Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol 2022; published online March 4. https://doi.org/10.1016/S1470-2045(22)00078-X.
**Supplementary Material 1**: Search strategy

1: (‘hcc’ or ‘hepatocellular carcinoma’ or ‘hepatic cell carcinoma’ or ‘liver neoplasm’ or ‘hepatoma’ or ‘liver cell carcinoma’ or ‘primary liver carcinoma’):ti,ab or ‘liver cell carcinoma’/exp

2: ‘nonalcoholic fatty liver/exp or (‘nafld’ or ‘nash’ or ‘fatty liver’ or ‘steatohep*’ or ((‘nonalcoholic’ or ‘non alcoholic’ or non-alcoholic’) and (‘fatty liver’ or ‘steatohep’))):ti,ab

3: (outcome* or ‘natural history’ or ‘prognosis’ or ‘progression’ or ‘disease’ or ‘course’ or ‘evolution’):ti,ab

4: ‘controlled study’/exp or ‘randomized controlled trial’/exp or (‘control$’ or ‘randomized’) near/2 (‘study’ or ‘studies’ or ‘trial’ or ‘trials’):ti,ab or (‘prospective’ and (‘study’ or ‘studies’ or ‘survey’ or ‘surveys’ or ‘analysis’ or ‘analyses’ or ‘trial’)):ti,ab

5: 1 and 2 and 3 and 4
## Supplementary Material 2: Summary of included articles

| Author, year | Country/ region | Study Duration | Non-NAFLD etiologies | Total population (HCC) | Sample Size (NAFLD) | Sample Size (Non-NAFLD) | Sample Size (HBV) | Sample Size (HCV) | Sample Size (ALD) | Age (mean, years, sd) | Gender Male (%) | Quality Assessment |
|--------------|-----------------|----------------|----------------------|------------------------|---------------------|------------------------|-----------------|-----------------|-----------------|---------------------|----------------|-----------------|
| Lim et al, 2021 | Singapore | 2008-2018 | HBV, HCV, ALD, AIH, PBC | 1186 | 321 | 865 | 553 | 124 | 179 | - | - | 7 |
| Lin et al, 2021 | Taiwan | 2011-2019 | HBV | 179 | 23 | 156 | 156 | - | - | - | 70.0 (14.2) | 72.6 | 8 |
| Pinyopornpanish et al, 2021 | USA | 2000-2015 | HBV, HCV, ALD, AIH, PBC | 2237 | 587 | 1650 | 129 | 873 | 293 | - | - | 8 |
| Jung et al, 2021 | South Korea | 2005-2015 | HBV | 232 | 32 | 200 | 200 | - | - | - | 61.0 (11.0) | 73.7 | 8 |
| Hiraoka et al, 2021 | Japan | 2018-2021 | HBV, HCV, ALD | 530 | 103 | 427 | - | - | - | 74.7 (8.3) | 78.8 | 8 |
| Kumar et al, 2020 | Singapore | 2000-2013 | ALD | 99 | 54 | 45 | - | - | 45 | 72.0 (9.0) | 78.3 | 8 |
| Paik et al, 2020 | USA | 2007-2017 | HBV, HCV, ALD | 11765 | 4291 | 7474 | 727 | 6099 | 648 | - | - | 70.3 (12.5) | 78.3 | 7 |
| Ahn et al, 2020 | South Korea | 2000-2016 | HBV, ALD | 622 | 56 | 566 | 393 | - | 173 | - | - | 68.0 (10.9) | 82.6 | 7 |
| Hanumanthappa et al, 2020 | Canada | 2011-2015 | HBV, HCV | 195 | 12 | 183 | 18 | 37 | - | - | - | - | 8 |
| Wang et al, 2020 | USA | 2010-2019 | HBV, HCV, ALD, AIH | 6346 | 1795 | 4551 | 355 | 1563 | 2399 | - | - | 74.7 (8.3) | 78.8 | 8 |
| Liew et al, 2019 | Singapore | 1980-2015 | HBV | 1079 | 163 | 916 | 916 | - | - | 67.6 (10.8) | 81.7 | 8 |
| Tateishi et al, 2019 | Japan | 2011-2015 | ALD, AIH, PBC | 1106 | 315 | 791 | - | - | 675 | - | - | 71.3 (7.5) | 77.1 | 8 |
| Bengtsson et al, 2019 | Sweden | 2004-2017 | HBV, HCV, ALD, AIH, PBC | 1562 | 225 | 1337 | - | - | - | 71.3 (7.5) | 77.1 | 8 |
| Patkar et al, 2019 | India | 2009-2017 | HBV, HCV, ALD | 105 | 40 | 65 | 42 | 10 | 13 | - | - | 67.9 (10.8) | 79.5 | 8 |
| Hestor et al, 2019 | USA | 2008-2016 | HBV, HCV, ALD | 1051 | 92 | 959 | 87 | 719 | 153 | - | - | 71.3 (7.5) | 77.1 | 8 |
| Pinero et al, 2018 | Latin America | 2005-2012 | HBV, HCV, ALD, AIH | 435 | 25 | 410 | 110 | 159 | 73 | 60.0 (4.0) | 81.8 | 7 |
| Author(s)               | Country | Year Period   | Conditions | Cases | Deaths | Survivors | Liver Transplantation | Mortality Rate | Complications |
|------------------------|---------|---------------|------------|-------|--------|-----------|----------------------|---------------|--------------|
| Pinero et al, 2018     | Argentina | 2009-2016    | HBV, HCV, ALD, AIH | 708   | 81     | 627       | 38                  | 262           | 147          |
| Ioannou et al, 2018    | USA     | 2001-2017    | HCV, ALD   | 9601  | 608    | 8993      | -                   | 7605          | 1388         |
| Kim et al, 2018        | USA     | 1998-2015    | HBV, HCV, ALD | 1884  | 95     | 1789      | 465                 | 1194          | 130          |
| Sadler et al, 2018     | USA     | 2004-2014    | HBV, HCV, ALD | 929   | 60     | 869       | 216                 | 522           | 90           |
| Yoon et al, 2018       | South Korea | 2005-2015  | HBV, HCV, ALD | 1260  | 63     | 1197      | 869                 | 137           | 191          |
| Marot et al, 2017      | Belgium | 1995-2014    | HCV, ALD   | 85    | 12     | 73        | -                   | 35            | 38           |
| Kimura et al, 2017     | Japan   | 1996-2012    | ALD        | 61    | 30     | 31        | -                   | -             | -            |
| Pais et al, 2016       | Italy   | 1995-2014    | HBV, HCV, ALD | 323   | 39     | 284       | -                   | -             | -            |
| Than et al, 2017       | United Kingdom | 2000-2014 | HCV      | 487   | 212    | 275       | -                   | 275           | -            |
| Piscaglia et al, 2016  | Italy   | 2010-2012    | HCV        | 756   | 145    | 611       | -                   | -             | -            |
| Meer et al, 2016       | Netherlands | 2005-2012 | HBV, HCV, ALD | 976   | 181    | 795       | 249                 | 197           | 349          |
| Lopes et al, 2016      | Brazil  | 2000-2014    | HBV, HCV, ALD | 66    | 8      | 58        | 11                  | 34            | 13           |
| Mittal et al, 2015     | USA     | 2005-2010    | HCV, ALD   | 1419  | 120    | 1299      | -                   | 1013          | 286          |
| Younossi et al, 2015   | USA     | 2004-2009    | HBV, HCV, ALD | 4725  | 701    | 4024      | 471                 | 2736          | 817          |
| Beste et al, 2015      | USA     | 1999-2014    | HBV, HCV, ALD, AIH | 7313  | 1029   | 6284      | 176                 | 5225          | 873          |
| Tateishi et al, 2015   | Japan   | 1991-2010    | ALD, AIH   | 2180  | 596    | 1584      | -                   | -             | 1423         |
| Dyson et al, 2014      | United Kingdom | 2000-2010 | HBV, HCV, ALD, AIH | 416   | 136    | 280       | 29                  | 65            | 178          |
| Paranaguá-Vezozzo et al, 2014 | Brazil | 1998-2008 | HBV, HCV, ALD | 69    | 1      | 68        | 16                  | 47            | 5            |
| Weinmann et al, 2014   | Germany | 2004-2009    | HBV, HCV, AIH | 283   | 28     | 255       | 79                  | 174           | -            |

