due to cohort restrictions (see Methods). All possible iterations of these data were fed through multi-state Cox models A and B as outlined in Figure 1 and detailed in Table 1. Resulting HRs were

analyzed and presented in Figures 3-5; all monotherapy HRs and corresponding p values are reported in supplemental table 1.

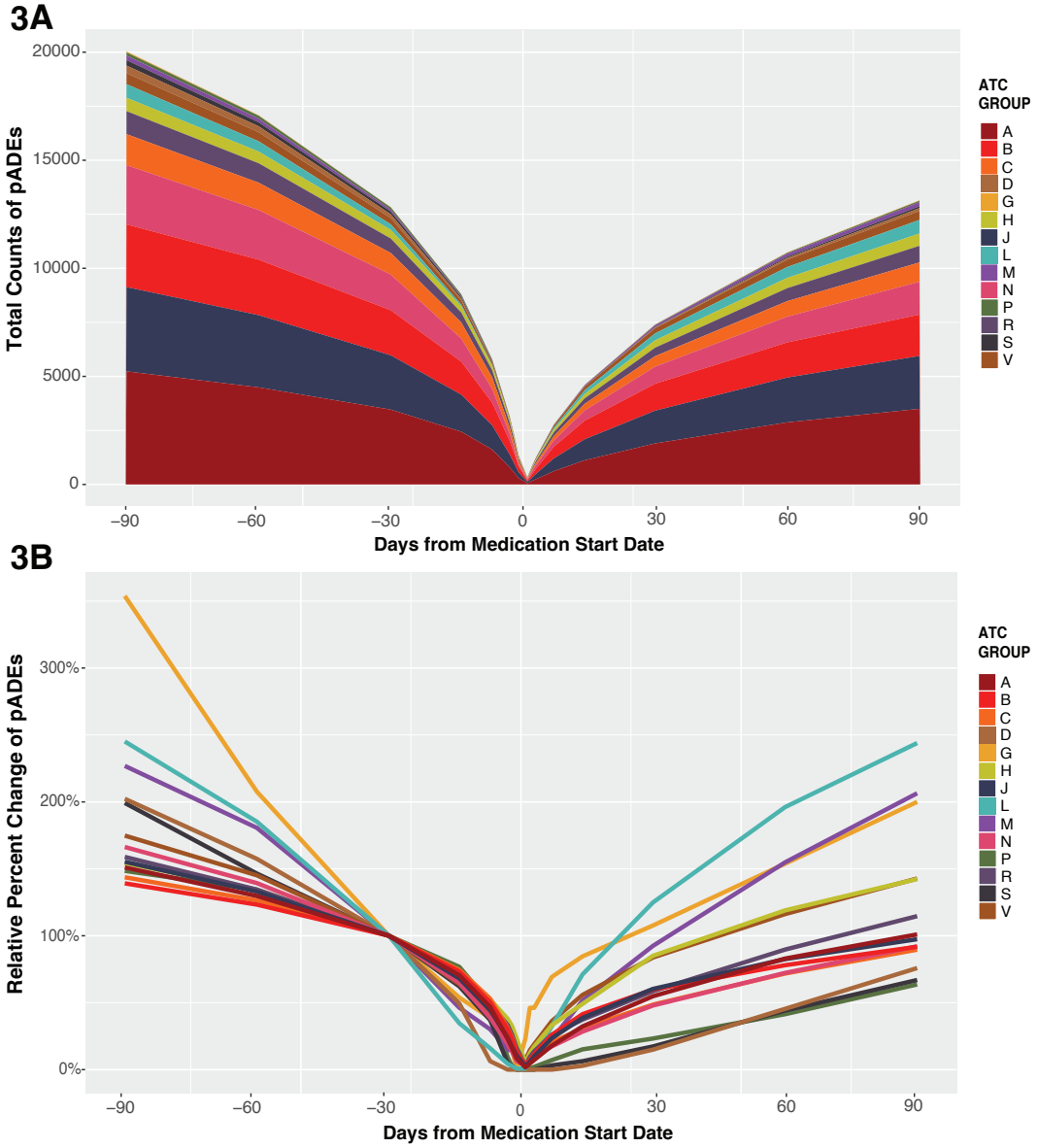

Figure 3: The total detected pADEs across the study period, in relation to medication start date (day 0). Figure 3a summarizes the total pADEs identified in the cohort for significant pADEs with HR > 2 (pval<0.05, FDR corrected). The same data is then assessed using relative percentage of pADEs as compared to day "-30" by ATC group in Figure 3b. The colors indicate the different ATC groups. Full legend provided in supplemental figure 1.

