Main Drug Classes Dispensed Prior To Hospital Admission For Acute Liver Injury

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Abstract

Background: Hepatic injury is a major safety issue. Most drugs and drug classes have been associated with liver toxicity. **Objectives:** To quantify exposure to different drug classes prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS. **Methods:** All hospital admissions for acute liver injury (K71.1,.2,.6,.9, K72.0) over 2009-2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were all drug classes at the highest ATC level, dispensed from 7 to 60 days before hospital admission. Reference populations were a) the French population over the study period, extrapolated from the 1/97th permanent representative sample, EGB in a case-population analysis. b) 5 controls/case from EGB, matched on age, gender, and index date, for case-control analysis. Results are provided as a) number of cases per million users (MPt) or ten thousand patient-years (TPY), with 95% confidence intervals [95%CI]; b) Odds Ratios [95% CI], compared to non-exposure. **Results:** 4807 ALI were matched to 24035 controls, with 3619 cases and 12793 controls exposed (OR 3.1 [2.9-3.4]). The greatest number of cases was exposed to analgesics (1954) followed by cardiovascular drugs (1858), the smallest was antimycobacterial (AMB, 86 cases). On the other hand, AMB were associated with by far the highest rates per MPt (399.9) and per MPY (909) and OR (72 [31-1646]) Second worst per million patients were antithrombotics (mostly aspirin) (86/MPt, 33/MPY, OR 1.54 [1.42-1.6], then cardiovascular drugs (74/MPt , 11/MPY, OR 1.8[1.66-1.94]. Analgesics including paracetamol were at 36/MPt, 88/MPY, OR 2.04 [1.91-2.18], and NSAIDs at 18.3 /MPt, 77/MPY, OR 1.4[1.28-1.52]. Drugs for functional gastrointestinal disorder and antiemetics had OR above 3, maybe reflecting protopathic bias rather than actual risk. **Conclusion:** The risk of hospital admission for hepatic injury with previous exposure to drugs was probably increased by the ICD10 codes chosen, which selected for toxic liver injury, with a three times higher exposure to any drugs in cases than in controls. Antimycobacterial had by far the highest risk of hepatotoxicity, and NSAIDs among the lowest. Data was collected for over 200 drugs.

1. *Gulmez SE, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. Drug Saf. 2013;36(2):135-44.*
2. *Gulmez SE, et al. Risk of hospital admission for liver injury in users of NSAIDs and nonoverdose paracetamol: Preliminary results from the EPIHAM study. Pharmacoepidemiol Drug Saf. 2018;27(11):1174-81.*

Declaration of Interest Statement

This study was supported by an unconditional public joint help from *Direction Générale de la Santé* (DGS), from *Mission recherche de la Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques* (MiRe-DREES) of *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAMTS*), Régime Social des Indépendants* (RSI) and *Caisse Nationale de Solidarité pour l'Autonomie* (CNSA*),* as part of the general call for projects by IReSP *(Appel à Projets, Institut de Recherche en Santé Publique)* in 2013. It was conducted by Bordeaux PharmacoEpi Platform. All authors, none declared other relationships to disclose for this study.

Background

- Acute Liver Injury (ALI) is a major source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPIHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

