2nd June 2022

Data analysis report

Prevalence of Acute Liver Injury

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1. Rationale and background

A study on prevalence of acute liver injury was requested to support regulatory decision making process on an orphan application in the indication of acute liver failure of any cause.

Acute liver injury is defined as a sudden appearance of liver test abnormalities (increased liver enzymes or markers of abnormal liver function) that range from mild abnormal biochemical liver values to acute liver failure [1-3].

It was of interest to obtain data on the yearly prevalence of acute liver injury in the European population, overall, and stratified by age group and gender. Drug-induced liver injury (DILI) is an important cause of acute liver injury. The incidence of DILI has been estimated at around 10-200 per million persons per year [4-8] with slightly higher rates of up to 260 per million persons per year in mainland China [9].

Acute liver injury can lead to liver failure that is generally estimated to occur in fewer than 10 cases per million persons per year [11] with a recent estimate from Germany at around 11.3 per million per year [12]. According to Orphanet, acute liver failure is a rare disease with a prevalence of 1-5 per 10,000 persons. Almost 50% of the patients died within 3 months of the diagnosis.

This study attempted to identify patients at risk of acute liver failure rather than patients already diagnosed with acute liver failure. A sensitivity analysis was conducted that did not include diagnoses codes of acute liver failure.

2. Research question and objectives

The main objective of the study was to estimate the yearly prevalence of acute liver injury in five EU countries (Germany, France, Italy, Romania, and Spain), overall and stratified by gender and age group (0-17 years, 18-49 years, 50-79 years, 80+ years).

3. Research methods

3.1. Study design

This was a descriptive study of the yearly prevalence of acute liver injury, overall and stratified by gender and age group. No hypothesis was tested.

3.2. Setting and study population

The study population included patients visiting general practices in France, Italy, Germany, Romania, and Spain. In Germany paediatric practices were also included as they are part of primary care in children. Patients were considered active during a year if they were observable for at least one day during the year. Patients were considered to be observable between their first and last visit dates or, alternatively, between the date of registering with the practice and until de-registration.

Study period was between January 2016 and December 2020.

3.3. Variables

To distinguish acute from chronic liver injury it was required that the patient had a disease duration of less than 26 weeks [13].

Case definition

A validation study of WHO ICD 10 diagnosis codes for acute liver injury in patients treated with antidepressants has been published [3]. A set of specific codes was identified that had a high positive predictive value for acute liver injury, including the WHO ICD 10 codes K71.0 (toxic liver disease with cholestasis), K71.1 (toxic liver disease with hepatic necrosis), K71.2 (toxic liver disease with acute hepatitis), K71.6 (toxic liver disease, not elsewhere classified), K71.9 (toxic liver disease, unspecified), K72.0 (acute and subacute hepatic failure) and K72.9 (hepatic failure, unspecified), K75.9 (inflammatory liver disease, unspecified), and K76.2 (central haemorrhagic necrosis of liver). However, of interest for this study were also specifically ischaemic, autoimmune, viral and other forms of acute and subacute liver injury, including Wilson's disease [10]. These conditions represent both patients without chronic liver disease that experience acute liver injury, and patients with chronic liver disease due to Wilson's disease, autoimmunity, or reactivation of chronic viral hepatitis who are at risk of acute liver failure [10]. For this reason, a broader set of diagnosis codes was used. However, to avoid acute-on-chronic liver injury, chronic hepatitis not elsewhere classified (WHO ICD 10 code K73), chronic liver failure (WHO ICD 10 code K72.1), and fibrosis and cirrhosis of liver (WHO ICD 10 code K74) were not considered.

We identified acute liver injury based on the WHO ICD 10 codes B15 (acute hepatitis A), B16 (acute hepatitis B), B17 (other acute hepatitis), B18 (chronic viral hepatitis), B19 (unspecified viral hepatitis), B25.1 (cytomegaloviral hepatitis), B58.1 (toxoplasma hepatitis), B94.2 (sequelae of viral hepatitis), E83.0 (disorders of copper metabolism), K71.0 (toxic liver disease with cholestasis), K71.1 (toxic liver disease with hepatic necrosis), K71.2 (toxic liver disease with acute hepatitis), K71.6 (toxic liver disease, not elsewhere classified), K71.9 (toxic liver disease, unspecified), K72.0 (acute and subacute hepatic failure), K72.9 (hepatic failure, unspecified), K75 (inflammatory liver disease), K76 (other diseases of liver), O14.2 (HELLP syndrome), T39.1 (poisoning by 4-aminophenol derivatives) and Y45.5 (adverse effects of therapeutic use of 4-aminophenol derivatives). Patients were considered to have acute liver injury up to a maximum of 25 weeks and 6 days (181 days) after the acute liver injury diagnosis, except for patients with Wilson's disease (ICD 10 code E83.0) that were considered to have acute liver injury during their entire follow-up time.

A sensitivity analysis excluded diagnoses codes for acute or subacute hepatic failure (WHO ICD 10 codes K72.0 and K72.9).

This case definition is based on etiological factors for acute liver failure described by Stravitz *et al*. [10]

In the THIN® Spain and THIN® Italy databases, diagnoses are recorded using ICD 9 codes. Corresponding ICD 9 codes were identified, please see Annex 2.

3.4. Data sources

The following databases and versions were used:

- IQVIA™ Disease Analyzer France version December 2021
- IQVIA™ Disease Analyzer Germany version December 2021
- THIN® Italy version February 2022
- THIN® Romania version February 2022
- THIN® Spain version February 2022

A brief descriptions of these databases are provided in **Annex 1**.