Figures 3a and 3b combine results from model A and B to visualize total HR counts and cumulative counts, respectively. In Figure 3b we can see expected trends in laboratory value changes, where more significant pADEs are identified before drug administration start dates than after which reflects the diagnostic period followed by reduced symptoms (after day 0) as the

medication takes effect; this finding serves as a proof-of-principle for the method approach. Further, the proportion of HRs after the drug start date increases in group L (Figure 3b) which mainly consists of cancer-fighting drugs; chemotherapies are widely known to cause severe side-effects, namely in white blood cell counts. Lastly there is a notable short increase in group G proportionally around days 1-7 post medication date of misoprostol (G02AD06), an abortion medication which typical involves several side effects that subside within a few days to a week.[34]

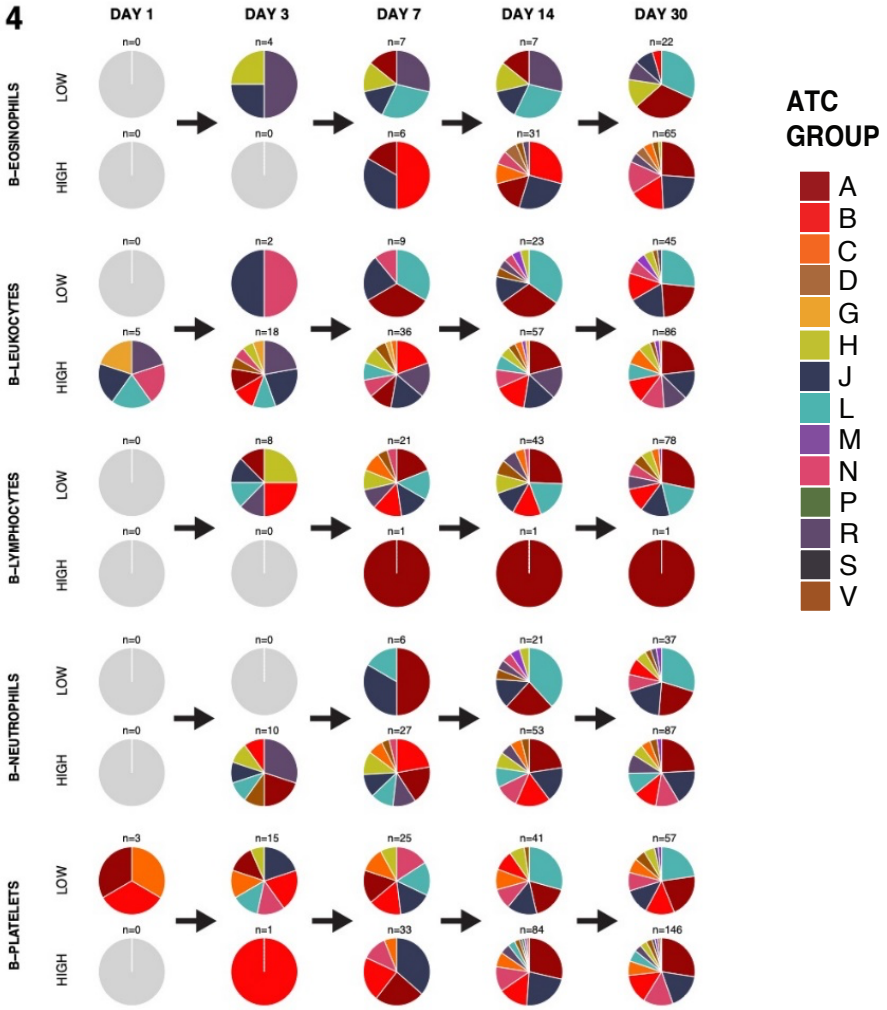

Figure 4: A time-frame overview of pADEs to each laboratory test over selected timeframes. The selection of tests highlighted here are selected white blood cell count tests and platelets, with results for both abnormally high and low counts. Grayed out pie charts indicate that no significant pADEs (HR>2, pval <0.05, FDR corrected) were detected at the given time point and lab test combination. Coefficient values for all data are reported in supplemental table 1. Full legend provided in supplemental figure 1.

