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Previous drug exposure in patients hospitalized for acute liver injury: a case-population study in the French national healthcare data system.

Running title: Drug-induced acute liver injury

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The present paper is a product of the EPIHAM Project that was submitted for public funding by the Bordeaux PharmacoEpi research Team, and served as support for the Eu2P PhD project of Prof Sinem Ezgi Gulmez. Prof Nicholas Moore had the original idea and supervised the project. Cécile Droz-Perroteau was the chief operating officer, discussed the study background and coordinated study logistics. Adeline Grolleau was the operational study manager, and collaborated to draft the manuscript. Régis Lassalle was the chief statistician and data manager. Vanessa Barbet and Mai Duong provided data-management and statistical analyses. Nicolas Thurin is a scientific adviser, and he contributed to the selection algorithm of the cases. Stéphanie Duret developed this specific analysis, collaborated to draft the manuscript.

All authors contributed comments and approved the final version of this paper.

Key Points:

- Liver Injury and in particular Acute Liver Injury (ALI) is an important source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- studies based on clinical identification of hospitalized cases rarely include more than a few hundred cases.
- The EPIHAM study provides information on the drugs associated with the greatest burden of ALI, and drugs with the highest individual associated risk, over the whole French population over 5 years. Most of these drugs are well known to be able to cause liver injury.

Abstract

Introduction: Acute liver injury (ALI) is a major reason for stopping drug development or removing drugs from the market. Hospitalisation for ALI is relatively rare for marketed drugs, justifying studies in large-scale databases such as the nationwide *Système National des Données de Santé* (SNDS) that covers 99% of the French population

Methods: SNDS was queried over 2010-2014 for all hospital admissions for acute toxic liver injuries not associated with a possible other cause, using a case-population approach. Exposures of interest were drugs dispensed from 7 to 60 days before date of admission. Individual drugs were analysed by their frequency (if ≥ 5 cases), and by the ratio of exposed cases to the number of exposed subjects and to exposed patient-time in the general population over the same time-frame.

Results: Over 5 years, 4,807 cases of ALI were identified, mean age 54.5, 59% women, 76% exposed to at least one of 249 different drugs. Drugs most commonly identified were non-overdose paracetamol (31% of cases), esomeprazole or omeprazole (18%), phloroglucinol, domperidone, coamoxiclav, furosemide, atorvastatin (more than 250 cases each). When compared to population exposures, the highest per-person risks were observed with antimycobacterial antibiotics with 1 case for 1,000 or fewer users, followed by colestyramine and erythromycin (around 1/5,300), antiepileptic drugs, anticoagulants, anti-Alzheimer drugs (1/6,000 - 1/10,000 users). When a person-time approach is considered, the drugs with the highest per-tablet risk were still the antituberculosis drugs followed by a number of other antibiotics.

Conclusions: This nationwide study describes drugs associated with ALI, according to absolute population burden, to per-patient and per-tablet risk. Some of these associations may be spurious, others causal, and others yet were unexpected. Systematic analysis of drug classes will look for outliers within each class that could raise signals of unexpected hepatic toxicity.

Keywords: Acute liver injury, case-population, drug exposure, claims database, pharmacoepidemiology.

1. Introduction

Liver Injury and in particular Acute Liver Injury (ALI) associated with medicines (drug-induced liver injury (DILI)) is a major source of regulatory action, of hospital admissions and burden of care [1-7]. Many drugs have been shown to cause or are suspected of causing liver injury, such as paracetamol, anti-mycobacterial drugs, erythromycin, or Valproic acid [8-10]. DILIs can range from simple elevation of liver enzymes, to acute liver failure leading to death or liver transplantation [11, 12]. A previous European study (SALT) of acute liver failure leading to liver transplantation (ALFT) in 7 countries over 3 years and confirmed that many drugs are involved in ALFT [1-3, 13]. The majority of the DILIs are not just acute liver failure or necrosis resulting in transplantation, but result in hospital admissions for ALI.[9]. Studies based on clinical identification of hospitalized cases often concern only a few hundred cases [14-16]. A study conducted in Thailand in the nationwide hospital admission database identified 6515 patients hospitalized with drug-induced liver injury, or drug intoxications (using the ICD-10 codes K71 and T36-T65), among which 33.5% were acute hepatitis [17]. This study confirmed well-known associations but also some unexpected ones. A preliminary study in the French Claims database 1/97th sample EGB confirmed the feasibility of such a study, but also the need of accessing the full *Système National des Données de Santé* (SNDS) database that includes 99% of the French population [18, 19]. EPIHAM (epidemiology of acute liver injury from medicines), the study described here, identified all hospital admissions for ALI in SNDS over 5 years, not related to acute drug overdose or other clinical causes. Exposures identified from drug dispensing in these patients were compared to drug utilisation in EGB, using the case-population approach [2, 20]. From these data, we identified the drugs most often associated with ALI, and those with the highest apparent risk.

2. Material and Methods

This was a case-population study in the French National Healthcare System Claims Database.

2.1. Data sources

This study was done in the *Système National des Données de Santé*, (SNDS), and its random permanent representative 1/97th sample, *Echantillon Généraliste de Bénéficiaires* (EGB). SNDS currently includes 66.6 million people (99% of the French population) [19]. SNDS (and its sample, EGB) contains information on (i) general demographics (gender, year of birth, region of residence, date of death but not cause of death), (ii) outpatient healthcare claims, with dates and codes for medical and other healthcare professionals visits, medical procedures, lab tests and other exams (but not results), drugs and medical devices, (iii) registration for a list of 30 long-term diseases (LTD) and their associated International Classification of Diseases 10th revision (ICD-10) codes allowing patients to receive full reimbursement for expenditure related to LTD, and (iv) hospital discharge data, which include start and end dates for all medical, obstetric and surgery hospitalizations, medical procedures, cost coding system, and the medical unit data when the patient is hospitalized successively in several medical units. The hospital discharge summary includes ICD-10 codes for main, related and associated diagnoses for all hospitalizations. The main diagnosis is the health problem that motivated the admission in the hospital, determined at hospital discharge. The related diagnoses exist if the main diagnosis is a procedure for a chronic or LTD disease and indicates the disease at the origin of the procedure. The associated diagnoses represent specific healthcare status modifiers, mainly underlying chronic diseases [21].

Hospital discharge ICD-10 codes are based on definitions. They are routinely coded by the physicians in charge of the patient, based on clinical data, assisted by trained professional medical information technicians who verify the codes to ensure consistency, with national

coding instructions and manuals. The medical information departments in the hospitals that are in charge of the quality of the coding conduct random validation checks on the diagnostic codes that are used, in addition to training programmes. This is part of the National accreditation and certification process for the Hospitals that includes the completeness and exactitude of the coding process. [22] The national Healthcare insurance system, which pays the hospitals and clinics based on disease or diagnosis-related groups (DRG) regularly audits these codes and may levy large fines in the case of discrepancies. Certain individual diagnoses have also been subject to validation studies, such as heart failure, stroke, coronary heart disease, or other diseases, which have found positive predictive values around 70-90% [21, 23-26], consistent with the national effort at coding quality.

2.2. Study design

The EPIHAM study was a case-population study in a claims database [19]. This approach consists in the comparison of exposure rates to a given drug in subjects presenting an event of interest (cases) with the exposure rate in the source population (reference population), as previously described [20, 27-29].