3.5. Statistical analysis

3.5.1. Main statistical methods

The prevalence was estimated as the number of patients with the condition anytime during the year according to the case definition (i.e. all patients that were observable during the year and had received a diagnosis of acute liver injury during the year or up to 181 days before* the start of the year) per million persons in the population that were observable during the year. The period of 181 days was only applied to the first date when the specific diagnosis was recorded in the patient, but the same patient could contribute to more than one 181-day period if more than one acute liver injury diagnosis was recorded.

* For Wilson's disease no time limit was applied.

All analyses were performed by EMA researchers using SAS Enterprise Guide version 7.15.

3.5.2. Sensitivity analysis

A sensitivity analysis excluded diagnoses codes for acute or subacute hepatic failure (WHO ICD 10 codes K72.0 and K72.9).

3.6. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round a review by an experienced reviewer, while the results from the statistical analysis were reviewed.

The quality control of the data is the responsibility of the data holder.

4. Results

4.1. Descriptive data

Descriptive information in patients with acute liver injury between 2016 and 2020 (or up to 181 days before or ever in the history for Wilson's disease) is shown in Table 1 below. The number of patients by diagnosis code is shown in Annex 3. In all countries, the age at diagnosis was similar with a mean age varying between 52 and 58 years and the median between 53 and 58 years. A high proportion of acute liver injury codes concerned other liver diseases, fatty liver disease (non-alcoholic liver disease), or unspecified liver disease. However, chronic hepatitis C was represented in 23.5% of patients with acute liver injury in Italy (vs. 0.8-6.1% in the other countries), and acute hepatitis C was represented in 17.1% in Spain (vs. 1.4-3.4% in the other countries).

Table 1 Demographics of patients with acute liver injury by data base

Database	No. of patients with acute liver injury	No. of male patients (%)	Mean (median) age at first acute liver injury diagnosis
IQVIA™ Disease Analyzer France	5785	2903 (50.2%)	51.71 (53)
IQVIA™ Disease Analyzer Germany	244,086	125,950 (51.6%)	52.96 (54)
THIN® Italy	3832	2114 (55.2%)	57.61 (58)
THIN® Romania	36,411	17,859 (49.0%)	52.33 (55)
THIN® Spain	19,086	10,428 (54.6%)	54.70 (55)

4.2. Main results

The overall prevalence of a diagnosis indicating acute liver injury showed a high degree of variation between the countries. The lowest prevalence was observed in Italy and France, where the annual prevalence varied from 16,90 to 19,62 per 10,000 (0.17-0.20%) in Italy and from 17,74 to 21,36 per 10,000 (0.18-0.21%) in France. The highest prevalence was observed in Germany and Romania, where the annual prevalence varied from 142,70 to 155,87 per 10,000 (1.43-1.56%) in Germany and from 151,56 to 171,68 per 10,000 (1.52-1.72%) in Romania, please see Table 2 below. The prevalence in Spain was somewhere in-between, with an annual prevalence varying from 37,06 to 53,73 per 10,000 (0.37-0.54%). The prevalence seemed to be slightly decreasing over time, especially in Germany, Italy and Spain, albeit with variation across years. The yearly prevalence by gender is shown in Annex 3, Tables S1-S2, and the yearly prevalence by age group is shown in Annex 3, Tables S3-S6.

In all countries the prevalence increased by age up to the age group 50-79 years that had the highest prevalence. Patients 50-79 years had a 6.4-21.4-fold higher mean prevalence compared to patients 0-17 years. The difference was greatest in Spain, followed by France, Germany, Romania and Italy.

Table 2 Yearly overall prevalence of acute liver injury

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	1447	769,241	18.81 (17.85 - 19.80)
	2017	1594	791,644	20.14 (19.16 - 21.15)
	2018	1710	800,551	21.36 (20.36 - 22.40)
	2019	1695	817,127	20.74 (19.77 - 21.75)
	2020	1343	757,192	17.74 (16.80 - 18.71)
Germany	2016	65,148	4,419,604	147.41 (146.29 - 148.53)
	2017	72,337	4,640,705	155.88 (154.75 - 157.01)
	2018	66,639	4,669,867	142.70 (141.63 - 143.78)
	2019	67,775	4,617,603	146.78 (145.68 - 147.88)
	2020	59,519	4,303,772	138.29 (137.19 - 139.40)
Italy	2016	1000	522,586	19.14 (17.97 - 20.36)
	2017	1057	538,766	19.62 (18.45 - 20.84)
	2018	996	560,415	17.77 (16.69 - 18.91)
	2019	1074	583,366	18.41 (17.33 - 19.54)
	2020	1008	596,571	16.90 (15.87 - 17.97)
Romania	2016	9764	612,760	159.34 (156.22 - 162.51)
	2017	10,695	622,950	171.68 (168.47 - 174.94)
	2018	10,613	634,226	167.34 (164.20 - 170.52)
	2019	10,583	623,169	169.83 (166.63 - 173.06)
	2020	8858	584,436	151.56 (148.45 - 154.73)
Spain	2016	5627	1,061,388	53.02 (51.64 - 54.42)
	2017	5937	1,105,001	53.73 (52.37 - 55.11)
	2018	5792	1,134,621	51.05 (49.74 - 52.38)
	2019	5175	1,152,732	44.89 (43.68 - 46.13)
	2020	4145	1,118,529	37.06 (35.94 - 38.20)

5.1. Other analyses, including sensitivity analyses

Removing diagnoses codes for acute or subacute hepatic failure (WHO ICD 10 codes K72.0 and K72.9) had little impact on the estimates of prevalence of acute liver injury, please see Table 3 below.

The impact was greatest in France, where the yearly prevalence was reduced by between 6.5% and 7.2%, followed by Spain (1.2-1.4% reduction), Romania (0.7-1.6% reduction), Germany (0.8-0.9% reduction) and Italy (0.1-0.4% reduction).