*Note: The table entries represent the number of cases, deaths, survivors, and liver transplantations for each study. The mortality rate and complications are also indicated.*
| Study                          | Country | Year          | Conditions | Patients (Gender) | HBV (Male) | HBV (Female) | HCV (Male) | HCV (Female) | ALD (Male) | ALD (Female) | AIH (Male) | AIH (Female) | NAFLD (Male) | NAFLD (Female) | Other (Male) | Other (Female) | Total (Male) | Total (Female) | Total (ALD) | Total (AIH) | Total (NAFLD) | Total (Other) | Total (Other) |
|-------------------------------|---------|---------------|------------|------------------|------------|-------------|------------|-------------|------------|--------------|-----------|--------------|-------------|---------------|-------------|----------------|--------------|----------------|-------------|--------------|----------------|----------------|----------------|
| Teixeira et al, 2012          | Brazil  | 2001-2009     | HBV, HCV   | 9                | 5          | 4           | 2          | 2           | -          | -            | -         | -            | -           | -              | -           | -              | 7            | 7             | 7             | 7             | 7             | 7             |
| Arase et al, 2012             | Japan   | 1994-2007     | HCV        | 277              | 10         | 267         | -          | 267         | -          | -            | -         | -            | -           | -              | -           | -              | 9            | 9             | 9             | 9             | 9             | 9             |
| Hernandez-Alejandro et al, 2012 | Canada  | 2000-2011     | HCV        | 81               | 17         | 64          | -          | 64          | -          | -            | -         | -            | -           | 58.6 (4.2)     | 94.0        | 7              | 7            | 7             | 7             | 7             | 7             | 7             |
| Reddy et al, 2012             | USA     | 2000-2012     | HCV, ALD   | 214              | 54         | 162         | -          | -           | -          | -            | -         | 64.0 (9.9)    | 75.7        | 9              | 9            | 9             | 9             | 9             | 9             | 9             |
| Hucke et al, 2011             | Austria | 1991-2009     | HBV, HCV, ALD | 387           | 23         | 364         | 30         | 127         | 207        | -            | -         | 70.1 (7.6)    | 60.0        | 8              | 8            | 8             | 8             | 8             | 8             | 8             |
| Ascha et al, 2010             | USA     | 2003-2007     | HCV        | 89               | 25         | 64          | -          | 64          | -          | -            | -         | -            | -           | -              | -           | -              | -            | -             | -             | -             | -             | -             |
| Tokushige et al, 2010         | Japan   | 1990-2007     | HCV        | 90               | 34         | 56          | -          | 56          | -          | -            | -         | 70.0 (7.6)    | 60.0        | 8              | 8            | 8             | 8             | 8             | 8             | 8             |
| Sanyal et al, 2006            | USA     | 1992-2004     | HCV        | 6                | 3          | 3           | -          | 3           | -          | -            | -         | -            | -           | -              | -           | -              | 9            | 9             | 9             | 9             | 9             | 9             |
| Hashimoto et al, 2004         | Japan   | 1989-2003     | ALD        | 58               | 8          | 50          | -          | -           | 50         | -            | -         | 67.3 (19.7)   | 78.5        | 8              | 8            | 8             | 8             | 8             | 8             | 8             |
| Shahid et al, 2009            | USA     | 1997-2008     | HBV, HCV, ALD, AIH | 447          | 27         | 430         | 52         | 138         | 99         | 63.1 (6.4)   | -         | 7            | -           | 7              | -           | 7              | 7            | 7             | 7             | 7             | 7             | 7             |
| Amarapurkar et al, 2013       | India   | 2010-2011     | HBV, HCV   | 46               | 6          | 40          | 26         | 14          | -          | -            | -         | -            | -           | -              | -           | -              | 9            | 9             | 9             | 9             | 9             | 9             |
| Jain et al, 2012              | India   | 2005-2010     | ALD        | 13               | 8          | 5           | -          | -           | 5          | -            | -         | 59.6 (3.0)    | 100        | 8              | 8            | 8             | 8             | 8             | 8             | 8             |
| Judith et al, 2010            | Germany | 2007-2008     | HBV, HCV, ALD | 119          | 36         | 83          | 29         | 35          | 19         | 68.6 (8.4)   | 84.0       | 7            | -           | 7              | -           | 7              | 7            | 7             | 7             | 7             | 7             | 7             |
| Schutte et al, 2014           | Germany | 1994-2003     | Viral, ALD | 440              | 43         | 397         | -          | -           | 299        | -            | -         | -            | -           | -              | -           | -              | -            | -             | -             | -             | -             | -             |
| Koh et al, 2019*              | Singapore | 2000-2015   | Non-NAFLD | 996              | 152        | 844         | -          | -           | -          | -            | -         | 68.0 (8.2)    | 77.7        | 9              | 9            | 9             | 9             | 9             | 9             | 9             |
| Yang et al, 2019              | China   | 2003-2014     | HBV        | 1483             | 96         | 1387        | 1387       | -           | -          | -            | -         | 57.3 (12.5)   | 88.5        | 8              | 8            | 8             | 8             | 8             | 8             | 8             |
| Wakai et al, 2011             | Japan   | 1990-2007     | HBV, HCV   | 225              | 17         | 208         | 61         | 147         | -          | -            | -         | -            | -           | -              | -           | -              | -            | -             | -             | -             | -             | -             |
| Morisco et al, 2018           | Italy   | 1987-2014     | Viral, ALD | 839              | 190        | 645         | -          | -           | 159        | -            | -         | -            | -           | -              | -           | -              | -            | -             | -             | -             | -             | -             |
| Gawrieh et al, 2019           | USA     | 2000-2014     | HBV, HCV, ALD, AIH | 3076         | 767        | 2309        | 315        | 1263        | 655        | -            | -         | -            | -           | 7              | -           | 7              | 7            | 7             | 7             | 7             | 7             | 7             | 7             |

