Clinical characteristics and outcome of drug-induced liver injury in the older patients: from the young-old to the oldest-old

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Abstract

Old patients with hepatotoxicity have been scarcely studied in idiosyncratic drug-induced liver injury (DILI) cohorts. We sought for the distinctive characteristics of DILI in older patients across age groups. A total of 882 DILI patients included in the Spanish DILI Registry (33% ≥65 years) were categorized according to age: “young” (<65y); “young-old” (65-74y); “middle-old” (75-84y); and “oldest-old” (≥85y). All elderly groups had increasingly higher comorbidity burden (p<0.001) and polypharmacy (p<0.001). There was a relationship between jaundice and hospitalization (p<0.001), and both were more prevalent in the elderly age groups, especially in the oldest-old (88% and 69%, respectively) and the DILI episode was more severe (p=0.029). The proportion of females decreased across age groups from the young to the middle-old, yet in the oldest-old there was a distinct female predominance. Pattern of liver injury shifted towards cholestatic with increasing age among top culprit drugs amoxicillin-clavulanate, atorvastatin, levofloxacin, ibuprofen, and ticlopidine. The best cut-off point for increased odds of cholestatic DILI was 65y. Older patients had increased non-liver related mortality (p=0.030) as shown by the predictive capacity of MELD (OR=1.116; p<0.001), and comorbidity burden (OR=4.188; p=0.001) in the 6-month mortality. Older patients with DILI exhibited an increasingly predominant cholestatic phenotype across a range of culprit drugs other that amoxicillin-clavulanate, with increased non-liver related mortality and require a different approach to predict outcome. The oldest DILI patients exhibited a particular phenotype with more severe DILI episodes and need to be considered when stratifying older DILI populations.

INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) is a potentially severe adverse drug reaction that challenges clinical drug development and post-marketing clinical use of medicines.[1] DILI typically presents as an array of phenotypes and affects subjects of all ages.[2] Due to an increasing life expectancy worldwide, the population is aging and the proportion of elderly (defined as ≥65 years) is predicted to double over the next 50 years.[3] Especially the group of patients aged 85 years or older ("oldest-old") is significantly growing.[4] Distinct characteristics of the elderly population are a high comorbidity burden and polypharmacy,[5,6] which may increase the likelihood of DILI and complicate its diagnosis.[7,8] In addition, the liver safety of drugs launched to the market is scarcely known in elderly patients as they are often excluded from clinical trials.[5]

More information on the phenotypic presentation of DILI across all ages is key to support both clinicians and the pharmaceutical industry in recognizing DILI in the elderly. However, research in this area is limited. Studies from both the prospective US DILI Network (DILIN)[9] and the Spanish DILI Registry[10] characterized DILI in the elderly by comparing the whole group of elderly to younger patients. Several studies have highlighted that elderly cannot be considered as one homogeneous group but rather as a heterogeneous group with regard to pattern of diseases and pharmacological therapy.[11,12] Consequently, a chronological definition establishing three age groups of elderly (65-75 years; 75-85 years; ≥85 years) has been proposed,[13] whereas in Japan the aging population is stratified in two groups, early-stage (65-75 years) and later-stage elderly (≥75 years).[14]

A retrospective study from Japan specifically compared the characteristics of DILI across different age groups of elderly (<65 years; 65-74 years; and ≥75 years),[14] yet the number of elderly patients was limited. In addition, this study did not specifically analyze the oldest-old. Therefore, the aim of this study was to assess the potential differences in the phenotypic presentation of DILI, its severity, and causative agents in patients of older age, ranging from the young-old to the oldest-old.

METHODS

Study population

All cases of idiosyncratic DILI from the Spanish DILI registry collected from 1994 to 2018 were included. In-depth details of this registry have been described elsewhere.[15] In short, suspected DILI cases were assessed for: (1) the compatibility of the time span between medicine intake and onset of symptoms, (2) all biochemical, histological, and imaging data to exclude alternative (liver) diseases, and (3) the outcome of the liver injury. Afterwards, CIOMS/RUCAM scale was applied.

Patients were categorised into age groups based on their age at DILI onset. For comparative purposes, patients were categorised in a 3-group scale, merging the middle- and oldest-old age groups (<65 years, 65-74 years, ≥75 years). Preliminary analysis with 5-year age groups resulted in too small groups with overlapping characteristics. Thus, patients were classified into the following 10-year groups: <65 years (young), 65-74 years (young-old), 75-84 years (middle-old) and ≥85 years (oldest-old).[13,16,17]

The Charlson Comorbidity Index (CCI), as measure of the comorbidity burden, was calculated.[18] In the CCI, underlying liver disease is only scored in case of chronic hepatitis or cirrhosis. Culprit drugs were classified using the Anatomical Therapeutic Chemical (ATC) of the World Health Organization. Hospitalization costs were estimated using the hospital adjusted expenses per inpatient day.[19]

Using the laboratory parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP)) at DILI recognition, the R-ratio was calculated, and the pattern of liver injury classified into: hepatocellular (R≥5), mixed (R>2 and R<5) or cholestatic injury (R≤2). The severity of the DILI episode was calculated using the DILI severity index.[20]

Patients were followed for a minimum of six months after DILI recognition. The number of patients adhering to the new Hy's law was calculated.[21]

The study protocol was approved by the local Ethics Committee at the Virgen de la Victoria University Hospital in Málaga, Spain, and all subjects gave informed consent.

Statistical analyses

Differences across age groups were assessed with the exact Chi-square linear trend test and the Kendall's Tau correlation coefficient for categorical variables, and the ANOVA or Kruskal-Wallis test, as appropriate, for continuous variables. Post hoc analysis with Bonferroni correction were performed afterwards. Multivariate logistic regression models were fitted including age as continuous or categorical variable. Tests were 2-sided, a p value<0.05 was deemed statistically significant. IBM SPSS v24 (IBM Corp) was used for the statistical analyses.

RESULTS

In total, 882 idiosyncratic DILI cases (mean age 54y, 48% female), were retrieved from the database. These were classified by age into the following groups: young (<65y; n=589), and the remaining 293 (33%, 44% females) cases into young-old (65-74y; n=169), middle-old (75-84y; n=108) and oldest-old (≥85y; n=16). The distribution of DILI cases according to age groups in the Spanish registry did not point towards increased DILI prevalence in older ages.