Table 3 Yearly overall prevalence of acute liver injury, excluding diagnoses codes for acute or subacute hepatic failure (WHO ICD 10 codes K720 and K72.9)

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	1344	769,241	17.47 (16.55 - 18.43)
	2017	1480	791,644	18.70 (17.76 - 19.67)
	2018	1599	800,551	19.97 (19.01 - 20.98)
	2019	1585	817,127	19.40 (18.45 - 20.38)
	2020	1263	757,192	16.68 (15.77 - 17.63)
Germany	2016	64,622	4,419,604	146.22 (145.10 - 147.34)
	2017	71,724	4,640,705	154.55 (153.43 - 155.68)
	2018	66,086	4,669,867	141.52 (140.45 - 142.59)
	2019	67,180	4,617,603	145.49 (144.40 - 146.58)
	2020	58,956	4,303,772	136.99 (135.89 - 138.09)
Italy	2016	996	522,586	19.06 (17.89 - 20.28)
	2017	1056	538,766	19.60 (18.44 - 20.82)
	2018	995	560,415	17.75 (16.67 - 18.89)
	2019	1073	583,366	18.39 (17.31 - 19.53)
	2020	1005	596,571	16.85 (15.82 - 17.92)
Romania	2016	9694	612,760	158.20 (155.09 - 161.36)
	2017	10,621	622,950	170.50 (167.29 - 173.74)
	2018	10,446	634,226	164.70 (161.59 - 167.87)
	2019	10,468	623,169	167.98 (164.80 - 171.20)
	2020	8783	584,436	150.28 (147.18 - 153.43)
Spain	2016	5551	1,061,388	52.30 (50.94 - 53.69)
	2017	5868	1,105,001	53.10 (51.76 - 54.48)
	2018	5714	1,134,621	50.36 (49.07 - 51.68)
	2019	5102	1,152,732	44.26 (43.06 - 45.49)
	2020	4091	1,118,529	36.57 (35.46 - 37.71)

The prevalence of liver failure could be estimated from the difference between the prevalence in the main analysis where liver failure was included and the sensitivity analysis where liver failure was excluded. The prevalence of liver failure was lowest in Italy (1.71-7.65 per million) and highest in Romania (114-263 per million).

6. Discussion and Conclusion

6.1. Key results

The estimated overall yearly prevalence of acute liver injury in this study varied from 0.17-0.20% in Italy to 1.52-1.72% in Romania. There was a high degree of variation between countries, despite the fact that all data sources were based on primary care data and patients visiting primary care. Also, although many cases with acute liver injury had a non-specific diagnosis or had a diagnosis of fatty liver disease (non-alcoholic liver disease), there were differences in the distribution of acute liver injury diagnoses between databases including a comparatively high proportion of chronic hepatitis C in Italy (23.5%) and a high proportion of acute hepatitis C in Spain (17.1%). According to a review by ECDC [14] the prevalence of hepatitis C in the population, available from 13 countries, varied from 0.1% in Belgium, Ireland and the Netherlands to 5.9% in Italy. According to ECDC chronic hepatitis may be asymptomatic and the individuals may not know that they are infected. Hence, data derived from notifications of diagnoses reflect national screening and testing practices rather than the actual true burden of disease.

The annual prevalence of acute liver injury increased with age up to an age of 50-79 years and with a mean age around 52-58 years at the time of the first diagnosis.

The overall prevalence of acute liver injury was similar in the sensitivity analysis where codes for liver failure were excluded, indicating that liver failure made only a small or no contribution to the overall prevalence of acute liver injury.

6.2. Interpretation

The yearly prevalence of acute liver injury was estimated based on diagnoses codes. The degree to which the diagnoses codes actually identified the patients of interest with signs of acute and ongoing liver injury was not verified as laboratory test results were not reviewed in the study. It is possible, therefore, that the study may have overestimated the prevalence of acute liver injury. The fact that in many cases nonspecific liver injury codes were used also makes it difficult to identify the type of liver injury or the specific cause of the liver injury.

6.3. Limitations

This study was based on data from patients visiting primary care. Patients not visiting primary care were not included in the study. Patients diagnosed only in secondary care may have been missed, which might limit how well the results are representative of the overall population.

In addition, the study may carry some misclassification of cases as some codes used to identify patients may not be specific enough, despite the use of a validation article (Stravitz *et al*. [10]) to identify them. Moreover, a threshold of 26 weeks to differentiate acute from chronic cases was used, however its robustness was not tested through a sensitivity analysis using a different threshold.

7. References

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Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

The Health Improvement Network (THIN®) Italy

In THIN® Italy data collection started in 2000 and this database is currently able to provide clinical monitoring data of anonymised patients managed by 500 GPs in primary care (including patients' history). The data source of THIN® Italy is electronic health care records. The entire database reaches 900,000 patients (active and non-active), from which 500,000 are currently actively followed. In order to be representative at national and macroregional level, physicians have been recruited in accordance with their universe distribution in terms of geography, age and gender.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries

patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

The Health Improvement Network (THIN®) Romania

THIN® Romania is a primary care healthcare database, including only General Practitioners (574 GPs). The source of data is electronic health care records. Enrolled GPs and their patients are representative of the whole Romanian population in terms of location, demographics and prevalence from the point of view of main chronic health pathologies. Data collection started in 2012.

