Table S1: Sensitivity analysis for the outcome of all-cause mortality, excluding patients who received ursodeoxycholic acid (UDCA) treatment prior to 2006—patient demographic and clinical characteristics by treatment status before and after inverse probability of treatment weighting

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Response | Unweighted | | Abs standard difference | Weighted | | Abs standard difference |
| Untreated | Treated | Untreated | Treated |
| (N= 988) | (N= 2150) | (N= 988) | (N= 2150) |
| US Census region | Midwest | 119 (12%) | 462 (21%) | 0.429 | (19%) | (19%) | 0.047 |
| Northeast | 59 (6%) | 145 (7%) | (6%) | (7%) |
| South | 256 (26%) | 231 (11%) | (16%) | (15%) |
| West | 554 (56%) | 1312 (61%) | (59%) | (59%) |
| Gender | Women | 765 (77%) | 1866 (87%) | 0.246 | (84%) | (84%) | 0.013 |
| Men | 223 (23%) | 284 (13%) | (16%) | (16%) |
| Race | ASINPI | 598 (61%) | 1430 (67%) | 0.224 | (65%) | (65%) | 0.043 |
| Black/ African American | 129 (13%) | 154 (7%) | (9%) | (9%) |
| White | 63 (6%) | 173 (8%) | (7%) | (8%) |
| Unknown | 198 (20%) | 393 (18%) | (19%) | (19%) |
| Hispanic ethnicity | Yes | 672 (68%) | 1433 (67%) | 0.09 | (67%) | (67%) | 0.039 |
| No | 204 (21%) | 526 (24%) | (24%) | (23%) |
| Unknown | 112 (11%) | 191 (9%) | (9%) | (10%) |
| Age at index | ≤40 | 73 (7%) | 161 (7%) | 0.224 | (7%) | (8%) | 0.043 |
| 41–50 | 123 (12%) | 365 (17%) | (15%) | (15%) |
| 51–60 | 279 (28%) | 659 (31%) | (30%) | (30%) |
| 61–70 | 262 (27%) | 591 (27%) | (27%) | (27%) |
| >70 | 251 (25%) | 374 (17%) | (21%) | (20%) |
| Insurance | Medicaid | 51 (5%) | 99 (5%) | 0.195 | (4%) | (5%) | 0.05 |
| Medicare Plus | 403 (41%) | 687 (32%) | (36%) | (35%) |
| Private | 510 (52%) | 1288 (60%) | (57%) | (57%) |
| Unknown | 24 (2%) | 76 (4%) | (3%) | (3%) |
| Household Income | $30K<$50K | 259 (26%) | 594 (28%) | 0.176 | (28%) | (27%) | 0.053 |
| $50K<$75K | 298 (30%) | 616 (29%) | (28%) | (29%) |
| ≥$75K | 356 (36%) | 828 (39%) | (39%) | (38%) |
| Missing | 75 (8%) | 112 (5%) | (5%) | (5%) |
| Charlson-Deyo comorbidity index\* | 0 | 455 (46%) | 1276 (59%) | 0.282 | (54%) | (55%) | 0.024 |
| 1 | 210 (21%) | 407 (19%) | (20%) | (20%) |
| 2 | 323 (33%) | 467 (22%) | (26%) | (25%) |
| Alkaline phosphatase | Normal | 251 (25%) | 374 (17%) | 0.287 | (20%) | (20%) | 0.039 |
| [1,2)\*ULN | 392 (40%) | 775 (36%) | (37%) | (37%) |
| [2,3)\*ULN | 114 (12%) | 348 (16%) | (14%) | (15%) |
| ≥3\*ULN | 110 (11%) | 384 (18%) | (16%) | (16%) |
| Unknown | 121 (12%) | 269 (13%) | (12%) | (12%) |
| Albumin | Normal | 461 (47%) | 1161 (54%) | 0.206 | (50%) | (51%) | 0.024 |
| <LLN | 310 (31%) | 467 (22%) | (26%) | (25%) |
| Unknown | 217 (22%) | 522 (24%) | (24%) | (24%) |
| Total Bilirubin (mg/dL) | >2.0 | 119 (12%) | 170 (8%) | 0.196 | (9%) | (9%) | 0.059 |
| 2.0>1.5 | 45 (5%) | 86 (4%) | (4%) | (4%) |
| 1.5>1.0 | 92 (9%) | 177 (8%) | (8%) | (8%) |
| 1.0>0.7 | 163 (16%) | 332 (15%) | (15%) | (16%) |
| 0.7>0.4 | 199 (20%) | 561 (26%) | (25%) | (25%) |
| ≤0.4 | 202 (20%) | 473 (22%) | (-21%) | (-0.22) |
| Unknown | 168 (17%) | 351 (16%) | (16%) | (17%) |
| AST/ALT≥1.1 | No | 469 (47%) | 1179 (55%) | 0.211 | (52%) | (53%) | 0.001 |
| Yes | 399 (40%) | 645 (30%) | (33%) | (33%) |
| Unknown | 120 (12%) | 326 (15%) | (15%) | (14%) |
| APRI Score |  | 2.3 ± 7.0 | 1.7 ± 4.6 | 0.11 | 1.9±6.1 | 2.1±8.1 | 0.017 |
| Index Year |  | 2010.2 ± 3.6 | 2010.8 ± 3.4 | 0.19 | 2010.2 ± 6.2 | 2010.8 ± 4.2 | 0.068 |