Figure 4 expands on pADEs identified in Figure 3 by looking at specific laboratory tests by specified timeframes. The figure provides a trajectory over time of newly abnormal laboratory tests and their relation to different anatomical groups.

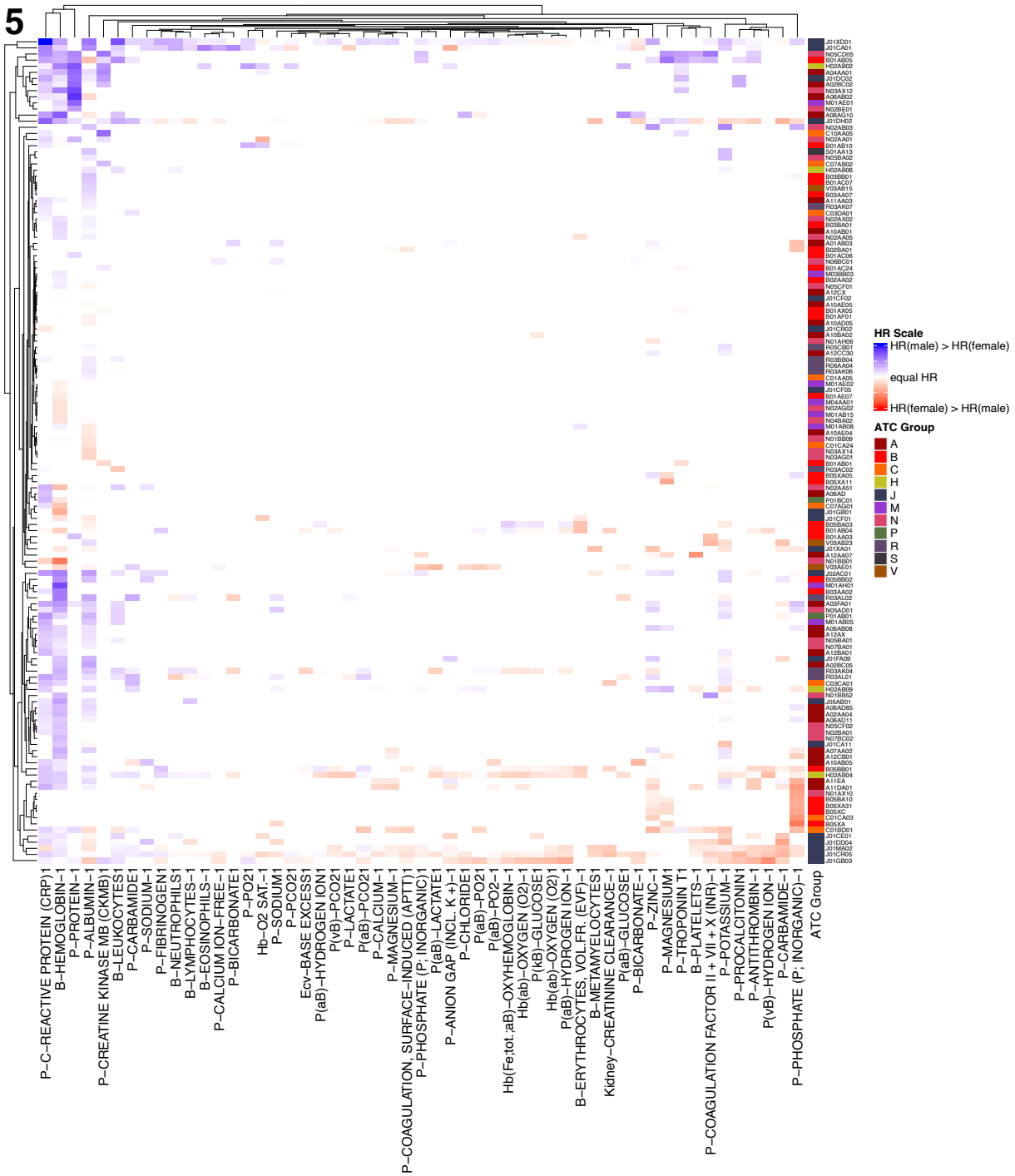

Figure 5: Heatmap providing a summary of sex-driven differences of pADEs that occur within two days of medication start. X-axis: Blood tests. Y-axis: Drugs. Bluer colors indicate a higher HR value for male vs female patients, while redder colors indicate the inverse. White: No significant difference between HRs for sexes or no pADEs were identified by the model (pval >0.05, FDR corrected). The actual HR values for all data can be found in supplemental table 1. Full legend provided in supplemental figure 1.

The timeframes of this pADE development are clearer here as the trends from hourly, daily, weekly, and monthly pADEs are elucidated, again primarily in group L around the 7-to-14-day mark in various white blood cell and platelet count tests. Except for lymphocytosis (high lymphocytes), the number of drugs that associates with an abnormal lab test increases as the time from exposure increases for all blood tests. However, the compositions of drug classes are only similar across time for some tests, e.g., thrombocytotosis (high platelets). Generally, the trajectories for leukocytes and neutrophils resemble each other, reflecting the fact that 40-60% of leukocytes are neutrophils. In both cases, drugs in anatomical groups J and L compromise at least 50% of the pairs, consistent with the characteristics of the population where these drugs are typically administered (i.e., treatment of infections and malignancies). Notably, the trajectory for lymphocytopenia remains constant over the observation time.

Figure 5 examines pADEs detected within 48 hours of drug administration by sex. Notably, HRs for hemoglobin, C-reactive protein, and albumin were generally higher for males than for females (left columns). Conversely, associations for antibiotics often administered as second or third line of treatment have many associations with abnormal lab values where HRs are higher for females (bottom rows). Yet, the trends for C-reactive protein, hemoglobin and leukocytes show higher HRs for males. In contrast, procalcitonin generally associates with higher HRs for females. In sum, these observations are consistent with existing knowledge of differences in inflammatory responses between sexes.[35–37] Importantly, the observed trends are evidence that these differences also affect treatment response.