In Romania, the insured population (background sampled population) numbered 17.1 million individuals (data from 2012). Among these, 8.5 million individuals benefited of healthcare services, in the public system. The number of GPs who worked in the public healthcare system, in 2017 was aproximately 11,000 physicians. They recorded 76 million consultations and issued 71 million prescriptions (data from 2017). The number of deceased patients was of 297,000 individuals, and number of newborns in 2020 was of 179,000 individuals.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

The Health Improvement Network (THIN®) Spain

THIN® Spain is mainly a primary care healthcare database, including practitioners (GP), specialists and pediatricians & nurses. It contains data from approximately 2,000 GPs and 2,400 specialists (cardiology, pulmonology, urology, etc.). THIN® Spain also includes partial activities related to the hospital. THIN® Spain is globally representative of the whole national demographics and prevalence on the main chronic health pathologies. THIN® Spain includes 3,000,000 individuals out of the overall population. Among these, 1,050,000 are active in the previous year and 1,800,000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals. New patients are automatically included into the database, and deceased patients identified in a specific field.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

The THIN® Spain Database has been approved by two Ethics Committees, one from the Community of Madrid (Hospital Ramón Cajal) and one from the Community of Catalonia (Hospital Clinic de Barcelona). These ethics committees reviewed the data collection, protection, and anonymization processes and positively approved THIN® Spain for observational research of medical products (upon protocol submission).

Annex 2 - Codelists

List of WHO ICD 10 codes for acute liver injury (IMS®Disease Analyzer France and Germany, THIN Romania)

WHO ICD 10 code *	Description
B15	Acute hepatitis A
B16	Acute hepatitis B
B17	Other acute hepatitis
B18	Chronic viral hepatitis
B19	Unspecified viral hepatitis
B25.1	Cytomegaloviral hepatitis
B58.1	Toxoplasma hepatitis
B94.2	Sequelae of viral hepatitis
E83.0	Disorders of copper metabolism
I82.0	Budd-Chiari syndrome
K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease, not elsewhere classified
K72.0 **	Acute and subacute hepatic failure
K72.9 **	Hepatic failure, unspecified
K75	Other inflammatory liver diseases
K76	Other diseases of liver
O14.2	HELLP syndrome
T39.1	Poisoning by 4-aminophenol derivatives
Y45.5	Adverse effects of therapeutic use of 4-aminophenol derivatives

* Please see https://icd.who.int/browse10/2019/en#/G10-G14

** A sensitivity analysis excluded diagnoses codes for acute or subacute hepatic failure (WHO ICD 10 codes K720 and K72.9).

List of corresponding WHO ICD 9 codes for acute liver injury (THIN Italy and Spain)

WHO ICD 9 code *	Description
070 (all subcodes)	Viral hepatitis
130.5	Hepatitis due to toxoplasmosis
275.1	Disorders of copper metabolism
453.0	Budd-chiari syndrome
570 **	Acute and subacute necrosis of liver
571.8	Other chronic nonalcoholic liver disease
572	Liver abscess and sequelae of chronic liver disease
572.0	Abscess of liver
572.1	Portal pyemia
572.2 **	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
573	Other disorders of liver
573.0	Chronic passive congestion of liver
573.1	Hepatitis in viral diseases classified elsewhere
573.2	Hepatitis in other infectious diseases classified elsewhere
573.3	Hepatitis, unspecified
573.4	Hepatic infarction
573.8	Other specified disorders of liver
573.9	Unspecified disorder of liver
642.5 (all subcodes)	Severe pre-eclampsia
965.4	Poisoning by aromatic analgesics, not elsewhere classified
E935.4	Pyrazole derivatives causing adverse effects in therapeutic use

* Please see http://www.icd9data.com/2015/Volume1/001-139/default.htm

** A sensitivity analysis excluded diagnoses codes for acute or subacute hepatic failure (WHO ICD 9 codes 570 and 572.2).

Annex 2 – Number of patients with acute liver injury by diagnosis code

IMS®Disease Analyzer France

ICD 10 code	Description	No. of patients
K76.8	OTHER SPECIFIED DISEASES OF LIVER	1918
K76.0	FATTY (CHANGE OF) LIVER NOT ELSEWHERE CLASSIFIED	1312
K76.9	LIVER DISEASE UNSPECIFIED	554
K75.9	INFLAMMATORY LIVER DISEASE UNSPECIFIED	495
K72.0	ACUTE AND SUBACUTE HEPATIC FAILURE	372
B16.9	ACUTE HEPATITIS B	297
K75.8	OTHER SPECIFIED INFLAMMATORY LIVER DISEASE DISEASES	242
B18.2	CHRONIC VIRAL HEPATITIS C	198
B17.1	ACUTE HEPATITIS C	197
B19.9	UNSPECIFIED VIRAL HEPATITIS WITHOUT COMA	153
K72.9	HEPATIC FAILURE UNSPECIFIED	142
K76.6	PORTAL HYPERTENSION	131
B15.9	HEPATITIS A WITHOUT HEPATIC COMA	89
B18.1	CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	48
K76.1	CHRONIC PASSIVE CONGESTION OF LIVER	42
B18.9	CHRONIC VIRAL HEPATITIS UNSPECIFIED	41
K71.6	TOXIC LIVER DISEASE WITH HEPATITIS NOT ELSEWHERE CLASSIFIED	21
B17.8	OTHER SPECIFIED ACUTE VIRAL HEPATITIS	20
E83.0	DISORDERS OF COPPER METABOLISM	16
B94.2	SEQUELAE OF VIRAL HEPATITIS	11
K75.0	ABSCESS OF LIVER	<10
B17.2	ACUTE HEPATITIS E	<10
K76.7	HEPATORENAL SYNDROME	<10