*\*Comorbidity index calculated after excluding liver related conditions*

*\*\*APRI included for illustration purposes but not used in the generation of propensity scores*

*Abs standard diff: absolute standard difference; ASINPI: Asian American, American Indian, Pacific Islander; ULN: upper limit of normal, as defined by the assay used at each site; LLN: lower limit of normal, as defined by the assay used at each site; AST/ALT: ratio of aspartate aminotransferase to alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index*

Table S2: Sensitivity analysis, all-cause mortality with multiple imputation for unknown values—patient demographic and clinical characteristics by ursodeoxycholic acid (UDCA) treatment status before and after inverse probability of treatment weighting

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Response | Unweighted | | Abs standard difference | Weighted | | Abs standard difference |
| Untreated | Treated | Untreated | Treated |
| (N= 990) | (N= 4238) | (N= 990) | (N= 4238) |
| US Census region | Midwest | 121 (12%) | 752 (23%) | 0.543 | (21%) | (21%) | 0.001 |
| Northeast | 59 (6%) | 284 (9%) | (8%) | (8%) |
| South | 256 (26%) | 260 (8%) | (12%) | (12%) |
| West | 554 (56%) | 1952 (60%) | (59%) | (59%) |
| Gender | Women | 766 (77%) | 2850 (88%) | 0.276 | (86%) | (86%) | 0.004 |
| Men | 224 (23%) | 398 (12%) | (14%) | (14%) |
| Race | ASINPI | 600 (61%) | 2290 (71%) | 0.281 | (69%) | (68%) | 0.027 |
| Black/ African American | 129 (13%) | 187 (6%) | (8%) | (8%) |
| White | 63 (6%) | 233 (7%) | (7%) | (7%) |
| Unknown | 198 (20%) | 538 (17%) | (16%) | (17%) |
| Hispanic ethnicity | Yes | 763 (77%) | 2489 (77%) | 0.01 | (77%) | (77%) | 0.0001 |
| No | 227 (23%) | 759 (23%) | (23%) | (23%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| Age at index | ≤40 | 74 (7%) | 212 (7%) | 0.229 | (6%) | (7%) | 0.082 |
| 41–50 | 123 (12%) | 518 (16%) | (13%) | (15%) |
| 51–60 | 279 (28%) | 1018 (31%) | (31%) | (30%) |
| 61–70 | 262 (26%) | 917 (28%) | (28%) | (28%) |
| >70 | 252 (25%) | 583 (18%) | (21%) | (20%) |
| Insurance | Medicaid | 51 (5%) | 151 (5%) | 0.104 | (4%) | (5%) | 0.049 |
| Medicare Plus | 421 (43%) | 1245 (38%) | (41%) | (40%) |
| Private | 518 (52%) | 1852 (57%) | (54%) | (56%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| Household Income | $30K<$50K | 288 (29%) | 957 (29%) | 0.024 | (30%) | (30%) | 0.024 |
| $50K<$75K | 323 (33%) | 1033 (32%) | (31%) | (32%) |
| ≥$75K | 379 (38%) | 1258 (39%) | (39%) | (39%) |
| Missing | 0(0%) | 0(0%) | (0%) | (0%) |
| Charlson-Deyo comorbidity index\* | 0 | 457 (46%) | 2030 (63%) | 0.371 | (58%) | (59%) | 0.026 |
| 1 | 210 (21%) | 599 (18%) | (20%) | (19%) |
| 2 | 323 (33%) | 619 (19%) | (22%) | (22%) |
| Alkaline phosphatase | Normal | 284 (29%) | 751 (23%) | 0.227 | (24%) | (24%) | 0.028 |
| [1,2)\*ULN | 445 (45%) | 1343 (41%) | (43%) | (42%) |
| [2,3)\*ULN | 132 (13%) | 564 (17%) | (16%) | (16%) |
| ≥3\*ULN | 129 (13%) | 590 (18%) | (17%) | (17%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| Albumin | Normal | 611 (62%) | 2328 (72%) | 0.227 | (69%) | (69%) | 0.028 |
| <LLN | 379 (38%) | 920 (28%) | (31%) | (31%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| Total Bilirubin (mg/dL) | >2.0 | 132 (13%) | 291 (9%) | 0.182 | (9%) | (10%) | 0.047 |
| 2.0>1.5 | 63 (6%) | 174 (5%) | (6%) | (6%) |
| 1.5>1.0 | 102 (10%) | 276 (8%) | (8%) | (9%) |
| 1.0>0.7 | 200 (20%) | 656 (20%) | (20%) | (20%) |
| 0.7>0.4 | 247 (25%) | 1003 (31%) | (30%) | (30%) |
| ≤0.4 | 246 (25%) | 848 (26%) | (26%) | (26%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| AST/ALT≥1.1 | No | 542 (55%) | 2039 (63%) | 0.164 | (61%) | (61%) | 0.003 |
| Yes | 448 (45%) | 1209 (37%) | (39%) | (39%) |
| Unknown | 0 (0%) | 0 (0%) | (0%) | (0%) |
| APRI Score |  | 2.3 ± 6.7 | 1.7 ± 4.4 | 0.102 | 1.8±10.1 | 1.8±6.8 | 0.011 |
| Index Year |  | 2010.2 ± 3.6 | 2010.0 ± 3.5 | 0.052 | 2009.9±7.4 | 2010.0±4.1 | 0.023 |

