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# Mortality and drug exposure in a 5-year cohort of patients with chronic liver disease

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## Summary

*Background:* Chronic liver diseases are common in the general population. Drug treatment in this group may be challenging, as many drugs are hepatically metabolised and hepatotoxic.

*Objectives:* We aimed to assess the mortality of patients with chronic liver disease according to specific drug exposures and the three laboratory parameters creatinine, bilirubin and International Normalised Ratio (INR).

*Methods:* We conducted a multicentre, 5-year retrospective cohort study in two tertiary university referral hospitals and a secondary referral hospital, using a research database to evaluate the crude and adjusted mortality.

*Results:* Of 1 159 362 individual patients 1.7% (n = 20 158) had chronic liver disease and in this group 36.8% had unspecified chronic non-alcoholic liver disease, 30.1% chronic hepatitis C and 11.9% cirrhosis of the liver. 8.4% of patients presented a diagnosis associated with alcohol. The 4-year survival rates were significantly higher in the group with the most normal laboratory values (94.3%) versus 34.5% in the group with elevated parameters (p <0.001). Overall, drug exposure was not associated with higher mortality; in adjusted multivariate analysis the hazard ratio for anti-cancer drugs was 2.69 (95% CI 1.32–5.46). Of individual drugs, mortality hazard ratios for amiodarone, morphine oral, acetazolamide, sirolimus and lamivudine were 2.46 (95% CI 1.68–3.61), 2.26 (95% CI 1.78–2.86), 2.10 (95% CI 1.19–3.70), 1.81 (95% CI 1.02–3.21) and 1.72 (95% CI 1.17–2.53) respectively.

*Conclusions:* Drug exposure in general was not associated with higher mortality except for a few categories. Mortality in patients with chronic liver disease was high and is associated with simple laboratory values.

*Key words: chronic liver disease; cirrhosis; drug exposure; mortality; MELD score; ambulatory; hospitalised; tertiary referral hospital; secondary referral hospital*

## Introduction

Cirrhosis and other chronic liver diseases (CLD) are common illnesses in the general population and involve additional hospitalisations, medical treatment and a high mortality rate in affected patients. According to the National Center for Health Statistics, the age-adjusted death rate

**Abbreviations**

| | |
|---|---|
| BBW | Black box warning for hepatotoxicity by FDA. |
| CI | Confidence interval |
| CLD | Chronic Liver Disease |
| D+ | Drug exposure group |
| D- | Group with no drug exposure to hepatotoxic drugs |
| FDA | Food and Drug Administration |
| HR | Hazard ratio |
| INR | International Normalised Ratio |
| L0 | Group with all three laboratory values (bilirubin, INR, creatinine) within normal limits |
| L1-2 | Group with 1 or 2 laboratory parameters above threshold |
| L3 | Group with all three laboratory parameters above threshold |
| MELD | Model for End-Stage Liver Disease |
| Metabolism | Flow-dependent hepatic metabolism drug group |
| LMR | Longitudinal Medical Record |
| RPDR | Research Patient Data Registry |
| SSA DMF | Social Security Administration Death Master File |
| Tox | Direct hepatic toxicity drug group |

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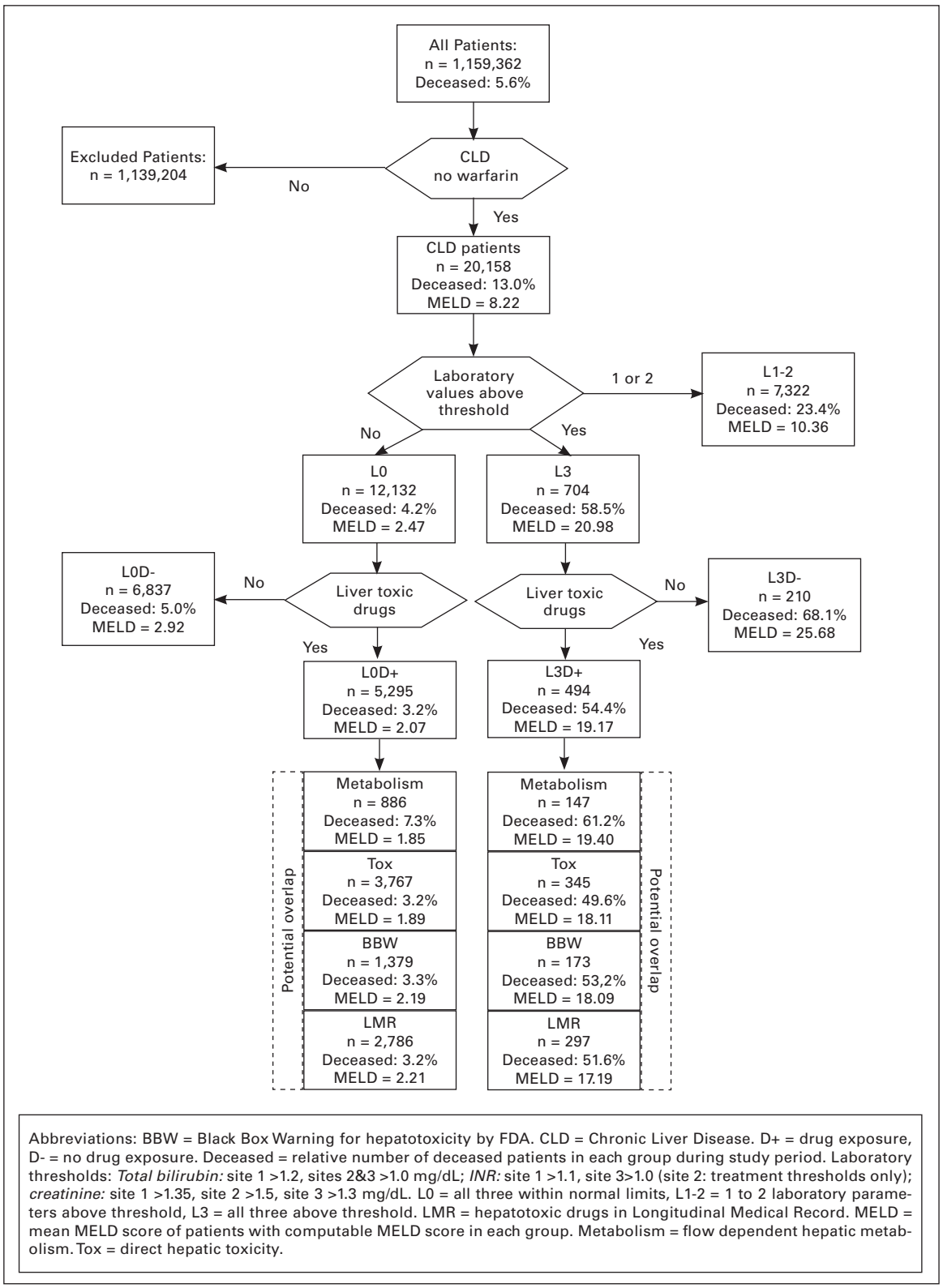
in 2004 was 9.0/100 000 US inhabitants/year dying of CLD, making it the twelfth leading cause of death [1].