IMS®Disease Analyzer Germany

ICD 10 code	Description	No. of patients
K76.0	FATTY (CHANGE OF) LIVER NOT ELSEWHERE CLASSIFIED	102,684
K76.9	LIVER DISEASE UNSPECIFIED	85,832
K76.8	OTHER SPECIFIED DISEASES OF LIVER	27,240
K75.9	INFLAMMATORY LIVER DISEASE UNSPECIFIED	12,855
B16.9	ACUTE HEPATITIS B	8225
B17.1	ACUTE HEPATITIS C	6175
B15.9	HEPATITIS A WITHOUT HEPATIC COMA	4937
B18.1	CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	4343
B18.2	CHRONIC VIRAL HEPATITIS C	3826
K72.9	HEPATIC FAILURE UNSPECIFIED	2965
K75.8	OTHER SPECIFIED INFLAMMATORY LIVER DISEASE DISEASES	1852
K75.4	AUTOIMMUNE HEPATITIS	1602
B19.9	UNSPECIFIED VIRAL HEPATITIS WITHOUT COMA	1490
K76.1	CHRONIC PASSIVE CONGESTION OF LIVER	1169
B17.2	ACUTE HEPATITIS E	1163
K71.0	TOXIC LIVER DISEASE WITH CHOLESTASIS	986
E83.0	DISORDERS OF COPPER METABOLISM	945
B17.8	OTHER SPECIFIED ACUTE VIRAL HEPATITIS	865
B17.9	ACUTE VIRAL HEPATITIS UNSPECIFIED	848
K76.6	PORTAL HYPERTENSION	700
K75.0	ABSCESS OF LIVER	552
K76.7	HEPATORENAL SYNDROME	499
B18.9	CHRONIC VIRAL HEPATITIS UNSPECIFIED	391
K72.0	ACUTE AND SUBACUTE HEPATIC FAILURE	273
O14.2	HELLP SYNDROME	273
K71.6	TOXIC LIVER DISEASE WITH HEPATITIS NOT ELSEWHERE CLASSIFIED	242
B94.2	SEQUELAE OF VIRAL HEPATITIS	236
I82.0	BUDD CHIARI SYNDROME	163
K75.2	NONSPECIFIC REACTIVE HEPATITIS	155
B18.0	CHRONIC VIRAL HEPATITIS B WITH DELTA AGENT	137
B18.8	OTHER CHRONIC VIRAL HEPATITIS	135
B25.1	CYTOMEGALOVIRAL HEPATITIS	120
K71.2	TOXIC LIVER DISEASE WITH ACUTE HEPATITIS	76
B16.2	ACUTE HEPATITIS B WITH HEPATIC COMA	51
B16.1	ACUTE HEPATITIS B WITH DELTA AGENT COINFECTION WITHOUT HEPATIC COMA	50
B58.1	TOXOPLASMA HEPATITIS	47
K75.1	PHLEBITIS OF PORTAL VEIN	36
Y45.5	ADVERSE EFFECTS IN THERAPEUTIC USE OF 4-AMINOPHENOL DERIVATIVES	32
K76.4	PELIOSIS HEPATIS	29
K71.1	TOXIC LIVER DISEASE WITH HEPATIC NECROSIS	28

ICD 10 code	Description	No. of patients
B16.0	ACUTE HEPATITIS B WITH DELTA AGENT COINFECTION WITH HEPATIC COMA	22
K75.3	GRANULOMATOUS HEPATITIS NOT ELSEWHERE CLASSIFIED	20
B17.0	ACUTE DELTA SUPERINFECTION IN CHRONIC HEPATITIS B	18
T39.1	POISONING WITH 4 AMINOPHENOL DERIVATIVES	14
B15.0	HEPATITIS A WITH HEPATIC COMA	8
K76.3	INFARCTION OF LIVER	7
B19.0	UNSPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA	7
K76.5	HEPATIC VENO OCCLUSIVE DISEASE	5
K76.2	CENTRAL HAEMORRHAGIC NECROSIS OF LIVER	5

THIN Italy

ICD 9 code	Description	No. of patients
571.8	OTHER CHRONIC NONALCOHOLIC LIVER DISEASE	1582
070.54	CHRONIC HEPATITIS C WITHOUT MENTION OF HEPATIC COMA	902
070.9	UNSPECIFIED VIRAL HEPATITIS WITHOUT MENTION OF HEPATIC COMA	465
573.9	UNSPECIFIED DISORDER OF LIVER	204
573.3	HEPATITIS, UNSPECIFIED	194
573.8	OTHER SPECIFIED DISORDERS OF LIVER	163
573	OTHER DISORDERS OF LIVER	115
070.7	UNSPECIFIED VIRAL HEPATITIS C	74
070.51	ACUTE HEPATITIS C WITHOUT MENTION OF HEPATIC COMA	55
573.1	HEPATITIS IN VIRAL DISEASES CLASSIFIED ELSEWHERE	29
572.3	PORTAL HYPERTENSION	28
070.70	UNSPECIFIED VIRAL HEPATITIS C WITHOUT HEPATIC COMA	23
275.1	DISORDERS OF COPPER METABOLISM	15
453.0	BUDD-CHIARI SYNDROME	13
572.0	ABSCESS OF LIVER	11
572.2	HEPATIC ENCEPHALOPATHY	<10
070.59	OTHER SPECIFIED VIRAL HEPATITIS WITHOUT MENTION OF HEPATIC COMA	<10
070.5	OTHER SPECIFIED VIRAL HEPATITIS WITHOUT MENTION OF HEPATIC COMA	<10
070.44	CHRONIC HEPATITIS C WITH HEPATIC COMA	<10
573.0	CHRONIC PASSIVE CONGESTION OF LIVER	<10
570	ACUTE AND SUBACUTE NECROSIS OF LIVER	<10
070.53	HEPATITIS E WITHOUT MENTION OF HEPATIC COMA	<10
573.2	HEPATITIS IN OTHER INFECTIOUS DISEASES CLASSIFIED ELSEWHERE	<10
642.5	SEVERE PRE-ECLAMPSIA	<10
070.52	HEPATITIS DELTA WITHOUT MENTION OF ACTIVE HEPATITIS B DISEASE OR HEPATIC COMA	<10
070.71	UNSPECIFIED VIRAL HEPATITIS C WITH HEPATIC COMA	<10
642.53	SEVERE PRE-ECLAMPSIA, ANTEPARTUM CONDITION OR COMPLICATION	<10
573.4	HEPATIC INFARCTION	<10
070.41	ACUTE HEPATITIS C WITH HEPATIC COMA	<10
572	LIVER ABSCESS AND SEQUELAE OF CHRONIC LIVER DISEASE	<10