* Koh et al, 2019 included in the Sanyal et al, 2006 study.
| Study Authors       | Region               | Period     | Hepatitis | HBV | HCV | ALD | AIH | Viral | PBC/PSC | Proportion of HCC Patients | Curative Treatment Allocation | Surveillance Before Diagnosis |
|---------------------|----------------------|------------|------------|-----|-----|-----|-----|-------|---------|----------------------------|-------------------------------|------------------------------|
| D’Silva et al,      | South Korea Multicentre (Japan, Korea, Germany and Italy) | 2004-2018 | HBV        | 575 | 36  | 539 | 36  | -     | -       | -                           | -                            | 7                            |
| Liew et al,         | Singapore General Hospital | 2010-2021 | HCV, HBV   | 1232| 236 | 996 | 268 | 453   | -       | 72.0 (8.25)                  | 78.0                         | 7                            |
| Koh et al           | Singapore General Hospital | 2010-2021 | HBV        | 575 | 36  | 539 | 36  | -     | -       | -                           | -                            | 7                            |
| Mittal et al        | United States Veterans Administration database | 2004-2018 | HBV, HCV, ALD, AIH, Viral, PBC/PSC | 20195| 1073| 19122| -   | -     | -       | 61.0 (5.9)                  | 83.7                         | 7                            |
| Beste et al         | Europe               | 202-2016   | Non-NAFLD  | 114 | 20  | 94  | 7   | 20    | 34      | -                           | -                            | 7                            |
| Kalaitzakis et al   | Europe               | 1994-2005  | HBV, HCV, ALD, AIH, Viral, PBC/PSC | 114  | 20  | 94  | 7   | 20    | 34      | -                           | -                            | 7                            |
| Nilsson et al       | Europe               | 2011-2010  | HCV, ALD, AIH, PBC/PSC | 202  | 32  | 170 | -   | 58    | 57      | -                           | -                            | 7                            |
| Koh et al           | Singapore General Hospital | 2010-2021 | HBV, HCV, ALD, AIH, PBC/PSC | 785  | 138 | 647 | 158 | 133   | 141     | 60 (7.97)                  | 87.2                         | 7                            |

* Lim et al. 2021, Liew et al. 2019, and Koh et al. 2019 included patients from the same institution (Singapore General Hospital). To avoid overlapping of cohorts, data from Liew et al. were only included in the analysis of the proportion of HCC patients that underwent surveillance before diagnosis, and data from Koh et al. were only included in the analysis of curative treatment allocation.

^ Mittal et al. 2015 and Beste et al. 2015 utilized data from the United States Veterans Administration database. To avoid overlapping of cohorts, data from Mittal et al. were only included in the analysis of the proportion of HCC patients that underwent surveillance before diagnosis.

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcohol-associated liver disease; AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; PBC/PSC, primary biliary cholangitis/primary sclerosing cholangitis; HCC, hepatocellular carcinoma
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### Supplementary Material 3: Proportion of NAFLD-related hepatocellular carcinoma across time periods and by study setting

|                | No. of studies | No. of patients | Pooled Proportion | Confidence Interval | Cochran-Q | I^2   | p value* |
|----------------|----------------|-----------------|-------------------|---------------------|-----------|-------|----------|
| **Overall analysis** |                |                 |                   |                     |           |       | 0.045    |
| Overall         | 42             | 86311           | 15.07             | 11.88 - 18.93       | <0.01     | 99.40%|          |
| Before 2000     | 1              | 440             | 9.77              | 7.33 - 12.92        | -         | -     |          |
| 2000 - 2004     | 6              | 4036            | 9.79              | 4.34 - 20.58        | <0.01     | 96.70%|          |
| 2005 - 2009     | 21             | 54822           | 15.60             | 10.89 - 21.85       | <0.01     | 99.10%|          |
| 2010 and beyond | 14             | 27013           | 16.97             | 12.17 - 23.16       | <0.01     | 98.90%|          |
| **Western Pacific** |              |                 |                   |                     |           |       | <0.001  |
| Overall         | 7              | 7880            | 16.69             | 10.56 - 25.37       | <0.01     | 98.20%|          |
| Before 2000     | Insufficient data |         |                   |                     |           |       |          |
| 2000 - 2004     | 1              | 2180            | 27.34             | 25.51 - 29.25       | -         | -     |          |
| 2005 - 2009     | 2              | 1618            | 11.93             | 8.19 - 17.05        | <0.01     | 92.40%|          |
| 2010 and beyond | 4              | 4082            | 17.26             | 8.59 - 31.68        | <0.01     | 98.60%|          |
| **Southeast Asia** |            |                 |                   |                     |           |       |          |
| Overall         | 3              | 936             | 21.94             | 12.59 - 35.41       | <0.01     | 91.80%|          |
| Before 2000     | Insufficient data |         |                   |                     |           |       |          |
| 2000 - 2004     | Insufficient data |     |                   |                     |           |       |          |
| 2005 - 2009     | Insufficient data |     |                   |                     |           |       |          |
| 2010 and beyond | 3              | 936             | 21.94             | 12.59 - 35.41       | <0.01     | 91.80%|          |
| **Europe**      |                |                 |                   |                     |           |       | 0.058    |
| Overall         | 14             | 26039           | 15.52             | 11.50 - 20.62       | <0.01     | 98.60%|          |
| Before 2000     | 1              | 440             | 9.77              | 7.33 - 12.92        | -         | -     |          |
| 2000 - 2004     | 3              | 1340            | 13.67             | 6.91 - 25.26        | <0.01     | 95.50%|          |
| 2005 - 2009     | 8              | 22599           | 17.00             | 10.85 - 25.63       | <0.01     | 99.00%|          |
| 2010 and beyond | 2              | 1930            | 14.46             | 12.96 - 16.10       | 0.89      | 0.00% |          |
| **Americas**    |                |                 |                   |                     |           |       | <0.001  |
| Overall         | 18             | 51186           | 13.23             | 8.19 - 20.68        | <0.01     | 99.90%|          |
| Before 2000     | Insufficient data |         |                   |                     |           |       |          |
| 2000 - 2004     | 2              | 516             | 3.49              | 2.21 - 5.47         | 0.34      | 0.00% |          |
| Time Period          | Total Studies | Total Cases | Proportion | 95% CI    | p Value | 95% CI    |
|----------------------|---------------|-------------|------------|-----------|---------|-----------|
| 2005 - 2009          | 11            | 30605       | 15.27      | 8.40 - 26.14 | <0.01   | 99.10%    |
| 2010 and beyond      | 5             | 20065       | 15.42      | 8.04 - 27.56 | <0.01   | 99.20%    |