Drug pairs are investigated in Figure 6 where a network approach is used to summarize the overlap between findings from the multi-state Cox model approach and known DDIs as reported by public health authorities. Generally, the network is dominated by drugs from ATC groups A, B, C, J, and N consistent with the trends in Figure 3. I.e., these drug classes are also the drugs classes that correlated with most abnormal lab tests when administered as a monotherapy. The figure shows that the severity of pADE is high for several drug pair therapies from the J chapter, when combined with drugs from the A and B chapter. Specifically, the J01 and J02 groups have a lot of edges (which we loosely denote “hub”) with a relatively large fraction being dark and indicating that there is a high risk of pADE when antibiotics for systemic used are combined with drugs used to treat bacterial and fungal infections. Further, Figure 6 illustrates that there likely are underreported drug pair therapies with pADE as indicated by “hubs” within the J chapter and chapter N. In addition, some of the trends displayed in the figure reflect clinical practice. For example, there is a dark edge between fentanyl (N01AH01) and triazolam (N05CD05) which are often administered jointly to patients subjected to surgery. Overall, there are a lot of thick and dark connections with ciprofloxacin (J01MA02) and similar group J drugs.

In addition, corticosteroid for systemic use (H02) is represented in four nodes making it the most prevalent drug class from chapter H (80% of drugs from chapter H). While the analysis does not present evidence that the indication for corticosteroids in these cases were allergic reactions, it is worth noting that voriconazole (J02AC03) pairs with corticosteroid for systemic use (H02). Voriconazole is a systemic antimycotic drug with a narrow therapeutic index often used to treat invasive aspergillus in immunocompromised patients.

