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Features and Outcomes of 280 Patients With Idiosyncratic Drug-Induced Liver Injury: The REFHEPS Prospective Study

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Abbreviations used in this paper: **ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CDK4/6, cyclin-dependent kinase 4/6; CIOMS, Council for International Organizations of Medical Sciences; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; HDS, herbal and dietary supplements; HER, human epidermal growth factor receptor; ICIs, immune checkpoint inhibitors; IQR, interquartile range; KRAS, Kirsten rat sarcoma viral oncogene homolog; LT, liver transplantation; OTC, over-the-counter (medications); REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; RUCAM, Roussel-Uclaf Causality Assessment Method; SD, standard deviation; TBL, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.**

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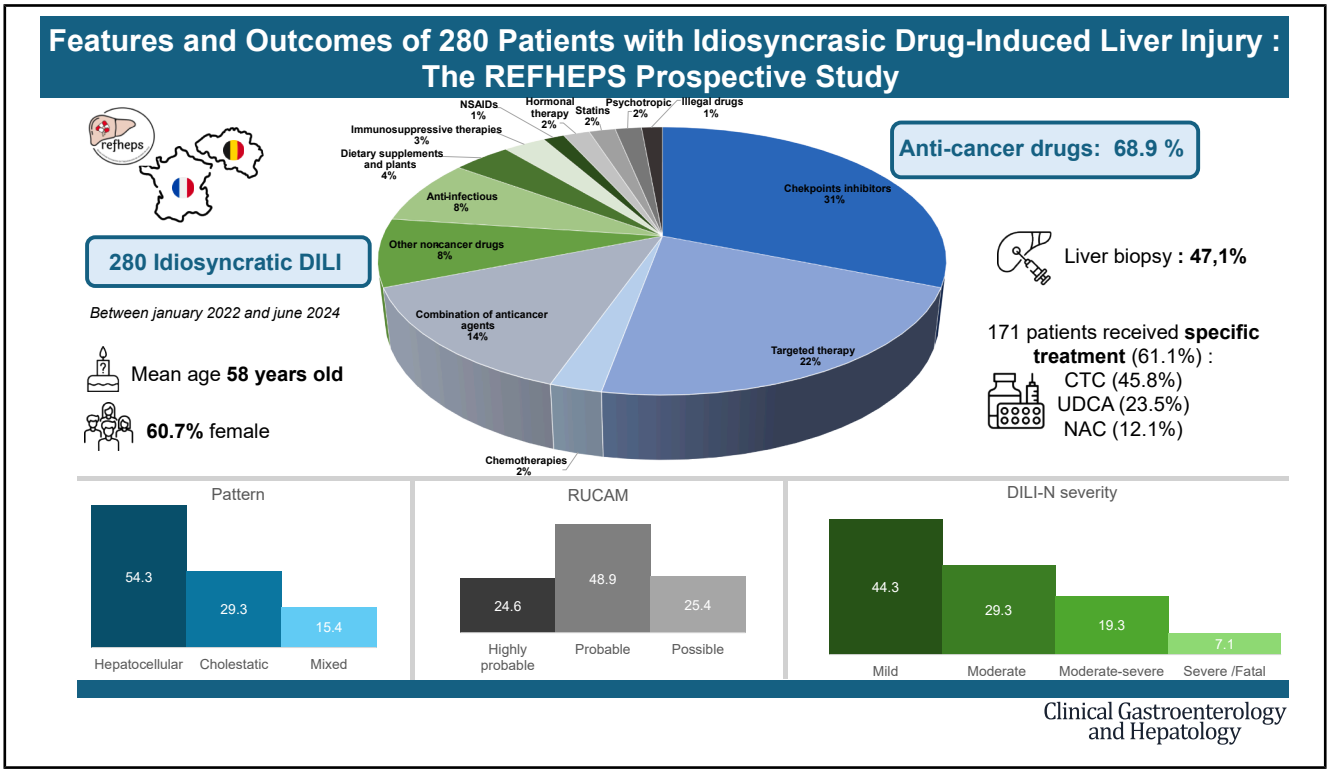

BACKGROUND & AIMS: **In October 2021, France and Belgium launched a joint prospective drug-induced liver injury (DILI) network (Réseau d'Etude Francophone de l'Hépatotoxicité des Produits de Santé - REFHEPS), which aims to collect liver toxicity data. Here, we present the clinical characteristics, outcome, histological features, and culprit drugs responsible for cases with DILI collected from January 2022 to June 30, 2024.**

METHODS: **Demographics, clinical presentation, histological findings, and outcome of prospectively recruited cases with DILI in the REFHEPS were analyzed. Case definition and severity of DILI were established according to the criteria of RUCAM and Drug-Induced Liver Injury Network (DILIN) criteria.**

RESULTS: **A total of 322 cases met the inclusion criteria for DILI, including 42 cases related to paracetamol. The current study focused on the 280 patients with idiosyncratic DILI. Our study highlights sex- and age-related differences: females were younger (57 vs 59.7 years; $P = .047$) and more likely to develop hepatocellular DILI (60% vs 45.5%; $P = .02$), whereas disease severity and outcomes were similar across sexes. In patients over 65 years, DILI had a later onset, was more cholestatic, and tended to be less symptomatic. A major finding is that anticancer drugs, particularly immune checkpoint inhibitors, account for most DILI cases (68.9%).**

CONCLUSIONS: **The REFHEPS registry collected 322 cases in 2.5 years. The study of the 280 idiosyncratic cases of DILI shows sex and age-related differences as reported in previous registries. The most significant difference compared with older registries is the predominance of anticancer drugs causing liver injury, demonstrating the emergence of "new" side effects associated with the use of innovative therapies, especially immune checkpoint inhibitors.**

Keywords: Anticancer Drugs; France-Belgium REFHEPS Registry; Hepatotoxicity; Immune Checkpoint Inhibitors; Prospective Registry.

See editorial on page 1787.