Subgroup analysis for the Americas

**North America**

| Time Period          | Total Studies | Total Cases | Proportion | 95% CI    | p Value | 95% CI    |
|----------------------|---------------|-------------|------------|-----------|---------|-----------|
| Overall              | 12            | 49388       | 17.22      | 10.46 - 27.01 | <0.01   | 99.70%    |
| Before 2000          | Insufficient data |         |            |           |         |           |
| 2000 - 2004          | 1             | 447         | 3.80       | 2.38 - 6.03  |         |           |
| 2005 - 2009          | 8             | 29979       | 18.20      | 10.15 - 30.69 | <0.01   | 99.40%    |
| 2010 and beyond      | 3             | 19162       | 21.90      | 10.52 - 40.08 | <0.01   | 99.40%    |

**South America**

| Time Period          | Total Studies | Total Cases | Proportion | 95% CI    | p Value | 95% CI    |
|----------------------|---------------|-------------|------------|-----------|---------|-----------|
| Overall              | 6             | 1598        | 6.94       | 2.66 - 16.92 | 0.01    | 83.60%    |
| Before 2000          | Insufficient data |         |            |           |         |           |
| 2000 - 2004          | 1             | 69          | 1.45       | 0.20 - 9.58  |         |           |
| 2005 - 2009          | 3             | 626         | 8.67       | 1.75 - 33.56 | <0.01   | 88.20%    |
| 2010 and beyond      | 2             | 903         | 9.21       | 5.94 - 14.02 | 0.03    | 77.70%    |

Subgroup analysis for study setting

| Study Setting         | Total Studies | Total Cases | Proportion | 95% CI    | p Value | 95% CI    |
|-----------------------|---------------|-------------|------------|-----------|---------|-----------|
| Clinical cohort       | 31            | 22569       | 14.82      | 11.08 - 19.55 | <0.01   | 97.60%    |
| Administrative database | 11        | 63742       | 15.81      | 10.61 - 22.89 | <0.01   | 99.80%    |

* = p value refers to the subgroup difference for changes in the proportion of NAFLD-related HCC across time periods, in each geographical region

** = p value refers to subgroup difference for proportion of NAFLD-related HCC in clinical cohort studies versus administrative database studies
Supplementary Material 4: Comparison of patient characteristics in NAFLD-related HCC versus HCC from other etiologies; stratified by etiology

| Etiology          | No. of Studies | No. of patients | Effect Size   | 95% Confidence Interval       | P-Value | Cochran-Q | I^2 (%) |
|-------------------|----------------|----------------|---------------|-------------------------------|---------|-----------|---------|
| **Hepatitis B**   |                |                |               |                               |         |           |         |
| Age               | 11             | 11993          | MD: 8.00      | 6.12 to 9.88                   | <0.001  | <0.01     | 87.7    |
| Body Mass Index   | 7              | 3227           | MD: 2.62      | 0.56 to 4.68                   | 0.013   | <0.01     | 95.9    |
| Male Gender       | 13             | 12236          | OR: 0.53      | 0.37 to 0.75                   | 0.002   | <0.01     | 69.6    |
| Diabetes          | 9              | 9742           | OR: 2.68      | 1.17 to 6.16                   | 0.026   | <0.01     | 93.6    |
| Hypertension      | 6              | 8293           | OR: 3.46      | 1.32 to 9.11                   | 0.021   | <0.01     | 89.4    |
| Hyperlipidaemia   | 1              | 179            | OR: 2.58      | 1.41 to 4.73                   | 0.002   | -         | -       |
| Cardiovascular Disease | 2      | 6190           | OR: 1.81      | 0.02 to 132.47                 | 0.330   | <0.01     | 92.7    |
| Cirrhosis         | 8              | 2830           | OR: 0.30      | 0.16 to 0.60                   | 0.004   | <0.01     | 69.2    |
| **Hepatitis C**   |                |                |               |                               |         |           |         |
| Age               | 11             | 31923          | MD: 5.58      | 3.70 to 7.45                   | <0.001  | <0.01     | 97.1    |
| Body Mass Index   | 8              | 16272          | MD: 3.64      | 2.05 to 5.23                   | <0.001  | <0.01     | 98.4    |
| Male Gender       | 14             | 32288          | OR: 0.79      | 0.53 to 1.17                   | 0.212   | <0.01     | 83.2    |
| Diabetes          | 10             | 28405          | OR: 6.28      | 3.25 to 12.13                  | <0.001  | <0.01     | 97.4    |
| Hypertension      | 6              | 13380          | OR: 2.97      | 1.07 to 8.22                   | 0.040   | <0.01     | 94.7    |
| Hyperlipidaemia   | 2              | 901            | OR: 4.07      | 0.00 to 127000                 | 0.335   | 0.05      | 74.7    |
| Cardiovascular Disease | 4      | 15716          | OR: 2.36      | 0.83 to 6.71                   | 0.080   | <0.01     | 95.9    |
| Cirrhosis         | 7              | 3623           | OR: 0.16      | 0.06 to 0.44                   | 0.004   | <0.01     | 88.2    |
| **Alcohol**       |                |                |               |                               |         |           |         |
| Age               | 13             | 13794          | MD: 4.74      | 3.80 to 5.89                   | <0.001  | <0.01     | 78.8    |
| Body Mass Index   | 9              | 4968           | MD: 2.54      | 1.88 to 3.19                   | <0.001  | <0.01     | 80.9    |
| Male Gender       | 14             | 14108          | OR: 0.17      | 0.11 to 0.28                   | <0.001  | <0.01     | 84.1    |
| Diabetes          | 12             | 12276          | OR: 2.75      | 1.55 to 4.87                   | <0.001  | <0.01     | 94.0    |
| Hypertension      | 9              | 8310           | OR: 2.27      | 1.31 to 3.93                   | <0.001  | <0.01     | 86.7    |
| Hyperlipidaemia   | 4              | 463            | OR: 2.70      | 1.19 to 6.10                   | 0.031   | 0.26      | 24.5    |
| Cardiovascular Disease | 3      | 6863           | OR: 2.40      | 0.33 to 17.7                   | 0.201   | <0.01     | 97.2    |
| Cirrhosis         | 9              | 3486           | OR: 0.32      | 0.17 to 0.60                   | 0.003   | 0.01      | 58.9    |
Supplementary Material 4B: Comparison of patient and tumor characteristics in NAFLD-related HCC versus HBV-related HCC; by geographical region