2.3. Definition of cases

Cases of ALI were identified and extracted over 5 years from SNDS, defined as patients aged 18 years and over with a first hospital admission for Acute Liver Injury (ALI) between 1 January 2010 and 31 December 2014. The date of first admission for ALI was considered as the index date. Hospitalization for ALI was defined as hospitalization with a main diagnosis ICD-10 code for acute toxic liver injury (K71.1, K71.2, K71.6, K71.9) or hepatic failure (K72.0), without previous hospitalization for ALI. If a patient had several hospitalisations for ALI over the study period, only the first was considered.

Exclusion criteria included:

- Any diagnosis code for non-drug-related liver disease or potential liver injury during the hospitalization of interest or in the previous 60 days as identified by the ICD-10 codes for associated, related or main diagnosis: chronic viral hepatitis (B18), malignant neoplasms (all C codes), mental and behavioural disorders due to use of alcohol (F10), other degenerative diseases of nervous system, not elsewhere classified (G31), heart failure (I50), portal vein thrombosis (I81), oesophageal varices (I85), alcoholic liver disease (K70), fibrosis and cirrhosis of liver (K74), other diseases of liver (K76), cholelithiasis (K80), other diseases of biliary tract (K83), ascites (R18), presence of cardiac and vascular implants and grafts (Z95), liver transplant failure and rejection (T86.4)
- Hospitalization with a diagnosis of liver transplant status in the previous 60 days (ICD-10 code for associated, related or main diagnosis: Z94.4);
- A diagnosis of poisoning during the hospitalization of interest and the concomitant stays (ICD-10 code for associated, related or main diagnosis: from T36 to T50).

Patients with at least one of the following criteria were also excluded from the analysis:

- Patients without health care usage, or not affiliated to the national healthcare insurance system during the year before hospitalization for ALI,
- Patients with no history or less than 60 days of history in the database before the first hospitalization for ALI,
- Patients with previous hospital stay for chronic liver disease (alcoholic cirrhosis, chronic hepatitis, alcoholics or malignant neoplasm (pancreatic or hepatobiliary)),

- Patients with a medical procedure including endoscopies, diagnostic procedures, or related to HIV disease during the first hospitalization for ALI,
- Patients with hospitalization (whatever the main diagnosis) ending within the previous 30 days, or starting more than 7 days before the first hospitalization for ALI, because the database does not contain information on the use of routine drugs in hospital, so that exposure in such cases could not be ascertained.

2.4. Definition of reference populations

The reference population was identified in the EGB database as all subjects aged 18 years and over. The total exposed population for each drug of interest was estimated from the number of patients dispensed that drug at least once during the study period. That number was extrapolated to the general population based on the age and gender structure in France at each considered year according to data published by the French national institute of statistics (*Institut National de la Statistique et des Etudes Economiques, INSEE*) [30].

In this situation, EGB is a convenience sample that is readily accessible, and is representative of the contents of the whole SNDS database. EGB has been used similarly for the case-population study of liver transplantation [2, 20, 29], for the feasibility study of EPIHAM [18], for other drug utilisation studies [31, 32], as well as for many other studies. In the present design it was clearly not feasible nor useful to ask for drug utilisation data in 66 million persons for each of the 200+ drugs identified.

2.5. Definition of exposure

Drug exposures in cases were defined as at least one recorded dispensing within the 7-60 days period before the index date. The 7-day lag time was chosen to minimise protopathic (drug

given for the symptoms of hepatic injury) and indication bias (drugs given for a disease that causes hepatic injury). The first would typically be antiemetic agents early before the onset of clinical hepatitis, the latter the use of loop diuretics in acute heart failure resulting in "cardiac liver".

Drug exposures in the reference population were defined according to two different metrics;

- As number of subjects with at least one drug dispensing during the study period, as might be recommended for idiosyncratic liver injury, which occurs in susceptible individuals early in the treatment [20] [33]

- As total number of Defined Daily Doses (DDD) dispensed over the study period. This corresponds to the more classical person-time approach [27], which would be appropriate to drugs with a direct, cumulative toxicity, but which probably overestimates risks for drugs with mostly short-term use [20].

Drugs of interest were identified by their anatomical therapeutic chemical (ATC) codes at the various levels, from drug classes (3 digit code, e.g., A02; drugs for acid related disorders), to the 4 digit chemical class, (e.g. M01A NSAIDs) to the 7-digit individual product code (eg, N02BE01 paracetamol). Classes, families and drugs of interest were identified by the frequency in the cases.

2.6. Statistical analyses

ALI cases were described, using standard statistical metrics for quantitative and qualitative variables.

Event rates of ALI for each drug, family or class of interest were estimated as the total number of cases exposed to the drug within 7-60 days before ALI to the total number of patients exposed during the study period, with their 95% Poisson confidence intervals, and to the total number of DDD dispensed over the study period with their 95% Poisson confidence intervals

Drugs, families or classes with fewer than 5 exposed cases were not analysed.

For descriptive purposes, the instant and cumulative hazards were determined for the typical hepatotoxic drugs valproic acid and erythromycin as representative of different toxic mechanisms, using duration of exposure previous to index date for cases, and distribution of exposure durations from the reference population. Cumulative incidences were assessed using the Kaplan-Meier method.

All Statistical analyses were carried out using SAS software versus 9.1 (SAS Institute, Cary, NC).

2.7. Regulatory aspects

In accordance with the French regulations, this study received authorization from the Institute of Health Data (Institut des Données de Santé) and from the French data protection commission (Commission Nationale de l'Informatique et des Libertés). This study was registered with ENCEPP (www.encepp.eu), at the European Medicines Agency (EMA, London, UK) with the registration number ENCEPP/SDPP/7549.

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3. Results

3.1. Characteristics of the cases

Over the study timeframe, 4,807 adult cases of hospitalized ALI were identified (Figure 1), 61.4% with acute toxic liver injury and 38.6% with hepatic failure (K72.0). More than half of the cases were women (58.7%). The mean age was 54.5 years (SD \pm 19.8), compared to an average age of the French population of 40.4 years. Among these cases, 47.8% had at least one registered chronic disease. The most common (\geq 5%) were diabetes (10.6%), chronic psychiatric disorders (9.1%), and malignant tumours, malignant lymphatic or hematopoietic tissue diseases (6.7%). Nearly all cases (97.6%) had at least one consultation or medical visit within 12 months before the index date, and most of them had seen their general practitioner (83.4%). The average number of medical visits within 12 months before the index date was 11.9 (SD \pm 10.8), the mean duration of ALI hospitalization was 6.9 days (SD \pm 7.1) and 79.8% of the cases had one or more associated diagnoses at index date (Table 1).

3.2. Exposures

There were 249 different drugs of interest with at least one dispensing within 7-60 days before index date in 3,633 ALI cases (75.6%), with at least 5 cases exposed per drug (Figure 2). The most frequent ATC classes or families were analgesics (N02, 40.6%), drugs for acid related disorders (A02, 31.6%), anxiolytics or hypnotics (at least one N05B or N05C, 23.6%), antibacterials for systemic use (J01, 23.1%), agents acting on the renin-angiotensin system (C09, 20.0%), lipid modifying agents (C10, 18.7%), antithrombotic agents (B01, 18.2%), NSAIDs (M01A, 17.0%), psychoanaleptics (N06, 16.6%) and drugs for functional gastrointestinal disorders (A03, 15.3%).