Demographics and comorbidities

Demographic characteristics and comorbid conditions of the patients are shown in Table 1. The proportion of males increased with age from 50% in the young population to 66% in the middle-old. Noticeably, in the oldest-old, only 25% of cases were male (p=0.011 vs. middle-old). This change in the trend of male predominance was already suggested in the group ≥80y (Table 2). With increasing age, the CCI also was raised: elderly age groups had a significantly higher scores compared to the young patients. In the oldest-old, cerebrovascular disease (19%), dementia (19%), renal disease (25%), and diabetes (31%) were more prevalent, and differed from the <65 years group. By contrast, there was a significant lower prevalence of underlying liver diseases with increasing age. The number of concomitant medications increased to a median of 3 (IQR 2-5) in the middle-old and oldest-old. Demographic characteristics showed similar differences across age groups (Table 2 and Table S1).

Causative agents

For all age groups, anti-infectives were the most frequently involved causative agents, contributing for around 40% of cases in the young, young-old and middle-old, and 69% in the oldest-old, with a large proportion of cases attributable to amoxicillin-clavulanate (Table 3). The high frequency of anti-infectives (particularly amoxicillin-clavulanate), remained in the group of patients ≥80 years (Table 2). The second most frequently causative agents in the young and the oldest-old were central nervous system drugs, while in the young-old and middle-old were cardiovascular agents. On the third place were musculoskeletal system drugs for the young, young-old and middle-old and cardiovascular agents for the oldest-old. The main culprit drugs according to age group are shown in Table 3 and Table S2.

Clinical features and phenotypic presentation

The prevalence of hypersensitivity features was not different among the groups, yet the proportion of patients presenting lymphopenia increased with age (p=0.002). The time to DILI onset and the duration of therapy were comparable across the age groups.

The proportion of cholestatic injury increased with age, from 14% in the young, 26% in both the young-old and middle-old (p=0.001 and p=0.008 vs. young) and reaching 50% of cases in the oldest-old (p<0.001 vs. young). Accordingly, ALP values increased with age, with the highest values in the oldest-old (p<0.001 vs. young), whilst ALT values decreased with age. Indeed, mean elevation of ALP levels in patients aged 65 and over was 2.8xULN, while cholestatic cases in this age range showed a mean elevation of 5xULN in ALP levels. There were higher levels of total bilirubin, creatinine, and glucose with increasing age (Table 4). Differences in the phenotypic presentation remained unchanged across age classifications (Table 2 and Table S1).

Predictors of the pattern of liver injury in the elderly

In the multivariable regression model, older age was found as a significant predictor of cholestatic injury independently of potential confounders (odds ratio [OR]=1.022; 95% confidence interval [CI] 1.011-1.034, p<0.001). Further, when age was included as a categorical variable, all elderly groups (65-75y; 75-85y; ≥85y) showed increasing odds of cholestatic injury compared to the youngest group (p for trend=0.003). Interestingly, when considering patients aged 55-64y, no higher risk of cholestatic injury compared to the reference group (<55y) was found (OR=1.320; 95% CI 0.805-2.167, p=0.272) (Table 5).

However, no higher odds of cholestatic DILI were seen when neither the number of concomitant medications (OR=1.028; 95% CI 0.939-1.125, p=0.550) nor the comorbidity burden (OR=1.161; 95% CI 0.990-1.362, p=0.066) increased.

Stratified analyses by amoxicillin-clavulanate use showed that increasing age was significantly related with the onset of cholestatic injury both in patients treated and non-treated with amoxicillin-clavulanate (OR=1.039; 95% CI 1.016-1.062, p=0.001 and OR=1.016; 95% CI 1.002-1.029, p=0.023, respectively). A similar shift towards cholestatic injury was found in patients who took atorvastatin, levofloxacin, ticlopidine or ibuprofen (p<0.001). However, in those patients who took drugs with a definite hepatocellular profile, no change in the phenotype in elderly patients was found (p=0.335) (Table S3).

We tested the hypothesis that chronic heart failure and/or a longer time to onset may contribute to the risk of cholestatic injury in the elderly.[14] However, none of these variables were found significantly related with cholestatic DILI in this cohort (OR=1.241, 95% CI 0.603-2.552, p=0.557, and OR=0.999, 95% CI 0.998-1.001, p=0.289, respectively).

Severity

In Figure 1, the prevalence of jaundice and hospitalization due to DILI and the grading of severity of the DILI episode is shown. There was a relationship between jaundice and hospitalization ($p<0.001$), and both features were more prevalent in the elderly age groups, especially in the oldest-old. Indeed, a correlation between hospitalization and bilirubin values at DILI recognition was found ($r_{pb}=0.39$; $p<0.001$). Hospitalization duration increased along age groups. Accordingly, estimated hospitalization costs raised in older groups, from nearly 50,000 US dollars in young cases to over 80,000 dollars in patients aged ≥80 (Table 2). Compared to the young, DILI in the young-old and middle-old was more often of moderate severity while in the oldest-old, the episode was more frequently severe compared to the young (25% vs. 7%; p=0.029). The percentage of patients meeting the new Hy's law did not differ between the groups (Table 4). Of note, the new Hy's law performed as expected, with about 10-13% of liver-related death/liver transplant, except 0% in the oldest-old group which had no true Hy's law cases. As expected, there were no transplant cases in the middle-old and oldest-old groups. The median age of patients who died (liver-related) or underwent a liver transplant was 73 (IQR 73-78) and 67 years old (IQR 65-68), respectively. All these patients had hepatocellular DILI and were predominantly females (56% of liver-related deaths, 100% of liver transplants). The median time to death or liver transplant since the DILI diagnosis were 34 (IQR 22-44) and 17 days (IQR 15-18), respectively.

There were more non-liver related deaths with increasing age during the time of follow-up (p=0.030). The median time to death in these cases was 31 days (IQR 23-51). DILI was deemed as contributing cause of death in seven patients (47%). Distribution of cases across age group is shown in Table 4. Causes of death were multiorgan failure (2 patients), post-transplant complications (2), cardiac arrest (1), amyloidosis and renal insufficiency (1), and respiratory infection in the context of liver failure (1). In the eight patients in whom DILI did not play a role, causes of death comprised malignancies (4 patients), cardiovascular disease (1), lung infarction (1), septic shock (1), cerebral toxoplasmosis (1) and tuberculous meningitis (1).