| Versus hepatitis B | No. of Studies | No. of patients | Effect Size | 95% Confidence Interval | P-Value | Cochran-Q | I² (%) | Subgroup difference* |
|--------------------|----------------|----------------|-------------|-------------------------|---------|-----------|--------|----------------------|
| **Age**            |                |                |             |                         |         |           |        |          |
| Western Pacific    | 6              | 4354           | 8.82        | 7.17 to 10.47           | <0.001  | 0.13      | 41.7   | 0.526    |
| Europe             | 1              | 65             | 8.80        | 3.76 to 13.84           | <0.001  | -         | -      |          |
| Americas           | 4              | 7574           | 6.95        | 4.12 to 9.78            | <0.001  | <0.01     | 93.5   |          |
| **Body Mass Index**|                |                |             |                         |         |           |        | 0.166    |
| Western Pacific    | 4              | 1792           | 1.57        | 0.55 to 2.59            | 0.003   | 0.2       | 35.5   |          |
| Europe             | 2              | 230            | 4.20        | 0.59 to 7.82            | 0.023   | <0.01     | 91.1   |          |
| Americas           | 1              | 1205           | 2.70        | 1.70 to 3.70            | <0.001  | -         | -      |          |
| **Male Gender**    |                |                |             |                         |         |           |        | 0.791    |
| Western Pacific    | 7              | 4432           | 0.51        | 0.35 - 0.76             | 0.006   | 0.15      | 35.2   |          |
| Europe             | 2              | 230            | 0.71        | 0.29 - 1.71             | 0.798   | 0.14      | 53.2   |          |
| Americas           | 4              | 7574           | 0.46        | 0.13 - 1.62             | 0.143   | <0.01     | 87.1   |          |
| **Diabetes**       |                |                |             |                         |         |           |        | 0.846    |
| Western Pacific    | 5              | 3275           | 3.27        | 1.75 - 6.10             | <0.001  | 0.09      | 50.1   |          |
| Europe             | 1              | 65             | 3.36        | 1.21 - 9.36             | 0.006   | -         | -      |          |
| Americas           | 3              | 6402           | 1.37        | 1.10 - 1.72             | 0.020   | <0.01     | 97.8   |          |
| **Hypertension**   |                |                |             |                         |         |           |        | 0.808    |
| Western Pacific    | 4              | 3096           | 3.19        | 1.47 - 6.94             | <0.001  | 0.07      | 57.3   |          |
| Europe             | 2              | 165            | -           | -                       | -       |           | -      |          |
| Americas           | 2              | 179            | -           | -                       | -       |           | -      |          |
| **Cirrhosis**      |                |                |             |                         |         |           |        | 0.017    |
| Western Pacific    | 5              | 2421           | 0.23        | 0.12 - 0.45             | 0.003   | 0.15      | 41.2   |          |
| Europe             | 2              | 230            | 0.33        | 0.14 - 0.75             | 0.009   | 0.03      | 80     |          |
| Americas           | 1              | 179            | 0.90        | 0.40 - 2.02             | 0.324   | -         | -      |          |
| **Tumor diameter** |                |                |             |                         |         |           | <0.01 | 0.001    |
| Western Pacific    | 5              | 3275           | 1.14        | 0.68 to 1.61            | <0.001  | 0.41      | 0.2    |          |
| Europe             | 1              | 165            | -1.00       | -1.44 to -0.56          | <0.001  | -         | -      |          |
| Americas           | 1              | 179            | -0.60       | -2.10 to 0.90           | 0.432   | -         | -      |          |

*=Subgroup difference refers to comparison of effect size between geographical region
Supplementary Material 4C: Comparison of patient and tumor characteristics in NAFLD-related HCC versus HCV-related HCC; by geographical region

| Versus hepatitis | No. of Studies | No. of patients | Effect Size | 95% Confidence Interval | P-Value | Cochran-Q | I² (%) | Subgroup difference* |
|-----------------|----------------|-----------------|-------------|-------------------------|---------|-----------|--------|----------------------|
| Age             |                |                 |             |                         |         |           |        | <0.001               |
| Western Pacific | 2              | 290             | -0.40       | -2.89 to 2.09           | 0.754   | 0.32      | 0.0    |                      |
| Europe          | 3              | 1314            | 4.09        | -6.34 to 14.52          | 0.442   | <0.01     | 98.6   |                      |
| Americas        | 6              | 29186           | 7.77        | 6.13 to 9.41            | <0.001  | <0.01     | 96.1   |                      |
| Body Mass Index | 0.002          |                 |             |                         |         |           |        |                      |
| Western Pacific | 2              | 290             | 1.01        | -0.44 to 2.45           | 0.171   | 0.14      | 54.4   |                      |
| Europe          | 4              | 1515            | 4.50        | 1.81 to 7.19            | 0.001   | <0.01     | 97.9   |                      |
| Americas        | 2              | 14467           | 4.29        | 2.92 to 5.66            | <0.001  | <0.01     | 95.0   |                      |
| Male Gender     | 0.004          |                 |             |                         |         |           |        |                      |
| Western Pacific | 3              | 454             | 0.98        | 0.39 - 2.46             | 0.944   | 0.43      | 0.0    |                      |
| Europe          | 4              | 1515            | 1.50        | 0.68 - 3.29             | 0.200   | 0.03      | 66.1   |                      |
| Americas        | 7              | 30319           | 0.52        | 0.32 - 0.86             | 0.020   | <0.01     | 81.7   |                      |
| Diabetes        | 0.663          |                 |             |                         |         |           |        |                      |
| Western Pacific | 2              | 290             | 1.86        | 1.14 - 3.02             | 0.014   | <0.01     | 93.3   |                      |
| Europe          | 3              | 1314            | 8.03        | 4.74 - 13.59            | 0.003   | 0.48      | 0.0    |                      |
| Americas        | 5              | 26801           | 7.99        | 2.62 - 24.41            | 0.007   | <0.01     | 98.7   |                      |
| Hypertension    | <0.001         |                 |             |                         |         |           |        |                      |
| Western Pacific | 2              | 290             | 1.37        | 0.84 - 2.26             | 0.203   | 0.68      | 0.0    |                      |
| Europe          | 1              | 756             | 5.42        | 3.62 - 8.13             | <0.001  | -         | -      |                      |
| Americas        | 3              | 12334           | 1.33        | 1.16 - 1.52             | <0.001  | <0.01     | 95.7   |                      |
| Cirrhosis       | <0.001         |                 |             |                         |         |           |        |                      |
| Western Pacific | 1              | 164             | 0.84        | 0.31 - 2.31             | 0.741   | -         | -      |                      |
| Europe          | 4              | 1515            | 0.06        | 0.02 - 0.16             | <0.001  | 0.16      | 41.6   |                      |
| Americas        | 2              | 1944            | 0.27        | 0.19 - 0.38             | <0.001  | 0.24      | 26.5   |                      |
| Tumor diameter  | 0.118          |                 |             |                         |         |           |        |                      |
| Western Pacific | 2              | 290             | 1.40        | -1.89 to 4.68           | 0.405   | <0.01     | 95.1   |                      |
| Europe          | 2              | 957             | 1.11        | 0.63 to 1.58            | <0.001  | 0.05      | 74.6   |                      |
| Americas        | 2              | 892             | -0.13       | -1.22 to 0.95           | 0.811   | 0.17      | 47.3   |                      |