3.3. Most common exposures

The drugs (ATC with 7 digit code) most frequently dispensed within 7-60 days period before ALI were paracetamol with 1,495 cases (31.1% of all cases), esomeprazole (10.4%), omeprazole (8.5%), phloroglucinol (6.5%), domperidone (6.2%), amoxicillin in combination with enzyme inhibitors (6.1%), furosemide (5.9%), atorvastatin (5.5%), pantoprazole (5.1%) and zolpidem (5.1%) (Table 2).

Some drugs were those widely dispensed both in cases and in the general population such as furosemide (284 cases), atorvastatin (263 cases) and bisoprolol (210 cases), with relatively high event rates around one case for 15,000 exposed patients.

3.4. Drugs with highest event rates per patient

The drugs with the highest event rates (exposed cases per exposed population) of ALI were antimycobacterials (J04). The combination of rifampicin, pyrazinamide and isoniazid was the highest ranked drug with one hospital admission for ALI in 578 exposed patients, followed by pyrazinamide alone (one case for 770 exposed patients), ethambutol (one case for 825 exposed patients), isoniazid (one case for 1,281 exposed patients) and rifampicin-isoniazid combination (one case for 1,928 exposed patients) (Table 3). The 25 highest ranked drugs also included colestyramine (one case of ALI for 5,312 exposed patients), erythromycin (one case for 5,374 exposed patients), cibenzoline (one case for 6,452 exposed patients) or methyldopa (one case for 6,719 exposed patients). Among these drugs one also finds antiepileptics (oxcarbazepine, phenobarbital, carbamazepine, valproic acid, and lamotrigine) with 1 case for 8 to 10 000 patients treated; anti-Alzheimer drugs rivastigmine, memantine, galantamine with 1/11000 to 1/12000 patients, and anticoagulants acenocoumarol and warfarin (around 1/11000 patients), and a number of drugs used to treat heart failure, such as

isosorbide mononitrate, carvedilol, betaxolol, captopril, which could suggest miscoding of heart-failure associated hepatic injury, or heart failure as a risk factor for drug-related ALI. These top 25 drugs were among the drugs with the lowest numbers of exposed cases, 71 or fewer.

3.5. Drugs with the highest event rate per patient-time

A common measure of exposure is patient-time rather than patients as presented in table 4. The drugs with the highest rate of ALI per DDD are the same as those per patient, i.e. anti-tuberculosis drugs. 21 out of the 25 drugs with high per-DDD event rate were antibacterial agents, with event rates below 1 case per million DDD. These are drugs with short treatment duration: in this case the number of patients per DDD is highest, which could explain such high per DDD risk if the event is not dose/duration dependent but patient dependent (idiosyncratic) [20].

3.6: Hazard functions

Comparing drug utilisation patterns in cases and the general user population may give indications on hazard functions and possible mechanisms of drug toxicity. As examples, we chose to consider erythromycin and valproic acid: the former is a typical type B (idiosyncratic) reaction, with a risk that is maximal at 10 days of treatment, and decreases thereafter (Figure 3). The initial zero-risk period between the date of dispensing and the index date for ALI is related to the 7-day exclusion period: none of the dispensings during these 7 days are considered (zero-exposure bias, akin to immortal time bias).

During valproic acid exposure, on the other hand, the risk of ALI was constant over time, so that the cumulative risk increases with duration of exposure (Figure 4).

4. Discussion

4.1. Main results

This population-based study provides a countrywide assessment of patients admitted for toxic acute liver injury, and the drugs dispensed during a period that would provide exposure that is compatible with a causality of the drug in the event (RUCAM) [34, 35]. In this initial report we describe individual drugs most concerned and a general overview of the possible use of such an approach for alert generation purposes, including the overall population burden of ALI for individual drugs by the absolute number of cases that were exposed to the drug of interest, and for the individual risk by the number of patients dispensed the drug for each case of ALI.

The diagnostic criteria we chose for ALI were rather restrictive: all cases with indications of a possible other cause were excluded, based on main, associated or secondary hospitalisation diagnosis or chronic disease ICD10 codes indicative of for instance alcoholic liver disease, other toxins, viral diseases or other clinically defined causes for liver injury. For legal privacy reasons we are not allowed to return from the recorded diagnoses to the individual patient files so that we have to rely on the quality of hospital diagnoses and coding.

Though errors may of course be possible and certainly occurred, it may be thought unlikely that they would be affected by drug exposure, though certainly exposure to known hepatotoxic drugs may have resulted in wrongly attributing the ALI to the exposure rather than to another cause, for instance viral. This is unlikely: viral tests are systematic at admission for ALI. On the other hand, drugs not thought to be associated with ALI, and that may not be cited in clinical files or spontaneous reports, will be identified from dispensing data.

Drugs whose first dispensing was within 0-7 days before the date of hospital admission were excluded. Hepatic lab tests before index date were done within 7 days before hospital admission, which could indicate that the hepatic symptoms started before that date. Drugs with a first dispensing after that day could have been prescribed because of ALI symptoms (protopathic bias). Indeed, drugs most often first dispensed within 7 days before index date were symptomatic medications (analgesics, antiemetics, propulsives) that could be related to the symptoms of hepatic injury (abdominal pain, nausea or vomiting, dyspepsia). This does not formally exclude that they may have been involved in the occurrence of ALI, but the chance of bias is such that we preferred to exclude them in a first analysis. This does not concern drugs that may have been renewed within the 0-7 days timeframe, but had already been prescribed before.

Our results are generally consistent with expectations [16, 36]: the drug most commonly dispensed between 7 and 60 days before admission for ALI was paracetamol with 1,495 cases, the drug by far the most dispensed in France [31]. Paracetamol was present in more than 30% of all ALI cases, with one case per 35,000 persons dispensed paracetamol at least once in 5 years. Other drugs often found before ALI were the proton pump inhibitor omeprazole (or esomeprazole, its active isomer), for 910 cases altogether (19%) and one case per 35 000 users of either. Phloroglucinol, and domperidone are drugs used for symptoms of the digestive sphere that may be associated with ALI, and for which further analyses will be needed to elucidate the exact chronology and likelihood of protopathic bias, also called reverse causality, a drug being prescribed for the event studied rather than causing it. Further down the list, drugs are found that are known to cause known liver injury and probably escape protopathic bias such as amoxicillin+clavulanic acid, furosemide or atorvastatin. Of course the absolute number of cases is not indicative of increased hepatotoxic risk per se, just that the

drugs may be widely used. These drugs are among the most frequently used, such as paracetamol (52 million exposed adult patients over 5 years, i.e., most adult population), coamoxiclav (19 million users), ibuprofen (26 million users), desloratadine (13 million users) or ketoprofen (19 million users). They did not head the ranking for event rates, with fewer than 7 cases per 100,000 exposed patients, or 1 case for 14,000 exposed patients. The large numbers of hepatic events may however impact overall medical resource utilisation and should be considered in the overall risk-benefit ratio of similar drugs.