Objectives

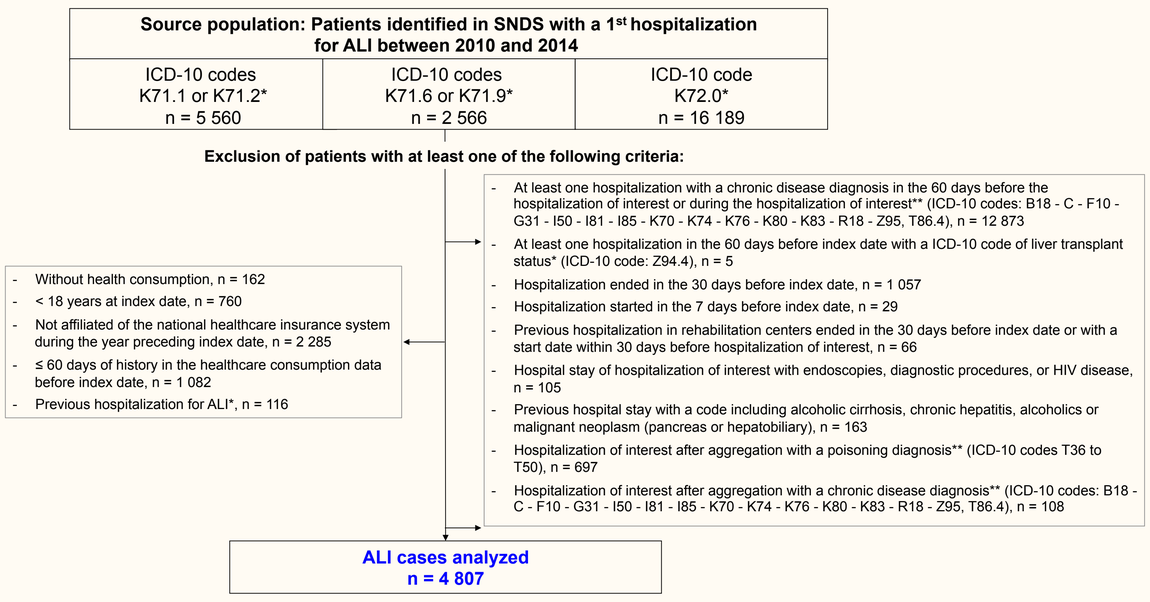
To quantify exposure to different drug classes prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database (SNDS).

Methods

- **Study design**
  - Case-population study of adults with a 1st hospitalization for ALI from 2010 to 2014.
  - Case-control study of adults exposed to interest drugs from 2010 to 2014.
- **Data source:** the SNDS French nationwide claims database which covers 99% of the French population and the EGB 1/97th permanent representative sample of SNDS.
- **Study population**
  - **Case** identified in SNDS among adult patients with a 1st hospital admission from 2010 to 2014 with main diagnosis of acute toxic liver injury (ICD-10 codes K71.1, K71.2, K71.6, K71.9) or hepatic failure (ICD-10 code K72.0) (Figure 1).
  - **Reference population** identified in EGB among adult patients affiliated at least one day for each year considered to the national healthcare insurance system for salaried workers (CNAMTS), extrapolated to the whole French population.
  - **Control** identified in EGB among adult patients affiliated to the CNAMTS and hospitalized between 2010 and 2014 for a reason other than ALI. Control were matched on age and gender using the same index date with a ratio of 5 controls / case identified (Figure 2).
- **Index date:** Date of first hospital admission for ALI.
- **Exposure**
  - **Case:** all drug classes at the highest ATC level dispensing between 7 and 60 days preceding the date of 1st hospital admission for ALI (to avoid indication and protopathic bias).
  - **Reference population:** number of patients with at least one interest drug dispensed over the study period (2010-2014), extrapolated to the whole French population.
  - **Control:** all drug classes dispensing in the same period as the identified cases.
- **Data analysis**
  - Incidence rate of ALI: number of exposed cases over the study period per million users (MP) or patient-years (MPY) with 95% confidence intervals (case-population analysis).
  - Risk of ALI in exposed patients (Odds Ratio – OR, conditional logistic regression) compared to non-exposed patients (case-control analysis).

Results

- **Identification of ALI cases – Case-population analysis**



** Main diagnosis; ** Main, associated or related diagnosis; *** Hospitalizations with a duration of 0 day or with a release "at home" were excluded from the aggregation*

Figure 1. Identification procedure of ALI cases in SNDS between 2010 and 2014

- **Exposure of adult ALI cases**
  - Considering ATC level 2: exposure ranged from 1954 (40.6%) cases for the analgesics to 86 (1.8%) cases for antimycobacterials (AMB) (Table 1).
  - Considering ATC level 5: exposure ranged from 31.1% for paracetamol to 4.7% for ibuprofen (Table 2).
- **Incidence of hospitalization for ALI**
  - Considering ATC level 2: event rates per MPY ranged from 909 [726-1124] for AMB to 18 [15-18] for RAS-acting agents, and per MP from 400 [320-494] for AMB to 13 [11-16] for antiemetics and antinauseants.
  - Considering ATC level 5: event rates per MPY ranged from 200 [175-226] for phloroglucinol to 25 [22-29] for atorvastatin, and per MP from 66 [58-76] for furosemide to 9 [8-10] for ibuprofen.