* = Subgroup difference refers to comparison of effect size between geographical region
## Supplementary Material 4D: Comparison of patient and tumor characteristics in NAFLD-related HCC versus alcohol-associated HCC; by geographical region

| Versus alcohol | No. of Studies | No. of patients | Effect Size | 95% Confidence Interval | P-Value | Cochran-Q | $I^2$ (%) | Subgroup difference* |
|----------------|----------------|----------------|-------------|-------------------------|---------|-----------|-----------|----------------------|
| **Age**        |                |                |             |                         |         |           |           | 0.008                |
| Western Pacific| 6              | 2720           | 0.10        | 0.08 - 0.12             | <0.001  | 0.82      | 0         |                      |
| Europe         | 2              | 55             | 0.33        | 0.17 - 0.62             | <0.001  | 0.22      | 34.9      |                      |
| Americas       | 6              | 11006          | 0.24        | 0.12 - 0.50             | 0.01    | <0.01     | 78.8      |                      |
| **Body Mass Index** |            |                |             |                         |         |           |           | 0.675                |
| Western Pacific| 5              | 2621           | 2.49        | 1.01 - 6.13             | 0.048   | 0.01      | 75.0      |                      |
| Europe         | 1              | 2720           | 0.12        | 0.03 - 0.17             | 0.003   | <0.01     | 97.4      |                      |
| Americas       | 5              | 9488           | 1.29        | 0.90 - 11.23            | 0.063   | <0.01     | 94.7      |                      |
| **Male Gender**|                |                |             |                         |         |           |           | 0.001                |
| Western Pacific| 6              | 2720           | 0.10        | 0.08 - 0.12             | <0.001  | 0.82      | 0         |                      |
| Europe         | 2              | 55             | 0.33        | 0.17 - 0.62             | <0.001  | 0.22      | 34.9      |                      |
| Americas       | 6              | 11006          | 0.24        | 0.12 - 0.50             | 0.01    | <0.01     | 78.8      |                      |
| **Diabetes**   |                |                |             |                         |         |           |           | 0.460                |
| Western Pacific| 6              | 2720           | 2.49        | 1.01 - 6.13             | 0.048   | 0.01      | 75.0      |                      |
| Europe         | 1              | 2720           | 0.12        | 0.03 - 0.17             | 0.003   | <0.01     | 97.4      |                      |
| Americas       | 5              | 9488           | 1.29        | 0.90 - 11.23            | 0.063   | <0.01     | 94.7      |                      |
| **Hypertension**|              |                |             |                         |         |           |           | 0.698                |
| Western Pacific| 6              | 2720           | 2.12        | 1.76 - 2.55             | <0.001  | 0.70      | 0         |                      |
| Europe         |                | Insufficient data |          |                        |         |           |           |                      |
| Americas       | 3              | 5590           | 2.80        | 0.13 - 59.94            | 0.285   | <0.01     | 94.7      |                      |
| **Cirrhosis**  |                |                |             |                         |         |           |           | 0.020                |
| Western Pacific| 5              | 2466           | 0.35        | 0.18 - 0.70             | 0.013   | 0.17      | 38.0      |                      |
| Europe         | 2              | 369            | 0.02        | 0.01 - 0.11             | <0.001  | 0.26      | 21.9      |                      |
| Americas       | 2              | 651            | 0.47        | 0.32 - 0.70             | <0.001  | 0.22      | 34.7      |                      |
| **Tumor diameter** |            |                |             |                         |         |           |           | 0.413                |
| Western Pacific| 5              | 2621           | 1.03        | -0.38 to 2.43           | 0.152   | <0.01     | 87.5      |                      |
| Europe         | 1              | 314            | 0.1         | 0.03 to 0.17            | 0.003   | -         | -         |                      |
| Americas       | 1              | 245            | 0.3         | -0.91 to 1.51           | 0.627   | -         | -         |                      |

*Subgroup difference refers to comparison of effect size between geographical region
Supplementary Material 5: Comparison of tumor characteristics in NAFLD-related HCC versus HCC from other etiologies; stratified by etiology

| Etiology       | No. of Studies | No. of patients | Effect Size | 95% Confidence Interval | P-Value | Cochran-Q | I^2 (%) |
|----------------|----------------|-----------------|-------------|-------------------------|---------|-----------|---------|
| **Hepatitis B** |                |                 |             |                         |         |           |         |
| Tumour Diameter | 7              | 3619            | MD: 0.52    | -0.48 to 1.52           | 0.310   | <0.01     | 87.5    |
| Alpha-fetoprotein | 6          | 2883            | MD -0.19    | -0.42 to 0.04           | 0.109   | <0.01     | 72.7    |
| Uni-nodular HCC | 6              | 4379            | OR 1.23     | 0.97 - 1.56             | 0.079   | 0.66      | 0.00%   |
| BCLC 0/A        | 4              | 2639            | OR 1.02     | 0.55 - 1.90             | 0.913   | 0.16      | 42.10%  |
| BCLC B          | 5              | 2818            | OR 1.12     | 0.74 - 1.72             | 0.488   | 0.43      | 0.00%   |
| BCLC C/D        | 5              | 2818            | OR 0.80     | 0.39 - 1.63             | 0.433   | 0.04      | 59.90%  |
| **Hepatitis C** |                |                 |             |                         |         |           |         |
| Tumour Diameter | 6              | 2139            | MD: 0.78    | 0.07 to 1.48            | 0.031   | <0.01     | 87.3    |
| Alpha-fetoprotein | 8           | 10709           | MD 0.02     | -0.09 to 0.13           | 0.744   | 0.06      | 49.0    |
| Uni-nodular HCC | 3              | 454             | OR 0.81     | 0.11 - 5.86             | 0.697   | 0.05      | 66.20%  |
| BCLC 0/A        | 2              | 956             | OR 0.69     | 0.31 - 1.51             | 0.104   | 0.7       | 0.00%   |
| BCLC B          | 3              | 1767            | OR 1.25     | 0.67 - 2.33             | 0.257   | 0.48      | 0.00%   |
| BCLC C/D        | 3              | 1767            | OR 1.10     | 0.33 - 3.68             | 0.766   | 0.02      | 73.70%  |
| **Alcohol**     |                |                 |             |                         |         |           |         |
| Tumour Diameter | 7              | 3180            | MD: 0.56    | 0.12 to 1.00            | **0.012** | <0.01      | 81.4    |
| Alpha-fetoprotein | 7           | 2939            | MD: 0.19    | -0.04 to 0.41           | **0.100** | <0.01      | 75.5    |
| Uni-nodular HCC | 4              | 2430            | OR 1.12     | 0.60 - 2.08             | 0.612   | 0.07      | 57.70%  |
| BCLC 0/A        | 3              | 582             | OR 0.79     | 0.16 - 3.89             | 0.591   | 0.07      | 61.50%  |
| BCLC B          | 4              | 827             | OR 1.37     | 1.07 - 1.76             | 0.028   | 0.94      | 0.00%   |
| BCLC C/D        | 4              | 827             | OR 1.11     | 0.36 - 3.43             | 0.783   | <0.01     | 75.60%  |