New models such as the Model for End-Stage Liver Disease (MELD) have been successfully developed and implemented to predict life expectancy in patients with liver disease and outcome in liver transplantation, transjugular intrahepatic portosystemic shunts, alcoholic hepatitis and fulminant hepatic failure caused by acetaminophen toxicity [2–7].

Drugs may present idiosyncratic or dose-dependent toxicity. Drug-induced liver failure represents the leading identifiable cause of acute liver failure in the United States [8, 9]. While much of this toxicity occurs in patients with normal hepatic function, it is a particular challenge to choose the correct drug and estimate the specific drug metabolism and excretion properties in order to adjust appropriately to individual liver function in patients with CLD.

**Figure 1**
Study design.




Abbreviations: BBW = Black Box Warning for hepatotoxicity by FDA. CLD = Chronic Liver Disease. D+ = drug exposure, D- = no drug exposure. Deceased = relative number of deceased patients in each group during study period. Laboratory thresholds: *Total bilirubin:* site 1 >1.2, sites 2&3 >1.0 mg/dL; *INR:* site 1 >1.1, site 3>1.0 (site 2: treatment thresholds only); *creatinine:* site 1 >1.35, site 2 >1.5, site 3 >1.3 mg/dL. L0 = all three within normal limits, L1-2 = 1 to 2 laboratory parameters above threshold, L3 = all three above threshold. LMR = hepatotoxic drugs in Longitudinal Medical Record. MELD = mean MELD score of patients with computable MELD score in each group. Metabolism = flow dependent hepatic metabolism. Tox = direct hepatic toxicity.

We conducted a retrospective cohort study using data from the Research Patient Data Registry (RPDR) and the Longitudinal Medical Record (LMR) at Partners Healthcare, a system of academic and community hospitals addressing the following questions: What is the mortality rate of patients with CLD in general? Is their mortality affected by administering hepatotoxic drugs? Does exposure to certain drugs or drug classes, their MELD score or its single laboratory parameters predict mortality?

## Methods

### Study design

We conducted a retrospective observational cohort study over five years (from 1 January 2002 to 31 December 2006; fig. 1). The Brigham and Women's Hospital Institutional Review Board approved the study.

### Study subjects

Study patients were all adult (age 18+) in- and outpatients of two tertiary referral teaching hospitals and one secondary referral hospital in the greater Boston area. Subjects were identified using the Research Patient Data Repository (RPDR), a clinical data warehouse at Partners Healthcare containing information from over 3.5 million patients and 600 million patient encounters [10]. Partners Healthcare system is a non-profit organisation which consists of its two founding academic hospitals, community hospitals and community health centres.

### Inclusion criteria

All patients seen during the study period were included. The time point of inclusion into the CLD group was the date in the LMR for one of the diagnoses of CLD as defined below.

### Exclusion criteria

We excluded patients treated with warfarin due to its influence on INR.

### Diagnosis of chronic liver disease (CLD)

Patients with CLD were identified from the RPDR using ICD-9-CM diagnoses. We included chronic rather than acute liver diseases to establish a more stable liver function pattern over time. Diagnostic codes included all 571 codes for chronic liver disease as well as 070.54 for chronic hepatitis C and 070.32 for chronic hepatitis B. If multiple liver diagnoses were present we assigned the diagnosis as the first specific diagnosis within the observation period; if the first diagnosis was non-specific (571.4 chronic non-viral hepatitis, 571.8 chronic non-alcoholic liver disease, 571.9 unspecified chronic liver disease with no mention of alcohol), we sequentially searched in time until we found a more specific diagnosis coded.

### Validation of data

Diagnoses from RPDR were validated by comparing them with a random sample of 110 electronic charts in LMR. From each of 11 groups as defined below, 10 charts were sampled and validated for identity, diagnosis and drug exposure. Validity testing showed a correct identity (name, gender and date of birth) in 99.1% (109/110 charts), a correct diagnosis in 96.4% (106/110) and 100% accuracy regarding drug exposure (110/110). An accurate diagnosis was defined as showing objective correlates in LMR patient charts in radiology, pathology or serology results.

### Definition of cancer diagnoses

Because of the impact of cancer diagnosis on mortality, we included the presence of any cancer diagnosis during the study period as a single binary predictor in the multivariate regression model including ICD-9 codes 140–239, with the exception of 210–229 "benign neoplasm" and 230–234 "carcinoma in situ", assuming that these diagnoses would have no substantial impact on mortality within a five-year period.

