

# Drug-induced acute liver injury (ALI) in the French claims database: description of cases

A. Grolleau<sup>1</sup>, V. Barbet<sup>1</sup>, N. Thurin<sup>2</sup>, R. Lassalle<sup>1</sup>, M. Duong<sup>1</sup>, C. Droz-Perroteau<sup>1</sup>, N. Moore<sup>2</sup>

<sup>1</sup>Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France – <sup>2</sup>Bordeaux PharmacoEpi, INSERM CIC1401, INSERM U1219, Université de Bordeaux, Bordeaux, France

## Abstract

**Background:** ALI is a major source of drug-induced regulatory action, hospital admissions and burden of care. More studies only concern a few hundred cases.  
**Objectives:** To identify drugs that most commonly lead to hospital admission for ALI.  
**Methods:** Case-population study of adults with a 1<sup>st</sup> hospital admission for non-overdose ALI from 2010 to 2014, identified in SNIIRAM, the French nationwide claims system database of 66.6 million persons (99% of the French population). ALI was identified by discharge summaries ICD-10-codes K71.1, 71.2, 71.6, 71.9 (acute toxic liver injury) and 72.0 (hepatic failure). Exposure was defined as a dispensing between 0-7 days and 7-60 days before admission, to allow for potential protopathic bias identification. Population exposure was number of patients dispensed the drug at least once over the study timeframe in EGB, the 1/97<sup>th</sup> sample of SNIIRAM, extrapolated to the whole population. Risk of hospital admission for ALI was estimated using the population exposure to the drugs [95% CI].  
**Results:** 4807 ALI were identified, 61.4% with acute toxic liver injury and 38.6% with hepatic failure. Mean (SD) age was 54.5 (19.8) years, 58.7% were women, and 47.8% had at least one long-term disease. Data on exposure is present on over 250 different drugs.  
Within 7 days preadmission, the 10 most frequent drugs were paracetamol (18.7%), phloroglucinol (6.6%), domperidone (6.0%), esomeprazole (4.5%), ibuprofen (4.2%), metopimazine (3.4%), omeprazole (3.4%), amoxicillin in association (2.6%) or alone (2.3%), and codeine in association (2.6%), many probably associated with treatment of hepatic symptoms.  
Over 7-60 days, the 10 most frequent drugs were paracetamol (31.1%), esomeprazole (10.4%), omeprazole (8.5%), phloroglucinol (6.5%), domperidone (6.2%), amoxicillin in association (6.1%), furosemide (5.9%), atorvastatin (5.5%), pantoprazole (5.1%), and zolpidem (5.1%).  
Among these, rates per million users were highest for metopimazine 20.8 [17.6; 24.4] and domperidone 21.3 [18.5; 24.2] within 7 days, and over 7-60 days for atorvastatin 63.5 [55.1; 72.7] and furosemide 66.3 [57.6; 75.6].  
**Conclusions:** This large study provides information on drugs associated with hospital admissions for ALI. It confirms known associations such as paracetamol. Protopathic bias is probable for GI active or analgesic drugs found within 7 days before admission rather than during the 7-60 period.

## Conflict 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, CIC Bordeaux CIC1401 of the Bordeaux University. All authors, none declared other relationships to disclose for this study.