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer
### Supplementary Material 6: Factors associated with receiving curative therapy* among patients with NAFLD-related HCC

| Factors            | No. of studies | No. of patients | Odds Ratio | 95% Confidence Interval | P-Value |
|--------------------|----------------|-----------------|------------|--------------------------|---------|
| Age                | 18             | 30082           | 0.54       | 0.39 to 0.74             | <0.001  |
| Male               | 18             | 30082           | 1.04       | 0.95 to 1.13             | 0.438   |
| Body Mass Index    | 13             | 25236           | 1.19       | 0.59 to 2.39             | 0.633   |
| Diabetes           | 14             | 7463            | 0.96       | 0.89 to 1.03             | 0.270   |
| Hypertension       | 11             | 6429            | 0.96       | 0.89 to 1.07             | 0.390   |
| Hyperlipidaemia    | 6              | 3186            | 0.97       | 0.90 to 1.04             | 0.421   |
| Cirrhosis          | 16             | 8808            | 0.93       | 0.89 to 0.98             | 0.004   |
| BCLC 0/A           | 7              | 5716            | 1.04       | 1.02 to 1.06             | <0.001  |
| BCLC C/D           | 7              | 5716            | 0.96       | 0.94 to 0.98             | <0.001  |
| Tumour diameter    | 11             | 4873            | 0.92       | 0.41 to 2.06             | 0.839   |
| Alpha-fetoprotein  | 12             | 7129            | 1.00       | 1.00 to 1.00             | 0.639   |

Legend: *defined as liver transplantation, liver resection or ablation

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group
Supplementary Material 7: Summary of risk factors affecting overall survival (OS) and disease-free survival (DFS) of NAFLD-related HCC

| Risk Factor                  | No. of Studies | Beta-Coefficient | 95% Confidence Interval | P-Value |
|------------------------------|----------------|-------------------|--------------------------|---------|
| **Overall survival**         |                |                   |                          |         |
| Age                          | 21             | -0.01             | -0.03 to 0.01            | 0.540   |
| Male Gender                  | 22             | -0.24             | -1.20 to 0.72            | 0.623   |
| Body Mass Index              | 14             | 0.01              | -0.03 to 0.05            | 0.605   |
| Diabetes                     | 16             | 0.01              | -1.10 to 1.11            | 0.990   |
| Hypertension                 | 12             | 0.05              | -0.64 to 0.74            | 0.886   |
| Hyperlipidaemia              | 5              | 0.74              | -1.20 to 2.69            | 0.454   |
| Cardiovascular Disease       | 4              | 0.41              | -2.07 to 2.88            | 0.746   |
| Early BCLC stage             | 10             | 0.26              | -0.54 to 1.07            | 0.517   |
| Late BCLC stage              | 10             | 0.09              | -0.92 to 1.10            | 0.863   |
| Tumour Diameter              | 12             | 0.01              | -0.10 to 0.13            | 0.836   |
| Alpha-fetoprotein            | 12             | 0.00              | 0.00 to 0.00             | 0.918   |
| **Disease free survival**    |                |                   |                          |         |
| Age                          | 8              | 0.01              | -0.03 to 0.05            | 0.653   |
| Male Gender                  | 9              | -0.89             | -3.73 to 1.95            | 0.540   |
| Body Mass Index              | 4              | -0.08             | -0.19 to 0.03            | 0.164   |
| Diabetes                     | 5              | -0.39             | -2.05 to 1.28            | 0.651   |
| Hypertension                 | 5              | -0.44             | -1.59 to 0.70            | 0.448   |
| Tumour Diameter              | 7              | 0.03              | -0.15 to 0.21            | 0.719   |
| Alpha-fetoprotein            | 4              | -0.02             | -0.03 to 0.00            | **0.029** |

Legend: * denote statistical significance at p<0.05; BCLC: Barcelona Clinic Liver Cancer
**Supplementary Material 8**: Overall and disease-free survival in NAFLD-related HCC vs HCC from other etiologies; stratified by individual etiology

| Subgroup                  | No. of Studies | No. of Patients | Hazard Ratio | 95% Confidence Interval | P-Value | Cochran-Q | I^2 (%) | Subgroup difference** |
|---------------------------|----------------|-----------------|--------------|--------------------------|---------|-----------|---------|----------------------|
| **Overall survival**      |                |                 |              |                          |         |           |         |                      |
| Hepatitis C virus         | 9              | 3997            | 1.24         | 0.86 to 1.81             | 0.253   | <0.01     | 99.8    | 0.388                |
| Western Pacific           | 1              | 90              | 0.90         | 0.49 to 1.66             | 0.746   | -         | -       |                      |
| Europe                    | 5              | 1921            | 1.42         | 0.88 to 2.31             | 0.150   | <0.01     | 99.7    |                      |
| Americas                  | 3              | 1986            | 0.94         | 0.78 to 1.14             | 0.938   | 0.14      | 49.9    |                      |
| Hepatitis B virus         | 10             | 4790            | 1.10         | 0.88 to 1.38             | 0.384   | <0.01     | 97.7    | 0.573                |
| Western Pacific           | 5              | 2918            | 0.92         | 0.70 to 1.21             | 0.531   | 0.61      | 0.0     |                      |
| Europe                    | 2              | 595             | 1.26         | 0.86 to 1.84             | 0.238   | <0.01     | 99.7    |                      |
| Americas                  | 2              | 198             | 1.45         | 0.35 to 6.05             | 0.614   | <0.01     | 94.1    |                      |
| South-East Asia           | 1              | 1079            | 1.05         | 0.87 to 1.28             | 0.596   | -         | -       |                      |
| Alcohol                   | 8              | 1933            | 1.19         | 0.94 to 1.52             | 0.148   | <0.01     | 88.1    | 0.299                |
| Western Pacific           | 1              | 229             | 0.93         | 0.67 to 1.28             | 0.653   | -         | -       |                      |
| Europe                    | 3              | 933             | 1.10         | 0.80 to 1.53             | 0.559   | <0.01     | 91.5    |                      |
| Americas                  | 3              | 672             | 1.71         | 0.82 to 3.55             | 0.150   | <0.01     | 92.0    |                      |
| South-East Asia           | 1              | 99              | 0.78         | 0.49 to 1.25             | 0.303   | -         | -       |                      |