### Exposures, outcomes and their measurement

The primary outcomes were crude and adjusted mortality with and without drug exposure. Covariates for adjustment next to drug exposure were age, gender, diagnoses of liver disease and cancer, the MELD score as well as its three single laboratory parameters creatinine, bilirubin and INR (fig. 1). To compute the MELD score the patient had to have all three parameters measured on one day during the observation period. Regarding the single laboratory values, the value was entered as a binary variable defined as either normal or above threshold meaning at least one measurement above normal within the observation period. Institution-based thresholds were: *total bilirubin*: site 1 = 0.2–1.2 mg/dL, site 2 = 0.3–1.0 mg/dL, site 3 = 0.0–1.0 mg/dL; *INR:* site 1 = 0.9–1.1, site 2: treatment thresholds only, site 3 = 1.0; *creatinine:* site 1 = 0.7–1.35 mg/dL, site 2 = <1.5 mg/dL, site 3 = 0.6–1.3 mg/dL. The final aim consisted of a mortality risk factor analysis and developing a prediction model based on this analysis.

### Group definitions

Groups L0, L1-2 and L3 were defined by laboratory parameters (creatinine, bilirubin and INR): group L0 had at no time parameters above thresholds, L1-2 either one or two of the three parameters above threshold at some time and in L3 all three parameters were above thresholds at least once concurrently or at different times. Groups L1 and L2 were lumped together because of overlap. Groups with drug exposure (D+) were classified according to the drug group exposed to; groups without drug exposure were marked D-.

### Drug exposures

Drug exposure groups were selected according to four distinct criteria: hepatic metabolism ("Metabolism"), direct liver toxicity ("Tox"), FDA Black Box Warning for hepatotoxicity group ("BBW") and hepatotoxic drugs as defined in the LMR ("LMR"). These four drug classes each contained between 9 and 43 single drugs or drug combinations (appendix 1**)**. Additionally, we designated functional drug classes, based on known hepatotoxic risk issues: statins, antiepileptics, opiates, anticancer drugs, immunosuppressants and HIV drugs.

### Survival Time

Survival time was computed from the time patients appeared in RPDR (2002–2006) with a diagnosis of liver

disease until death or censoring at the end of the observation period. Vital status data are updated monthly in RPDR using Social Security and National Death Index [11, 12].

### Model for End Stage Liver Disease (MELD)

The MELD score was computed from the last laboratory data within the observation period ($3.8 \times \log_e$ (bilirubin, mg/dL) + $11.2 \times \log_e$ (INR) + $9.6 \times \log_e$ (creatinine, mg/dL) +6.4) [7]; all three laboratory parameters had to be measured on the same day.

### Statistical analysis

For the comparison of approximately normal variables across group (such as MELD score), we used the t-test to compare means; for categorical variables across groups, we used Pearson's chi-square. To compare unadjusted mortality and survival times across groups (e.g., the three laboratory groups), we used the log rank test. Survival distributions were characterised by Kaplan-Meier curves and the 48-months survival rate. Thresholds of significance were set at $\alpha = 0.05$.

*Cox regression model for mortality.* The Cox proportional hazards regression model included all the clinically relevant predictors: age, gender, race, laboratory value groups, MELD score, diagnoses of liver disease and cancer, drug exposure to single drugs, drug groups and functional drug classes. The adequacy of the Cox regression model was assessed with the residual-based method proposed by Lin et al. [13]; the functional forms of each covariate appeared appropriate, and the proportional hazards assumption for each covariate was not violated (all goodness-of-fit p-values >.05). Single drugs were adjusted in the same way as the drug groups, except for MELD due to the low number of patients with single drug exposure and computable MELD score.

We used the SAS statistical software package for Windows, version 9.1 (SAS Institute Inc., Cary, NC).