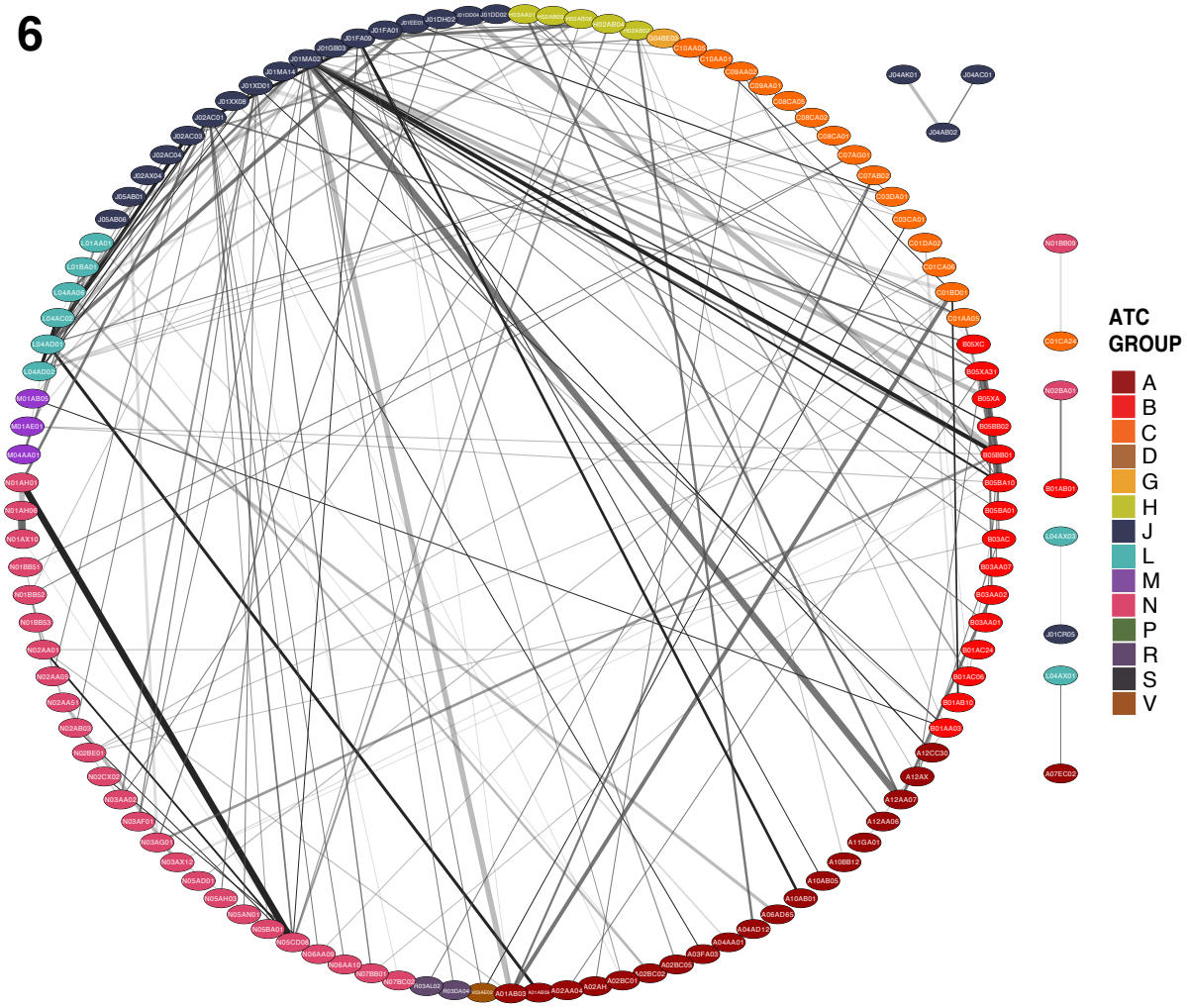

Figure 6: Circle network overview of pADEs by drug pairs. Line thickness correlate to the total number of pADEs detected using the model shown in figure 2, while the coloring corelates to the known severity of the drug interaction in accordance with the Danish Drug-Drug interaction database (lighter= less severe, darker= more severe). Data used to create this figure are provided in supplemental table 3. Only pADEs with HR>3 are included in this figure; any interactions that were known to not cause side effects (level = "ingen") were removed. A minimum of 4 pADEs were also required for each pair to be included in this visualization. Full legend provided in supplemental figure 1.

