**Age and the relative importance of liver-related deaths in nonalcoholic fatty liver disease**

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**Figure S1. Cause-specific mortality by cirrhosis status.** A) Number of deaths by cirrhosis and causes. B) Percentage of different causes of death by cirrhosis. Cirrhosis was diagnosed with both ICD-9 diagnose codes of liver cirrhosis and cirrhotic complications during follow-up.

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**Figure S2. Cause-specific mortality by baseline FIB-4 levels.** A) Number of deaths by FIB-4 levels and causes. B) Percentage of different causes of death by FIB-4 levels. 789 mortality cases with available FIB-4 levels were analyzed. FIB-4, Fibrosis-4 index.

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**Table S1. ICD-9 diagnosis codes**

|  |  |
| --- | --- |
| Diseases | ICD-9 codes |
| Cirrhotic complications |  |
| Ascites | 789.5 |
| Spontaneous bacterial peritonitis | 567.2:9, 567.8:0 |
| Oesophageal variceal bleeding | 456.0, 456.20 |
| Gastric variceal bleeding | 456.8:1, 456.8:2 |
| Hepatic encephalopathy | 348.3, 349.82, 572.2 |
| Hepatorenal syndrome | 572.4 |
| Excessive use of alcohol | 291, 291.0, 291.1, 291.2, 291.3, 291.4 291.5, 291.8, 291.81, 291.89, 291.9, 303, 303.0, 303.00, 303.01, 303.02, 303.03 303.90, 303.91, 303.92, 303.93, 305, 305.00, 305.01, 305.02, 305.03, 357.5, 425.5, 535.30, 535.31, 571.0, 571.1 571.2, 571.3, 655.4, 760.71, V11.3, V15.84 |
| Hepatitis B | 070.20-070.23, 070.30-070.33, V02.61 |
| Hepatitis C | 070.41, 070.44, 070.51, 070.54, V02.62 |
| HCC | 155.0, 155.2 |
| HIV | 042, 079.53, V02.9:1, V08 |
| Liver cirrhosis | 571.5, 456.1, 456.21, 456.8:5, 572.3 |
| NAFLD | 571.8 |
| Other hepatobiliary diseases | 275.0, 275.1, 571.40,571.41,571.49,571.6, 571.9, 572.0-572.4, 572.8, 573.0-573.3, 573.8, 573.9, 576.1 |
| Liver transplantation | V42.7; 50.51, 50.59 |

Note: Liver transplantation was defined by ICD-9 procedure codes.

Abbreviations:HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease.

**Table S2. ICD-10 codes for causes of death**

|  |  |
| --- | --- |
| **Causes of death** | **ICD-10 codes** |
| Liver diseases | C22, K70-K77 |
| Pneumonia | J12-J18 |
| Extrahepatic cancer | C00-C97 (excluding C22) |
| Cardiovascular diseases | I00-I09, I11, I13, I20-I51 |
| Renal diseases | N00-N07, N17-N19, N25-N27 |
| Cerebrovascular diseases | I60-I69 |
| Septicemia | A40-A41 |
| Others | All other codes |

Note: 4 patients who died in the earlier era had ICD-9 codes for the causes of death.

**Table S3. Comorbidities and medication use during follow-up among NAFLD patients who died**

|  |  |
| --- | --- |
| N | 2097 |
| Male sex, n (%) | 1008 (48.1) |
| Comorbidities, n (%) |  |
| Cirrhosis | 213 (10.2) |
| FIB-4 Index | 1.8 (1.1-3.1) |
| Cirrhotic complications | 194 (9.3) |
| Hepatocellular carcinoma | 73 (3.5) |
| Extrahepatic cancer | 922 (44.0) |
| Type 2 diabetes mellitus | 1432 (68.3) |
| Hypertension | 1950 (93.0) |
| Coronary artery disease | 642 (30.6) |
| Congestive heart failure | 719 (34.3) |
| Cerebrovascular disease | 805 (38.4) |
| Hyperlipidemia | 1332 (63.5) |
| Medication use, n (%) |  |
| Metformin | 1013 (48.3) |
| Sulfonylureas | 1034 (49.3) |
| Thiazolidinediones | 91 (4.3) |
| DPP-4 inhibitors | 173 (8.2) |
| SGLT2 inhibitors | 10 (0.5) |
| Insulin | 907 (43.3) |
| Lipid-lowering drugs | 1237 (59.0) |
| Aspirin | 1273 (60.7) |
| Thiazides | 862 (41.1) |
| Beta-blockers | 1428 (68.1) |
| Calcium channel blockers | 1538 (73.3) |
| ACEI/ARB | 1687 (80.4) |

Note: Categorical variables are presented as number (percentage), continuous variables are expressed as median (interquartile range). FIB-4 Index was presented at baseline.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; FIB-4 Index, Fibrosis-4 Index; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; LLA, lipid lowing agents; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