**Table 1**

Characteristics and demographics of individual patients

| Characteristics | All patients* N = 1,159,362 (%) | All CLD patients n = 20,158 (%) | L0 n = 12,132 (%) | L1-2 n = 7,322 (%) | L3 n = 704 (%) | L0D+ n = 5,295 (%) | L0D- n = 6,837 (%) | L3D- n = 210 (%) | L3D+ n = 494 (%) |
|---|---|---|---|---|---|---|---|---|---|
| Age [years], mean | † | 52.6 | 50.5 | 55.4 | 59.7 | 50.6 | 50.4 | 61.4 | 59.0 |
| 18–19 | 19,021 (1.6)‡ | 115 (0.6) | 71 (0.6) | 43 (0.6) | 1 (0.1) | 20 (0.4) | 51 (0.7) | 0 | 1 (0.2) |
| 20–29 | 170,746 (14.7) | 1,406 (7.0) | 1,040 (8.6) | 352 (4.8) | 14 (2.0) | 455 (8.6) | 585 (8.6) | 2 (0.9) | 12 (2.4) |
| 30–39 | 218,729 (18.9) | 3,021 (15.0) | 2,141 (17.6) | 836 (11.4) | 44 (6.3) | 972 (18.4) | 1,169 (17.1) | 6 (2.9) | 38 (7.7) |
| 40–49 | 217,572 (18.8) | 5,689 (28.2) | 3,603 (29.7) | 1,921 (26.2) | 165 (23.4) | 1514 (28.6) | 2,089 (30.5) | 46 (21.9) | 119 (24.1) |
| 50–59 | 199,550 (17.2) | 5,460 (27.1) | 3,157 (26.0) | 2,086 (28.5) | 217 (30.8) | 1373 (25.9) | 1,784 (26.1) | 69 (32.9) | 148 (30.0) |
| 60–69 | 150,271 (13.0) | 2,709 (13.4) | 1,423 (11.7) | 1,155 (15.8) | 131 (18.6) | 660 (12.5) | 763 (11.2) | 44 (21.0) | 87 (17.6) |
| 70–79 | 105,315 (9.1) | 1,343 (6.7) | 566 (4.7) | 682 (9.3) | 95 (13.5) | 251 (4.7) | 315 (4.6) | 33 (15.7) | 62 (12.5) |
| 80–89 | 64,040 (5.5) | 384 (1.9) | 123 (1.0) | 228 (3.1) | 33 (4.7) | 50 (0.9) | 73 (1.1) | 8 (3.8) | 25 (5.1) |
| =/>90 | 14,107 (1.2) | 31 (0.1) | 8 (0.1) | 19 (0.3) | 4 (0.6) | 0 | 8 (0.1) | 2 (0.9) | 2 (0.4) |
| Total | 1,159,351 (100) | 20,158 (100) | 12,132 (100) | 7,322 (100) | 704 (100) | 5,295 (100) | 6,837 (100) | 210 (100) | 494 (100) |
| Sex | | | | | | | | | |
| Female | 675,059 (58.2) | 9,141 (45.3) | 6,435 (53.0) | 2,485 (33.9) | 221 (31.4) | 3168 (59.8) | 3,267 (47.8) | 55 (26.2) | 166 (33.6) |
| Male | 484,305 (41.8) | 11,017 (54.7) | 5,697 (47.0) | 4,837 (66.1) | 483 (68.6) | 2127 (40.2) | 3,570 (52.2) | 155 (73.8) | 328 (66.4) |
| Race | | | | | | | | | |
| Caucasian | 759,028 (65.5) | 14,085 (69.9) | 8,214 (67.7) | 5,400 (73.7) | 471 (66.9) | 3526 (66.6) | 4,688 (68.6) | 152 (72.4) | 319 (64.6) |
| Hispanic | 81,918 (7.1) | 2,064 (10.2) | 1,375 (11.3) | 619 (8.5) | 70 (9.9) | 814 (15.4) | 561 (8.2) | 19 (9.1) | 51 (10.3) |
| African American | 73,081 (6.3) | 1559 (7.7) | 816 (6.7) | 635 (8.7) | 108 (15.3) | 398 (7.5) | 418 (6.1) | 20 (9.5) | 88 (17.8) |
| Asian | 33,087 (2.9) | 1,025 (5.1) | 732 (6.0) | 274 (3.7) | 19 (2.7) | 281 (5.3) | 451 (6.6) | 5 (2.4) | 14 (2.8) |
| American Indian | 847 (0.1) | 29 (0.1) | 22 (0.2) | 7 (0.1) | 0 | 16 (0.3) | 6 (0.1) | 0 | 0 |
| Other | 30,310 (2.6) | 408 (2.0) | 268 (2.2) | 126 (1.7) | 14 (2.0) | 113 (2.1) | 155 (2.3) | 4 (1.9) | 10 (2.0) |
| Not recorded | 181,125 (15.6) | 988 (4.9) | 705 (5.8) | 261 (3.6) | 22 (3.1) | 147 (2.8) | 558 (8.1) | 10 (4.7) | 12 (2.4) |
| Total | 1,159,396 (100) | 20,158 (100) | 12,132 (100) | 7,322 (100) | 704 (100) | 5,295 (100) | 6,837 (100) | 210 (100) | 494 (100) |
| Vital status | | | | | | | | | |
| Alive | 1,094,776 | 17,529 | 11,626 | 5,611 | 292 | 5128 | 6,498 | 67 | 225 |
| Deceased | 64,592 | 2,629 | 506 | 1,711 | 412 | 167 | 339 | 143 | 269 |
| Malignancy (%)§ | N/A | 7,770 (38.6) | 3,328 (27.4) | 3,935 (53.7) | 507 (72.0) | 1,888 (35.7) | 1,440 (21.1) | 119 (56.7) | 388 (78.5) |
| Total | 1,159,368 (100) | 20,158 (100) | 12,132 (100) | 7,322 (100) | 704 (100) | 5,295 (100) | 6,837 (100) | 210 (100) | 494 (100) |
| Crude mortality % (95% CI) during observation period | 5.6 (5.56–5.64) | 13.0 (12.54–13.46) | 4.2 (3.84–4.56) | 23.4 (22.43–24.37) | 58.5 (54.86–62.14) | 3.2 (2.73–3.67) | 5.0 (4.48–5.52) | 68.1 (61.80–74.40) | 54.4 (50.00–58.79) |

*Data accuracy in RPDR ± 3 in de-identified patients. Age at the time of data retrieval; in all other groups age is computed at the time of liver diagnosis.
N/A= not assessed. † Not computable; these patients were not personalized. ‡ Age group 18–19 may contain single patients between 10 and 18 years old.
CI=confidence interval. L0: no laboratory values above threshold, L1-2: 1-2 laboratory values above threshold, L3: three laboratory values above threshold.
D+: exposure to drug groups, D- no exposure to drug groups. § ICD-9-CM codes 140–239 excluding 210–229 "Benign neoplasms" and 230–234 "Carcinoma in situ".

**Table 2**

Unadjusted 48 months survival rates and mortality in end stage liver disease (MELD) scores.

| Group* | 48 months survival rate [95%CI] | Deaths per 1000 person months | p-Value†* (Deaths per 1000 person months) | MELD score Mean [95%CI] (n*) | p-Value‡ (MELD) |
|---|---|---|---|---|---|
| All CLD patients | 83.4 [82.7–83.9] | 4.5 | – | 8.22 [8.03–8.41] (9,514) | – |
| L0 | 94.3 [93.8–94.8] | 1.4 | L0 vs L3: p <0.001 | 2.47 [2.36–2.58] (3,484) | L0 vs L3: p <0.001 |
| L1-2 | 71.2 [69.9–72.4] | 8.5 | L0 vs L1-2: p <0.001 | 10.36 [10.11–10.61] (5,355) | L0 vs L1-2: p <0.001 |
| L3 | 34.5 [30.3–38.7] | 29.0 | – | 20.98 [20.00-21.96] (675) | – |
| L0D+ | 95.6 [94.8–96.3] | 1.0 | L0D+ vs L0D-: p <0.001<br>L0D+ vs L3D+: p <0.001 | 2.07 [1.92-2.22] (1,834) | L0D+ vs L0D-: p <0.001<br>L0D+ vs L3D+: p <0.001 |
| L0D- | 93.3 [92.6–94.1] | 1.6 | L0D- vs L3D-: p <0.001 | 2.92 [2.76–3.08] (1,650) | L0D- vs L3D-: p <0.001 |
| L3D+ | 38.7 [33.5–43.8] | 24.6 | L3D+ vs L3D-: p <0.001 | 19.17 [18.06–20.28] (487) | L3D+ vs L3D-: p <0.001 |
| L3D- | 24.6 [18.0–31.7] | 43.5 | – | 25.68 [23.84–27.52] (188) | – |

* Group L1-2 was not analysed regarding drug exposure. **Number of patients with computable MELD score within each group.
† Log rank test. ‡ T-test.