To have an indication of the actual risk with individual drugs, one needs to turn to per-user event rates. Of course this is only indicative, and any attempt to compare drugs should be extremely cautious, using the appropriate adjustment methods and a good knowledge of the disease states the drugs are prescribed in. Different drugs are prescribed to different patients with different susceptibilities to liver injury related to patient backgrounds and to the diseases treated. However, within drug families, which share common indications and are used in similar patients, there may be no major differences in the patients or only few confounders. Different event rates may raise signals of possible concern, and may lead to further explorations. For instance, the first drugs for events per patient are the antimycobacterial drugs, where ALI occurs in one out of 600 to 2,000 exposed patients. Antimycobacterial drugs are known to be hepatotoxic. Rifampicin alone may be less toxic than the others. The next drug by importance of risk is colestyramine, one in 5000 users. Of course colestyramine is given for pruritus in chronic jaundice, which might also suggest protopathic bias or at least a risk factor for acute injury. This will certainly warrant further exploration to test what other drugs may have been associated with colestyramine in these cases. It has been reported as an antidote to paracetamol, [37, 38] and is used to facilitate the elimination of toxins. However increased transaminases have also been reported, but without overt liver injury. [39]

Among the well-known hepatotoxic agents one finds methyldopa (1/6,700), the antiepileptic drugs carbamazepine, oxcarbazepine, phenobarbital, valproic acid, and lamotrigine, all with around one case in 7-9 000 patients. Drugs used in heart failure (isosorbide mononitrate, carvedilol, or betaxolol) with 1/10-11,000 patients suggest potential confounding by indication, and the possibility of misdiagnosed heart failure and cardiac liver disease. Warfarine and acenocoumarol have the same event rate (1/11,400), but fluindione and the direct acting anticoagulants do not appear in this list. The anti-Alzheimer drugs memantine, rivastigmine, galantamine also appear together with around one case in 12 000 exposed patients, a toxicity also previously described with tacrine [40].

Erythromycine, with one case in 5,400 patients, is the only macrolide in this list. The first descriptions of erythromycin hepatotoxicity date back to the early 1960's [41]. Hepatotoxicity seems to have been associated with all its esters or salts [42]. There have been recent meta-analyses of the hepatic risks of antibiotics or macrolides within the European IMI-Protect project, but not comparing the individual drugs [43, 44]. Further analyses will be needed to verify whether the apparent risk we found is related to uses of erythromycin in patients at high risk of ALI, or whether it is a specific risk of the drug, different from the other macrolides, in which case the real benefits of this ancient drug might need to be reconsidered.

4.2. Strengths

The main strength of our study is its power: studying 5 years of hospital admissions for ALI in a whole country database yields a much greater number of cases than previous studies, enabling the study of over 200 different drugs.

The study population was exhaustive and representative of the French population, through data sources that cover nearly all the country's population. Because this database was not set

up for this study, neither selection bias nor recall bias should be an issue. The case-population design has been proven feasible, adequate, and efficient by the SALT study, even on a wider scale, for ALFT, a very rare event with 100% ascertainment rates [2, 3, 20]. Selection bias was also reduced by the choice of inclusion and exclusion criteria that provided an accurate definition of acute hepatotoxicity from medicines. The defined exposure period reduced protopathic bias, as drugs dispensed in the 7 days before hospital admission for ALI could have been prescribed to relieve the symptoms of liver failure.

Since the drug utilisation patterns can be described in cases and the reference populations, it is feasible to compare the drug dispensing patterns in cases compared to the general population and derive hazard function curves.

4.3. Limitations

As all claims and hospital admissions databases, there are limitations.

The first concerns the diagnosis of acute liver injury. Because we cannot identify patients from the database, we cannot directly validate the diagnoses, and have to rely on hospital coder proficiency and professionalism. The basic coding is generated by hospital personnel, usually for statistical and billing purposes. In recent years, professional coders have been deployed in some hospitals, mostly to ensure the quality and consistency of coding and the proper coding of associated diagnoses. There are national coding instructions for various diseases, to ensure homogeneous coding over the thousands of hospitals concerned.

The algorithms we used excluded other causes of acute liver injury, such as viral diseases, non-drug toxicity (chemical, plants), cardiac disorders, Budd-chiari syndrome and other vascular diseases, as well as acute drug intoxications, especially paracetamol. In addition to the codes used for the main diagnosis, other information such as secondary codes, or

indication of chronic disease or alcohol related disorders were used to exclude cases. Hospital stays for whatever reason within the 7-60 days before ALI were also a reason for exclusion, since during the hospital period there is no indication on drug exposures, so that potential exposures of interest could be missed.

Exposure was measured by drug dispensing, which is one step closer to actual exposure than prescriptions or electronic health records. Ideally one would want to have direct contact with the patient, knowing that even that is sometimes uncertain [45, 46]. Though most claims databases cannot identify OTC drugs, in France over 84% of the paracetamol and 70% of analgesic strength ibuprofen is prescribed and identified in the database [31, 32, 47]. Drug dispensing is specific and precise, in that only commercial preparations are dispensed, indicating the exact number of tablets, and their individual strength, so that the total quantity of drug that is dispensed is known.

Further analyses will consider individual drug classes (e.g., NSAIDs, antidepressants, antiepileptic drugs or antibiotics, as well as different analytical strategies, beyond the case-population approach used here, such as case-control, case crossover or self-controlled case series. These will be used to compare event rates or odds ratios of different drugs within the same indications or drug families.

4.4. Future developments

Such a resource may be used to test known hepatotoxic drugs, compare marketed drugs within drug families, and confirm the validity of the method. A potential use could also be for early recognition of drug alerts of hepatotoxicity, once the background rates of hepatotoxicity have been established for drug classes or clinical situations. We voluntarily restricted the analysis to only the drugs with at least 5 cases exposed over 5 years. This would be too

restrictive for alert generation where even one case for instance in the first years of marketing may be of interest. Early surveillance of new cases in the SNDS exposed to newly marketed drugs, may alert to the hepatotoxic potential of such new drugs. The main restriction is the data delay: the hospital data (cases) are available for a given year in the third quarter of the following year year. This may be enough for routine surveillance of new drugs, may too long for emerging acute drug alerts, and needs to be compared to the performance of the spontaneous reporting system.

5. Conclusion

To conclude, this first analysis of the collection of all toxic ALI admitted to hospital in France over 5 years already provides information on the drugs associated with the greatest burden of ALI, and drugs with the highest apparent individual risk. Paracetamol is by far the drug most often associated with hospitalisation for ALI, but it is also by far the drug most often prescribed in France, at least once in 5 years to 80% of the population. At the other end of the spectrum, antituberculosis antibiotics were by far the most hepatotoxic drugs, with the highest individual risk of hepatotoxicity, whether per patient or per DDD.

This study provides a rich source of information on suspected hepatotoxicity, which will be explored using different analytical methods. Individual drugs and drugs families will be further explored, as will be the use of this method to generate alerts. Interested researchers are invited to contribute and participate in this research.

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7. Compliance with ethical standards.

The corresponding author has full access to all of the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

7.1 Conflicts of interest

Nicholas Moore, Stephanie Duret, Adeline Grolleau, Regis Lassalle, Vanessa Barbet, Mai Duong, Nicolas Thurin, Cécile Droz-Perroteau, Sinem Ezgi Gulmez have no conflicts of interest that are directly relevant to the content of this study

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no other relationships or activities that could appear to have influenced the submitted work. Bordeaux PharmacoEpi receives funding from various pharmaceutical companies and governmental bodies to conduct research on marketed drugs at the request of regulatory authorities, or as a consequence of research grant applications. None of these concern the subject at hand.

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7.3 Ethical approval.