Drug-induced liver injury (DILI) is a major cause of drug discontinuation and is often the main reason why a drug fails to achieve marketing authorization.[1] A large proportion of drug-induced hepatotoxicity occurs in an unpredictable manner, where a drug has been used as recommended, defining an idiosyncratic event

and explaining the low likelihood of observing a significant number of cases during clinical trials. Furthermore, DILI can mimic a wide range of non-iatrogenic liver diseases and can lead to acute liver failure, which is the leading cause of drug-related death.[2,3] Consequently, DILI is a major challenge for physicians, health authorities, and pharmaceutical companies.[2,3]

More recently, the DILI landscape has become more complex due to the increasing role of herbal medicines, complementary products, recreational and illicit compounds, and chemicals in liver toxicity.[4,5] The past decade has also seen dramatic changes in the therapeutic armamentarium of several medical fields, such as oncology, where an increasing number of neoplastic diseases are being successfully treated with immune checkpoint inhibitors (ICIs). Unfortunately, this major advance is associated with side effects such as immune-mediated liver injury, the pathophysiology and management of which remain incompletely defined.[6]

In Western countries, the incidence of DILI in the general population has been estimated to be in the range of 2%–10%.[1,7] In a retrospective population-based case-control study published in 2004, the incidence of DILI in the United Kingdom was approximately 2.4 cases per 100,000 people per year. Similarly, another retrospective study from the Swedish Liver Disease Clinic Database reported an incidence of 2.3 cases per 100,000 persons per year.[8] Only a few prospective studies have been published. A population-based prospective study from France showed an incidence of DILI of 13.9 per 100,000 population per year, which was 16 times higher than that estimated by spontaneous reporting methods.[9] In Iceland, a 2-year prospective study based on the entire population documented a DILI incidence of 19.1 per 100,000 inhabitants.[8] Interestingly, these incidences are significantly higher when compared with retrospective studies.

In addition to epidemiological studies, several prospective registries have been developed to improve knowledge of DILI, such as the Spanish DILI Registry, the DILI Network (DILIN) in the United States, the Latin American DILI Network (LATINDILI), the Chinese DILI Network, and the Indian DILI Network.[8–14] In October 2021, France and Belgium launched a joint prospective DILI network (Réseau d'Etude Francophone de l'Hépatotoxicité des Produits de Santé [REFHEPS]), which aims to collect liver toxicity data from a population of 88 million inhabitants.[15,16] Among the 322 collected cases, 42 paracetamol intoxications were observed. In this paper, the clinical characteristics, outcomes, histological features, and culprit drugs responsible for idiosyncratic DILI in patients included in the REFHEPS network from January 2022 to June 30, 2024 are presented.

What You Need to Know

Background

Given the heterogeneity of drug-induced liver injury (DILI) presentation, management, and progression and evolving epidemiology due to newly approved drugs, herbal supplements, and recreational substances, a recent Franco-Belgian registry has been established.

Findings

Antineoplastic agents were the most represented drug class, unlike previous cohorts. Cancer-related DILI was often incidental. Hepatocellular DILI occurred predominantly in younger females. Many cases had histological confirmation.

Implications for patient care

This registry provides new insights into DILI recognition and characterization, paving the way for a deeper understanding of this complex complication. Oncology patients require close monitoring.

Material and Methods

Study Population

REFHEPS is a prospective registry designed to identify and collect data on cases of DILI.[17] The registry collects information at the time of DILI recognition and during follow-up. For each suspected DILI case submitted to REFEHPS, data are collected using a standardized case report form to ensure comprehensive case adjudication. The data set includes: (1) a detailed medication history and symptoms, including the use of herbal and dietary supplements (HDS) and over-the-counter (OTC) medications; (2) biochemical parameters, imaging, and histological data to exclude alternative causes of liver injury; and (3) patient outcomes.

Case Definitions

In the REFHEPS registry, we used the biochemical criteria for DILI originally established by the Council for International Organizations of Medical Sciences (CIOMS) and subsequently adapted to those proposed by Aithal et al[18]: alanine aminotransferase (ALT) $\geq$5 times the upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq$2 times ULN, or ALT $\geq$3 times ULN in combination with total bilirubin (TBL) $\geq$2 times ULN. The liver injury pattern was defined according to the R value calculated from the first available blood test after DILI recognition using the formula (ALT/ULN)/(ALP/ULN). Liver injury was categorized as hepatocellular (R $\geq$5), cholestatic (R $\leq$2), or mixed (R between 2 and 5).[19] The severity of each DILI episode was graded according to an index defined by an internationally recognized expert working group.[3] Causality assessment was performed by a panel of independent experts from the REFHEPS coordinating centers. Case probability was categorized using the Roussel-Uclaf Causality Assessment Method (RUCAM).[20] Chronic DILI was defined as the persistence of abnormal liver parameters (above ULN) for more than 6 months

after the initial diagnosis of DILI. Cases with insufficient data to assess causality or those with a more likely differential diagnosis were excluded from the study. For the purpose of the analysis, cases of hepatotoxicity attributed to paracetamol (n = 42) were excluded to retain only cases of idiosyncratic toxicity.

Data Management and Statistical Analyses

Demographic and clinical data of patients enrolled in the REFHEPS registry between January 2022 and June 2024 were extracted on November 1, 2024. Descriptive statistics were used to characterize the cohort, including means with standard deviations (SDs) for normally distributed variables, medians with interquartile ranges (IQRs) for skewed distributions, and frequency distributions for categorical variables. Comparisons between groups were made using the χ^2 test for categorical variables and the Wilcoxon/Kruskal-Wallis test for continuous variables. Statistical significance was defined as a P value $<.05$. All statistical analyses were performed with Easymedstat. The study protocol was approved by the local ethics committees (Institutional Review Board number: 198711).

Results

Clinical and Demographic Characteristics

Between January 1, 2022, and June 30, 2024, a total of 383 DILI cases were submitted to the REFHEPS and 280 cases met the inclusion criteria for the current study (Figure 1). The mean age of the patients was 58 years, with a predominance of female patients (60.7%). The mean time to onset of DILI after drug initiation was 146.5 days (median, 61.5 days; range, 1–2042 days). The mean time of follow-up was 123 days (median, 85.5 days; range, 1–1052 days). Liver biopsy was performed in 132 patients (47.1%). A total of 84 patients (30%) required hospitalization for management of DILI (Table 1). The pattern of liver injury was hepatocellular in 54.3%, cholestatic in 29.3%, and mixed in 15.4% of the cases.