**Table 3**

Hazard ratios for drug groups and single drugs. (all adjusted for age, cancer, liver diagnosis and race)*

| Drug group/Single drug name (Number of patients exposed) | Hazard ratio [95% CI] | Lab adjusted hazard ratio† [95% CI] |
|---|---|---|
| Drug groups | | |
| Metabolism drug group (n = 1,033) | 2.18 [1.81–2.64] | 1.74 [1.45–2.10] |
| BBW drug group (n = 1,552) | 1.47 [1.20–1.80] | 1.20 [0.96–1.45] |
| Hepatotoxic drug group (n = 4,112) | 0.91 [0.77–1.06] | 0.76 [0.65–0.88] |
| LMR drug group (n = 3,083) | 0.68 [0.57–0.81] | 0.58 [0.49–0.68] |
| Functional drug group | | |
| Anticancer drugs (n = 184) | 3.49 [2.57–4.75] | 3.49 [2.53–4.81] |
| Single drugs | | |
| Cyclosporine oral (immunosuppression) (n = 20) | 5.16 [2.58–10.31] | 2.30 [0.16–4.56] |
| Etoposide oral (anticancer) (n = 32) | 4.03 [2.40–6.77] | 3.55 [2.15–5.87] |
| Sirolimus (immunosuppression) (n = 22) | 3.80 [2.06–7.03] | 1.81 [1.02–3.21] |
| Docetaxel (anticancer) (n = 21) | 3.40 [1.81–6.40] | 7.53 [3.91–14.48] |
| Morphine oral (opiate analgesic) (n = 239) | 3.10 [2.48–3.87] | 2.26 [1.78–2.86] |
| Amiodarone oral (antiarrhythmic) (n = 81) | 2.46 [1.68–3.61] | ‡ |
| Acetazolamide (diuretic) (n = 45) | 2.10 [1.19–3.70] | ‡ |
| Lamivudine (antiviral) (n = 164) | 1.72 [1.17–2.53] | ‡ |
| Ibuprofen (NSAID) (n = 2,605) | 0.60 [0.50–0.72] | 0.73 [0.60–0.88] |
| Metformin (antidiabetic) (n = 816) | 0.51 [0.35–0.74] | 0.59 [0.41–0.87] |
| Atorvastatin (lipid lowering) (n = 1,370) | 0.44 [ 0.34–0.57] | 0.63 [0.48–0.83] |
| Pravastatin (lipid lowering) (n = 183) | 0.34 [0.15–0.76] | 0.32 [0.14-0.73] |
| Azathioprine (antimetabolite) (n = 103) | 0.25 [0.11–0.59] | 0.22 [0.09-0.51] |
| Simvastatin (lipid lowering) (n = 580) | ‡ | 0.57 [0.42–0.78] |

* In descending order of hazard; reference group for hazard ratios are patients with no exposure to drugs. † Additional adjustment for high laboratory values. Containing no patients from group L1-2. ‡ Variable not significant at p = 0.05. NSAID = non-steroidal anti-inflammatory drug.

## Results

The patient population included 1 159 362 individual patients, and 22 211 with CLD (1.9%, table 1). Among patients with CLD, 2052 were excluded on account of warfarin use during the observation period; one patient was excluded as he lacked a unique identifier. The remaining 20 158 patients (1.7% of all patients) had a mean age of 52.6 years, and a crude mortality of 5.6% (95% CI 5.56–5.64) during the observation period. In the three laboratory groups L0, L1-2 and L3 mean age was 50.5, 55.4 and 59.7 years, respectively; more patients were male (54.7%; range 47.0–68.6%). Mean age was similar for the L0D+ and L0D- groups (50.6 and 50.4 years) and somewhat higher in laboratory positive groups L3D+ and L3D- (59.0 and 61.4 years). The crude mortality rate increased with the number of positive laboratory values: group L0 4.2% (95% CI 3.84–4.56), L1-2 23.4% (95% CI 22.43–24.37) and L3 58.5% (95% CI 54.86–62.14). Crude mortality rate was lowest in group L0D+ with 3.2% (95% CI 2.73–3.67) and highest in L3D- (68.1%, 95% CI 61.80–74.40).

Chronic hepatitis C was the most common specific diagnosis according to ICD among patients with CLD, with a mean prevalence of 30.1% (range among subgroups 5.5–32.9%). The prevalence of chronic hepatitis B (mean 7.5%, range 3.3–8.7%) was fairly consistent. The most frequent non-infectious diagnosis was "other non-alcoholic liver disease" with mean 36.8% (range 4.7–52.8%), followed by "cirrhosis of liver" with no mention of alcohol (mean 11.9%; range 5.3–24.3%) and "alcoholic cirrhosis of liver" in 4.1% of patients (range 0.6–24.3%). 8.4% of patients showed a diagnosis associated with alcohol use.

The prevalence of a malignancy diagnosis was 38.6% for all groups, with a range from 21.1% in group L0D- to 78.5% in group L3D+.