## Background

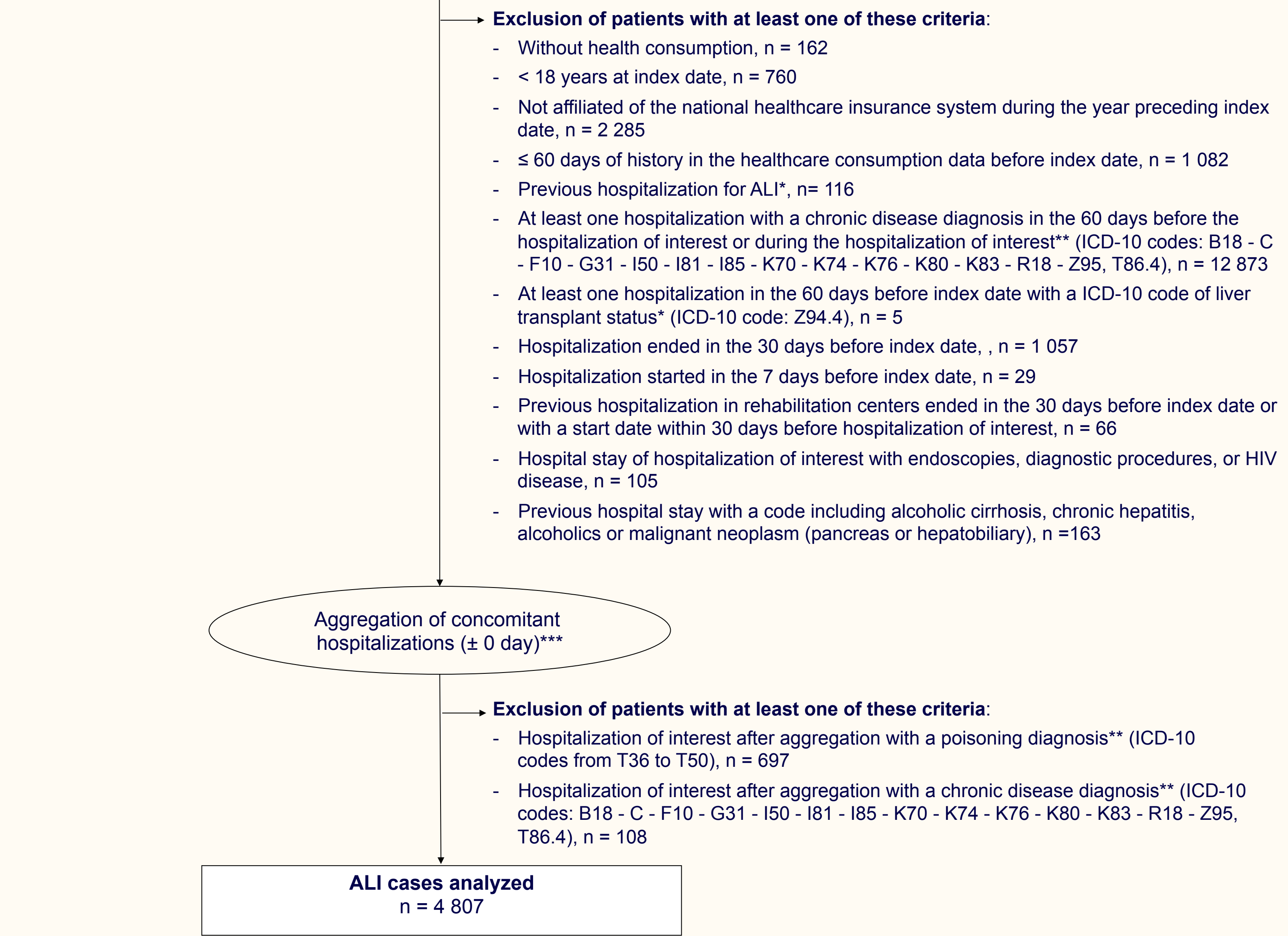
- Acute Liver Injury (ALI) is a major source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries<sup>1</sup>. 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.

1. Gulmez SE, Larrey D, Pageaux GP, Lignot S, Lassalle R, Jove J, 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.

## Results

### Identification of ALI cases

Population source : Patients identified in SNIIRAM with 1 <sup>st</sup> hospitalization for ALI between 2010 and 2014		
ICD-10 codes K71.1 or K71.2* n = 5 560	ICD-10 codes K71.6 or K71.9* n = 2 566	ICD-10 code K72.0* n = 16 189



\* 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 SNIIRAM between 2010 and 2014.

### ALI cases characteristics

- ✓ More than half of cases were female, and mean age was 54.5 years.
- ✓ The main diagnosis of 1<sup>st</sup> hospitalization at the index date was acute toxic liver injury for two-third cases (Table 1).