**Table S4. Top 3 non-liver cancers that contributed to mortality by age and gender**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cohorts** | **Cancer types** | | |
| **Whole cohort** | Lung cancer | Colon cancer | Pancreas cancer |
| **Sex** |  |  |  |
| **Male** | Lung cancer | Colon cancer | Pancreas cancer |
| **Female** | Lung cancer | Pancreas cancer | Breast cancer |
| **Age at death** |  |  |  |
| **<50** | Pancreas cancer | Brain cancer | Breast cancer |
| **50-59** | Lung cancer | Pancreas cancer | Breast/Colon cancer |
| **60-69** | Lung cancer | Pancreas cancer | Colon cancer |
| **70-79** | Lung cancer | Colon cancer | Pancreas cancer |
| **80-89** | Lung cancer | Colon cancer | Gastric cancer |
| **≥90** | Lung cancer | Colon cancer | Gastric cancer |

**Table S5.** **All-cause and cause-specific mortality in the NAFLD patients by age**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Mortality** | **Age at death (years)** | | | | | |
| **<50** | **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| All-cause death, N | 99 | 196 | 380 | 601 | 657 | 164 |
| Incidence rate, per 10,000 PY (95%CI) | 3.21  (2.63-3.90) | 11.13  (9.68-12.81) | 34.28  (31.01-37.9) | 127.86  (118.10-138.43) | 443.81  (411.84-478.25) | 1021.64  (883.73-1181.08) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 2 | 6 | 13 | 30 | 38 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 0.06  (0.02-0.26) | 0.34  (0.15-0.75) | 1.17  (0.68-2.02) | 6.38  (4.46-9.13) | 25.66  (18.68-35.26) | 18.68  (6.03-57.88) |
| Pneumonia, N | 13 | 18 | 67 | 131 | 208 | 72 |
| Incidence rate, per 10,000 PY (95%CI) | 0.42  (0.24-0.72) | 0.99  (0.64-1.62) | 6.04  (4.75-7.68) | 27.87  (23.49-33.07) | 140.51  (122.76-160.80) | 448.53  (357.89-562.12) |
| Extrahepatic cancer, N | 18 | 77 | 104 | 133 | 90 | 17 |
| Incidence rate, per 10,000 PY (95%CI) | 0.58  (0.36-0.92) | 4.37  (3.50-5.47) | 9.38  (7.74-11.37) | 28.29  (23.87-33.53) | 60.79  (49.47-74.70) | 105.90  (66.00-169.92) |
| Cardiovascular diseases, N | 17 | 33 | 57 | 91 | 87 | 22 |
| Incidence rate, per 10,000 PY (95%CI) | 0.55  (0.34-0.88) | 1.87  (1.33-2.63) | 5.14  (3.96-6.66) | 19.36  (15.76-23.77) | 58.76  (47.66-72.46) | 137.05  (90.50-207.54) |
| Renal diseases, N | 4 | 10 | 23 | 53 | 56 | 7 |
| Incidence rate, per 10,000 PY (95%CI) | 0.13  (0.05-0.34) | 0.56  (0.31-1.05) | 2.07  (1.37-3.12) | 11.27  (8.61-14.75) | 37.82  (29.12-49.13) | 43.61  (20.82-91.32) |
| Cerebrovascular diseases, N | 5 | 12 | 24 | 27 | 33 | 6 |
| Incidence rate, per 10,000 PY (95%CI) | 0.16  (0.07-0.39) | 0.68  (0.38-1.20) | 2.16  (1.45-3.23) | 5.74  (3.94-8.37) | 22.29  (15.85-31.34) | 37.37  (16.82-83.07) |
| Septicemia, N | 3 | 6 | 20 | 30 | 25 | 12 |
| Incidence rate, per 10,000 PY (95%CI) | 0.09  (0.03-0.30) | 0.34  (0.15-0.75) | 1.81  (1.16-2.79) | 6.38  (4.46-9.12) | 16.88  (11.42-24.98) | 74.75  (42.54-131.35) |
| Other causes, N | 37 | 30 | 59 | 88 | 106 | 24 |
| Incidence rate, per 10,000 PY (95%CI) | 1.20  (0.86-1.65) | 1.71  (1.19-2.43) | 5.32  (4.13-6.87) | 18.72  (15.19-23.06) | 71.60  (59.23-86.55) | 149.51  (100.51-222.39) |

Abbreviations: NAFLD, nonalcoholic fatty liver disease; PY, person-years; CI, confidence interval.

**Table S6. The incidence rate ratio of liver-related mortality in the whole, men/women and cirrhosis/no cirrhosis cohorts by age groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age groups (years)** | **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| **Whole cohort** | 5.01  (1.11-37.84)  **0.035** | 16.99  (4.64-118.26)  **<0.001** | 91.85  (27.71-611.91)  **<0.001** | 368.77  (113.14-2443.89)  **<0.001** | 281.52  (42.86-2422.90)  **<0.001** |
| **Men** | 6.16  (0.72-176.58)  0.099 | 28.89  (5.34-723.44)  **<0.001** | 78.18  (14.80-1941.57)  **<0.001** | 295.67  (55.97-7342.07)  **<0.001** | 362.23  (9.28-14126.93)  **0.005** |
| **Women** | 3.83  (0.44-110.05)  0.231 | 7.92  (1.09-215.91)  **0.039** | 88.43  (18.56-2105.94)  **<0.001** | 353.69  (76.41-8332.19)  **<0.001** | 231.58  (18.74-7268.69)  **<0.001** |
| **Cirrhosis** | 1.18  (0.18-10.18)  0.859 | 3.45  (0.91-24.35)  0.070 | 8.63  (2.54-58.05)  **<0.001** | 28.77  (8.72-191.38)  **<0.001** | 39.02  (5.94-335.79)  **<0.001** |
| **No cirrhosis** | - | 1.09  (0.13-7.17)  0.926 | 8.71  (2.35-42.69)  **0.001** | 24.08  (6.14-120.87)  **<0.001** | **-** |