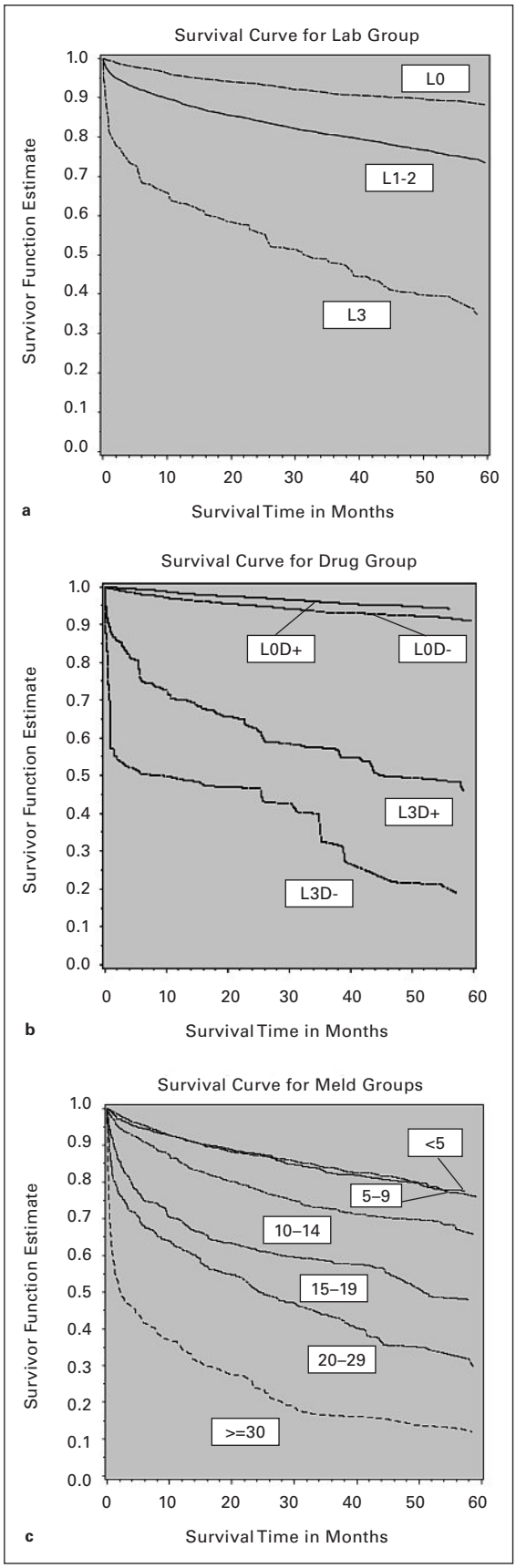



**Figure 2**

Survival Curves: 2a Laboratory Groups; 2b Drug Exposure Groups; 2c MELD Score Groups.

Individual patients were followed from inclusion time to time of death or censoring at the end of the observation period (see Methods section).

We computed the unadjusted 4-year survival rates and deaths per 1000 person months (table 2). The 4-year survival rates were significantly higher in groups with the most normal laboratory values: L0 showed a 4-year survival rate of 94.3% versus 34.5% in group L3 ($p < 0.001$). Drug-exposed patients showed significantly higher survival rates: L0D+ with 95.6% 4-year survival vs L0D- with 93.3% ($p < 0.001$) and L3D+ with 38.7% vs L3D- with 24.6% ($p < 0.001$). The drug exposure subgroups differed significantly (all $p < 0.001$) from each other: the Tox group (L0 Tox and L3 Tox) had the highest survival rates with 98.5% (95% CI 98.0–98.8) and 42.4% (95% CI 35.9–48.8%); the Metabolism groups (L0 Metabolism and L3 Metabolism) had the lowest with 89.7% (95% CI 86.8–92.0%) and 35.4% (95% CI 26.9-43.0). Since laboratory parameters for MELD could be obtained only for 47.2% (9514/20 158) of patients, we compared the hazard ratios of the patient groups with and without MELD scores regarding age, gender, cancer and liver diagnoses, race and exposure to the four drug groups. Estimated hazard ratios and significance levels for the above variables were very similar between the MELD and non-MELD groups.

Adjusted hazard ratios (HR) for drug groups versus subjects with no drug exposure showed that of the four drug groups studied HR was highest in the metabolism drug group (1.83, 95% CI 1.01–3.30; table 3). The other three groups showed lower HRs without significance. The functional drug groups showed a high HR for anti-cancer drugs (2.69, 95% CI 1.32–5.46). The HRs of the HIV drug group, immunosuppressants, antiepileptics and statins (HR 0.39, 95% CI 0.08–2.01) were not significant; the opiate group (morphine oral and pentazocine) was reduced to morphine oral, since no patient was treated with pentazocine. Among single drugs docetaxel and etoposide had the highest adjusted HRs with 7.53 (95% CI 3.91–14.48) and 3.55 (95% CI 2.15–5.87) respectively, followed by morphine (2.26, 95% CI 1.78–2.86) and sirolimus (HR = 1.81, 95% CI 1.02–3.21). Amiodarone (HR = 2.46, 95% CI 1.68–3.61), acetazolamide (2.10, 95% CI 1.19–3.70) and lamivudine (1.72, 95% CI 1.17–2.53) showed high HRs even after adjustment including cancer diagnoses. Some drugs showed a laboratory-adjusted HR lower than 1.0: ibuprofen, metformin, atorvastatin, pravastatin, azathioprine and simvastatin. The list of the 44 drugs excluded due to small sample size (<20 patient exposures) can be obtained from the authors.

The survival curves adjusted for age, liver diagnosis, cancer and race are plotted in figure 2: the more laboratory parameters above threshold, the higher the mortality (fig. 2a). Overall exposure to drug groups was not associated with a higher mortality rate (fig. 2b). MELD scores below ten had a close to identical outcome; the other four strata showed a regular pattern with an inverse relationship between MELD and survival (fig. 2c).