*Table 1. Main drug classes (ATC level 2) exposure of adult ALI cases within 7-60 days **preceding the index date** and incidence of hospitalizations for ALI between 2010 and 2014*

Drug dispensed (ATC level 2) within 7 and 60 days before index date	Case n = 4 807	Case / million patients [95% CI][1]	Case / million patients-year [95% CI][1]
≥ 1 drug dispensed between 7 and 60 days before index date, n (%)	**3877 (80.7)**	**73.53**	**14.7**
N02 – Analgesics	**1954 (40.6)**	**35.90 [32.15 ; 39.7]**	**87.28 [76.65 ; 94.90]**
A02 – Drugs for acid related disorders	**1521 (31.6)**	**41.18 [36.83 ; 45.61]**	**61.58 [54.75 ; 69.35]**
N05 – Psycholeptics	**1187 (24.7)**	**46.84 [41.81 ; 51.98]**	**39.25 [36.50 ; 43.80]**
At least one anxiolytic (N05B) or hypnotic (N05C)	1135 (23.6)	45.48 [40.58 ; 50.49]	42.57 [36.50 ; 47.45]
J01 – Antibacterials for systemic use	**1109 (23.1)**	**22.68 [20.24 ; 25.19]**	**133.97 [120.45 ; 149.65]**
C09 – Agents acting on the renin-angiotensin system	**963 (20.0)**	**72.18 [64.32 ; 80.27]**	**17.98 [14.60 ; 18.25]**
C10 – Lipid modifying agents	**897 (18.7)**	**69.45 [61.83 ; 77.29]**	**26.18 [21.90 ; 29.20]**
B01 – Antithrombotic agents	**877 (18.2)**	**86.06 [76.61 ; 95.81]**	**33.62 [29.20 ; 36.50]**
M01A –Antiinflammatory and antirheumatic products, non-steroids	**815 (17.0)**	**18.34 [16.31 ; 20.43]**	**75.48 [65.70 ; 83.95]**
N06 – Psychoanaleptics	**798 (16.6)**	**59.35 [52.77 ; 66.15]**	**41.71 [36.50 ; 47.45]**
A03 – Drugs for fonctional gastrointestinal disorders	**737 (15.3)**	**24.68 [21.93 ; 27.54]**	**92.91 [83.95 ; 102.20]**
R06 – Antihistaminies for systemic use	**576 (12.0)**	**20.70 [18.32 ; 23.19]**	**51.39 [43.80 ; 58.40]**
N03 – Antiepileptics	**341 (7.1)**	**57.36 [50.17 ; 65.05]**	**70.14 [62.05 ; 80.30]**
A04 – Antiemetics and antinauseants	**108 (2.2)**	**13.00 [10.66 ; 15.69]**	**223.07 [182.50 ; 270.10]**
J04 – Antimycobacterials	**86 (1.8)**	**399.94 [319.91 ; 493.93]**	**909.03 [726.35 ; 1124.20]**

[1] Taking into account the extrapolation of patient number for the reference population in the EGB database between 2010 and 2014

*Table 2. Main drug classes (ATC level 5) exposure of adult ALI cases within 7-60 days **preceding the index date** and incidence of hospitalizations for ALI between 2010 and 2014*