Based on the RUCAM scale, drug causality was classified as highly probable in 24.6% of cases, probable in 48.9% and possible in 25.4%. In 3 patients with chronic presentation, RUCAM was not applicable, and causality was determined by a consistent time frame and the exclusion of competitive causes. Based on the DILIN severity classification, the severity was mild in 44.3%, moderate in 29.3%, moderate-severe in 19.3%, severe in 2.1%, and fatal in 5% of the cases. There was no difference in severity according to the different patterns of hepatitis ($P = .462$). Eight patients (2.9%) developed acute liver failure (ALF), all of whom died, including 1 after liver transplantation (LT). The implicated drugs were olanzapine, amoxicillin–clavulanate, atezolizumab, atezolizumab plus bevacizumab, carboplatin plus pembrolizumab plus paclitaxel (n = 2), pembrolizumab, and cocaine. Most patients (171; 61.1%) received a specific treatment for DILI, including corticosteroids (45.8%), ursodeoxycholic acid (UDCA) (23.5%), or N-acetylcysteine (12.1%) (Table 1).

Females were younger (57 vs 59.7 years; $P = .047$) and more likely to be diagnosed with hepatocellular DILI (60.0% vs 45.5%; $P = .02$). The severity and the outcome were similar between males and females (Table 2). Patients over 65 years of age (n = 111) had a significantly longer time to onset (119.4 vs 161.9 days; $P < .001$) and were more likely to present with cholestatic or mixed patterns (Table 2). The implicated treatment was reintroduced in 29 cases: estradiol valerate, duloxetine, ocrelizumab, nivolumab (n = 4), vinblastine, colchicine, encorafenib/binimetinib (n = 2), azathioprine, pembrolizumab (n = 7), leflunomide, ivacaftor/tezacaftor/

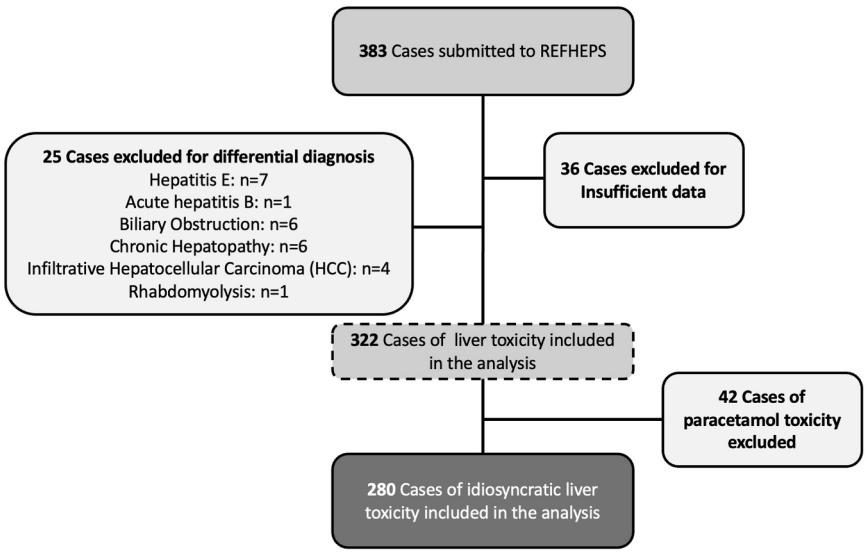

Figure 1. Flowchart of case selection for inclusion in the REFHEPS analysis. This flowchart illustrates the selection process of cases submitted to the REFHEPS study. Of 383 cases initially submitted, 36 were excluded due to insufficient data, and 25 were excluded following differential diagnosis (including cases of hepatitis E, acute hepatitis B, biliary obstruction, chronic hepatopathy, infiltrative hepatocellular carcinoma, and rhabdomyolysis). Cases of paracetamol intoxication were excluded from the analysis. A total of 280 cases of idiosyncratic DILI were ultimately included in the analysis.

Table 1. Characteristics of Patients With DILI by Injury Pattern in the REFHEPS Cohort

Characteristics	DILI cases, N = 280	Hepatocellular,[a] n = 152	Cholestatic,[a] n = 82	Mixed,[a] n = 43	*P*
Age, *y*	58 (±16.1) (12–95)	55.2 (±16.6) (12–88)	60.4 (±15.6) (17–88)	63.3 (±14.5) (28–95)	**.004**
Sex					**.023**
Male	110 (39.3)	50 (32.9)	42 (51.2)	18 (41.9)	
Female	170 (60.7)	102 (67.1)	40 (48.8)	25 (58.1)	
Alcohol consumption (N = 156)					**.027**
Chronic	22 (7.9)	9 (5.9)	5 (6.1)	8 (18.6)	
Occasionally	56 (20.0)	30 (19.7)	22 (26.8)	4 (9.3)	
Never	67 (23.9)	41 (27.0)	17 (20.7)	7 (16.3)	
Time to onset, *d*	146.5 (±264.2) (0–2042)	113.1 (±225.0) (0–1931)	170.0 (±290.4) (1–2042)	140.9 (±194.8) (5–885)	.072
Laboratory parameters at onset					
AST, *IU/L*	435.6 (±749.9)	607 (±937.3)	142.1 (±124.2)	417.1 (±526.7)	**<.001**
ALT, *IU/L*	523.3 (±621.1)	745.2 (±720.3)	173.8 (±149.3)	434.4 (±466.8)	**<.001**
ALP, *IU/L*	347.2 (±442.7)	149.7 (±81.8)	644.2 (±627.9)	395.3 (±359.6)	**<.001**
GGT, *IU/L*	432.0 (±610.9)	194.3 (±192.8)	685.3 (±678.3)	719.2 (±958.3)	**<.001**
TBL, *μmol/L*	47.5 (±86.4)	45.9 (±82.2)	53.3 (±101.3)	43.8 (±73.0)	.766
INR (N = 84)	1.1 (±0.4)	1.22 (±0.5)	1.1 (±0.1)	1.03 (±0.1)	**.049**
Laboratory parameters at peak					
ALT, *IU/L*	814.8 (±1112.5)	1183.0 (±1377.3)	280.5 (±208.3)	595.3 (±474.4)	<.001
ALP, *IU/L*	473.1 (±582.6)	195.7 (±123.7)	943.3 (±793.4)	543.5 (±483.5)	<.001
INR	1.2 (±0.5)	1.3 (±0.6)	1.1 (±0.3)	1.1 (±0.2)	.675
TBL, *μmol/L*	82.5 (±137.2)	77.6 (±117.1)	83.3 (±148.6)	102.1 (±179.5)	.998
Liver biopsy	132 (47.1)	69 (45.4)	40 (48.8)	20 (46.5)	.885
Delay DILI-biopsy, *d*	45.3/24 (0–578)	49.0 (±91.2) (2–578)	43.4 (±57.7) (0–293)	29.4 (±28.5) (4–110)	.928
Hospitalization	84 (30.0)	47 (30.9)	18 (22.0)	18 (41.9)	.065
RUCAM imputability (N = 277)					**.028**
Highly probable	69 (24.6)	34 (22.4)	22 (26.8)	13 (30.2)	
Probable	137 (48.9)	84 (55.3)	30 (36.6)	23 (53.5)	
Possible	71 (25.4)	34 (22.4)	30 (36.6)	7 (16.3)	
DILI-N imputability (N = 277)					**.004**
Highly probable	81 (28.9)	41 (27.0)	27 (32.9)	13 (30.2)	
Probable	136 (48.6)	86 (56.6)	27 (32.9)	23 (53.5)	
Possible	60 (21.4)	25 (16.5)	28 (34.2)	7 (16.3)	
DILI-N severity					.794
Mild	124 (44.3)	68 (44.7)	36 (43.9)	19 (44.2)	
Moderate	82 (29.3)	45 (29.6)	26 (31.7)	11 (25.6)	
Moderate-severe	54 (19.3)	25 (16.5)	16 (19.5)	12 (27.9)	
Severe	6 (2.1)	4 (2.6)	1 (1.2)	0 (0)	
Fatal	14 (5.0)	10 (6.6)	3 (3.7)	1 (2.3)	
DILI clinical symptoms	91 (32.5)	54 (35.5)	21 (25.6)	15 (34.9)	.284
DILI treatment	171 (61.1)	89 (58.6)	55 (67.1)	27 (62.8)	.861
Steroids	127 (45.8)	70 (46.7)	37 (45.7)	20 (46.5)	.898
UDCA	65 (23.5)	16 (10.7)	34 (42.0)	15 (34.9)	**<.001**
N-acetylcysteine	15 (12.1)	13 (17.1)	2 (6.9)	0 (0)	.122
Outcome					**.014**
Recovery	141 (50.4)	86 (56.6)	33 (40.2)	22 (51.2)	
Improvement	62 (22.1)	31 (20.4)	21 (25.6)	10 (23.3)	
Chronic	34 (12.1)	8 (5.3)	18 (22.0)	5 (11.6)	
Death	8 (2.9)	4 (2.6)	3 (3.7)	1 (2.3)	
Liver transplantation	6 (2.1)	6 (4.0)	0 (0)	0 (0)	