Note: The incidence rate ratios were calculated with <50 age group as the reference (50-59 age group as the reference in no cirrhosis subgroup analysis). All rate ratios were presented with 95% confidence intervals and P value.

**Table S7. Association between age at death and specific cause of death in 2097 mortality NAFLD cases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Specific cause of death** | **Age at death (years)** | | | | |
| **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| **OR (95%CI) and *P* value** | | | | |
| Liver diseases | 2.13 (0.38-12.17)  0.392 | 2.23 (0.45-11.17)  0.326 | 3.21 (0.68-15.08)  0.139 | 4.96 (1.06-23.28)  **0.042** | 1.58 (0.22-11.01)  0.645 |
| Pneumonia | 0.69 (0.32-1.48)  0.342 | 1.53 (0.80-2.94)  0.193 | 2.08 (1.11-3.88)  **0.022** | 3.62 (1.95-6.75)  **<0.001** | 6.36 (3.23-12.54)  **<0.001** |
| Extrahepatic cancer | 3.47 (1.90-6.36)  **<0.001** | 2.09 (1.17-3.74)  **0.012** | 1.68 (0.95-2.98)  0.072 | 0.89 (0.49-1.59)  0.701 | 0.61 (0.29-1.29)  0.203 |
| Cardiovascular diseases | 0.92 (0.48-1.76)  0.805 | 0.79 (0.43-1.44)  0.442 | 0.77 (0.43-1.38)  0.385 | 0.68 (0.38-1.22)  0.203 | 0.72 (0.36-1.45)  0.361 |
| Renal diseases | 1.16 (0.35-3.84)  0.799 | 1.30 (0.43-3.89)  0.634 | 1.84 (0.64-5.27)  0.252 | 1.78 (0.62-5.10)  0.277 | 0.86 (0.24-3.08)  0.827 |
| Cerebrovascular diseases | 1.13 (0.38-3.31)  0.826 | 1.06 (0.39-2.89)  0.897 | 0.71 (0.26-1.91)  0.502 | 0.77 (0.29-2.07)  0.614 | 0.54 (0.16-1.86)  0.333 |
| Septicemia | 0.93 (0.22-3.82)  0.921 | 1.49 (0.43-5.19)  0.523 | 1.32 (0.39-4.46)  0.654 | 0.96 (0.28-3.30)  0.956 | 1.91 (0.52-7.09)  0.329 |
| Other causes | 0.29 (0.17-0.53)  **<0.001** | 0.30 (0.18-0.49)  **<0.001** | 0.27 (0.17-0.45)  **<0.001** | 0.31 (0.19-0.49)  **<0.001** | 0.27 (0.15-0.51)  **<0.001** |

Note: With age **<**50 group as reference, the multivariable logistic regression adjusted with sex, hypertension and diabetes. Cirrhotic complication and hepatocellular carcinoma were additionally adjusted in the analysis for liver-related death.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; OR: odds ratio; CI: confidence interval.