Table 1. Cases characteristics during 1<sup>st</sup> hospitalization for ALI.

	Cases n = 4 807
<b>Female, n (%)</b>	2 822 (58.7)
<b>Mean age, years (± SD*)</b>	54.5 (19.8)
<b>At least one LTD** mentioned before index date, n (%)</b>	2 298 (47.8)
LTD: « Diabetes type 1 and diabetes type 2 »	510 (10.6)
LTD: « Long-term psychiatric conditions »	439 (9.1)
LTD: « Malignant tumours, malignant lymphatic or haematopoietic tissue »	324 (6.7)
<b>Main diagnosis of hospital admission for (ICD-10 codes***), n (%)</b>	
Acute toxic liver injury	2 950 (61.4)
K71.1 "Toxic liver disease with hepatic necrosis"	392 (8.2)
K71.2 "Toxic liver disease with acute hepatitis"	1 599 (33.3)
K71.6 "Toxic liver disease with hepatitis, not elsewhere classified"	673 (14.0)
K71.9 "Toxic liver disease, unspecified"	286 (5.9)
K72.0 « hepatic failure, not elsewhere classified"	1 857 (38.6)

\* SD: Standard Deviation

\*\* LTD: Long Term Disease, only LTD with a frequency > 5% are presented

\*\*\* ICD-10 codes: International Classification of Diseases, 10<sup>th</sup> revision

## Objectives

To identify drugs that most commonly lead to hospital admission for ALI in France using the nationwide claims database.

## Methods

- Design:** Case-population study of adults with a 1<sup>st</sup> hospital admission for non-overdose ALI from 2010 to 2014.
- Data sources**
  - ✓ Study performed using the French nationwide claims database (*Système National d’Information Inter-Régimes de l’Assurance Maladie*, SNIIRAM) of 66.6 million persons (99% of the French population) and of the 1/97<sup>th</sup> representative sample of SNIIRAM (*Echantillon Généraliste de Bénéficiaires*, EGB).
  - ✓ These databases contain anonymised data on: general characteristics (gender, year of birth, month and year of death), long term diseases (LTD), outpatient reimbursed healthcare expenditure (visits, medical procedure, lab tests, drugs, medical devices), hospital discharge summaries (ICD-10 diagnostic codes for hospitalization, medical acts, date of entry and exit of hospitalization and length of stay).
- Study populations**
  - ✓ **Cases** identified in SNIIRAM among adult patients with a 1<sup>st</sup> hospital admission from January 1<sup>st</sup>, 2010 to December 31<sup>st</sup>, 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, extrapolated to the whole French population.
- Exposure**
  - ✓ **Cases:** drug dispensing between 7 and 60 days or 0 and 7 days preceding date of the 1<sup>st</sup> hospital admission for ALI.
  - ✓ **Exposed population:** number of patients among the reference population dispensed the drug at least once over the study timeframe in EGB (01/01/2010 - 31/12/2014), extrapolated to the whole French population.
- Statistical analysis**
  - ✓ Index date: date of 1<sup>st</sup> hospitalization for ALI (with aggregation of concomitant stays for patients hospitalized in several medical units).
  - ✓ Risk of hospital admission for ALI: expressed as the rate [95% CI] of number of drug-exposed cases over the study timeframe by million of drug-exposed patients among the exposed population.

### Exposure of adult ALI cases

- ✓ Over 7-60 days, 80.7% of ALI cases were exposed to at least one drug,
- ✓ Within 7 days, 52.7% of ALI cases were exposed to at least one drug.

Tableau 2. Top 10 of drugs dispensed for ALI cases identified in the SNIIRAM between 2010 and 2014.