Table 1. Continued

Characteristics	DILI cases, N = 280	Hepatocellular,[a] n = 152	Cholestatic,[a] n = 82	Mixed,[a] n = 43	*P*
Time to recovery, *d* (N = 140)	84.1 (±114.5) (5–1183)	69.1 (±53.7) (9–266)	94.8 (±93.8) (13–403)	121.7 (±243.8) (5–1183)	.303
Rechallenge	29 (10.4)	14 (9.2)	7 (8.5)	8 (18.6)	.419

NOTE. Data are presented as number (%) or mean (standard deviation) (minimum-maximum).
NOTE. Boldface *P* values indicate statistical significance.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILI-N, Drug-Induced Liver Injury Network; GGT, gamma-glutamyl transferase; REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; TBL, total bilirubin level; UDCA, ursodeoxycholic acid.
[a]A total of 280 patients were included; however, phenotype classification was possible for only 277 patients. Three patients presented with a chronic form without liver function test abnormalities, preventing their classification into a specific phenotype (hepatocellular, cholestatic, or mixed).

elexacaftor, amiodarone, sotorasib, venetoclax, rosuvastatin, amoxicillin, crizotinib, dupilumab, and abemaciclib.

Therapeutic Classes Involved

Of the 280 cases, a single drug was implicated in the majority of cases (82.5%), whereas more than 1 drug was implicated in 17.5% of cases (n = 49). Anticancer drugs accounted for 193 cases (68.9%), with ICIs alone involved in 87 cases (31.1%). For 35 patients (12.5%), the treatment involved a combination of anticancer agents, most commonly an ICI combined with a targeted therapy (Figure 2). Among the other anticancer agents involved, 21.8% of patients (n = 61) received a targeted therapy, including cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (n = 37), tyrosine kinase inhibitors, human epidermal growth factor receptor (HER) inhibitors, or Kirsten rat sarcoma viral oncogene homolog (KRAS) inhibitors. Finally, in 2% of cases, conventional chemotherapy was administered. Among nononcology agents, the most common categories were anti-infectives, HDSs, and immunosuppressive therapies. HDSs accounted for 11 cases (*Tinospora cordifolia*, *Boswellia serrata*, *Indigofera spicata*, blue-green algae, *Serenoa repens*, *Curcuma lunga*, *Trenbolone* anabolic steroids, combination of herbal preparation and green algae, 2 cases due to dietary supplement used or physical activities and 2 cases due to mushrooms supplements).

Comparison Between Anticancer and Non-Anticancer DILI

Compared with nononcology drug cases, patients with oncology drug-related DILI were significantly older (61.8 vs 49.7 years; $P < .001$) with no difference in sex distribution (60.6% vs 60.9% female; $P > .999$). The time to onset was significantly longer for anticancer drugs (142.9 vs 120.5 days; $P = .048$). Hepatocellular injury was the most common pattern in all groups, but cholestatic injury was more common in anticancer DILI (33.7% vs 19.5%; $P < .001$). There was no significant difference in RUCAM causality scores between the groups. DILI severity scores (DILI-N) showed less severe classifications in oncology cases (severe/fatal: 4.7% vs 12.6%; $P = .047$). There was no significant difference in the frequency of liver biopsies among patients receiving oncologic and nononcologic treatments (48.2% vs 44.9%; $P = .695$).

Regarding treatment, corticosteroids (55.7%) and UDCA (26%) were more commonly used for oncologic DILI, whereas N-acetylcysteine (26.8%) was more commonly used for nononcologic DILI ($P < .001$) (Table 3).

Discussion

In a recently created French-speaking network for DILI assessment (REFHEPS), 280 patients were included over 30 months. Most of the liver injury occurred in women, was asymptomatic, and had a hepatocellular pattern. The severity was mainly mild to moderate; however, two-thirds of the cases received specific treatment. A favorable outcome was observed, except in 10% of patients who developed persistent abnormal liver parameters. Our study highlights sex- and age-related differences: females were younger and more likely to develop hepatocellular DILI, whereas disease severity and outcomes were similar across sexes. Notably, in patients over 65 years of age, DILI had a later onset, was more cholestatic/mixed, and tended to be less symptomatic. The main therapeutic classes involved in our cohort were anticancer drugs, antimicrobials, HDSs, and hormonal therapy/statin/psychotropic drugs.