## Discussion

Our study revealed no association between overall drug exposure and mortality in patients with chronic liver disease, although exposure to certain drug groups such as anti-cancer drugs and the metabolism drug group was associated with an almost twofold or higher mortality hazard ratio, as were five individual drugs (amiodarone, morphine, acetazolamide, lamivudine and sirolimus). To the best of our knowledge overall drug exposure and these drug groups have not been evaluated regarding mortality in a retrospective cohort study of this size in patients with chronic liver illness.

However, the risk of single drugs has been assessed in many studies. Here our findings are quite consistent with the literature; for example, amiodarone has been reported to cause drug-induced liver injury with fatal outcome by the World Health Organization Collaborating Centre for International Drug Monitoring [14]. In addition, patients with liver illness can develop acetazolamide-induced severe lactic acidosis and ketosis by inhibition of the mitochondrial carbonic anhydrase V [15], which has been suspected to cause bone marrow depression. In the case of lamivudine, underlying disease such as chronic hepatitis B as well as concomitant anti-HIV drugs may be especially prevalent as confounding factors, and causality has been difficult to establish [14]. Sirolimus has been used in solid organ transplantation, but its side effect of hepatic artery thrombosis led to a black-box warning by the US Food and Drug Administration [16].

Drugs may cause different kinds of liver damage and histopathology may show a very heterogeneous pattern. Next to liver enzyme induction (e.g., phenytoin, amiodarone) drugs may cause direct liver toxicity with microvasular steatosis (e.g., valproic acid, tetracyclines), acute hepatitis with hepatocellular swelling (e.g., isoniacid), cholestasis (e.g., amoxicillin/clavulanic acid, chlorpromazine) or eosinophilic inflammation (e.g., phenytoin) [17, 18]. Allopurinol, halothane and carbamazepine are known to cause granulomatous hepatitis [19, 20].

Causality must be viewed with circumspection because of the potential for confounding. Patients exposed to certain hepatotoxic drugs actually had a lower mortality than non-exposed patients. This might be interpreted as a protective effect of drugs, and this could indeed be the case e.g., for statins. A vast literature exists on the incidence reduction of cardiovascular disease and mortality by statins [21, 22]. On the other hand, confounding cannot be excluded since physician judgment clearly plays a central role in selecting which patients will receive the drugs prescribed, and physicians are likely to be most conservative in the patients at highest risk. The most striking example was group L3D–, which had the highest mortality of all groups but no drug exposure as studied here. This suggests that physicians assess their patients according to disease severity and are appropriately reluctant to use potentially hepatotoxic medications in patients with the most severe liver disease and greatest risk of death [23, 24]. Lower mortality in patients taking non-steroidal anti-inflammatory drugs has been observed in several pharmacoepidemiological studies, with a relative risk reduction of 41% and a risk reduction of death by 26% [23, 24]. These reductions remained after adjustment for age, gender, co-morbidity and polypharmacy, and seem to be associated with physician judgment [24]. The most consistent finding in our study was the high adjusted mortality in patients receiving anticancer drugs and five individual drugs. While one possibility for this association are toxic drug effects, confounding by an underlying life-limiting disease is more likely despite statistical adjustment for cancer diagnosis in our study, or, in the case of opiates, their use in terminal care [24].

In general, drug dosage schemes for patients with chronic liver disease are badly needed, but have been challenging to develop. This study was intended as a preliminary step, to determine whether particular drugs represent a significant measurable risk. While only certain drugs could be singled out as potentially harmful in patients with CLD, it is clear that for patients whose underlying liver disease was caused by drugs, the consequences can be serious. In one study with 461 patients with drug related liver injury 53% of patients had to be hospitalised and 18 (4%) suffered fulminant liver failure of whom 12 died and 6 received a liver transplant [25]. In contrast to our patients, in this study by Andrade et al chronic liver disease was excluded. Acetaminophen alone or in combination accounted for 49% of liver transplantation cases in the UNOS database 1990–2002 [8]. However, the risks in patients with known liver disease are less certain and measures to reduce drug induced liver injury are urgently needed.

We found that three readily accessible laboratory parameters – bilirubin, creatinine and INR – could effectively stratify life expectancy for patients with CLD, even without computing the MELD score. It has been suggested that other laboratory parameters such as aspartate-aminotransferase predict mortality and the need for liver transplantation in drug-induced liver disease [26]. We chose the MELD parameters since the score has been widely implemented and used in different clinical settings. MELD has been used primarily in the context of single diseases and with rather low patient numbers [3, 6, 7, 27]. We showed that MELD can be used in large populations with different reasons for CLD to predict survival.

When large research databases are used, it is important to scrutinise data quality. In our study inclusion search results for drug exposure appeared accurate, as were demographic data. Death data files are controverted regarding timeliness

and accuracy. Sensitivity for mortality is reported to be up to 92.1% with a specificity of 99.9% with data from Social Security Administration Death Master File (SSA DMF), as compared to >95% with National Death Index as the gold standard [11, 12, 28]. RPDR is updated monthly using SSA DMF, which itself is updated weekly [12, 29]. Hence we cannot exclude slight inaccuracy during the first and the last 1–2 months of the observation period.

Our study has several limitations. Patient selection may be influenced by the geographical area where recruitment study sites are located. As an example, 8.4% of our patients presented alcohol-associated CLD whereas Said et al found 29.9% of patients with an alcohol-associated CLD in their cohort[30]. Our study sites are located in the greater Boston area, and thus the study results may not be generalisable to other patient populations. Our study was designed to give an overview of mortality of CLD patients with and without exposure to potentially hepatotoxic drugs. The design of observational drug outcome studies has been challenged [24]. Nevertheless, observational studies have an important hypothesis-generating role in pharmacoepidemiological research [31]. In this study setting we did not analyse possible morbidities caused by these prescription drugs, which may have been considerable. Causality between mortality and drug exposure was not established here; in order to do so, in-depth studies of drug exposure regarding duration and total amount will have to be performed [18]. Although we used the most probable covariates in the Cox regression model, further confounding such as physician judgment and over-the-counter (OTC) drug use may still be present. In fact propensity scores have been suggested in order to adjust for physician judgment, but their use does not seem to influence results substantially [32]. OTC drugs, especially pain relievers such as acetaminophen or ibuprofen may have influenced our study endpoints [33]; however, the majority of the observed drugs are not available OTC. Some drug groups overlapped and patients may have been exposed to more than one drug; we therefore chose groups excluding overlapping patients. Finally, laboratory thresholds varied slightly among the study sites. Since the differences were minute we do not believe they are decisive for our study results.