**Table S8. All-cause and cause-specific mortality in the NAFLD patients by age and sex**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Mortality** | **NAFLD patients in different age groups** | | | | | |
| **<50** | **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| **Male** |  |  |  |  |  |  |
| All-cause death, N | 61 | 121 | 212 | 308 | 257 | 49 |
| Incidence rate, per 10,000 PY (95%CI) | 3.64  (2.83-4.67) | 16.14  (13.51-19.28) | 45.72  (39.97-52.28) | 162.05  (145.05-181.03) | 511.32  (453.91-575.98) | 1058.51  (812.28-1379.36) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 1 | 3 | 9 | 10 | 10 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | 0.06  (0.008-0.42) | 0.40  (0.13-1.24) | 1.94  (1.01-3.73) | 5.26  (2.83-9.77) | 19.89  (10.71-36.95) | 21.60  (3.04-153.03) |
| Pneumonia, N | 8 | 15 | 41 | 84 | 84 | 28 |
| Incidence rate, per 10,000 PY (95%CI) | 0.48  (0.24-0.95) | 2.00  (1.21-3.32) | 8.84  (6.51-12.01) | 44.19  (35.70-54.71) | 167.12  (135.18-206.60) | 604.86  (422.41-866.11) |
| Extrahepatic cancer, N | 10 | 43 | 49 | 64 | 43 | 5 |
| Incidence rate, per 10,000 PY (95%CI) | 0.59  (0.32-1.11) | 5.74  (4.25-7.73) | 10.56  (7.98-13.98) | 33.67  (26.36-43.00) | 85.55  (63.53-115.21) | 108.01  (45.17-258.27) |
| Cardiovascular diseases, N | 13 | 24 | 31 | 50 | 32 | 6 |
| Incidence rate, per 10,000 PY (95%CI) | 0.77  (0.45-1.33) | 3.20  (2.15-4.78) | 6.69  (4.70-9.51) | 26.30  (19.94-34.69) | 63.66  (45.07-89.93) | 129.61  (58.53-287.01) |
| Renal diseases, N | 3 | 8 | 12 | 19 | 25 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | 0.18  (0.06-0.55) | 1.06  (0.53-2.13) | 2.59  (1.47-4.56) | 9.99  (6.37-15.66) | 49.74  (33.64-73.54) | 21.60  (3.04-153.03) |
| Cerebrovascular diseases, N | 4 | 8 | 17 | 10 | 7 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 0.24  (0.09-0.64) | 1.06  (0.53-2.13) | 3.67  (2.28-5.89) | 5.26  (2.83-9.77) | 13.93  (6.64-29.19) | 64.81  (20.97-200.20) |
| Septicemia, N | 2 | 2 | 12 | 15 | 6 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | 0.12  (0.03-0.48) | 0.27  (0.07-1.06) | 2.59  (1.47-4.56) | 7.89  (4.76-13.08) | 11.93  (5.36-26.55) | - |
| Other causes, N | 20 | 17 | 33 | 49 | 42 | 5 |
| Incidence rate, per 10,000 PY (95%CI) | 1.19  (0.77-1.85) | 2.26  (1.41-3.64) | 7.12  (5.06-10.01) | 25.78  (19.49-34.09) | 83.56  (61.83-112.93) | 108.01  (45.17-258.27) |
| **Female** |  |  |  |  |  |  |
| All-cause death, N | 38 | 75 | 168 | 293 | 400 | 115 |
| Incidence rate, per 10,000 PY (95%CI) | 2.70  (1.96-3.71) | 7.42  (5.92-9.31) | 26.06  (12.41-30.31) | 104.65  (93.39-117.28) | 409.10  (371.66-450.31) | 1006.71  (846.51-1197.23) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 1 | 3 | 4 | 20 | 28 | 2 |
| Incidence rate, per 10,000 PY (95%CI) | 0.07  (0.001-0.50) | 0.29  (0.09-0.92) | 0.62  (0.23-1.65) | 7.14  (4.61-11.07) | 28.63  (19.78-41.45) | 17.51  (4.38-69.92) |
| Pneumonia, N | 5 | 3 | 26 | 47 | 124 | 44 |
| Incidence rate, per 10,000 PY (95%CI) | 0.35  (0.14-0.85) | 0.29  (0.09-0.92) | 4.03  (2.74-5.92) | 16.78  (12.62-22.33) | 126.82  (106.47-151.06) | 385.17  (288.29-514.62) |
| Extrahepatic cancer, N | 8 | 34 | 55 | 69 | 47 | 12 |
| Incidence rate, per 10,000 PY (95%CI) | 0.56  (0.28-1.13) | 3.36  (2.41-4.71) | 8.53  (6.55-11.11) | 24.64  (19.47-31.19) | 48.07  (36.14-63.93) | 105.05  (59.83-184.4) |
| Cardiovascular diseases, N | 4 | 9 | 26 | 41 | 55 | 16 |
| Incidence rate, per 10,000 PY (95%CI) | 0.28  (0.10-0.75) | 0.89  (0.46-1.71) | 4.03  (2.74-5.92) | 14.64  (10.78-19.88) | 56.25  (43.22-73.21) | 140.06  (86.10-227.84) |
| Renal diseases, N | 1 | 2 | 11 | 34 | 31 | 6 |
| Incidence rate, per 10,000 PY (95%CI) | 0.07  (0.001-0.50) | 0.19  (0.05-0.79) | 1.71  (0.94-3.08) | 12.14  (8.67-16.99) | 31.71  (22.31-45.05) | 52.52  (23.64-116.67) |
| Cerebrovascular diseases, N | 1 | 4 | 7 | 17 | 26 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 0.07  (0.001-0.50) | 0.39  (0.14-1.05) | 1.08  (0.52-2.27) | 6.07  (3.77-9.76) | 26.59  (18.11-39.03) | 26.26  (8.48-81.31) |
| Septicemia, N | 1 | 4 | 8 | 15 | 19 | 12 |
| Incidence rate, per 10,000 PY (95%CI) | 0.07  (0.001-0.50) | 0.39  (0.14-1.05) | 1.24  (0.62-2.48) | 5.35  (3.23-8.88) | 19.43  (12.40-30.45) | 105.05  (59.83-184.42) |
| Other causes, N | 17 | 13 | 26 | 39 | 64 | 19 |
| Incidence rate, per 10,000 PY (95%CI) | 1.21  (0.75-1.94) | 1.28  (0.74-2.21) | 4.03  (2.74-5.92) | 13.93  (10.18-19.06) | 65.45  (51.27-83.56) | 166.32  (106.49-259.78) |

Abbreviations: NAFLD, nonalcoholic fatty liver disease; PY, person years; CI, confidence interval.