Drug dispensations over 7 - 60 days before the index date	Cases n = 4 807	Drug dispensations within 7 days before the index	Cases n = 4 807
N02BE01 - Paracetamol, n (%)	1 495 (31.1)	N02BE01 - Paracetamol, n (%)	901 (18.7)
A02BC05 - Esomeprazole, n (%)	502 (10.4)	A03AX12 - Phloroglucinol, n (%)	317 (6.6)
A02BC01 - Omeprazole, n (%)	408 (8.5)	A03FA03 - Domperidone, n (%)	288 (6.0)
A03AX12 - Phloroglucinol, n (%)	311 (6.5)	A02BC05 - Esomeprazole, n (%)	215 (4.5)
A03FA03 - Domperidone, n (%)	298 (6.2)	M01AE01 - Ibuprofen, n (%)	201 (4.2)
J01CR02 - Amoxicillin and enz. inhib., n (%)	293 (6.1)	A02BC01 - Omeprazole, n (%)	163 (3.4)
C03CA01 - Furosemide, n (%)	284 (5.9)	A04AD05 - Metopimazine, n (%)	163 (3.4)
C10AA05 - Atorvastatin, n (%)	263 (5.5)	J01CR02 - Amoxicillin and enz. inhib., n (%)	125 (2.6)
A02BC02 - Pantoprazole, n (%)	245 (5.1)	N02AA59 - Codeine, combinations excl. psycholeptics, n (%)	123 (2.6)
N05CF02 - Zolpidem, n (%)	244 (5.1)	J01CA04 - Amoxicillin, n (%)	112 (2.3)

### Risk of hospital admission for ALI

Among the 10 most frequent dispensed drugs, rates per million users were highest for:

- ✓ Furosemide and atorvastatin over 7-60 days (Figure 2a),
- ✓ Domperidone and metopimazine within 7 days (Figure 2b).