Another interesting pair is the amiodarone (C01BD01) and metronidazole (J01XD01), which has no documented DDI warning (therefore hidden from Figure 6) but has 46 pADEs listed in supplemental table 3. Owing to the risk of pro-arrythmias, amiodarone treatment is typically initiated under tight monitoring[38]. The fact that co-administration of amiodarone and metronidazole correlates with many abnormal blood tests might indicate that administration of amiodarone to infected patients presents yet another risk.

To assess if the trends identified in the present study were also reflected in drug dosage changes, we compared the 694 pairs defined as pADE in the present study with the potential undescribed

drug interaction pairs identified by Rodríguez et al.[24] Of the 694 pairs, there were 357 that were also identified as pADE in the present study. The most prevalent pADE was ampicillin and dexamethasone, which was also described by Rodríguez et al. The fact that this drug combination was identified in both studies is consistent with the fact, that infections and inflammatory responses are not necessarily trivial to distinguish in clinical practice. For example, in cancer patients you would expect dexamethasone discontinuation, if antibiotics (e.g. ampicillin) is initiated. We also noted that the co-administration of, for example, morphine and insulins was overlapping in the two datasets.

4. Discussion

In this study, we have developed and presented an approach that systematically assesses correlations of drug impact on laboratory test results for secondary care patients managed at hospitals. Outcomes shown in Figures 3 and 4 present positive control cases of the model providing initial validation for the statistical approach. These results build the foundation for Figure 5 where the model directly compares pADEs for male vs female patients in cases where one sex experiences a significant risk as compared to the other sex. Notably inflammation markers were most consistently different between sexes which has been established in the literature previously.[35–37] This is important because it highlights that the physiological response to drugs can be fundamentally different between sexes, emphasizing the need for improved representation in clinical trial approval protocols. Drugs have historically been mostly approved using men as test subjects and additionally at a singular dose, regardless of BMI or other differing features.[39] Reasonings from these findings, with similar findings in the literature, suggest that in several instances it is likely that physicians are over or under medicating females as opposed to their male counterparts for the same disease.[40] Further, since gender changes are included in this dataset starting from 2014, it is possible that there are some hidden transgender population trends that would be interesting to investigate separately once a more robust data set is developed. Transgender populations are often identified as a group that suffers greatly from health disparities and as such should be a focus in similar studies going forward as data availability increases . At this time, we are also unable to stratify by race or ethnicity in this dataset, but this would be an important future research question as well.

In Figure 6, the first attempt is made to model pADEs driven by concomitant therapies using a multi-state Cox model, whose use is validated using the monotherapy model presented here and confirmed results in Figures 3-5. Figure 6 takes a network view of drug pairs already known in the Danish DDI database and overlaid with the results generated in the model overviewed in Figure 2. These results open the door for future applications of this method where specific sub-groups of patients can be compared for increased risk of certain ADEs, better informing their physicians when determining the proper therapeutic approach to follow. Additionally, the polypharmaceutical model captures pADEs at both the monotherapy and polypharmaceutical level in the same statistical test, allowing for more direct assessments for additive, synergistic, or antagonistic drug pairs.

While still a preliminary approach, this study demonstrates the potential for identifying and alerting authorities more efficiently to possible DDIs that are yet unknown especially when new drugs enter the market. Technically, we introduced model restrictions in the multistate Cox models

(cf. Methods) to reduce the impact of potential bias from the physicians who had already seen and reacted to the respective patient's symptoms or side effects, effectively focusing the model on pADEs associated to first time drug exposures. We further identified overlapping trends in lab values and drug dosage changes, which exemplifies a novel way of assessing potential drug effect and adverse drug effects. In a population with an increasing age and prevalence of polypharmacy, we argue that it is of uttermost importance to develop methods for monitoring drug effects.

The method also provides the foundation for a tool for exploring which targets and mechanisms of action are more prone to severe ADEs and can therefore be studied more thoroughly when testing new drugs in the pre-clinical phase, as to avoid costly human trials that eventually may end in the removal of drugs from the market.

In summary, this study presents the first retrospective study investigating how a patient's laboratory data history can be used to investigate possible drug-induced biochemical changes within specific population groups, improving their safety and health in the long run. Further potential benefits include reduced hospital admittance for the treatment of these same ADEs, reducing both the cost and physical/mental toll on these patients.[42]

Supplemental material

Supplemental material is available at https://github.com/vmuse12/ADE_data

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