**Table S9. All-cause and cause-specific mortality in the NAFLD patients by age and cirrhosis status**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Mortality** | **NAFLD patients in different age groups** | | | | | |
| **<50** | **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| **Cirrhosis** |  |  |  |  |  |  |
| All-cause death, N | 11 | 19 | 38 | 66 | 66 | 13 |
| Incidence rate, per 10,000 PY (95%CI) | 83.30  (46.20-150.01) | 116.20  (74.30-181.70) | 192.01  (140.10-263.10) | 401.60  (317.10-508.70) | 963.90  (766.40-1212.40) | 2621.80  (1643.60-4182.15) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 2 | 3 | 11 | 23 | 32 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 15.10  (3.70-60.50) | 18.30  (5.90-56.80) | 55.51  (30.80-100.20) | 139.90  (93.20-210.01) | 467.30  (333.20-655.50) | 605.01  (202.01-1811.80) |
| Pneumonia, N | 2 | 1 | 2 | 8 | 10 | 5 |
| Incidence rate, per 10,000 PY (95%CI) | 15.10  (3.70-60.50) | 6.10  (0.80-43.40) | 10.10  (2.50-40.30) | 48.60  (24.30-97.10) | 146.01  (78.90-270.20) | 1008.40  (439.20-2315.20) |
| Extrahepatic cancer, N | 3 | 8 | 9 | 18 | 1 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 22.70  (7.30-70.30) | 48.90  (24.50-97.70) | 45.40  (23.70-87.20) | 109.50  (69.20-173.40) | 14.60  (2.10-103.50) | 605.01  (202.01-1811.80) |
| Cardiovascular diseases, N | 1 | 1 | 3 | 3 | 3 | 2 |
| Incidence rate, per 10,000 PY (95%CI) | 7.50  (1.10-53.70) | 6.10  (0.80-43.40) | 15.10  (4.80-46.90) | 18.20  (5.80-56.50) | 43.80  (14.10-135.50) | 403.30  (103.70-1567.90) |
| Renal diseases, N | 1 | 1 | 4 | 3 | 4 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | 7.50  (1.10-53.70) | 6.10  (0.80-43.40) | 20.20  (7.50-53.80) | 18.20  (5.80-56.50) | 58.40  (21.90-155.20) | - |
| Cerebrovascular diseases, N | 0 | 0 | 1 | 0 | 1 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 5.10  (0.70-35.80) | - | 14.60  (2.10-103.50) | - |
| Septicemia, N | 0 | 1 | 3 | 4 | 1 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 6.10  (0.80-43.40) | 15.10  (4.01-46.90) | 24.30  (9.10-64.70) | 14.60  (2.10-103.50) | - |
| Other causes, N | 2 | 3 | 2 | 3 | 10 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | 15.10  (3.70-60.50) | 18.30  (5.90-56.80) | 10.10  (2.50-40.30) | 18.20  (5.80-56.50) | 146.01  (78.90-270.20) | - |
| **No Cirrhosis** |  |  |  |  |  |  |
| All-cause death, N | 88 | 177 | 342 | 535 | 591 | 151 |
| Incidence rate, per 10,000 PY (95%CI) | 2.86  (2.32-3.53) | 10.15  (8.76-11.76) | 31.42  (28.26-34.92) | 117.94  (108.42-128.31) | 418.58  (386.82-452.95) | 970.64  (834.14-1129.49) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 0 | 3 | 2 | 7 | 6 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 0.17  (0.05-0.53) | 0.18  (0.04-0.74) | 1.54  (0.74-3.23) | 4.25  (1.91-9.45) | - |
| Pneumonia, N | 11 | 17 | 65 | 123 | 198 | 67 |
| Incidence rate, per 10,000 PY (95%CI) | 0.36  (0.19-0.64) | 0.97  (0.60-1.56) | 5.97  (4.68-7.61) | 27.11  (22.73-32.35) | 140.23  (122.12-161.04) | 430.68  (340.74-544.35) |
| Extrahepatic cancer, N | 15 | 69 | 95 | 115 | 89 | 14 |
| Incidence rate, per 10,000 PY (95%CI) | 0.48  (0.29-0.81) | 3.95  (3.12-50.11) | 8.72  (7.13-10.67) | 25.35  (21.12-30.43) | 63.04  (51.24-77.54) | 89.99  (53.43-151.59) |
| Cardiovascular diseases, N | 16 | 32 | 54 | 88 | 84 | 20 |
| Incidence rate, per 10,000 PY (95%CI) | 0.52  (0.32-0.85) | 1.84  (1.29-2.59) | 4.96  (3.80-6.47) | 19.40  (15.74-23.90) | 59.49  (48.07-76.33) | 128.56  (83.17-198.71) |
| Renal diseases, N | 3 | 9 | 19 | 50 | 52 | 7 |
| Incidence rate, per 10,000 PY (95%CI) | 0.09  (0.03-0.30) | 0.52  (0.26-0.99) | 1.47  (1.11-2.73) | 11.02  (8.35-14.54) | 36.83  (28.09-48.31) | 44.99  (21.48-94.22) |
| Cerebrovascular diseases, N | 5 | 12 | 23 | 27 | 32 | 6 |
| Incidence rate, per 10,000 PY (95%CI) | 0.16  (0.07-0.39) | 0.68  (0.39-1.21) | 2.11  (1.40-3.18) | 5.95  (4.08-8.67) | 22.66  (16.03-32.03) | 38.56  (17.35-85.72) |
| Septicemia, N | 3 | 5 | 17 | 26 | 24 | 12 |
| Incidence rate, per 10,000 PY (95%CI) | 0.09  (0.03-0.30) | 0.28  (0.12-0.69) | 1.56  (0.97-2.51) | 5.73  (3.90-8.42) | 16.99  (11.39-25.35) | 77.14  (43.90-135.53) |
| Other causes, N | 35 | 27 | 57 | 85 | 96 | 24 |
| Incidence rate, per 10,000 PY (95%CI) | 1.14  (0.82-1.58) | 1.54  (1.06-2.25) | 5.23  (4.03-6.78) | 18.74  (15.15-23.17) | 67.99  (55.70-82.99) | 154.27  (103.73-229.45) |