Until recently, antibiotics have been described as the main cause of idiosyncratic DILI. However, an increasing incidence of liver injury associated with antineoplastic drugs has been reported.[21] Interestingly, more than one-half of the cases recruited to the REFHEPS cohort were due to an anticancer drug, and of these, slightly less than one-half were immune-related liver injury due to an ICI. Targeted therapies also accounted for a non-negligible proportion of cases, particularly anti-CDK4/6 inhibitors used to treat some metastatic breast cancers.[17] Several factors may explain the predominance of

Table 2. Characteristics of Patients With DILI According to Sex and Age in the REFHEPS Cohort

Characteristics	Men, n = 110	Women, n = 170	*P* value	Age <65, n = 170	Age ≥65, n = 109	*P* value
Age, *y*	59.7 (±16.8)(12–88)	57.0 (±15.7) (17–95)	.047			
Sex						.101
Male				60 (35.3)	50 (45.9)	
Female				110 (64.7)	59 (54.1)	
Alcohol consumption			.002			.706
Chronic	15 (13.6)	7 (4.1)		13 (7.7)	9 (8.3)	
Occasionally	27 (24.6)	29 (17.1)		31 (18.2)	25 (22.9)	
Never	17 (15.5)	50 (29.4)		44 (25.9)	23 (21.1)	
Time to onset, *d*	114.2 (±149.9) (0–749)	150.5 (±285.9) (0–2042)	.657	119.4 (±242.5) (0–1931)	161.9 (±242.4) (0–2042)	<.001
Laboratory parameters at onset						
AST, *IU/L*	431.8 (±919.3)	438.2 (±618.0)	.207	464.2 (±843)	393.8 (±580.9)	.51
ALT, *IU/L*	479.0 (±635.7)	552.2 (±613.5)	.151	590.8 (±706.1)	421.8 (±446.1)	.141
ALP, *IU/L*	447.1 (±497.8)	278.9 (±389.7)	.004	331.9 (±475.7)	371.6 (±396.2)	.165
GGT, *IU/L*	600.6 (±765.5)	317.3 (±448.6)	<.001	361.4 (±593.5)	540.6 (±628.2)	.018
TBL, *μmol/L*	49 (±78.4)	46.5 (±91.8)	.139	50.2 (±92.9)	43.5 (±76.1)	.516
INR	1.15 (±0.4)	1.14 (±0.4)	.647	1.14 (±0.4)	1.15 (±0.4)	.508
Laboratory parameters at peak						
ALT, *IU/L*	859.2 (±1447.6)	785.9 (±832.8)	.118	966.9 (±1352.9)	583.3 (±507.6)	<.001
ALP, *IU/L*	557.9 (±609.8)	416.3 (±569.1)	.035	437.8 (±597.6)	529.8 (±561.7)	.067
INR	1.22 (±0.5)	1.16 (±0.5)	.071	1.17 (±0.5)	1.21 (±0.5)	.955
TBL, *μmol/L*	91.45 (±139.6)	6.55 (±136.1)	.031	91.69 (±144.6)	69.34 (±125.8)	.705
Pattern			.02			.005
Others	0 (0.0)	3 (1.5)		2 (1.2)	1 (0.9)	
Cholestatic	42 (38.2)	40 (23.5)		44 (25.9)	38 (34.9)	
Hepatocellular	50 (45.5)	102 (60)		105 (61.8)	46 (42.2)	
Mixed	18 (16.4)	25 (14.7)		19 (11.2)	24 (22)	
Liver biopsy	60 (54.6)	72 (42.4)	.061	81 (47.7)	51 (46.8)	.986
Delay DILI-biopsy, *d*	33.3 (±47.0) (0–293)	55.2 (±90.7) (1–578)	.069	49.1 (±86.1) (0–578)	39.3 (±52.7) (3–293)	.598
Hospitalization	46 (41.8)	38 (22.4)	<.001	53 (31.2)	31 (28.4)	.725
RUCAM imputability			.022			.769
Highly probable	37 (33.6)	32 (18.8)		39 (22.9)	30 (27.5)	
Probable	47 (42.7)	90 (52.9)		87 (51.2)	49 (45)	
Possible	26 (23.6)	45 (26.5)		42 (24.7)	29 (26.6)	
DILI-N imputability			.055			.494
Highly probable	41 (37.3)	40 (23.5)		45 (26.5)	36 (33)	
Probable	48 (43.6)	88 (51.8)		88 (51.8)	47 (43.1)	
Possible	21 (19.1)	39 (22.9)		35 (20.6)	25 (22.9)	
DILI-N severity			.393			.382
Mild	42 (38.2)	82 (48.2)		73 (42.9)	50 (45.9)	
Moderate	33 (30.0)	49 (28.8)		51 (30)	31 (28.4)	
Moderate-severe	26 (23.6)	28 (16.5)		32 (18.8)	22 (20.2)	
Severe	2 (1.8)	4 (2.4)		6 (3.5)	0 (0)	
Fatal	7 (6.4)	7 (4.1)		8 (4.7)	6 (5.5)	
DILI clinical symptoms	40 (36.4)	51 (30)	.327	64 (37.7)	27 (24.8)	.035
DILI treatment	76 (69.1)	95 (55.9)	.037	100 (58.8)	70 (64.2)	.438
Steroids	59 (53.6)	68 (40.7)	.047	71 (42.3)	55 (50.9)	.198
UDCA	34 (30.9)	31 (18.6)	.026	33 (19.6)	32 (29.6)	.078
N-acetylcysteine	5 (12.8)	10 (11.8)	>.999	13 (15.7)	2 (4.9)	.141
Outcome			.771			.377
Recovery	55 (50.0)	86 (50.6)		90 (52.9)	50 (45.9)	
Improvement	23 (20.9)	39 (22.9)		37 (21.8)	25 (22.9)	
Chronic	15 (13.6)	19 (11.2)		17 (10)	17 (15.6)	