In accordance with the French regulations, this study received authorization from the Institute of Health Data (*Institut des Données de Santé*) and from the French Data Protection Agency (*Commission Nationale de l'Informatique et des Libertés*). This study was registered with ENCEPP (www.encepp.eu), at the European Medicines Agency (EMA, London, UK) with the registration number ENCEPP/SDPP/7549.

7.4 Patient consent

Not applicable.

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Table 1. Characteristics of cases of hospital admissions for acute liver injury cases identified in the French national health data SNDS from 2010 to 2014

	Cases
	n = 4,807
Gender – Female, n (%)	2,822 (58.7)
Age at index date (in years), mean (\pm SD)	54.5 (19.8)
At least one LTD declared before ID, n (%)	2,298 (47.8)
LTD “Diabetes type 1, diabetes type 2”, n (%)	510 (10.6)
LTD “Long-term psychiatric conditions”, n (%)	439 (9.1)
LTD “Malignant tumours, malignant lymphatic or hematopoietic tissue, n (%)	324 (6.7)
At least one transaminase test within 7 days before ID, n (%)	205 (4.3)
At least one medical visit during the 12 months before ID, n (%)	4,691 (97.6)
General practitioner, n (%)	4,008 (83.4)
Ophthalmology, n (%)	948 (19.7)
Hospital practitioner (Unknown specialty), n (%)	817 (17.0)
Gastroenterology and hepatology, n (%)	667 (13.9)
Dermatology, n (%)	591 (12.3)
Cardiology, n (%)	580 (12.1)
Anaesthetics, n (%)	552 (11.5)
Number of medical visits per patient during the 12 months before ID, mean (\pm SD)	11.9 (10.8)
ICD-10 code diagnosis of hospitalization for ALI	
K71.1 – toxic liver disease with hepatic necrosis, n (%)	392 (8.2)
K71.2 – toxic liver disease with acute hepatitis, n (%)	1,599 (33.3)
K71.6 – toxic liver disease with hepatitis, not elsewhere described, n (%)	673 (14.0)
K71.9 – toxic liver disease, unspecified. n (%)	286 (5.9)
K72.0 – acute and subacute liver failure, n (%)	1,857 (38.6)

	Cases
	n = 4,807
Duration of hospitalization for ALI (in days), mean (\pm SD)	6.9 (7.1)
Number of associated diagnoses per patient at ID, n (%)	
0	971 (20.2)
1 to 4	2,665 (55.4)
5 to 8	816 (17.0)
> 8	355 (7.4)
ICD-10 code of associated diagnoses at ID (several diseases possible – ICD-10 main chapters)	
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, n (%)	1,617 (33.6)
Endocrine, nutritional and metabolic diseases, n (%)	1,382 (28.7)
Diseases of the circulatory system, n (%)	1,117 (23.2)
External causes of morbidity and mortality, n (%)	962 (20.0)
Diseases of the digestive system, n (%)	888 (18.5)
Factors influencing health status and contact with health services, n (%)	821 (17.1)
Mental and behavioural disorders, n (%)	661 (13.8)
Certain infectious and parasitic diseases, n (%)	584 (12.1)
Diseases of the genito-urinary system, n (%)	551 (11.5)

SNDS, *Système National des Données de Santé*; SD, Standard deviation; LTD, Long-Term disease; ID, Index Date; ICD, International Classification of Diseases ; ALI, Acute Liver Injury

Table 2. Top 25 drugs dispensed within 7-60 days before hospital admission for ALI between 2010 and 2014, by number of exposed ALI.

	Number of ALI n (%) n = 4,807	Number of DDD dispensed n=119,310,075,800	Number of users over 5 years n = 65,375,384	Number of cases per million DDD [95% CI]	Number of cases per 10 000 users [95% CI]	Number of users/ case
N02BE01 - Paracetamol	1,495 (31.1)	5,219,032,555	52,020,957	0.29 [0.26 ; 0.32]	0.29 [0.26 ; 0.32]	34,797
A02BC05 - Esomeprazole	502 (10.4)	2,982,803,352	14,161,092	0.17 [0.15 ; 0.19]	0.35 [0.31 ; 0.40]	28,209
A02BC01 - Omeprazole	408 (8.5)	2,260,375,155	17,494,549	0.18 [0.16 ; 0.20]	0.23 [0.21 ; 0.26]	42,879
A03AX12 - Phloroglucinol	311 (6.5)	568,912,425	20,033,756	0.55 [0.48 ; 0.62]	0.16 [0.14 ; 0.18]	64,417
A03FA03 - Domperidone	298 (6.2)	850,851,417	13,555,192	0.35 [0.31 ; 0.40]	0.22 [0.19 ; 0.25]	45,487
J01CR02 - Amoxicillin and enzyme inhibitor	293 (6.1)	724,464,594	19,059,269	0.40 [0.35 ; 0.46]	0.15 [0.13 ; 0.18]	65,049
C03CA01 - Furosemide	284 (5.9)	3,432,035,850	4,284,346	0.08 [0.07 ; 0.09]	0.66 [0.58 ; 0.76]	15,086
C10AA05 - Atorvastatin	263 (5.5)	3,839,738,298	4,140,201	0.07 [0.06 ; 0.08]	0.64 [0.55 ; 0.73]	15,742
A02BC02 - Pantoprazole	245 (5.1)	1,130,527,478	8,622,136	0.22 [0.19 ; 0.25]	0.28 [0.25 ; 0.33]	35,192
N05CF02 - Zolpidem	244 (5.1)	1,623,764,111	6,741,764	0.15 [0.13 ; 0.17]	0.36 [0.31 ; 0.42]	27,630
N02AA59 – Codeine combinations	236 (4.9)	480,605,654	15,435,944	0.49 [0.42 ; 0.56]	0.15 [0.13 ; 0.18]	65,407
M01AE01 - Ibuprofen	228 (4.7)	658,447,116	25,768,233	0.35 [0.30 ; 0.40]	0.09 [0.08 ; 0.10]	113,019
J01CA04 - Amoxicillin	223 (4.6)	924,921,578	27,387,752	0.24 [0.21 ; 0.28]	0.08 [0.07 ; 0.09]	122,815
N02AX52 - Tramadol, combinations	217 (4.5)	476,468,850	14,487,560	0.46 [0.39 ; 0.53]	0.15 [0.13 ; 0.17]	66,763
N05BA12 - Alprazolam	215 (4.5)	1,054,354,871	7,742,811	0.20 [0.18 ; 0.24]	0.28 [0.24 ; 0.32]	36,013
C07AB07 - Bisoprolol	210 (4.4)	1,483,228,124	2,977,061	0.14 [0.12 ; 0.16]	0.71 [0.61; 0.82]	14,176
N05BA08 - Bromazepam	189 (3.9)	1,092,243,431	6,312,999	0.17 [0.15 ; 0.20]	0.30 [0.26 ; 0.35]	33,402
C10AA07 - Rosuvastatin	182 (3.8)	2,294,431,995	3,705,341	0.08 [0.07 ; 0.09]	0.49 [0.42 ; 0.57]	20,359
R06AX27 - Desloratadine	182 (3.8)	1,354,186,403	12,676,021	0.13 [0.11 ; 0.16]	0.14 [0.12 ; 0.17]	69,648
N05BB01 - Hydroxyzine	166 (3.5)	458,934,834	6,194,431	0.36 [0.31 ; 0.42]	0.27 [0.23 ; 0.31]	37,316
N05CF01 - Zopiclone	163 (3.4)	1,110,657,434	4,717,977	0.15 [0.12 ; 0.17]	0.34 [0.29 ; 0.40]	28,945
N02AX02 - Tramadol	162 (3.4)	648,184,200	8,737,883	0.25 [0.21 ; 0.29]	0.19 [0.16 ; 0.22]	53,938
A02BC03 - Lansoprazole	161 (3.3)	900,407,668	6,889,923	0.18 [0.15 ; 0.21]	0.23 [0.20 ; 0.27]	42,795
A02BX13 - Alginic acid	154 (3.2)	299,064,119	7,628,487	0.51 [0.43 ; 0.61]	0.20 [0.17 ; 0.24]	49,536
M01AE03 - Ketoprofen	153 (3.2)	813,655,782	18,897,000	0.19 [0.16 ; 0.22]	0.08 [0.07 ; 0.10]	123,510