The 6-month predictive model developed by Ghabril *et al.*[22] was applied in this cohort. MELD score (OR=1.153; 95% CI 1.071-1.240; p<0.001), comorbidity burden (OR=5.721; 95% CI 1.459-22.459; p=0.012) and serum albumin (OR=0.530; 95% CI 0.292-0.962; p=0.037) were independent predictors of liver-related death. However, when overall mortality (including non-liver related) was considered, only MELD score (OR=1.116; 95% 1.066-1.168; p<0.001) and comorbidities (OR=4.188; 95% CI 1.738-10.091; p=0.001) remained as significant predictors (Table 6). Noticeably, serum albumin levels were significantly lower in liver-related death patients than in those with non-liver related deaths (3.01±0.32 vs 3.94±0.28; p=0.049).

Differences in hospitalization, jaundice, severity, and non-liver related death remained significant regardless of age cut-off ≥80 years or ≥75 years (Table 2 and Table S1).

DISCUSSION

With an aging population the prevalence of DILI in the elderly is forecast to increase, making it worthy to focus on the clinical signature of DILI in this population. Furthermore, the National Institute of Health and guidelines are enforcing the inclusion of individuals of all ages, including older patients, in clinical studies.[6,16,17,23,24]

The long history of the Spanish DILI Registry allowed us to prospectively study a substantial number of DILI cases in patients aged 65 years or older, including patients ≥85 years ("oldest-old"), a group that has never been described before. The phenotypic presentation of DILI in these patients exhibited some differential characteristics compared to younger age groups. The high proportion of females in the oldest age group was unexpected considering the male predominance observed in the young-old and middle-old. Indeed, this change was also suggested in the population ≥80 years. Interestingly, when comparing our results in the oldest-old subgroup to data from the Spanish Statistical Institute, the same pattern of gender distribution was found: a lower male to female ratio among the very old,[25] which reflects of women having a longer lifespan than men and underscore the importance of assessing this distinct oldest-old category.

Second, the DILI episode was frequently deemed as more severe in the elderly patients, especially in the oldest-old, being more jaundiced and leading to hospitalization in almost 70% of these patients. Although the overall mortality rate in patients aged ≥65 years was similar to that reported in the US DILIN prospective cohort (6.8% vs 8.7%, respectively),[9] more non-liver related deaths were found with increasing age. In comparison, the US DILIN[9] found a relatively lower severity of DILI in the elderly (≥65 years) compared to the younger patients, although the elderly population represented only 17% of the cases (compared to the 33% in this Registry), with a similar age (73±6 vs 74±6, respectively) and they did not specifically look at different age subgroups. The reason behind an increase in DILI severity in elders is unclear but, in addition to pharmacokinetic and dynamic changes accompanying an aging liver and reduced renal excretion,[5,26] an impaired liver regeneration may contribute.[27]

A higher comorbidity burden in the elderly population may also explain the more severe DILI course and higher non-liver related mortality. A recent study found that a high comorbidity burden is a strong predictor for mortality in patients with DILI.[22] Indeed, our data validates the 6-month predictive model of mortality proposed[22] but only for liver-related fatalities. Interestingly, the albumin component of the model did not perform as a predictor for overall mortality (i.e., including non-liver related death) which indirectly supports the accuracy of the contributory determinants of mortality in the current study.[28] On the other hand, despite a more severe course, the proportion of Hy's law cases did not differ among the groups, the percentage being roughly 10% lower in all elderly age groups compared to the young. This can be related to the predominance of a cholestatic injury pattern suggesting that different approaches to predict a severe DILI outcome in the elderly need to be explored.

Our analysis reinforces the previously described influence of older age in the phenotypic presentation of DILI increasing the odds for a cholestatic presentation.[9,10,14] Furthermore, the odds for presenting this pattern of liver injury were almost 5-times higher in the oldest-old compared to youngest group. Importantly, 65 years seemed to be the best cut-off point for a significantly increased risk of cholestatic DILI, independently of potential confounders such as the number of comedications and the use of amoxicillin-clavulanate, which in fact was the most commonly involved causative agent across age groups. Interestingly, a similar age-dependent change in the clinical signature and biochemical injury pattern compared to younger patients was observed among top culprit drugs of different pharmacological groups, including statins (atorvastatin), NSAID (ibuprofen), antibiotics (levofloxacin) and antithrombotic agents (ticlopidine). Hence, the more frequent cholestatic pattern of injury in older DILI patients seems to be a phenotypic characteristic specifically driven by the host.

The mechanisms underlying the increased risk of cholestatic injury in the old are still unclear. In our study, and contrary to Onji *et al.* hypothesis,[14] neither a longer time to DILI onset nor a diagnosis of chronic heart failure, albeit present in a higher number of elderly patients, increased the odds for cholestatic injury. Remarkably, the pattern of damage of a given drug can change with increasing age, a feature only demonstrated for amoxicillin-clavulanate so far.[29,30] In addition, genetic factors, particularly HLA class I and II alleles, have been also found to influence the phenotypic drug signature.[31-33] An alternative explanation includes the interference with an underlying aging process such as a diminished renal clearance and biliary function, which may favor a more cholestatic liver reaction to drugs.[29] This also would apply for amoxicillin-clavulanate, whose prolonged canalicular excretion and exposure of the bile duct cells might favor an immune response.[34] Previous research indeed noted a higher reporting frequency of DILI events due to drugs with biliary pump inhibition potential and biliary excretion in the elderly.[26,35] Indeed, we do not know the mechanism for shift to cholestatic phenotype with several individual drugs. Although pharmacokinetic changes are age dependent how this or other age-related factors might contribute to this at this time are unknown. More research is needed to better explain the increased risk of cholestatic DILI in older patients and to develop biomarkers for cholestatic DILI.

Our data also add to prior knowledge indicating a more prolonged recovery of cholestatic DILI in the older population,[36] and that older age is a risk factor for chronic DILI.[37] However, according to our data, DILI was less prevalent at older ages captured by enrolment in the registry.

The strength of the study is a well characterized cohort of DILI patients with an adequate follow-up. The large number of DILI cases in the elderly enrolled in the Registry has enabled stratification of older DILI populations in three age groups, demonstrating at the same time the suitability of the proposed age classification. Although our results do emphasize the potential distinct phenotype of DILI in the oldest-old patients, the number of subjects in this group was limited and the results should be further validated in large DILI cohorts.[38] A factor that was not taken into account was the frailty of the patients. Frailty is defined as a multidimensional condition that makes a patient, when exposed to a stressor, vulnerable to adverse health outcomes.[39,40] An underlying phenotype of frailty may also be an explanation for the more severe DILI course in the elderly, yet this should be verified in additional studies.