THIN Romania

ICD 10 code	Description	No. of patients
K76.9	LIVER DISEASE UNSPECIFIED	16165
K76.0	FATTY (CHANGE OF) LIVER NOT ELSEWHERE CLASSIFIED	10635
K75.9	INFLAMMATORY LIVER DISEASE UNSPECIFIED	2464
B18.2	CHRONIC VIRAL HEPATITIS C	2224
B18.1	CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	1487
B18.9	CHRONIC VIRAL HEPATITIS UNSPECIFIED	811
K75.0	ABSCESS OF LIVER	734
B15.9	HEPATITIS A WITHOUT HEPATIC COMA	644
K75.2	NONSPECIFIC REACTIVE HEPATITIS	572
B17.1	ACUTE HEPATITIS C	522
K72.9	HEPATIC FAILURE UNSPECIFIED	377
B18.0	CHRONIC VIRAL HEPATITIS B WITH DELTA AGENT	347
B16.9	ACUTE HEPATITIS B WITHOUT DELTA AGENT WITHOUT HEPATIC COMA	332
E83.0	DISORDERS OF COPPER METABOLISM	238
B17.8	OTHER SPECIFIED ACUTE VIRAL HEPATITIS	219
K75.3	GRANULOMATOUS HEPATITIS NOT ELSEWHERE CLASSIFIED	184
K71.0	TOXIC LIVER DISEASE WITH CHOLESTASIS	180
K76.6	PORTAL HYPERTENSION	172
K71.2	TOXIC LIVER DISEASE WITH ACUTE HEPATITIS	145
B15.0	HEPATITIS A WITH HEPATIC COMA	132
B16.0	ACUTE HEPATITIS B WITH DELTA AGENT COINFECTION WITH HEPATIC COMA	125
B19.9	UNSPECIFIED VIRAL HEPATITIS WITHOUT COMA	112
K76.7	HEPATORENAL SYNDROME	84
K72.0	ACUTE AND SUBACUTE HEPATIC FAILURE	82
B16.1	ACUTE HEPATITIS B WITH DELTA AGENT COINFECTION WITHOUT HEPATIC COMA	73
K76.1	CHRONIC PASSIVE CONGESTION OF LIVER	56
B17.0	ACUTE DELTA SUPERINFECTION IN CHRONIC HEPATITIS B	49
B94.2	SEQUELAE OF VIRAL HEPATITIS	42
I82.0	BUDD CHIARI SYNDROME	36
K71.1 *	TOXIC LIVER DISEASE WITH HEPATIC NECROSIS	28
B25.1	CYTOMEGALOVIRAL HEPATITIS	17
B19.0	UNSPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA	13
B16.2	ACUTE HEPATITIS B WITH HEPATIC COMA	13
K76.5	HEPATIC VENO OCCLUSIVE DISEASE	13
B17.2	ACUTE HEPATITIS E	13
K75.1	PHLEBITIS OF PORTAL VEIN	11
K76.4	PELIOSIS HEPATIS	10
B58.1	TOXOPLASMA HEPATITIS	<10
K71.6	TOXIC LIVER DISEASE WITH HEPATITIS NOT ELSEWHERE CLASSIFIED	<10
K76.2	CENTRAL HAEMORRHAGIC NECROSIS OF LIVER	<10

ICD 10 code	Description	No. of patients
K76.3	INFARCTION OF LIVER	<10
Y45.5	ADVERSE EFFECTS IN THERAPEUTIC USE OF 4-AMINOPHENOL DERIVATIVES	<10

* There is some uncertainty about this ICD 10 code as the label provided for this code (‘steatoza hepatica’) was not consistent with the code.

THIN Spain

ICD 9 code	Description	No. of patients
571.8	Other chronic nonalcoholic liver disease	8650
070.51	Acute hepatitis C without mention of hepatic coma	3273
573.9	Unspecified disorder of liver	2788
070.3	Viral hepatitis b without mention of hepatic coma	1599
573.3	Hepatitis, unspecified	1328
573.8	Other specified disorders of liver	1130
570	Acute and subacute necrosis of liver	330
070.1	Viral hepatitis A without mention of hepatic coma	202
572.3	Portal hypertension	201
070.54	Chronic hepatitis C without mention of hepatic coma	151
572.0	Abscess of liver	139
070.30	Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta	96
070.9	Unspecified viral hepatitis without mention of hepatic coma	89
070.41	Acute hepatitis C with hepatic coma	65
275.1	Disorders of copper metabolism	64
70	Viral hepatitis	51
453.0	Budd-chiari syndrome	44
573.0	Chronic passive congestion of liver	40
572.1	Portal pyemia	24
573	Other disorders of liver	24
E935.4	Aromatic analgesics, not elsewhere classified, causing adverse effects in therapeutic use	20
572.4	Hepatorenal syndrome	19
572.2	Hepatic encephalopathy	16
070.32	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta	15
070.44	Chronic hepatitis C with hepatic coma	14
070.53	Hepatitis E without mention of hepatic coma	<10
070.52	Hepatitis delta without mention of active hepatitis B disease or hepatic coma	<10
070.0	Viral hepatitis A with hepatic coma	<10
070.31	Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta	<10
070.20	Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta	<10
070.6	Unspecified viral hepatitis with hepatic coma	<10
130.5	Hepatitis due to toxoplasmosis	<10
642.54	Severe pre-eclampsia, postpartum condition or complication	<10
642.53	Severe pre-eclampsia, antepartum condition or complication	<10
070.2	Viral hepatitis b with hepatic coma	<10
070.5	Other specified viral hepatitis without mention of hepatic coma	<10
572	Liver abscess and sequelae of chronic liver disease	<10