Note: Cirrhosis was diagnosed with both ICD-9 diagnose codes of liver cirrhosis and cirrhotic complication.

NAFLD, nonalcoholic fatty liver disease; PY, person years; CI, confidence interval.

**Table S10. All-cause and cause-specific mortality in the NAFLD patients by age and FIB-4 levels**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Mortality** | **NAFLD patients in different age groups** | | | | | |
| **<50** | **50-59** | **60-69** | **70-79** | **80-89** | **≥90** |
| **<1.3** |  |  |  |  |  |  |
| All-cause death, N | 22 | 38 | 63 | 63 | 58 | 8 |
| Incidence rate, per 10,000 PY (95%CI) | 3.29  (2.16-4.99) | 15.05  (10.95-20.68) | 50.09  (39.16-64.09) | 156.09  (122.17-199.43) | 564.15  (439.36-724.38) | 1553.39  (821.66-2936.76) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 0 | 1 | 1 | 1 | 2 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 0.39  (0.05-2.81) | 0.79  (0.11-5.64) | 2.47  (0.34-17.58) | 19.45  (4.87-77.68) | - |
| Pneumonia, N | 3 | 2 | 13 | 15 | 13 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 0.45  (0.14-1.39) | 0.79  (0.19-3.16) | 10.33  (6.00-17.79) | 37.16  (22.42-61.59) | 126.44  (73.67-217.02) | 582.52  (194.26-1746.74) |
| Extrahepatic cancer, N | 3 | 20 | 22 | 12 | 8 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | 0.45  (0.14-1.39) | 7.92  (5.11-12.27) | 17.49  (11.52-26.55) | 29.73  (16.90-52.31) | 77.81  (39.02-155.18) | - |
| Cardiovascular diseases, N | 3 | 5 | 9 | 9 | 8 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | 0.45  (0.14-1.39) | 1.98  (0.82-4.75) | 7.15  (3.72-13.75) | 22.30  (11.61-42.83) | 77.81  (39.02-155.18) | 194.17  (27.88-1352.36) |
| Renal diseases, N | 1 | 2 | 4 | 5 | 6 | 2 |
| Incidence rate, per 10,000 PY (95%CI) | 0.15  (0.02-1.06) | 0.79  (0.19-3.16) | 3.18  (1.19-8.47) | 12.38  (5.15-29.74) | 58.36  (26.28-129.60) | 388.35  (99.80-1511.16) |
| Cerebrovascular diseases, N | 1 | 3 | 4 | 2 | 2 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | 0.15  (0.02-1.06) | 1.18  (0.38-3.68) | 3.18  (1.19-8.47) | 4.95  (1.24-19.80) | 19.45  (4.87-77.68) | - |
| Septicemia, N | 0 | 0 | 2 | 2 | 3 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 1.59  (0.39-6.35) | 4.95  (1.24-19.80) | 29.18  (9.42-90.32) | - |
| Other causes, N | 11 | 5 | 5 | 15 | 16 | 2 |
| Incidence rate, per 10,000 PY (95%CI) | 1.64  (0.91-2.97) | 1.98  (0.82-4.75) | 3.97  (1.65-9.55) | 37.16  (22.42-61.59) | 155.62  (95.71-253.06) | 388.35  (99.80-1511.16) |
| **1.3-2.66** |  |  |  |  |  |  |
| All-cause death, N | 5 | 17 | 41 | 92 | 111 | 25 |
| Incidence rate, per 10,000 PY (95%CI) | 3.83  (1.59-9.22) | 12.95  (8.05-20.83) | 35.66  (26.27-48.41) | 135.66  (110.74-166.19) | 453.04  (377.74-543.35) | 915.47  (630.06-1330.16) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 0 | 1 | 0 | 4 | 4 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 0.76  (0.11-5.41) | - | 5.89  (2.21-15.71) | 16.32  (6.13-43.46) | - |
| Pneumonia, N | 0 | 5 | 6 | 19 | 38 | 13 |
| Incidence rate, per 10,000 PY (95%CI) | - | 3.81  (1.58-9.15) | 5.21  (2.34-11.61) | 28.01  (17.88-43.89) | 155.09  (113.13-212.62) | 476.04  (280.06-809.17) |
| Extrahepatic cancer, N | 0 | 5 | 13 | 19 | 19 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 3.81  (1.58-9.15) | 11.31  (6.56-19.47) | 28.01  (17.88-43.89) | 77.54  (49.55-121.36) | - |