In summary, elderly patients with DILI have a high comorbidity burden, are polymedicated and have a significant increase in non-liver related mortality as shown by the predictive capacity of MELD and CCI in the 6-month mortality. This supports a possible contributing role of DILI in non-liver related deaths. The oldest-old is a unique group of patients in their response to DILI, with a large proportion of female cases and a more severe liver injury reinforcing the need for further characterization of DILI in the distinct oldest-old category.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Drug-induced liver injury (DILI) in the elderly has been studied only in population categorized as ⩾65 years.

What question did this study address?

We assessed the phenotypic characteristics and outcome of DILI in the young (<65 years), young-old (65-74 years), middle-old (74-84 years) and oldest-old (⩾85 years) patients included in the Spanish DILI Registry and define the most suitable age classification to stratify *older DILI populations.*

What does this study add to our knowledge?

This is the largest study on DILI in elderly patients at different age subgroups and the first to characterize that the oldest-old is a unique group of patients in their response to DILI with female predominance and a more severe injury leading to hospitalization.

Liver damage shifts towards cholestatic with increasing age among top culprit drugs. Elderly patients with DILI have poorer outcomes with increased non-liver related mortality.

How might this change clinical pharmacology or translational science?

Older DILI patients exhibit an increasingly predominant cholestatic phenotype, a more severe DILI episode and require a different approach to predict outcome.

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Table 1. Demographic characteristics of 882 DILI patients, stratified by age groups.

	Young <65 years (n=589)	**Young-old** 65-74 years (n=169)	**Middle-old** 75-84 years (n=108)	**Oldest-old** ≥85 years (n=16)	**p value**
Age (years), mean (range)	45 (11-64)	69 (65-74)	79 (75-84)	87 (85-91)	
Female, n (%)	293 (50)	79 (47)	37 (34)	12 (75)	0.129
BMI (kg/m^2), mean±SD	25±3.8 (n=376)	27±3.8[a] (n=106)	27±3.8[a] (n=64)	26±4.8 (n=10)	<0.001
Underlying liver disease, n (%)	53 (9)	11 (7)	3 (3)	0 (0)	0.011
Charlson Comorbidity Index score, median (IQR)	0 (0-1)	0 (0-1)[a]	1 (0-2)[a,b]	1 (0-3)[a]	<0.001
Myocardial infarction, n (%)	9 (2)	9 (5)[a]	9 (8)[a]	0 (0)	0.001
Congestive heart failure, n (%)	22 (4)	11 (7)	15 (14)[a]	2 (13)	<0.001
Peripheral vascular disease, n (%)	2 (0)	7 (4)[a]	4 (4)[a]	0 (0)	0.004
Cerebrovascular disease, n (%)	8 (1)	7 (4)	8 (7)[a]	3 (19)[a]	<0.001
Dementia, n (%)	1 (0)	3 (2)	2 (2)	3 (19)[a,b,c]	<0.001
Chronic pulmonary disease, n (%)	29 (5)	12 (7)	13 (12)[a]	1 (6)	0.015
Connective tissue disease, n (%)	15 (3)	5 (3)	3 (3)	0 (0)	0.999
Peptic ulcer disease, n (%)	10 (2)	6 (4)	4 (4)	1 (6)	0.063
Hemiplegia or paraplegia, n (%)	0 (0)	0 (0)	1 (1)	0 (0)	0.141
Renal disease (moderate/severe), n (%)	2 (0)	5 (3)[a]	5 (5)[a]	4 (25)[a,b,c]	<0.001
Malignancy, n (%)	17 (3)	12 (7)[a]	11 (10)[a]	0 (0)	0.004
Leukaemia, n (%)	6 (1)	0 (0)	1 (1)	0 (0)	0.639
Lymphoma, n (%)	2 (0)	1 (1)	0 (0)	0 (0)	0.999
Diabetes, uncomplicated / complicated, n (%)	44 (7) / 2 (0)	24 (14)[a] / 0 (0)	31 (29)[a,b] / 2 (2)	5 (31)[a] / 0 (0)	<0.001
Liver disease, mild / moderate-severe, n (%)	10 (2) / 9 (2)	2 (1) / 2 (1)	0 (0) / 2 (2)	0 (0) / 0 (0)	0.867
Acquired immune deficiency syndrome, n (%)	9 (2)	0 (0)	0 (0)	0 (0)	0.076
Number of concomitant medications, median (IQR)[d]	1 (0-3)	2 (1-4)[a]	3 (2-5)[a,b]	3 (2-5)[a]	<0.001

IQR: interquartile range, SD: standard deviation.

a. p<0.05 vs. the young, b. p<0.05 vs. the young-old, c. p<0.05 vs. the middle-old, d. only systemic medication is included in the number of concomitant medications

Table 2. Characteristics of 882 DILI patients, stratified in 5 age groups.

	<65 years (n=589)	65-69 years (n=93)	70-74 years (n=76)	75-79 years (n=64)	≥80 years (n=60)	p value
Age (years), mean (range)	45 (11-64)	67 (65-69)	72 (70-74)	76 (75-79)	83 (80-91)	
Female, n (%)	293 (50)	42 (45)	37 (49)	21 (33)	28 (47)[¶]	0.089
BMI (kg/m^2), mean±SD	25.3±3.8	26.9±3.9	26.9±3.6	27.7±4.0	25.9±3.6	<0.001
Underlying liver disease, n (%)	53 (9)	6 (7)	5 (7)	2 (3)	1 (2)	0.012
CCI score, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	1 (1-2)	1 (0-2)	<0.001
Number of concomitant medications, median (IQR)	1 (0-3)	1 (1-3)	3 (1-5)	3 (2-5)	3 (2-5)	<0.001
Jaundice, n (%)	374 (63)	72 (77)	53 (70)	54 (85)	48 (80)	<0.001
Hospitalization, n (%)	282 (48)	59 (64)	47 (62)	40 (63)	38 (64)	<0.001
Hospitalization duration in days[∫], median (IQR)	21 (10-42)	20 (12-45)	19 (11-45)	23 (11-41)	33 (15-55)	0.760
Hospitalization costs[∫#], median (IQR)	51,599 (25,170-105,714)	50,340 (30,204-113,265)	47,823 (27,687-113,265)	57,891 (27,687-103,197)	83,061 (37,755-138,435)	0.760
Hypersensitivity features, n (%)[a]	244 (42)	44 (47)	31 (41)	26 (41)	27 (45)	0.767
Fever	75 (13)	13 (14)	10 (13)	5 (8)	3 (5)	0.086
Rash	47 (8)	8 (9)	3 (4)	5 (8)	2 (3)	0.204
Lymphopenia	98 (17)	26 (28)	14 (18)	17 (27)	16 (27)	0.012
Eosinophilia	124 (21)	27 (29)	15 (20)	14 (22)	12 (20)	1.000
Arthralgia	12 (2)	1 (1)	0 (0)	2 (3)	0 (0)	0.368
Main pharmacological groups, n (%)						
Anti-infectives	212 (36)	42 (45)	32 (42)	24 (38)	34 (57)	0.007
Amoxicillin-clavulanate	110 (19)	28 (30)	20 (26)	13 (20)	24 (40)	0.001
Central nervous system	81 (14)	9 (10)	8 (11)	6 (9)	3 (5)	0.027