Drug dispensed (ATC level 5) within 7 and 60 days before index date	Case n = 4 807	Case / million patients [95% CI][1]	Case / million patients-year [95% CI][1]
N02BE01 – Paracetamol, n (%)	**1495 (31.1)**	**28.74 [25.70 ; 31.84]**	**104.55 [94.90 ; 116.80]**
At least one drug with paracetamol (N02AA59, N02BE01, N02BE51, N02BE71)	1698 (35.3)	31.84 [28.49 ; 35.24]	104.90 [94.90 ; 116.80]
A02BC05 – Esomeprazole, n (%)	**502 (10.4)**	**35.45 [31.29 ; 39.82]**	**61.43 [54.75 ; 69.35]**
A02BC01 – Omeprazole, n (%)	**408 (8.5)**	**23.32 [20.50 ; 26.32]**	**65.88 [58.40 ; 73.00]**
A03AX12 – Phloroglucinol, n (%)	**311 (6.5)**	**15.52 [13.54 ; 17.66]**	**199.53 [175.20 ; 226.30]**
A03FA03 – Domperidone, n (%)	**298 (6.2)**	**21.98 [19.15 ; 25.04]**	**127.84 [113.15 ; 146.00]**
J01CR02 – Amoxicillin and beta-lactamase inhibitor, n (%)	**293 (6.1)**	**15.37 [13.38 ; 17.52]**	**147.62 [127.75 ; 167.90]**
C03CA01 – Furosemide, n (%)	**284 (5.9)**	**66.29 [57.64 ; 75.63]**	**30.20 [25.55 ; 32.85]**
C10AA05 – Atorvastatin, n (%)	**263 (5.5)**	**63.52 [55.08 ; 72.68]**	**25.00 [21.90 ; 29.20]**
A02BC02 – Pantoprazole, n (%)	**245 (5.1)**	**28.42 [24.57 ; 32.61]**	**79.10 [69.35 ; 91.25]**
N05CF02 – Zolpidem, n (%)	**244 (5.1)**	**36.19 [31.29 ; 41.54]**	**54.85 [47.45 ; 62.05]**
N02AA59 – Codeine. combinations excl psycholeptics, n (%)	**236 (4.9)**	**15.29 [13.20 ; 17.57]**	**179.23 [153.30 ; 204.40]**
M01AE01 – Ibuprofen, n (%)	**228 (4.7)**	**8.85 [7.63 ; 10.18]**	**126.39 [109.50 ; 146.00]**

[1] Taking into account the extrapolation of patient number for the reference population in the EGB database between 2010 and 2014

- **Identification of controls – Case-control analysis**

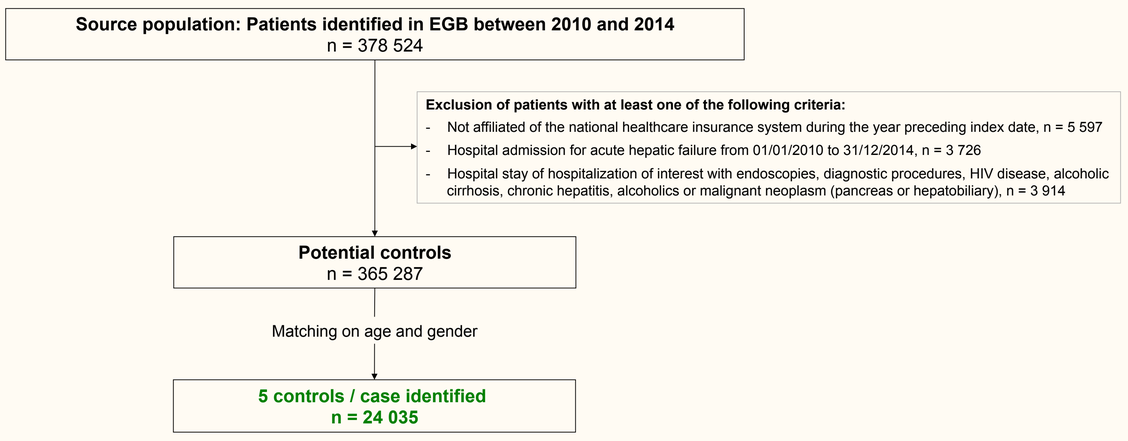


Figure 2. Identification procedure of controls in EGB between 2010 and 2014

- **Risk of hospital admission for ALI**
  - Considering ATC level 2: OR ranged from 71.7 [31.3-164.0] for AMB to 1.4 [1.3-1.5] for lipid modifying agents and NSAIDs (Figure 3).
  - Considering ATC level 5: OR ranged from 3.6 [3.2-4.3] for amoxicillin and beta-lactamase inhibitors to 1.4 [1.2-1.6] for ibuprofen (Figure 4).