*\*Comorbidity index calculated after excluding liver related conditions*

*\*\*APRI included for illustration purposes but not used in the generation of propensity scores*

*Abs standard diff: absolute standard difference; ASINPI: Asian American, American Indian, Pacific Islander; ULN: upper limit of normal, as defined by the assay used at each site; LLN: lower limit of normal, as defined by the assay used at each site; AST/ALT: ratio of aspartate aminotransferase to alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index*

Table S3: Details of multivariable analysis of ursodeoxycholic acid treatment for main outcomes of all-cause mortality and liver transplant/ death—sub-sample sizes, adjusted hazard ratios (HR), and 95% confidence intervals (CI).



*ASINPI: Asian American, American Indian, Pacific Islander; ULN: upper limit of normal, as defined by the assay used at each site; LLN: lower limit of normal, as defined by the assay used at each site; AST/ALT: ratio of aspartate aminotransferase to alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index (*

Table S4: Details of sensitivity analysis of ursodeoxycholic acid treatment for all-cause mortality, excluding patients with history of treatment prior to study observation start date (2006) and with multiple imputation (MI) for missing data—sub-sample sizes, adjusted hazard ratios (HR), and 95% confidence intervals (CI).



*ASINPI: Asian American, American Indian, Pacific Islander; ULN: upper limit of normal, as defined by the assay used at each site; LLN: lower limit of normal, as defined by the assay used at each site; AST/ALT: ratio of aspartate aminotransferase to alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index (*

Table S5: Pairwise comparison of ursodeoxycholic acid treated versus untreated patients for all-cause mortality, liver transplant/ death, and sensitivity analyses that excluded patients with history of treatment prior to study observation start date (2006) and with multiple imputation (MI) for missing data—sub-sample sizes, adjusted hazard ratios (HR), and 95% confidence intervals (CI).



*ASINPI: Asian American, American Indian, Pacific Islander; AST/ALT: ratio of aspartate aminotransferase to alanine aminotransferase;*

**Table S6: Summary of multivariable models and validated results of predictive accuracy**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Model** | **Variables** | **AUROC (validation)** | | **See Figure** |
| **2 Year** | **5 Year** |
| **All-cause mortality** | BL | Index date variables: region, household income, comorbidity index, age, bilirubin, ALP, AST/ALT, albumin, and interactions of UDCA with gender, race, and AST/ALT | 0.82 | 0.81 | 1a |
| BL+P2 | BL variables + Paris-II criteria at Year 1 (with Paris II by UDCA interaction) | 0.89 | 0.84 |  |
| BL+1 | Baseline + ALP, AST/ALT, and bilirubin at Year 1 | 0.90 | 0.85 |  |
| P2 | Paris-II criteria at Year 1 | 0.84 | 0.74 |  |
| **Liver transplant or all-cause mortality** | TXF | Index date variables: region, household income, comorbidity index, age, bilirubin, gender, ALP, albumin and interaction of UDCA with race | 0.81 | 0.81 | 1b |
| TXF+P2 | TXF + UDCA interaction with Paris-II criteria at Year 1, gender, AST/ALT | 0.85 | 0.84 |  |
| TXF+1 | TXF + ALP, AST/ALT, and bilirubin at Year 1, and interaction of UDCA with race | 0.86 | 0.84 |  |
| P2 | Paris-II criteria at Year 1 | 0.79 | 0.73 |  |