Cardiovascular agents	54 (9)	11 (12)	13 (17)	11 (17)	7 (12)	0.040
Musculoskeletal system	63 (11)	10 (11)	9 (12)	8 (13)	6 (10)	0.865
Type of liver injury, n (%)						<0.001
Hepatocellular	413 (70)	51 (55)	36 (47)	37 (58)	26 (43)	
Cholestatic	81 (14)	22 (24)	22 (29)	14 (22)	22 (37)	
Mixed	95 (16)	20 (22)	18 (24)	13 (20)	12 (20)	
Laboratory parameters at onset, median (IQR)						
Total bilirubin (x ULN)	4.1 (1.0-9.2)	6.5 (3.1-11.6)	5.7 (1.2-11.3)	7.8 (3.4-13.7)	6.4 (2.7-12.1)	<0.001
AST (x ULN)	6.8 (3.0-25.3)	5.7 (3.0-18.2)	5.0 (2.6-14.0)	5.4 (2.6-19.5)	6.2 (3.4-9.4)	0.301
ALT (x ULN)	10.7 (4.9-28.6)	9.6 (5.3-23.4)	7.5 (4.4-15.6)	8.0 (3.5-17.0)	7.6 (4.8-16.6)	0.009
ALP (x ULN)	1.4 (0.9-2.2)	1.8 (1.2-2.7)	1.9 (1.2-3.5)	2.0 (1.1-3.0)	2.5 (1.2-4.6)	<0.001
GGT (x ULN)	5.0 (2.1-9.3)	6.1 (3.8-9.8)	7.1 (3.8-11.1)	5.7 (3.4-9.4)	9.4 (4.8-14.4)	<0.001
Albumin (g/dL)	4.1 (3.6-4.4)	4.1 (3.2-4.4)	4.2 (3.8-4.5)	4.2 (3.9-4.6)	4.5 (3.7-4.6)	0.241
Creatinine (mg/dL)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.9 (0.8-1.1)	1 (0.8-1.3)	1.0 (0.8-1.4)	<0.001
INR	0.84±0.85	0.86±0.81	0.90±0.81	0.92±0.69	0.94±0.89	0.876
Severity, n (%)						0.132[†]
Mild	205 (36)	19 (20)	17 (24)	10 (16)	9 (15)	
Moderate	311 (54)	66 (71)	48 (68)	42 (68)	44 (75)	
Severe	38 (7)	5 (5)	2 (3)	7 (11)	5 (9)	
Fatal/Transplant	20 (3)	3 (3)	4 (6)	3 (5)	1 (2)	
Death liver related, n (%)	9 (2)	1 (1)	4 (5)	3 (5)	1 (2)	0.130
Transplantation, n (%)	11 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0.093
Death non-liver related, n (%)	6 (1)	3 (3)	1 (1)	3 (5)	2 (3)	0.036

CCI: Charlson Comorbidity index; SD: standard deviation; IQR: interquartile range; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; ULN: upper limit of normal range; INR: International Normalized Ratio.

[a] Hypersensitivity features were defined as the presence of at least one of the following characteristics during the DILI episode: fever, rash, serum eosinophilia (defined as eosinophils >5%), lymphopenia (defined as lymphocytes <10%), or arthralgia

[†] Kendall's Tau correlation coefficient ranges from -1 to 1.

[¶] ≥81 years (n=51); female, n (%): 25 (49)
≥82 years (n=40); female, n (%): 21 (52)
≥83 years (n=31); female, n (%): 19 (61)
≥84 years (n=21); female, n (%): 14 (67)

[∫] Excluding patients who died (liver related and non-liver related deaths) and who underwent a liver transplant.

[#] In US dollars.

Table 3. Main suspected pharmacological groups and individual drugs as causative agent for the DILI cases.

ATC	Main pharmacological groups, n (%)	Young <65 years (n=589)	Young-old 65-74 years (n=169)	Middle-old 75-84 years (n=108)	Oldest-old ≥85 years (n=16)
A	Alimentary tract and metabolic agents, excluding anabolic agents	62 (11)	9 (5)	3 (3)	-
	Drugs for peptic ulcer drugs	22 (4)	6 (4)	2 (2)	-
B	Antithrombotic agents	6 (1)	7 (4)	5 (5)	-
C	Cardiovascular agents	54 (9)	24 (14)	16 (15)	2 (13)
	ACE inhibitors + angiotensin II antagonists	10 (2)	5 (3)	5 (5)	-
	Statins	28 (5)	15 (9)	6 (6)	2 (13)
	Fibrates	7 (1)	0 (0)	1 (1)	-
D	Dermatologicals	5 (1)	1 (1)	0 (0)	-
G	Genito-urinary system and sex hormones	18 (3)	1 (1)	2 (2)	-
H	Thyroid therapy	9 (2)	0 (0)	1 (1)	-
J	Anti infectives	212 (36)	74 (44)	47 (44)	11 (69)
	Antibacterials for systemic use	158 (27)	64 (38)	40 (37)	11 (69)
	Amoxicillin-clavulanate	110 (19)	48 (28)	28 (26)	9 (56)
	Hepatocellular	59 (54)	13 (27)	6 (21)	2 (22)
	Cholestatic	22 (20)	18 (38)	12 (43)	4 (44)
	Mixed	29 (26)	17 (35)	10 (36)	3 (33)
	Penicillins/cephalosporins, excluding amoxicillin-clavulanate	10 (2)	4 (2)	2 (2)	-
	Macrolides	12 (2)	4 (2)	2 (2)	-
	Fluoroquinolones	16 (3)	7 (4)	8 (7)	1 (6)
	Antimycobacterials	46 (8)	10 (6)	7 (6)	-
L	Antineoplastic and immunomodulating agents	43 (7)	15 (9)	12 (11)	-
	Antineoplastic agents	13 (2)	3 (2)	2 (2)	-
	Endocrine therapy	8 (1)	9 (5)	9 (8)	-
	Immunosuppressants	15 (3)	3 (2)	1 (1)	-
M	Musculoskeletal system	63 (11)	19 (11)	14 (13)	-
	Nonsteroidal antiinflammatory drugs	54 (9)	14 (8)	13 (12)	-
N	Central nervous system	81 (14)	17 (10)	6 (6)	3 (19)
	Antiepileptics	21 (4)	4 (2)	0 (0)	-
	Psycholeptics	14 (2)	5 (3)	4 (4)	2 (13)
	Antipsychotics	7 (1)	2 (1)	2 (2)	-