Table 2. Continued

Characteristics	Men, n = 110	Women, n = 170	*P* value	Age <65, n = 170	Age ≥65, n = 109	*P* value
Death Liver transplantation	5 (4.6) 2 (1.8)	3 (1.8) 4 (2.4)		3 (1.8) 5 (2.9)	5 (4.6) 1 (0.9)	
Time to recovery, *d*	75.7 (±74.6) (13–403)	89.2 (±133.8) (5–1183)	.371	85.2 (±132.7) (9–1183)	82.3 (±75.6) (5–403)	.418
Rechallenge	16 (14.5)	13 (7.6)	.212	16 (9.4)	13 (11.9)	.066
Anticancer drugs	76 (69.1)	117 (68.8)	>.999	105 (61.9)	87 (79.8)	.002
Polymedication	26 (23.6)	23 (13.5)	.044	31 (18.2)	18 (16.5)	.836

NOTE. Data are presented as number (%) or mean (standard deviation) (minimum-maximum).
NOTE. Boldface *P* values indicate statistical significance.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILI-N, Drug-Induced Liver Injury Network; GGT, gamma-glutamyl transferase; REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; TBL, total bilirubin level; UDCA, ursodeoxycholic acid.

antineoplastic agents as the cause of liver injury in the REFHEPS cohort. First, the majority of patients were recruited in French and Belgian centers with high oncological activity, and therefore, a large population at risk of developing antineoplastic-associated DILI. Not only are these patients treated with molecules susceptible to developing liver injury, but these oncology patients are also very frequently monitored for the development of side effects by blood tests. This probably explains the rapid detection of liver injury, but also its high incidence, while patients are often asymptomatic. Another key element is likely to be the French and Belgian health care systems, which have a more favorable access profile to oncology treatment protocols than many other countries, exposing more patients to drug-related side effects. Indeed, our network also provides assistance for the management of complex cases, which tends to attract reports of rarer or more complex DILI rather than those related to well-known anti-infective agents.

Finally, the past decade has seen a dramatic change in the therapeutic oncology landscape with the development of many new molecules and therapeutic

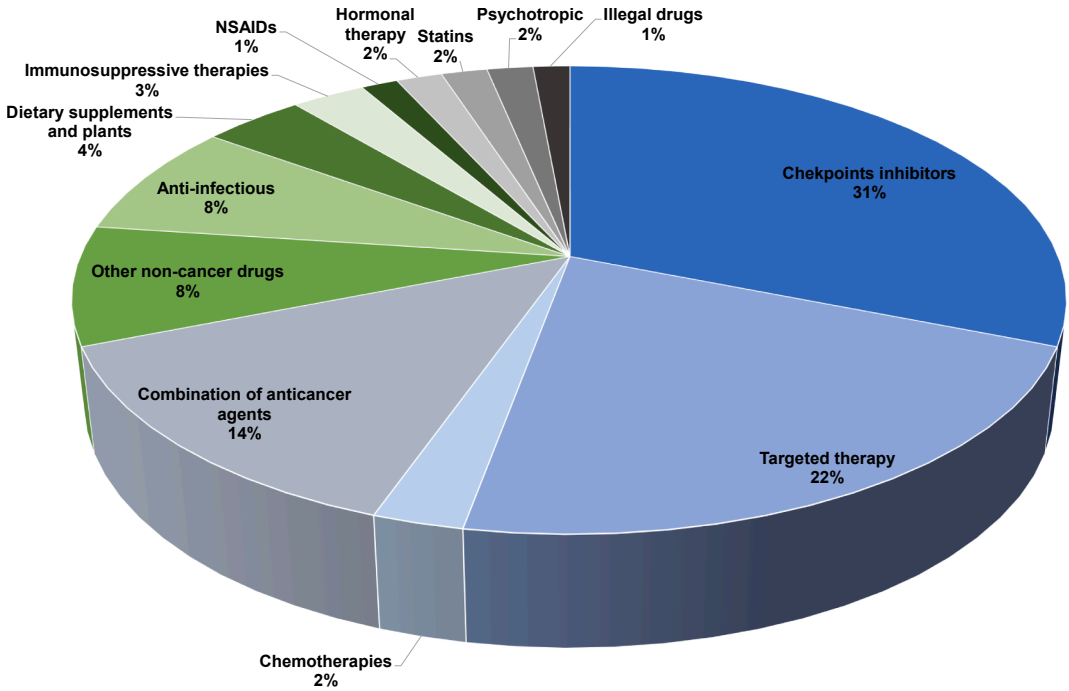

Figure 2. Distribution of therapeutic classes implicated in submitted cases. Distribution of drug classes implicated in DILI cases reported in the REFHEPS cohort. ICIs were the most frequently involved agents (31%), followed by targeted therapies (22%), combinations of anticancer agents (14%), anti-infectious drugs (8%), and other noncancer drugs (8%). Less frequent categories included dietary supplements and plants (4%), immunosuppressive therapies (3%), hormonal therapies (2%), statins (2%), psychotropic drugs (2%), chemotherapies (2%), nonsteroidal anti-inflammatory drugs (1%), and illegal drugs (1%).

Table 3. Characteristics of DILI Cases Related to Anticancer Drugs and Non-Anticancer Drugs in the REFHEPS Cohort