ALI, Acute Liver Injury

Table 3. Top 25 drugs (ATC code, ingredients) dispensed within 7-60 days before hospital admission for ALI with the highest ratios of exposed cases to exposed population between 2010 and 2014

	Number of ALI	Number of patients	Number of cases per 10 000 users [95% CI]	Number of users per case	Case-population ratio (users)
All cases/reference population	4807	65,375,384	0.73	13,600	1.00
J04AM05 Rifampicin, pyrazinamide and isoniazid	35	20,247	17.3 [12.0 ; 24.0]	578	23.5 [16.8-32.7]
J04AK01 - Pyrazinamide	10	7,702	13.0 [6.23 ; 23.9]	770	17.7 [9.50-32.8]
J04AK02 - Ethambutol	27	22,268	12.1 [7.99 ; 17.6]	825	16.5 [11.3-24.1]
J04AC01 - Isoniazid	14	17,940	7.8 [4.26 ; 13.09]	1,281	10.6 [6.28-17.9]
J04AM02 - Rifampicin and isoniazid	31	59,782	5.2 [3.52 ; 7.36]	1,928	7.1 [4.96-10.0]
C10AC01 - Colestyramine	30	159,373	1.9 [1.27 ; 2.69]	5,312	2.6 [1.79-3.66]
J01FA01 - Erythromycin	56	300,937	1.9 [1.41 ; 2.42]	5,374	2.5 [1.95-3.29]
J04AB02 - Rifampicin	22	139,309	1.6 [0.99 ; 2.39]	6,332	2.1 [1.41-3.26]
C01BG07 - Cibenzoline	5	32,261	1.5 [0.50 ; 3.62]	6,452	2.1 [0.88-5.06]
C02AB02 - Methyldopa (racemic)	10	67,189	1.5 [0.71 ; 2.73]	6,719	2.0 [1.09-3.76]
N03AF02 - Oxcarbazepine	9	71,005	1.3 [0.58 ; 2.41]	7,890	1.7 [0.90-3.31]
N03AA02 - Phenobarbital	17	137,193	1.2 [0.72 ; 1.98]	8,070	1.7 [1.05-2.71]
N03AF01 - Carbamazepine	41	340,863	1.2 [0.86 ; 1.63]	8,313	1.6 [1.20-2.22]
N06AB08 - Fluvoxamine	5	42,395	1.2 [0.38 ; 2.75]	8,479	1.6 [0.67-3.85]
N03AG01 - Valproic acid	71	645,763	1.1 [0.86 ; 1.39]	9,095	1.5 [1.18-1.89]
N03AX09 - Lamotrigine	27	245,831	1.1 [0.72 ; 1.60]	9,105	1.5 [1.02-2.18]
C01DA14 - Isosorbide mononitrate	8	73,373	1.1 [0.47 ; 2.15]	9,172	1.5 [0.74-2.97]
C07AG02 - Carvedilol	5	50,409	0.99 [0.32 ; 2.32]	10,082	1.3 [0.56-3.24]
B01AA07 - Acenocoumarol	21	221,980	0.95 [0.59 ; 1.45]	10,570	1.3 [0.84-1.97]
B01AA03 - Warfarin	36	400,734	0.90 [0.63 ; 1.24]	11,362	1.2 [0.88-1.69]
C07AB05 - Betaxolol	13	147,703	0.88 [0.47 ; 1.51]	11,362	1.2 [0.70-2.06]
N06DA03 - Rivastigmine	20	229,195	0.87 [0.53 ; 1.35]	11,460	1.2 [0.77-1.84]
N06DX01 - Memantine	27	311,492	0.87 [0.57 ; 1.26]	11,537	1.2 [0.81-1.72]
C09AA01 - Captopril	8	93,556	0.86 [0.37 ; 1.68]	11,695	1.2 [0.58-2.33]
N06DA04 - Galantamine	10	119,721	0.84 [0.40 ; 1.54]	11,972	1.1 [0.61-2.11]

ALI. Acute Liver Injury ATC: anatomical chemical therapeutic classification of medicines.

Case-population ratio: ratio of exposure in cases to exposure in the reference population in number of patients exposed.

Table 4. Top 25 drugs (ATC Code, ingredients) dispensed within 7-60 days before hospital admission for ALI with the highest ratio of exposed cases to patient exposure (in DDD) between 2010 and 2014

	Number of ALI	Number of DDD dispensed	Average treatment duration (days)	Number of cases per million DDD (for 5 years)	Million DDD per case	Case-population ratio (DDD)*
All cases/reference population	4807	119,310,075,800		0.04	24.8	1
J04AM05 - Rifampicin, pyrazinamide and isoniazid	35	1,178,553	58.21	29.7 [20.7 ; 41.3]	0.034	737.1 [528.6-1027.8]
J04AK01 - Pyrazinamide	10	654,693	85	15.3 [7.33 ; 28.1]	0.065	379.1 [203.8-705.1]
J04AK02 - Ethambutol	27	2,120,578	95.23	12.7 [8.39 ; 18.5]	0.079	316.0 [216.5-461.3]
J01FA01 - Erythromycin	56	7,076,693	23.52	7.9 [5.98 ; 10.3]	0.126	196.4 [151.0-255.8]
J04AM02 Rifampicin and isoniazid	31	5,929,932	99.19	5.2 [3.55 ; 7.42]	0.191	129.8 [91.2-184.8]
J04AC01 - Isoniazid	14	3,061,062	170.63	4.6 [2.50 ; 7.67]	0.219	113.6 [67.2-191.9]
R06AD08 - Oxomemazine	82	18,262,910	1.92	4.5 [3.57 ; 5.57]	0.223	111.5 [89.7-138.7]
A02BD08 - Bismuth, tetracycline and metronidazole	5	1,303,065	10.34	3.8 [1.24 ; 8.96]	0.261	95.3 [39.6-229.1]
J01XX01 - Fosfomycin	58	15,514,861	2.94	3.7 [2.84 ; 4.83]	0.267	92.9 [71.7-120.3]
J01DD04 - Ceftriaxone	37	12,088,318	6.03	3.1 [2.15 ; 4.22]	0.327	76.0 [55.0-105.1]
J01DC07 - Cefotiam	10	4,225,146	3.92	2.4 [1.14 ; 4.35]	0.423	58.9 [31.6-109.3]
J01MA07 - Lomefloxacin	14	7,601,244	4.45	1.8 [1.01 ; 3.09]	0.543	45.8 [27.1-77.3]
J04AB02 - Rifampicin	22	12,357,882	88.71	1.8 [1.12 ; 2.70]	0.562	44.2 [29.1-67.2]
C02AB02 - Methyldopa (racemic)	10	5,944,899	88.48	1.7 [0.81 ; 3.09]	0.594	41.9 [22.5-77.7]
C10AC01 - Colestyramine	30	18,169,739	114.01	1.6 [1.11 ; 2.36]	0.606	41.0 [28.6-58.7]
J01FF01 - Clindamycin	10	6,489,170	20.37	1.5 [0.74 ; 2.83]	0.649	38.3 [20.6-71.2]
J01XC01 - Fusidic acid	10	7,554,527	8.34	1.3 [0.64 ; 2.43]	0.755	32.9 [17.7-61.1]
J01EE01 - Sulfamethoxazole and trimethoprim	53	42,279,776	20.78	1.3 [0.94 ; 1.64]	0.798	31.1 [23.7-40.8]
J01FA02 - Spiramycin	14	12,660,637	8.85	1.1 [0.60 ; 1.86]	0.904	27.5 [16.3-46.4]
J01FA15 - Telithromycin	7	6,422,211	9.08	1.1 [0.44 ; 2.25]	0.917	27.1 [12.9-56.8]
A02AB03 - Aluminium phosphate	7	6,753,221	17.63	1.0 [0.42 ; 2.14]	0.965	25.7 [12.3-54.0]
J01FA07 - Josamycin	18	17,985,220	10.53	1.0 [0.59 ; 1.58]	0.999	24.9 [15.7-39.5]
J01XE01 - Nitrofurantoin	29	29,633,830	18.41	0.98 [0.66 ; 1.41]	1.022	24.3 [16.9-35.0]
J01MA02 - Ciprofloxacin	52	54,450,964	14.34	0.95 [0.71 ; 1.25]	1.047	23.7 [18.1-31.2]
J01MA06 - Norfloxacin	50	53,321,277	13.09	0.94 [0.70 ; 1.24]	1.066	23.3 [17.6-30.8]