	Psychoanaleptics	23 (4)	4 (2)	1 (1)	1 (6)
	Antidepressants	22 (4)	3 (2)	1 (1)	1 (6)
–	Herbal products	24 (4)	2 (1)	2 (2)	-

ACE: angiotensin-converting enzyme, ATC: Anatomical Therapeutical Chemical classification

Table 4. Clinical presentation and laboratory parameters of 882 DILI patients, stratified by age groups.

	Young <65 years (n=589)	**Young-old** 65-74 years (n=169)	**Middle-old** 75-84 years (n=108)	**Oldest-old** ≥85 years (n=16)	**p value**
Jaundice, n (%)	374 (63)	125 (74)	88 (81)[a]	14 (88)	<0.001
Hospitalization, n (%)	282 (48)	106 (63)[a]	67 (62)[a]	11 (69)	<0.001
Hypersensitivity features, n (%)[c]	244 (42)	75 (44)	45 (42)	8 (50)	0.630
Fever	75 (13)	23 (14)	7 (6)	1 (6)	0.110
Rash	47 (8)	11 (7)	7 (6)	0 (0)	0.282
Lymphopenia	98 (17)	40 (24)	27 (25)	6 (38)	0.002
Eosinophilia	124 (21)	42 (25)	24 (22)	2 (13)	0.875
Arthralgia	12 (2)	1 (1)	2 (2)	0 (0)	0.510
Positive antibody titres, n (%)	104 (18)	26 (15)	28 (26)	4 (25)	0.117
Daily dose (mg), median (IQR)	375 (50-1800)	500 (100-1875)	400 (80-1875)	1500 (80-3000)	0.054
Duration of treatment in days, median (IQR)	29 (9-76)	23 (9-62)	17 (8-74)	12 (6-62)	0.450
Time to onset in days, median (IQR)	25 (10-64)	25 (11-57)	21 (7-59)	27 (5-61)	0.454
Type of liver injury, n (%)					<0.001
Hepatocellular	413 (70)	87 (51)[a]	58 (54)[a]	5 (31)[a]	
Cholestatic	81 (14)	44 (26)[a]	28 (26)[a]	8 (50)[a]	
Mixed	95 (16)	38 (22)	22 (20)	3 (19)	
Laboratory parameters at onset, median (IQR)					
Total bilirubin (x ULN)	4.1 (1.0-9.2)	6.1 (2.4-11.5)[a]	6.9 (3.0-13.1)[a]	6.5 (3.4-8.9)	<0.001
AST (x ULN)	6.8 (3.0-25.3)	5.6 (2.8-18.0)	5.4 (3.0-13.2)	6.1 (3.7-19.5)	0.216
ALT (x ULN)	10.7 (4.9-28.6)	9.0 (4.6-21.3)	7.6 (3.7-16.6)[a]	9.2 (5.0-16.0)	0.008
ALP (x ULN)	1.4 (0.9-2.2)	1.9 (1.2-2.8)[a]	1.9 (1.2-3.3)[a]	3.0 (2.4-4.6)[a,b]	<0.001
GGT (x ULN)	5.0 (2.1-9.3)	6.4 (3.8-10.8)[a]	6.8 (3.7-10.2)[a]	11.5 (6.2-25.0)[a]	<0.001
Albumin (g/dL)	4.1 (3.6-4.4) (n=244)	4.1 (3.5-4.4) (n=70)	4.3 (3.9-4.7) (n=34)	4.4 (4.0-4.6) (n=8)	0.201
Other laboratory parameters, median (IQR)					
Glucose (mg/dL)	96 (86-110) (n=413)	101 (91-115) (n=125)	116 (97-151) (n=82)	113 (107-132) (n=11)	<0.001

Creatinine (mg/dL)	0.8 (0.7-1.0) (n=390)	0.9 (0.7-1.1) (n=122)	1.0 (0.8-1.3) (n=80)	0.9 (0.7-1.2) (n=11)	<0.001
Haemoglobin (g/dL)	14 (13-15) (n=415)	13 (12-14) (n=125)	13 (12-15) (n=85)	13 (13-14) (n=10)	0.002
Platelets (x10^3/µL)	227 (182-282) (n=403)	217 (163-263) (n=124)	216 (162-279) (n=82)	245 (148-272) (n=10)	0.134
New Hy's law, n (%)	208 (40)	52 (34)	33 (33)	5 (31)	0.078
Severity, n (%)					0.138[d]
Mild	205 (36)	36 (22)[a]	18 (17)[a]	1 (6)	
Moderate	311 (54)	114 (70)[a]	75 (71)[a]	11 (69)	
Severe	38 (7)	7 (4)	8 (8)	4 (25)[a,b]	
Fatal	20 (3)	7 (4)	4 (4)	0 (0)	
Death liver related, n (%)	9 (2)	5 (3)	4 (4)	0 (0)	0.218
Transplantation, n (%)	11 (2)	2 (1)	0 (0)	0 (0)	0.148
Death non-liver related, n (%)	6 (1)	4 (2)	5 (5)[a]	0 (0)	0.030
DILI contributory	2 (29)	2 (29)	3 (43)	0 (0)	
DILI nonrelated	4 (50)	2 (25)	2 (25)	0 (0)	
Time to resolution in days, median (IQR)	103 (51-189)	142 (66-451)[a]	109 (53-331)	111 (46-140)	0.044

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; IQR: interquartile range; ULN: upper limit of normal range.

a. p<0.05 vs. the young, b. p<0.05 vs. the young-old, c. hypersensitivity features were defined as the presence of at least one of the following characteristics during the DILI episode: fever, rash, serum eosinophilia (defined as eosinophils >5%), lymphopenia (defined as lymphocytes <10%), or arthralgia, d. Kendall's Tau correlation coefficient ranges from -1 to 1.