In summary, we found in our observational study that drug exposure overall was not associated with a higher mortality except in a few categories; in these, randomised controlled trials should follow to analyse causality issues. Patients with chronic liver disease have a high mortality and the parameters bilirubin, creatinine and INR per se may stratify these patients regarding mortality.

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**Ethical approval:** The Brigham and Women's Hospital Institutional Review Board approved the study.

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## Appendix 1: Drug groups

A) Hepatic Metabolism (11 drugs). High extraction drugs are typically flow dependent and flow is diminished in cirrhosis. This implies that the first pass effect of primarily flow dependent drugs is reduced in CLD and the free serum levels are higher than normal. ClHep = Q x E where ClHep is the hepatic clearance of a drug, Q = blood flow through liver and E = hepatic extraction of drug [1]. The following drugs have a high hepatic extraction rate of >60% (= first pass effect) in healthy humans and therefore show a clinically relevant flow dependent hepatic metabolism requiring dose reduction [1, 2]; oral formulations were included wherever possible by excluding search terms "solution", "injection", "mg/ml", "IV" and "vial" because of the hepatic first-pass effect involved (cyclosporine, fluorouracil, idarubicin, lovastatin, morphine, pentazocine, quetiapine, tacrolimus, verapamil, vinblastine, vincristine).

B) Direct Liver Toxicity (9 drugs). A common, dangerous and costly problem is direct drug toxicity to the liver. Drugs like antiepileptics and tuberculostatics are used quite commonly. This group contains iv and po drugs with known direct liver toxicity: acetaminophen, amoxicillin-clavulanate, carbamazepine, diclofenac, etoposide, ibuprofen, isoniazide, propylthiouracil and valproic acid.

C) FDA Black Box Warnings (BBW) for liver toxicity (43 drugs) [3]. The FDA issues BBW to give health care professionals a clear understanding of serious side effects of a drug. 0.7% of outpatients receive a prescription in violation of FDA BBW [4]. Of these less than 1% has an ADE. The following drugs are FDA listed for potential hepatotoxicity and were therefore included: adefovir & dipivoxil, amiodarone, bosentan, dacarbazine, danazole, dantrolene, daunorubicine (conventional), didanosine, docetaxel, emtricitabine, entecavir, epirubicin, felbamate, flutamide, gemtuzumab, idarubicin, isoniazid, ketokonazole, lamivudine, metformin, methotrexate, naltrexone, nandrolone decanoate, oxandrolone and oxymethalone (anabole steroids), nefazodone, nevirapine, pemoline, sirolimus, stavudine, streptozocin, telbivudine, telithromycin, tenofovir & disoproxil fumarate, tipranavir, tolcapone, trovafloxacin, valproic acid, zalcitabine, zidovudine, zidovudine & lamivudine.

D) Potentially hepatotoxic drugs included in LMR (42 drugs). The following drugs were studied from March 24th 2003 to September 23rd 2003 and went live in the LMR warning system for potential liver toxicity by January 1st 2004 in all three hospitals studied. Warnings are triggered by the combination of the drugs with the Public Health Service (PHS) diagnosis codes for cirrhosis (81), ascites (889) or oesophageal varices (676) as well as liver function tests. The following drugs were included: acetazolamide, allopurinol, amiodarone, atorvastatin, azathioprine, carbamazepine (oral: chew, XR), cervistatin, chlorpropamide,

clidinium bromide, clonazepam, colchicine ± probenecid, cyclosporine (oral: Micro oral, Micro, oral sol), danazol, dantrolene, disulfiram, divalproex sodium, ergotamine and caffeine combined, ergotamine tartrate, erythromycine estolate, ezetimibe and simvastatin (10–10/20/40/80 mg) combined, fenofibrate, fluvastatin, gemfibrozil, isoniazid, isoniazide and rifampin combined, isoniazide and rifampin and pyrazinamide combined, levonorgestrel implants, lovastatin, medroxyprogesterone acetate, methazolamide, methyldopa, naltrexone, nefazodone, phenelzine, pioglitazone, pravastatin, pyrazinamide, rosiglitazone, simvastatin, terbinafine, tranylcypromine, valproic acid, warfarin sodium.

E) Functional drug classes: The group Statins included lovastatin, atorvastatin, cervistatin, simvastatin, ezetimibe and simvastatin combined and fluvastatin, the group Antibiotics amoxicillin-clavulanate, telithromycin, trovafloxacin and erythromycine estolate. Antiepileptics enclosed carbamazepine, valproic acid, divalproex sodium and felbamate. Opiates included morphine and pentazocine, Anti-cancer agents fluorouracil, flutamide, gemtuzumab, dacarbazine, idarubicin, vinblastine, vincristine, vinorelbine, etoposide, daunorubicine, docetaxel and epirubicin. Immunosuppressants embraced cyclosporine, tacrolimus, methotrexate and sirolimus and HIV drugs emtricitabine, adefovir & dipivoxil, didanosine, entecavir, lamivudine, nevirapine, stavudine, telbivudine, tenofovir & disoproxil fumarate, tipranavir, zalcitabine, zidovudine as well as zidovudine and lamivudine combined. TBC drugs encompassed isoniazide and the two combinations isoniazide/rifampin as well as isoniazide/rifampin/pyrazinamide.

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