ICD 9 code	Description	No. of patients
070.42	Hepatitis delta without mention of active hepatitis B disease with hepatic coma	<10
642.50	Severe pre-eclampsia, unspecified as to episode of care or not applicable	<10
070.59	Other specified viral hepatitis without mention of hepatic coma	<10
573.1	Hepatitis in viral diseases classified elsewhere	<10

Annex 3 – Yearly prevalence of acute liver injury by gender and age group

Table S 1 Yearly overall prevalence of acute liver injury in males

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	712	367,791	19.36 (17.96 - 20.83)
	2017	792	377,798	20.96 (19.53 - 22.47)
	2018	863	381,810	22.60 (21.12 - 24.16)
	2019	839	387,153	21.67 (20.23 - 23.19)
	2020	690	355,585	19.40 (17.98 - 20.91)
Germany	2016	33,323	2,114,265	157.61 (155.94 - 159.30)
	2017	37,224	2,228,846	167.01 (165.33 - 168.70)
	2018	34,292	2,250,524	152.37 (150.78 - 153.98)
	2019	34,851	2,230,629	156.24 (154.62 - 157.87)
	2020	30,632	2,070,297	147.96 (146.32 - 149.61)
Italy	2016	547	243,628	22.45 (20.61 - 24.41)
	2017	573	251,245	22.81 (20.98 - 24.75)
	2018	536	261,167	20.52 (18.82 - 22.33)
	2019	596	270,593	22.03 (20.29 - 23.86)
	2020	571	275,629	20.72 (19.05 - 22.49)
Romania	2016	4769	275,280	173.24 (168.40 - 178.19)
	2017	5139	280,254	183.37 (178.43 - 188.40)
	2018	5035	285,002	176.67 (171.86 - 181.57)
	2019	5074	280,031	181.19 (176.29 - 186.20)
	2020	4474	263,358	169.88 (164.98 - 174.89)
Spain	2016	3099	513,041	60.40 (58.30 - 62.56)
	2017	3250	536,742	60.55 (58.49 - 62.66)
	2018	3167	552,766	57.29 (55.32 - 59.32)
	2019	2846	562,672	50.58 (48.74 - 52.47)
	2020	2190	548,466	39.93 (38.28 - 41.63)

Table S 2 Yearly overall prevalence of acute liver injury in females

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	735	401,450	18.31 (17.01 - 19.68)
	2017	802	413,846	19.38 (18.06 - 20.77)
	2018	847	418,741	20.23 (18.89 - 21.64)
	2019	856	429,974	19.91 (18.60 - 21.29)
	2020	653	401,607	16.26 (15.04 - 17.55)
Germany	2016	31,825	2,305,339	138.05 (136.55 - 139.56)
	2017	35,113	2,411,859	145.58 (144.08 - 147.10)
	2018	32,347	2,419,343	133.70 (132.26 - 135.16)
	2019	32,924	2,386,974	137.93 (136.46 - 139.42)
	2020	28,887	2,233,475	129.34 (127.86 - 130.83)
Italy	2016	453	278,958	16.24 (14.78 - 17.80)
	2017	484	287,521	16.83 (15.37 - 18.40)
	2018	460	299,248	15.37 (14.00 - 16.84)
	2019	478	312,773	15.28 (13.94 - 16.71)
	2020	437	320,942	13.62 (12.37 - 14.95)
Romania	2016	4995	337,480	148.01 (143.96 - 152.14)
	2017	5556	342,696	162.13 (157.92 - 166.41)
	2018	5578	349,224	159.73 (155.59 - 163.94)
	2019	5509	343,138	160.55 (156.37 - 164.81)
	2020	4384	321,078	136.54 (132.55 - 140.61)
Spain	2016	2528	548,347	46.10 (44.33 - 47.93)
	2017	2687	568,259	47.28 (45.52 - 49.10)
	2018	2625	581,855	45.11 (43.41 - 46.87)
	2019	2329	590,060	39.47 (37.89 - 41.10)
	2020	1955	570,063	34.29 (32.79 - 35.85)

Table S 3 Yearly overall prevalence of acute liver injury in the age group 0-17 years

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	46	152,028	3.03 (2.22 - 4.04)
	2017	32	184,655	1.73 (1.19 - 2.45)
	2018	46	183,048	2.51 (1.84 - 3.35)
	2019	55	180,238	3.05 (2.30 - 3.97)
	2020	46	152,028	3.03 (2.22 - 4.04)
Germany	2016	2328	976,079	23.85 (22.89 - 24.84)
	2017	2643	1,011,011	26.14 (25.16 - 27.16)
	2018	2478	1,006,451	24.62 (23.66 - 25.61)
	2019	2310	980,281	23.56 (22.61 - 24.54)
	2020	1858	875,808	21.21 (20.26 - 22.20)
Italy	2016	<10	-	3.22 (1.47 - 6.10)
	2017	<10	-	2.90 (1.25 - 5.72)
	2018	13	27,456	4.73 (2.52 - 8.10)
	2019	17	27,684	6.14 (3.58 - 9.83)
	2020	<10	-	2.65 (1.07 - 5.46)
Romania	2016	467	139,610	33.45 (30.49 - 36.62)
	2017	451	140,772	32.04 (29.15 - 35.13)
	2018	491	142,890	34.36 (31.39 - 37.53)
	2019	488	139,442	35.00 (31.96 - 38.24)
	2020	340	129,071	26.34 (23.62 - 29.29)
Spain	2016	88	200,431	4.39 (3.52 - 5.41)
	2017	90	205,864	4.37 (3.52 - 5.37)
	2018	92	208,057	4.42 (3.56 - 5.42)
	2019	96	207,234	4.63 (3.75 - 5.66)
	2020	77	195,697	3.93 (3.11 - 4.92)