Severity index. Mild: elevated ALT/ALP meeting DILI criteria with total bilirubin <2 x ULN; Moderate: elevated ALT/ALP with total bilirubin ≥2 x ULN; Severe: elevated ALT/ALP, total bilirubin ≥2 x ULN and one of the following: ascites, encephalopathy, international normalization ratio ≥1.5 and/or other organ failure considered to be due to DILI; Fatal: death or transplantation due to DILI.

[#] In US dollars.

Table 5. Associations of age and age groups and cholestatic liver injury.

	Odds ratio	95% confidence interval	p value
Age	1.022	(1.011-1.034)	<0.001
Male sex	1.239	(0.860-1.786)	0.250
Charlson comorbidity index	1.147	(0.977-1.347)	0.095
Amoxicillin-clavulanate	2.136	(1.438-3.175)	<0.001
Concomitant medication	1.021	(0.933-1.119)	0.647
	Odds ratio	**95% confidence interval**	**p value**
Age			
<55 years		1 (reference)	
55-64 years	1.320	(0.805-2.167)	0.272
65-74 years	2.130	(1.319-3.438)	0.002
75-84 years	1.754	(0.986-3.120)	0.056
≥85 years	4.811	(1.630-14.203)	0.004
Male sex	1.263	(0.872-1.830)	0.217
Charlson comorbidity index	1.161	(0.990-1.362)	0.066
Amoxicillin-clavulanate	2.102	(1.409-3.136)	<0.001
Concomitant medication	1.028	(0.939-1.125)	0.550

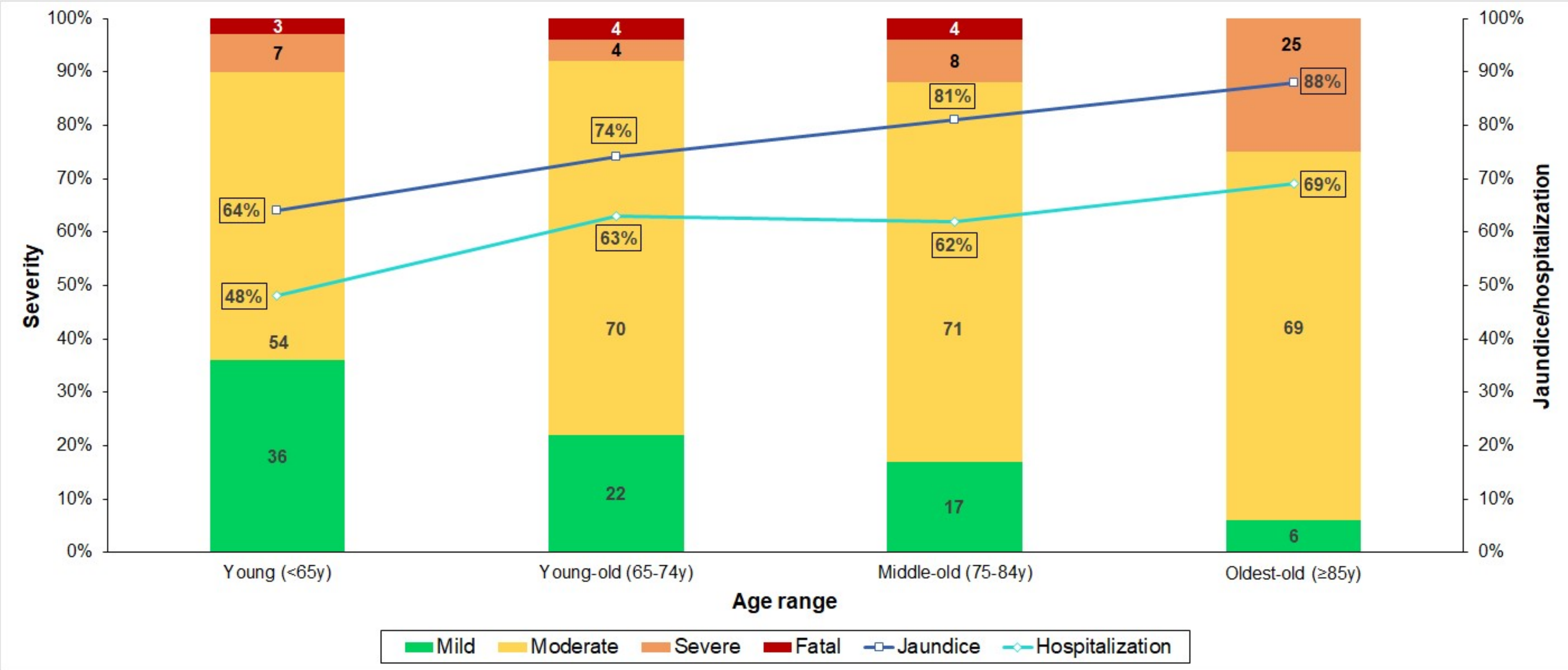
Male sex (yes/no); Charlson comorbidity index (continuous); amoxicillin clavulanate (yes/no); concomitant medication (continuous).

Table 6. Predictors of 6-month mortality in DILI patients.[22]

Liver related death	**OR (95% CI)**	**p value**
MELD score	1.153 (1.071-1.240)	<0.001
Comorbidity burden		
No/mild comorbidity (CCI≤1) [Reference]	-	-
Significant comorbidity (CCI>1)	5.721 (1.459-22.429)	0.012
Albumin (g/dL)	0.530 (0.292-0.962)	0.037
Overall mortality	**OR (95% CI)**	**p value**
MELD score	1.116 (1.066-1.168)	<0.001
Comorbidity burden		
No/mild comorbidity (CCI≤1) [Reference]	-	-
Significant comorbidity (CCI>1)	4.188 (1.738-10.091)	0.001
Albumin (g/dL)	0.739 (0.502-1.089)	0.126

CCI: Charlson comorbidity index; OR: odds ratio; CI: confidence interval

Figure 1. Severity of DILI episode and prevalence of jaundice and hospitalization due to DILI, stratified by age groups.



Severity index. Mild: elevated ALT/ALP meeting DILI criteria with total bilirubin <2 x upper limit of normality (ULN); Moderate: elevated ALT/ALP with total bilirubin ≥2 x ULN; Severe: elevated ALT/ALP, total bilirubin ≥2 x ULN and one of the following: ascites, encephalopathy, international normalization ratio ≥1.5 and/or other organ failure considered to be due to DILI; Fatal: death or transplantation due to DILI.

Table S1. Characteristics of 882 DILI patients, stratified in 3 age groups.