| Cardiovascular diseases, N | 4 | 0 | 8 | 20 | 16 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 3.07  (1.15-8.18) | - | 6.95  (3.48-13.91) | 29.49  (19.04-45.68) | 65.30  (40.07-106.43) | 109.85  (35.65-338.50) |
| Renal diseases, N | 0 | 0 | 1 | 5 | 6 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 0.87  (0.12-3.17) | 7.37  (3.07-17.71) | 24.48  (11.01-54.45) | - |
| Cerebrovascular diseases, N | 0 | 0 | 2 | 5 | 3 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 1.74  (0.43-6.95) | 7.37  (3.07-17.71) | 12.24  (3.95-37.93) | 36.61  (5.17-259.03) |
| Septicemia, N | 0 | 0 | 3 | 5 | 3 | 2 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 2.61  (0.84-8.09) | 7.37  (3.07-17.71) | 12.24  (3.95-37.93) | 73.23  (18.41-291.35) |
| Other causes, N | 1 | 6 | 7 | 14 | 19 | 6 |
| Incidence rate, per 10,000 PY (95%CI) | 0.76  (0.11-5.45) | 4.57  (2.05-10.17) | 6.08  (2.90-12.77) | 20.64  (12.23-34.84) | 77.54  (49.55-121.36) | 219.71  (99.58-484.75) |
| **≥2.67** |  |  |  |  |  |  |
| All-cause death, N | 7 | 15 | 32 | 64 | 100 | 28 |
| Incidence rate, per 10,000 PY (95%CI) | 22.07  (10.53-46.26) | 42.47  (25.63-70.37) | 73.72  (52.20-104.12) | 160.06  (125.52-204.09) | 492.31  (406.66-595.98) | 1030.67  (725.72-1463.75) |
| Cause-specific mortality |  |  |  |  |  |  |
| Liver diseases, N | 0 | 0 | 2 | 9 | 12 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 4.61  (1.15-18.41) | 22.50  (11.72-43.22) | 59.07  (33.60-103.85) | 36.81  (5.20-260.37) |
| Pneumonia, N | 0 | 1 | 5 | 17 | 34 | 13 |
| Incidence rate, per 10,000 PY (95%CI) | - | 2.83  (3.99-20.09) | 11.52  (4.79-27.66) | 42.51  (26.45-68.32) | 167.38  (119.93-233.59) | 478.52  (281.54-813.33) |
| Extrahepatic cancer, N | 2 | 5 | 8 | 11 | 11 | 4 |
| Incidence rate, per 10,000 PY (95%CI) | 6.30  (1.57-25.21) | 14.15  (5.89-33.99) | 18.43  (9.22-36.83) | 27.51  (15.24-49.64) | 54.15  (30.03-97.63) | 147.23  (55.66-389.47) |
| Cardiovascular diseases, N | 1 | 4 | 5 | 7 | 15 | 3 |
| Incidence rate, per 10,000 PY (95%CI) | 3.15  (0.44-22.37) | 11.32  (4.25-30.15) | 11.52  (4.79-27.66) | 17.51  (8.35-36.69) | 73.84  (44.60-122.26) | 110.43  (35.84-340.25) |
| Renal diseases, N | 0 | 1 | 3 | 5 | 7 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | - | 2.83  (3.99-20.09) | 6.91  (2.23-21.42) | 12.50  (5.21-30.03) | 34.46  (16.45-72.19) | 36.81  (5.20-260.37) |
| Cerebrovascular diseases, N | 0 | 2 | 1 | 2 | 6 | 0 |
| Incidence rate, per 10,000 PY (95%CI) | - | 5.66  (1.42-22.63) | 2.30  (0.33-16.35) | 5.00  (1.25-19.99) | 29.53  (13.28-65.67) | - |
| Septicemia, N | 0 | 0 | 2 | 4 | 2 | 1 |
| Incidence rate, per 10,000 PY (95%CI) | - | - | 4.60  (1.15-18.41) | 10.00  (3.75-26.64) | 9.84  (2.46-39.34) | 36.81  (5.20-260.37) |
| Other causes, N | 4 | 2 | 4 | 7 | 9 | 4 |
| Incidence rate, per 10,000 PY (95%CI) | 12.61  (4.73-33.58) | 5.66  (1.42-22.63) | 9.21  (3.46-24.54) | 17.51  (8.35-36.69) | 44.31  (23.08-85.03) | 147.23  (55.66-389.47) |

Note: FIB-4 levels were calculated at baseline, 8283 patients including 789 mortality cases with available FIB-4 levels were analyzed.

FIB-4, Fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; PY, person years; CI, confidence interval.