ALI: acute liver injury; DDD: Defined daily dose; * Case-population ratio: ratio of exposure in cases compared to whole population, in DDD (person-time)

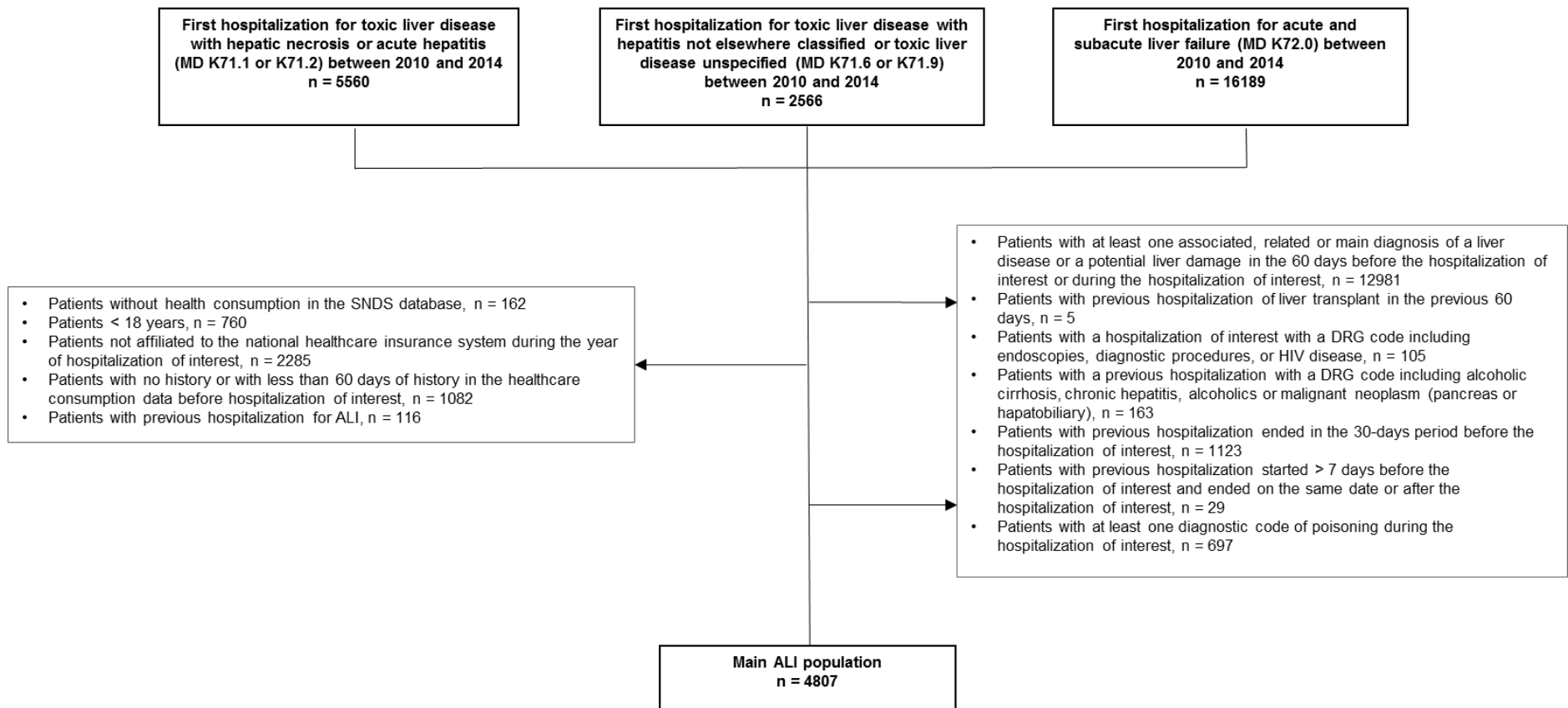


Figure 1. Flow chart of adult ALI cases identification between 2010-2014.

ALI: Acute liver injury; DRG: Diagnosis related group; ICD: International Classification of Diseases 10th revision; MD: main diagnosis, SNDS: *Système National des Données de Santé*