Table S 4 Yearly overall prevalence of acute liver injury in the age group 18-49 years

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	536	304,419	17.61 (16.15 - 19.16)
	2017	603	328,429	18.36 (16.92 - 19.88)
	2018	683	330,506	20.67 (19.15 - 22.27)
	2019	654	335,008	19.52 (18.06 - 21.08)
	2020	536	304,419	17.61 (16.15 - 19.16)
Germany	2016	23,418	1,607,178	145.71 (143.86 - 147.57)
	2017	25,898	1,693,384	152.94 (151.09 - 154.80)
	2018	23,432	1,699,404	137.88 (136.14 - 139.65)
	2019	23,079	1,663,369	138.75 (136.98 - 140.54)
	2020	19,873	1,533,496	129.59 (127.81 - 131.40)
Italy	2016	283	223,377	12.67 (11.24 - 14.23)
	2017	316	226,419	13.96 (12.46 - 15.58)
	2018	301	231,027	13.03 (11.60 - 14.59)
	2019	257	235,102	10.93 (9.64 - 12.35)
	2020	257	234,403	10.96 (9.67 - 12.39)
Romania	2016	3472	218,037	159.24 (154.03 - 164.58)
	2017	3847	218,599	175.98 (170.51 - 181.58)
	2018	3649	216,588	168.48 (163.10 - 173.98)
	2019	3537	207,445	170.50 (164.98 - 176.17)
	2020	2915	191,692	152.07 (146.64 - 157.65)
Spain	2016	1859	483,309	38.46 (36.74 - 40.25)
	2017	1967	504,167	39.01 (37.31 - 40.77)
	2018	1951	518,337	37.64 (35.99 - 39.34)
	2019	1739	526,198	33.05 (31.52 - 34.64)
	2020	1304	503,746	25.89 (24.50 - 27.33)

Table S 5 Yearly overall prevalence of acute liver injury in the age group 50-79 years

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	700	255,125	27.44 (25.44 - 29.54)
	2017	875	238,906	36.63 (34.24 - 39.13)
	2018	904	245,526	36.82 (34.46 - 39.29)
	2019	897	257,409	34.85 (32.61 - 37.20)
	2020	700	255,125	27.44 (25.44 - 29.54)
Germany	2016	35,109	1,550,135	226.49 (224.15 - 228.84)
	2017	38,756	1,619,755	239.27 (236.92 - 241.64)
	2018	36,010	1,629,743	220.96 (218.70 - 223.22)
	2019	37,126	1,622,036	228.89 (226.59 - 231.20)
	2020	32,852	1,544,932	212.64 (210.37 - 214.93)
Italy	2016	614	228,704	26.85 (24.77 - 29.05)
	2017	632	238,535	26.50 (24.47 - 28.64)
	2018	593	251,062	23.62 (21.76 - 25.60)
	2019	681	264,908	25.71 (23.81 - 27.71)
	2020	650	275,189	23.62 (21.84 - 25.51)
Romania	2016	5544	220,517	251.41 (244.91 - 258.03)
	2017	6058	227,550	266.23 (259.65 - 272.92)
	2018	6137	237,074	258.86 (252.51 - 265.34)
	2019	6194	237,652	260.63 (254.26 - 267.12)
	2020	5269	226,322	232.81 (226.64 - 239.11)
Spain	2016	3383	322,869	104.78 (101.30 - 108.35)
	2017	3601	338,756	106.30 (102.87 - 109.81)
	2018	3490	351,860	99.19 (95.94 - 102.52)
	2019	3096	362,741	85.35 (82.38 - 88.40)
	2020	2527	361,941	69.82 (67.13 - 72.58)

Table S 6 Yearly overall prevalence of acute liver injury in the age group 80 + years

Country	Year	Numerator	Denominator	Prevalence per 10,000 (95% CI)
France	2016	61	45,620	13.37 (10.23 - 17.17)
	2017	84	39,654	21.18 (16.90 - 26.22)
	2018	77	41,471	18.57 (14.66 - 23.20)
	2019	89	44,472	20.01 (16.07 - 24.62)
	2020	61	45,620	13.37 (10.23 - 17.17)
Germany	2016	4293	286,212	149.99 (145.57 - 154.51)
	2017	5040	316,555	159.21 (154.88 - 163.63)
	2018	4719	334,269	141.17 (137.20 - 145.23)
	2019	5260	351,917	149.47 (145.48 - 153.53)
	2020	4936	349,536	141.22 (137.33 - 145.18)
Italy	2016	94	42,517	22.11 (17.87 - 27.05)
	2017	101	46,247	21.84 (17.79 - 26.53)
	2018	89	50,870	17.50 (14.05 - 21.53)
	2019	119	55,672	21.38 (17.71 - 25.57)
	2020	94	60,577	15.52 (12.54 - 18.99)
Romania	2016	281	34,596	81.22 (72.04 - 91.25)
	2017	339	36,029	94.09 (84.38 - 104.60)
	2018	336	37,674	89.19 (79.94 - 99.20)
	2019	364	38,630	94.23 (84.83 - 104.37)
	2020	334	37,351	89.42 (80.12 - 99.49)
Spain	2016	297	54,779	54.22 (48.24 - 60.73)
	2017	279	56,214	49.63 (43.99 - 55.79)
	2018	259	56,367	45.95 (40.53 - 51.88)
	2019	244	56,559	43.14 (37.91 - 48.89)
	2020	237	57,145	41.47 (36.37 - 47.09)