**Table S11. Liver-related deaths in NAFLD patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author** | **Publication year** | **Country or region** | **Method to diagnose NAFLD** | **Number of NAFLD patients** | **Number of deaths** |
| Present study | - | Hong Kong | ICD-9 codes | 30,943 | 2,097 |
| Ong JP (1) | 2008 | USA | Biochemical test | 817 | 80 |
| Fujii H (2) | 2022 | Japan | Biopsy | 1,398 | 47 |
| Rinella ME (3) | 2022 | USA | Imaging or biopsy | 938 | 195 |
| Haflidadottir S (4) | 2014 | Iceland | Biopsy | 151 | 42 |
| Grgurevic I (5) | 2021 | Croatia | Biochemical test | 454 | 17 |
| Chang Y (6) | 2019 | Korean | Ultrasound | 91,392 | 738 |
| Feldman A (7) | 2021 | Austria | Biopsy | 299 | 36 |
| Hirose S (8) | 2020 | Japan | Biopsy | 223 | 23 |
| Lin Y (9) | 2021 | China | Ultrasound | - | 2,015 |
| Simon TG (10) | 2020 | Sweden | Biopsy | 10,568 | 4,338 |
| Paik JM (11) | 2019 | USA | ICD-10 codes | - | 353,234 |
| Ekstedt M (12) | 2006 | Sweden | Biopsy | 129 | 11 |
| Ekstedt M (13) | 2014 | Sweden | Biopsy | 229 | 96 |
| Tada T (14) | 2017 | Japan | Ultrasound | 4,073 | 179 |
| Golabi P (15) | 2020 | USA | Biochemical test or ultrasound | 3,140 | 939 |
| Kogiso T (16) | 2020 | Japan | Biopsy | 365 | 44 |
| Nguyen AL (17) | 2019 | USA | ICD-9 codes | 91,558 | 11,463 |
| Adams LA (18) | 2010 | USA | Imaging or biopsy | 116 | 27 |
| Otgonsuren M (19) | 2013 | USA | Ultrasound | 2,510 | 1,659 |
| Adams LA (20) | 2005 | USA | Imaging or biopsy | 420 | 53 |
| Rafiq N (21) | 2009 | USA | Biopsy | 173 | 78 |
| Stepanova M (22) | 2013 | USA | Biopsy | 289 | 115 |
| Kim D (23) | 2013 | USA | Ultrasound | 4,081 | 1,016 |
| Dunn W (24) | 2008 | USA | Biochemical test | 980 | 95 |
| Lazo M (25) | 2011 | USA | Ultrasound | 2,515 | 526 |
| **First author** | **Number of liver-related mortality cases** | **Median follow-up years** | **Follow-up person-years** | **Incidence of liver-related death** | **Rank of liver-related death** |
| Present study | 92 | 22.0 | 662,471 | 1.4/10,000 person-year | 8 |
| Ong JP (1) | 5 | 8.4 | - | 7.2/10,000 person-year | 3 |
| Fujii H (2) | 21a | 4.6 | 8,874 | 2.3/1000 person-year | 1 |
| Rinella ME (3) | 22 | 3.8 | - | - | 4 |
| Haflidadottir S (4) | 3 | 9.9 | - | - | 4 |
| Grgurevic I (5) | 0 | 2.1 | - | - | - |
| Chang Y (6) | 26 | 5.2 | 681,422.4 | 3.8/105 person-year | Not top 3 |
| Feldman A (7) | 15 | 8.4 | - | - | 1 |
| Hirose S (8) | 3 | 19.5 | 4248.3 | 7.1/10,000 person-year | 3 |
| Lin Y (9) | 105 | - | - | - | 5 |
| Simon TG (10) | Cirrhosis: 413  HCC: 186 | 14.2 | 147,500b | Cirrhosis: 2.8/1000 person-year  HCC: 1.3/1000 person-year | 3 |
| Paik JM (11) | Cirrhosis: 155,894  HCC: 10,867 | - | - | - | 1 |
| Ekstedt M (12) | 2 | 13.7 | - | - | 3 |
| Ekstedt M (13) | Cirrhosis: 4  HCC: 5 | 26.4 | - | - | 3 |
| Tada T (14) | 9 | 7.1 | - | - | Not top 3 |
| Golabi P (15) | 16 | 22.4 | - | - | 4 |
| Kogiso T (16) | 28 | 7.1 | - | - | 1 |
| Nguyen AL (17) | 1,849 | 4.0 | - | - | 3 |
| Adams LA (18) | 5 | 9.2 | - | - | 2 |
| Otgonsuren M (19) | 26 | 13.8 | 15,3615 | 3.7/10,000 person-year | - |
| Adams LA (20) | 7 | 7.6 | 3,192 | 2.2/1000 person-year | 3 |
| Rafiq N (21) | 12 | - | - | 5.3/1000 person-year | 3 |
| Stepanova M (22) | 30 | 12.5 | - | - | 2 |
| Kim D (23) | 19 | 14.5 | - | 3.2/10,000 person-year | Not top 3 |
| Dunn W (24) | 5 | 8.7 | - | 5.8/10,000 person-year | 4 |
| Lazo M (25) | 10 | 14.5 | - | 2.7/10,000 person-year | Not top 3 |

Abbreviations: NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma

a, Calculated by the follow-up person-years and incidence rate.

b, Calculated by the number of deaths and incidence rate.

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