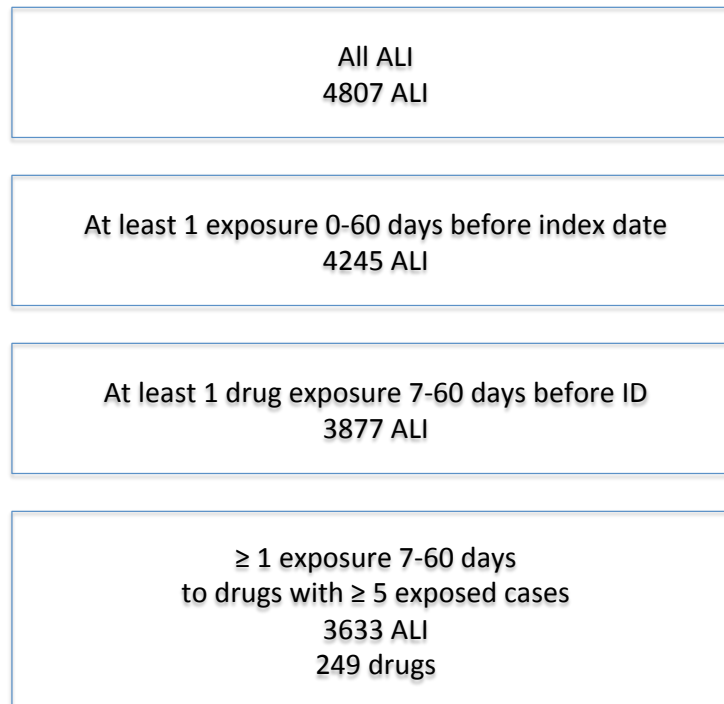


Figure 2: selection of hospitalisations for acute liver injury

ALI: Acute liver injury; ID: Index date

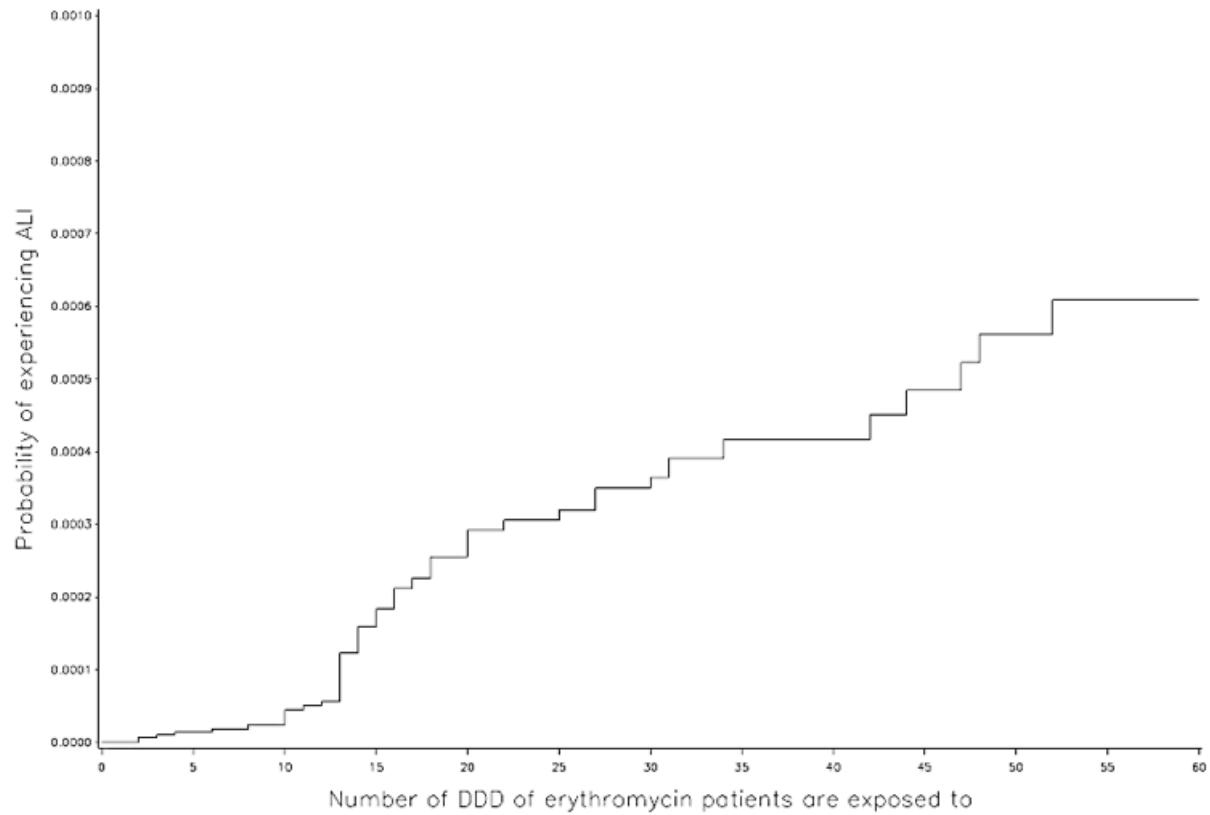


Figure 3. Cumulative incidences for erythromycin according to the number of DDD dispensed in cases and in the extrapolated reference population between 2010-2014.

DDD: Defined daily dose

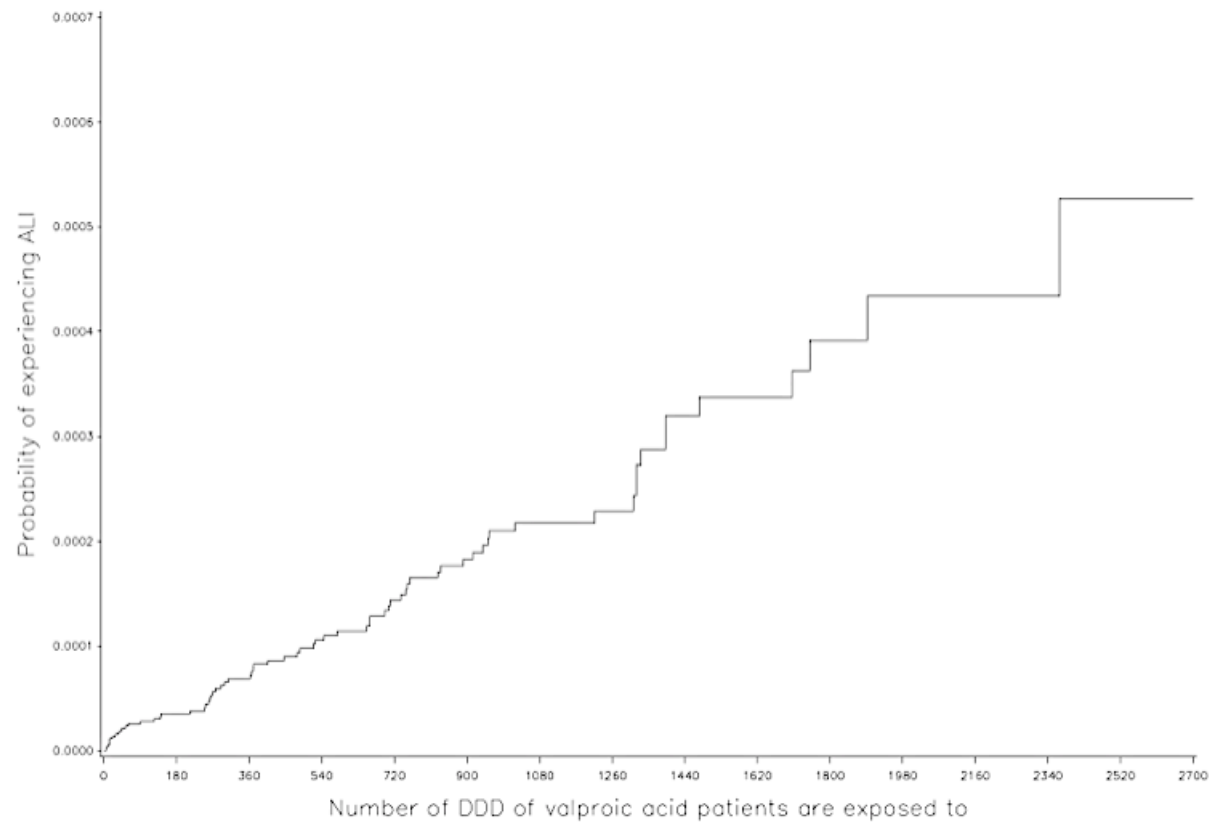


Figure 4. Cumulative incidences for valproic acid according to the number of DDD dispensed in cases and in the extrapolated reference population between 2010-2014.

DDD: Defined daily dose