Characteristics	Anticancer drugs, n = 193	Non-anticancer drugs, n = 87	*P* value
Age, *y*	61.8 (±12.9) (17–88)	49.7 (±19.2) (12–95)	<.001
Sex			>.999
Male	76 (39.4)	34 (39.1)	
Female	117 (60.6)	53 (61.0)	
Alcohol consumption			.881
Chronic	15 (7.8)	7 (8.1)	
Occasionally	38 (19.7)	18 (20.7)	
Never	44 (22.8)	23 (26.4)	
Unknown	96 (49.7)	39 (44.8)	
Time to onset, *d*	142.9 (±241.6)	120.5 (±245.4)	.048
Laboratory parameters at onset			
AST, *IU/L*	297.0 (±429.2)	747.6 (±1135.8)	<.001
ALT, *IU/L*	393.3 (±415.6)	815.5 (±867.2)	<.001
ALP, *IU/L*	348.3 (±453.6)	344.6 (±421.0)	.859
GGT, *IU/L*	395.4 (±485.4)	518.2 (±836.4)	.448
TBL, *μmol/L*	28.1 (±60.7)	93.5 (±116.9)	<.001
INR	1.13 (±0.3)	1.19 (±0.542)	.721
Laboratory parameters at peak			
ALT, *IU/L*	691.2 (±936.3)	1092.0 (±1403.4)	.008
ALP, *IU/L*	494.8 (±584.1)	424.9 (±583.2)	.251
TBL, *μmol/L*	56.5 (±101)	144.4 (±185.6)	**<.001**
INR	1.19 (±0.5)	1.19 (±0.5)	.487
Liver biopsy	93 (48.2)	39 (44.9)	.695
Delay DILI-biopsy, *d*	48.9 (±61.7)	36.4 (±100.3)	<.001
Hospitalization	47 (24.4)	37 (42.5)	.003
DILI pattern			.046
Hepatocellular	99 (51.3)	53 (60.9)	
Cholestatic	65 (33.7)	17 (19.5)	
Mixed	26 (13.5)	17 (19.5)	
Other	3 (1.6)	0 (0)	
RUCAM imputability			.154
Highly probable	54 (28.0)	15 (17.2)	
Probable	89 (46.1)	48 (55.2)	
Possible	47 (24.4)	24 (27.6)	
Improbable	3 (1.6)	0 (0)	
DILI-N imputability			.121
Highly probable	63 (32.6)	18 (20.7)	
Probable	87 (45.1)	49 (56.3)	
Possible	40 (20.7)	20 (23.0)	
Improbable	3 (1.6)	0 (0)	
DILI-N severity			.082
Mild	92 (47.7)	32 (36.8)	
Moderate	58 (30.1)	24 (27.6)	
Moderate-severe	34 (17.6)	20 (23.0)	
Severe	3 (1.6)	3 (3.5)	
Fatal	6 (3.1)	8 (9.2)	
DILI clinical symptoms	44 (22.8)	47 (54.0)	<.001
DILI treatment	125 (64.8)	46 (52.9)	.079
Steroids	107 (55.7)	20 (23.5)	<.001
UDCA	50 (26.0)	15 (17.7)	.172
N-acetylcysteine	0 (0)	15 (26.8)	<.001
Outcome			.049
Recovery	105 (54.4)	36 (41.4)	
Improvement	39 (20.2)	23 (26.4)	

Table 3. Continued

Characteristics	Anticancer drugs, n = 193	Non-anticancer drugs, n = 87	*P* value
Chronic	22 (11.4)	12 (13.8)	
Death	5 (2.6)	3 (3.5)	
Liver transplantation	1 (0.5)	5 (5.8)	
Time to recovery, *d*	85.4 (±123.2)	80.1 (±87.0)	.317
Rechallenge	19 (9.8)	10 (11.5)	>.999

NOTE. Data are presented as number (%) or mean (standard deviation) (minimum-maximum).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILI-N, Drug-Induced Liver Injury Network; GGT, gamma-glutamyl transferase; NA, not applicable; REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; TBL, total bilirubin level; UDCA, ursodeoxycholic acid.

combinations that can induce DILI. The recent use of such treatments has been associated with the description of new side effects, especially hepatic ones, that were not previously reported. For example, nivolumab- and ipilimumab-induced liver injury appeared for the first time in the results of the Pro-Euro DILI registry published in 2022, whereas these molecules had not been reported to such an extent in previous papers.[22]

The Belgian-French DILI registry (REFHEPS) was established to enhance knowledge of DILI in Europe. It leverages the specific health care context of France and Belgium, which facilitates the identification of rare cases and promotes close collaboration between hepatologists and oncologists to improve understanding and clinical management.

As mentioned above, REFHEPS is the most recent DILI registry, and its cohort has some similarities with most of the previous studies, such as the age, distribution pattern of liver injury, and the severity reflected by the mortality rate and the LT rate (Table 4). In addition, similar to the Spanish DILI registry, we observed an age-related effect on the pattern of liver injury, with a more cholestatic profile in older people.[9] However, the REFHEPS cohort has 4 notable differences from previous cohorts (Table 4). The first is the important detection rate; in fact, 280 idiosyncratic DILI cases were collected and analyzed in 2.5 years. As mentioned above, this high rate can be partly explained by the high oncological activity in the centers where the cases were collected. This high rate also highlights the likely gap between the true incidence of DILI and the number of reported cases. Indeed, we can hypothesize that a large proportion of cases would not have been reported without the REFEHPS registry. In addition, REFHEPS offers its 380 members a consultation service on the diagnosis and management of DILI within 24 to 48 hours, which contributes to the collection of new cases. Secondly, histological confirmation of DILI was more frequent compared with other registries. Liver biopsy was performed in 132 cases (47.1%). Finally, as already discussed, antineoplastic agents, particularly ICIs, were the main therapeutic class responsible for 68.9% of cases, while they were under-represented in the previous cohorts. As a result, we were able to compare cases of DILI caused by anticancer drugs with those caused by non-anticancer drugs. We observed that the cholestatic pattern was more common in oncological DILI and that patients in this group were older. Interestingly, treatment (corticosteroids or UDCA) was started more often, whereas liver injury was less severe overall in oncological DILI. Liver biopsy was also more common in this group, at least partly because liver damage is associated with the use of newer drugs with a less well-described overall toxicity profile. As the issue of drug reintroduction may be critical in some oncology patients, we can at least partly explain the high rate of liver biopsy performed by the need to have histological confirmation of the diagnosis of DILI and to exclude other causes of liver injury. The higher rate of the use of corticosteroids or UDCA may certainly be explained by the discrepancies between oncological and hepatological guidelines not only in terms of treatment but also in terms of severity classification.[15] We can also hypothesize that the high rate of histological data in the anticancer drug group induced a high rate of treatment of DILI. It is also important to note that anticancer drugs are one of the causes of acute liver failure and even DILI-related death, whereas they were less prevalent in previous cohorts.

The strengths of our study are the prospective collection in a homogeneous database, the adjudication made by expert hepatologists, and the large number of liver biopsies to confirm diagnosis. Some limitations should also be acknowledged. Indeed, DILI cases managed by general practitioners are certainly under-represented in our cohort, as data were mainly reported by specialists. As a result, the hepatotoxicity of some "classical" drugs may be largely under-reported. The number of patients treated during the studied period was not available; therefore, solid conclusions about incidence of DILI could not be withdrawn. Finally, the study did not include biomarkers to predict clinical course.