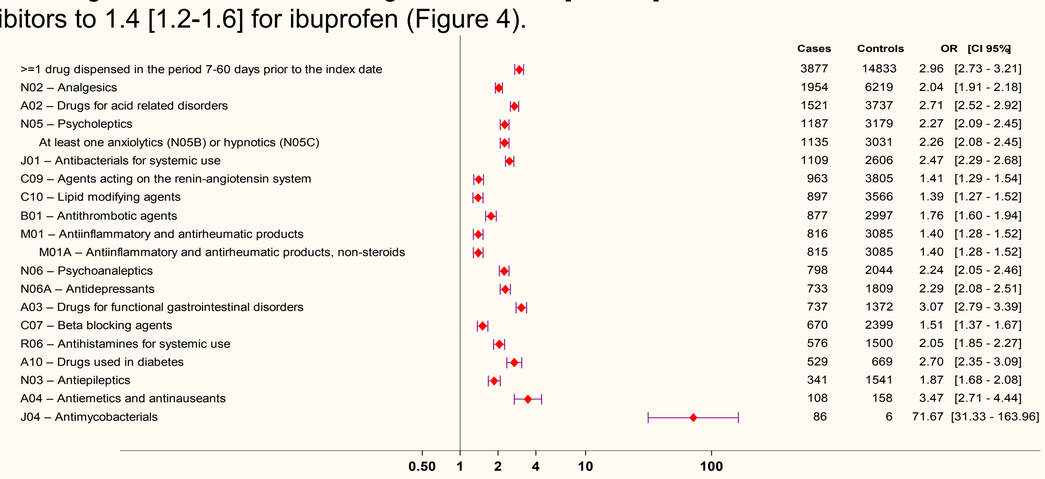


Figure 3. Risk of hospital admission for ALI between 2010 and 2014 (ATC level 2)

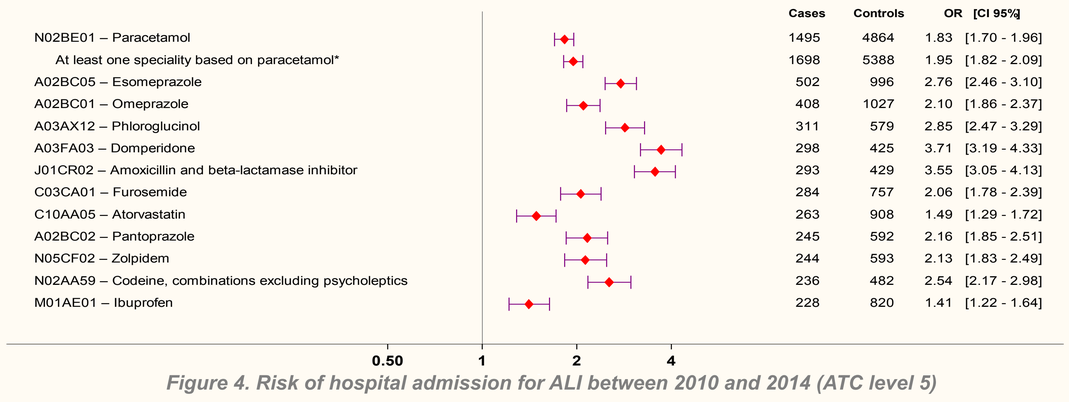


Figure 4. Risk of hospital admission for ALI between 2010 and 2014 (ATC level 5)

Conclusion

- **The hospitalization risk for ALI with previous exposure to drugs was probably increased by the ICD-10 codes chosen, which selected for toxic liver injury, with a three times higher exposure to any drugs in cases than in controls.**
- **Antimycobacterials had by far the highest risk of hepatotoxicity (OR 72), and NSAIDs among the lowest (OR 1.4). Data was collected for over 200 drugs.**

35th ICPE International Society for Pharmacoepidemiology
August 24-28, 2019, Philadelphia, PA, USA
[Abstract # 6885]