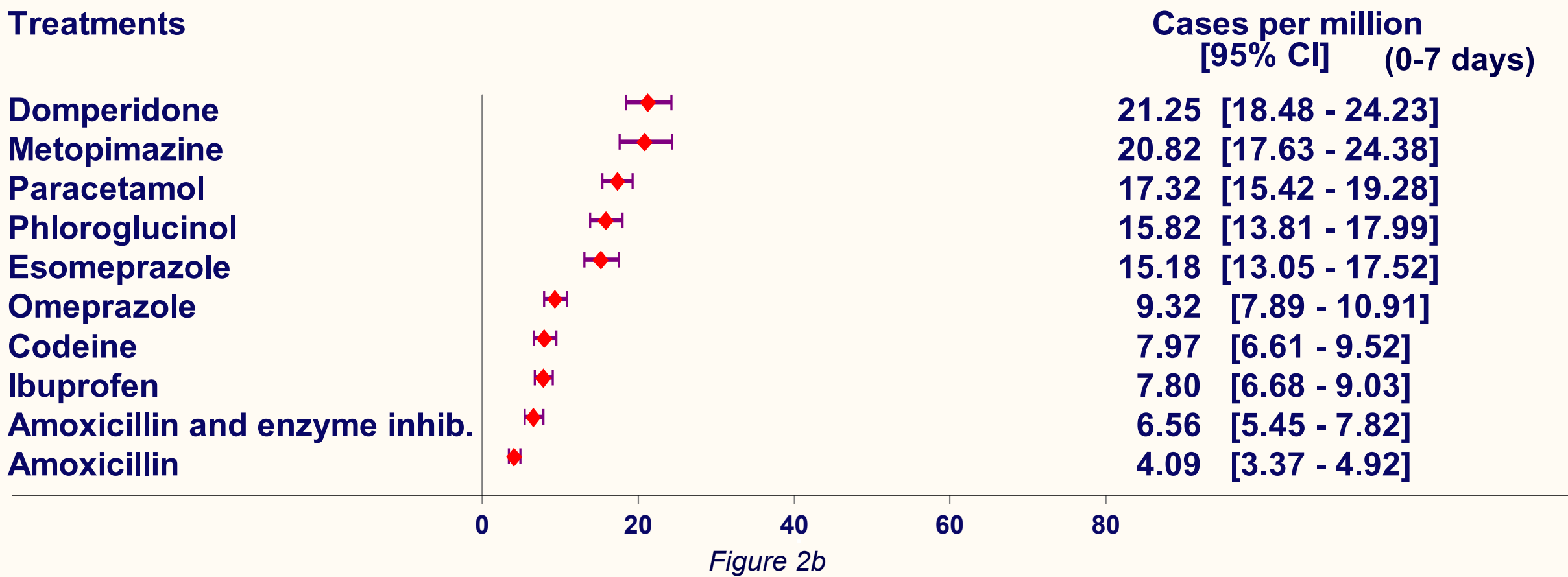
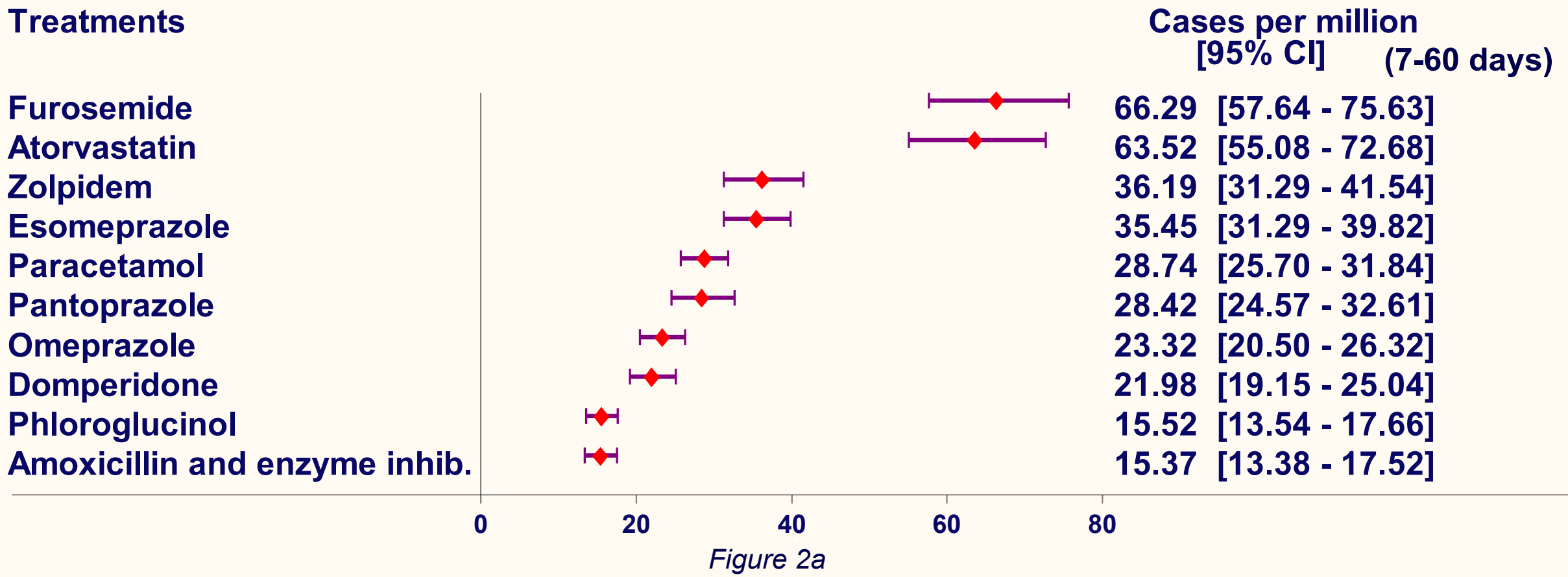


Figure 2. Risk of hospital admission for ALI over 7-60 days (Figure 2a) and 0-7 days (Figure 2b) before the index date among the 10 most frequent dispensed drugs.

## Conclusions

- Many drugs are dispensed before 1<sup>st</sup> hospital admission for acute liver injury.
- The known associations such as paracetamol were confirmed.
- Gastro-intestinal active or analgesic drugs were frequently found within 7 days preadmission, suggesting that protopathic bias is probable. Further sensitive analyses are needed to confirm this hypothesis.