Conclusions

In conclusion, we report here the first data from REFHEPS, a new French and Belgian DILI registry established at the end of 2021. Between January 2022

Table 4. Comparison of DILI Registries

	DILIN, United States, prospective registry, N = 899	Iceland, prospective population-based study, N = 96	China, retrospective case series, N = 25 927	INDILI, India, prospective case series, N = 1288	Spanish DILI prospective registry, N = 843	LATINDILI, Latin America prospective registry, N = 468	REFHEPS, French and Belgian prospective registry, N = 280
Recruiting period	September 1, 2004–May 16, 2013	March 1, 2010–February 29, 1012	January 1, 2012–December 31, 2014	2013–2018	1994–2018	2011–July 2022	January 1, 2022–June 30, 2024
Acetaminophen-induced DILI	No	No	Not mentioned	No	No	No	Yes
Inclusion criteria	ALT or AST >5 ULN or ALP >2 times ULN or TBL >2.5 mg/dL or INR >1.5 with any elevations in AST/ALT/ALP level	ALT or AST >5 ULN and/or ALP >2 times ULN	Based on diagnoses at discharge: "drug induced liver injury," "drug-induced hepatitis," …	ALT or AST >5 ULN or ALP >2 times ULN without symptoms or TBL >2 mg/dL or symptoms of liver injury with AST or ALT > 3 ULN	ALT >5 ULN and/or ALP >2 ULN, or ALT >3 ULN in combination with TBL >2 ULN	ALT >5 ULN and/or ALP >2 ULN, or ALT >3 ULN in combination with TBL >2 ULN	ALT >5 ULN and/or ALP >2 ULN, or ALT >3 ULN in combination with TBL >2 ULN
Age, *y* (SD, range, or distribution) and gender	49 ± 17 Females 59%	55 (16–91) Females 56%	>60: 22.09% 40–59: 42.73% 18–39: 30.89% <18: 4.29% Females 49.17%	43 ± 16.5 Females 48.6%	54 ± 18 (11–91) Females 48%	49 ± 18 Females 62%	58 ± 16.1 Females 60.7%
Patterns of DILI							
Hepatocellular	53.8%	42%	51.39%	29.7%	57%	62%	54.3%
Cholestatic	23.4%	32%	20.31%	42.8%	21%	24%	29.3%
Mixed	22.8%	26%	28.30%	27.4%	22%	14%	15.4%
Liver-related death/non-liver related death/liver transplantation	3%/3.2%/4%	0%/1%/0%	0.28%/0.11%/0.01%	6.3%/6.1%/0%	2.1%/1.7%/1.5%	2.1%/1.3%/1.9%	Death 2.9%/liver transplantation 2.1%
Top 5 implicated drug classes	Antimicrobials (45%) HDS (16%) Cardiovascular agents (10%) Central nervous system agents (9%) Antineoplastic agents (5%) Analgesics (3%)	Antimicrobials (37%) HDS (16%) Immunosuppressant drugs (10%) Psychotropic drugs (7%) Analgesics (6%)	Traditional Chinese medicine and HDS (26.81%) Anti-tuberculosis (TBC) drugs (21.99%) Antineoplastics or immunomodulators (8.34%) Anti-infectious agents (6.08%) Psychotropics (4.90%)	Anti-TBC drugs (46.4%) HDS (13.9) Anti-epileptic drugs (8.1%) Antimicrobials non anti-TBC (6.5%) Anti-metabolites (3.8%)	Antimicrobials (40%) Central nervous system drugs (16%) Musculoskeletal drugs (12%) Cardiovascular agents (11%) Antineoplastics or immunomodulators (7.8%)	Antimicrobials (31%) Musculoskeletal drugs (12%) Antineoplastics or immunomodulators (11%) Analgesics (NSAIDs) (10%) HDS (9%)	Antineoplastics (69%) Antimicrobials (8%) HDS (4%) Immunomodulators (3%) Hormonal therapy/statin/psychotropic drug (2%)
Drugs responsible for acute liver failure/liver transplantation/death	Antimicrobials, cardiovascular agents, central nervous system agents,	One DILI-associated death due to a combination of amoxicillin, clarithromycin, and rabeprazol,	Mainly anti-TBC drugs and traditional Chinese medicine	Anti-TBC drugs, complementary and alternative medicine, anti-epileptic drugs, central nervous system agents, dapsone, antifungal, anti-	Amoxicillin-clavulanate, anti-TBC drugs, ibuprofen, flutamide, levofloxacin,	NSAIDs and anti-rheumatic drugs, anti-infectious, genitourinary system and sex hormones, antineoplastic and immunomodulators, anticonvulsants, cardiovascular	Olanzapine, amoxicillin–clavulanate, atezolizumab, atezolizumab plus bevacizumab,

Table 4. Continued

	DILIN, United States, prospective registry, N = 899	Iceland, prospective population-based study, N = 96	China, retrospective case series, N = 25 927	INDILI, India, prospective case series, N = 1288	Spanish DILI prospective registry, N = 843	LATINDILI, Latin America prospective registry, N = 468	REFHEPS, French and Belgian prospective registry, N = 280
	antineoplastics, and analgesics	as well as fluconazole		retroviral drugs, chemotherapeutic, hormone, methotrexate, NSAIDs, statins	nimesulide, and carbamazepine	system, anti-virals, anesthetics, antithyroid	carboplatin plus pembrolizumab plus paclitaxel, pembrolizumab, and cocaine
% of antineoplastic agents	5%	5%	8.34% (antineoplastics or immunomodulators)	3.8% (antimetabolites)	2%	11% (antineoplastics or immunomodulators)	69%
Liver biopsy, *n*	249 (until October 29, 2010)	11	Not mentioned	Not mentioned	141	80	132

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; HDS, herbal and dietary supplements; NSAID, nonsteroidal anti-inflammatory drugs; REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; SD, standard deviation; TBC, tuberculosis; TBL, total bilirubin; ULN, upper limit of normal.

and June 2024, 280 cases of idiosyncratic DILI were collected, highlighting the importance of DILI and thus the major challenge it can represent. Our study shows sex- and age-related differences: women were younger and more likely to develop hepatocellular DILI, whereas patients over 65 years of age had less severe cholestatic/mixed liver injury with a later onset. The most significant difference compared with previous registries is the predominance of anticancer drugs causing liver injury, demonstrating the emergence of "new" side effects associated with the use of innovative therapies, especially ICIs. The large number of cases of DILI in oncology patients reinforces the need for prospective studies to better characterize the hepatic damage caused by anti-cancer drugs. Better characterization will also enable better management of these liver toxicities.

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Yves Horsmans (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Dominique Larrey (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Validation: Equal; Writing – original draft: Equal)

Conflicts of interest
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