Characteristics	Young <65 years (n=589)	Young-old 65-74 years (n=169)	Middle/oldest-old ≥75 years (n=124)	p value
Age (years), mean (range)	45 (11-64)	69 (65-74)	80 (75-91)	
Female, n (%)	293 (50)	79 (47)	49 (40)	0.042
BMI (kg/m^2), mean±SD	25.3±3.8	26.9±3.8	26.8±3.9	<0.001
Underlying liver disease, n (%)	53 (9)	11 (7)	3 (2)	0.011
CCI score, median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	<0.001
Number of concomitant medications, median (IQR)	1 (0-3)	2 (1-4)	3 (2-5)	<0.001
Jaundice, n (%)	374 (63)	125 (74)	102 (82)	<0.001
Hospitalization, n (%)	282 (48)	106 (63)	78 (63)	<0.001
Hospitalization duration in days[∫], median (IQR)	21 (10-42)	20 (12-45)	27 (13-45)	0.595
Hospitalization costs[∫#], median (IQR)	51,599 (25,170-105,714)	49,082 (30,204-113,265)	66,701 (31,463-113,265)	0.595
Hypersensitivity features, n (%)[a]	244 (42)	75 (44)	53 (43)	0.674
Fever	75 (13)	23 (14)	8 (7)	0.118
Rash	47 (8)	11 (7)	7 (6)	0.333
Lymphopenia	98 (17)	40 (24)	33 (27)	0.004
Eosinophilia	124 (21)	42 (25)	26 (21)	0.737
Arthralgia	12 (2)	1 (1)	2 (2)	0.491
Main pharmacological groups, n (%)				
Anti-infectives	212 (36)	74 (44)	58 (47)	0.010
Amoxicillin-clavulanate	110 (19)	48 (28)	37 (30)	0.001
Central nervous system	81 (14)	17 (10)	9 (7)	0.028
Cardiovascular agents	54 (9)	24 (14)	18 (15)	0.032
Musculoskeletal system	63 (11)	19 (11)	14 (11)	0.824
Type of liver injury, n (%)				<0.001
Hepatocellular	413 (70)	87 (51)	63 (51)	
Cholestatic	81 (14)	44 (26)	36 (29)	
Mixed	95 (16)	38 (22)	25 (20)	
Laboratory parameters at onset, median (IQR)				
Total bilirubin (x ULN)	4.1 (1.0-9.2)	6.1 (2.4-11.5)	6.7 (3.1-12.9)	<0.001

AST (x ULN)	6.8 (3.0-25.3)	5.6 (2.8-18.0)	5.8 (3.1-13.3)	0.122
ALT (x ULN)	10.7 (4.9-28.6)	9.0 (4.6-21.3)	7.8 (3.9-16.6)	0.003
ALP (x ULN)	1.4 (0.9-2.2)	1.9 (1.2-2.8)	2.2 (1.2-3.5)	<0.001
GGT (x ULN)	5.0 (2.1-9.3)	6.4 (3.8-10.8)	6.9 (3.8-11.6)	<0.001
Albumin (g/dL)	4.1 (3.6-4.4)	4.1 (3.5-4.4)	4.3 (3.9-4.6)	0.102
Creatinine (md/dL)	0.8 (0.7-1.0)	0.9 (0.7-1.1)	1.0 (0.8-1.3)	<0.001
INR, mean±SD	0.84±0.85	0.88±0.81	0.93±0.79	0.580
Severity, n (%)				0.137[†]
Mild	205 (36)	36 (22)	19 (16)	
Moderate	311 (54)	114 (70)	86 (71)	
Severe	38 (7)	7 (4)	12 (10)	
Fatal/Transplant	20 (3)	7(4)	4 (3)	
Death liver related, n (%)	9 (2)	5 (3)	4 (3)	0.190
Transplantation, n (%)	11 (2)	2 (1)	0 (0)	0.127
Death non-liver related, n (%)	6 (1)	4 (2)	5 (4)	0.018

CCI: Charlson Comorbidity index; SD: standard deviation; IQR: interquartile range; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; ULN: upper limit of normal range; INR: International Normalized Ratio.

[a] Hypersensitivity features were defined as the presence of at least one of the following characteristics during the DILI episode: fever, rash, serum eosinophilia (defined as eosinophils >5%), lymphopenia (defined as lymphocytes <10%), or arthralgia

[†] Kendall's Tau correlation coefficient ranges from -1 to 1.

[∫] Excluding patients who died (liver related and non-liver related deaths) and who underwent a liver transplant.

[#] In US dollars.

Table S2. Most frequent culprit drugs according to age groups.

Young (<65 years) (n=589)	**Young-old** (65-74 years) (n=169)	**Middle-old** (75-84 years) (n=108)	**Oldest-old** (≥85 years) (n=16)
Amoxicillin-clavulanate 110 (19%)	Amoxicillin-clavulanate 48 (28%)	Amoxicillin-clavulanate 28 (26%)	Amoxicillin-clavulanate 9 (56%)
Anti-TBC 27 (5%)	Flutamide 8 (5%)	Flutamide 8 (7%)	Atorvastatin 2 (13%)
Ibuprofen 21 (4%)	Anti-TBC 6 (4%)	Diclofenac 7 (6%)	Chlorpromazine; Clomethiazole; Escitalopram; Levofloxacin; Nitrofurantoin 1 (6%)
Isoniazid 17 (3%)	Simvastatin; Ticlopidine 5 (3%)	Anti-TBC 5 (5%)	-
Androgenic anabolic steroids (Stanozolol) 12 (2%)	Atorvastatin; Isoniazid 4 (2%)	Levofloxacin 4 (4%)	-

Anti-TBC: tuberculosis treatments consisting of rifampicin, isoniazid, pyrazinamide and ethambutol combinations.

Table S3. Pattern of liver injury according to age and culprit drugs.

Culprit drug	<65 (n=585)	≥65 (n=284)	p value
Amoxicillin-clavulanate			<0.001
Hepatocellular	59 (54)	19 (23)	
Cholestatic/mixed	50 (46)	63 (76)	
Atorvastatin, levofloxacin, ibuprofen, ticlopidine			0.027
Hepatocellular	27 (68)	11 (39)	
Cholestatic/mixed	13 (32)	17 (61)	
Isoniazid, anti-TBC, diclofenac, flutamide			0.335
Hepatocellular	53 (91)	32 (84)	
Cholestatic/mixed	5 (9)	6 (16)	

Anti-TBC: tuberculosis treatments consisting of rifampicin, isoniazid, pyrazinamide and ethambutol combinations.