**Disease-free survival**
| Condition                        | Count | Cases | HR   | 95% CI  | p-value | ORR  |
|---------------------------------|-------|-------|------|---------|---------|------|
| Hepatitis C Virus               | 5     | 700   | 0.67 | 0.31 to 1.42 | 0.286 | <0.01 |
| Hepatitis B Virus               | 5     | 2135  | 1.02 | 0.61 to 1.72 | 0.942 | 0.70  | 0.0  |
| Western Pacific                 | 3     | 1793  | 0.80 | 0.55 to 1.17 | 0.244 | 0.16  | 0.0  |
| Europe                          | 1     | 323   | 1.24 | 0.77 to 1.97 | 0.378 | -     | -    |
| Americas                        | 1     | 19    | 0.48 | 0.12 to 1.84 | 0.281 | -     | -    |
| Alcoholic Liver Disease         | 2     | 344   | 0.92 | 0.69 to 1.23 | 0.571 | 0.43  | 0.00 |

**Curative therapy Only***

|                |       |       |      |        |        |      |
|----------------|-------|-------|------|--------|--------|------|
| Overall survival |  |       |      |        |        |      |
| Hepatitis C Virus | 2   | 1243  | 1.22 | 1.01 to 1.48 | **0.041** | 0.97 | 0.00 |
| Hepatitis B Virus | 2   | 1715  | 1.01 | 0.61 to 1.67 | 0.955 | 0.78  | 0.00 |

Legend: *defined as liver transplantation, liver resection and ablation; **subgroup difference refers to comparison of effect sizes between geographical regions for each etiology

Abbreviations: NAFLD, non-alcoholic fatty liver disease; hepatocellular carcinoma, HCC
Supplementary Material 9: Funnel plots for publication bias

Funnel plot of age between NAFLD and non-NAFLD-related HCC

Funnel plot of body mass index (BMI) between NAFLD and non-NAFLD-related HCC
Funnel plot of diabetes between NAFLD and non-NAFLD-related HCC

\[ \text{Standard Error} \]

\[ \text{Odds Ratio} \]

\[ p = 0.0042 \]

Funnel plot of hypertension between NAFLD and non-NAFLD-related HCC

\[ \text{Standard Error} \]

\[ \text{Odds Ratio} \]

\[ p = 0.020 \]
Funnel plot of male gender between NAFLD and non-NAFLD-related HCC

\[ p = 0.497 \]
Funnel plot of non-cirrhosis between NAFLD and non-NAFLD-related HCC

Funnel plot of mean tumor diameter between NAFLD and non-NAFLD-related HCC

\[ p = 0.742 \]

\[ p = 0.690 \]
Funnel plot of unimodular tumor between NAFLD and non-NAFLD-related HCC

Funnel plot of BCLC B between NAFLD and non-NAFLD-related HCC
Funnel plot of BCLC C/D between NAFLD and non-NAFLD-related HCC

\[ \text{Odds Ratio} \]

\[ \text{Standard Error} \]

\( p = 0.131 \)

\( p = 0.749 \)
Funnel plot of allocation of curative treatment between NAFLD and non-NAFLD-related HCC

Funnel plot of allocation of palliative treatment between NAFLD and non-NAFLD-related HCC

\[ p = 0.705 \]

\[ p = 0.472 \]
Funnel plot of overall survival (OS) between NAFLD and non-NAFLD-related HCC

Funnel plot of disease-free survival (DFS) between NAFLD and non-NAFLD-related
NAFLD HCC Meta-analysis Protocol

Background:
Non-alcoholic fatty liver disease (NAFLD) is the fastest rising cause of hepatocellular carcinoma (HCC) in the U.S. and parts of Europe, and is expected to rise exponentially in parallel with the global obesity epidemic.\textsuperscript{1-5} However, the characteristics and outcomes of NAFLD HCC versus HCC from other etiologies, including hepatitis B (HBV), hepatitis C (HCV), and alcoholic liver disease (ALD), remain unclear. Existing studies have reported contrasting results, in part due to these studies being limited by geographical region or treatment.\textsuperscript{6-8}

Therefore, we aim to conduct a systematic review and meta-analysis to compare the clinical features, prevalence, surveillance rates and outcomes of NAFLD-related HCC versus non-NAFLD HCC.

Aims:
(1) To determine the prevalence of HCC secondary to NAFLD, globally, by region, and over time
(2) To evaluate the differences in patient characteristics (e.g. age, gender, presence of metabolic conditions including diabetes, hypertension, hyperlipidemia, presence of cirrhosis) and tumor characteristics (e.g. tumor number, tumor diameter, BCLC staging) and surveillance between NAFLD HCC and other etiologies, overall and by etiology
(3) To determine differences in treatment allocation (curative treatment, palliative treatment, best supportive care) between NAFLD HCC and other etiologies, overall and by etiology
(4) To determine differences in survival outcomes (overall survival, disease-free survival) between NAFLD HCC and other etiologies, overall and by etiology

Inclusion and exclusion criteria:
Only studies written or translated to English language will be included, with no date filter. Prospective and retrospective cohort studies and randomized control trials will be considered for inclusion. Studies will be included if they (1) describe the prevalence of HCC secondary to NAFLD, the patient and tumor characteristic of NAFLD HCC, and the treatment allocation and survival outcomes of NAFLD HCC; and (2) compared these outcomes with HCC secondary to other etiologies (HBV, HCV, ALD). Studies that diagnosed NAFLD based on either (i) imaging, (ii) histology or (iii) ICD codes in the absence of
significant alcohol consumption and coexisting causes of chronic liver disease will be included for analysis.

Studies that were not published will be excluded. Editorials, case series/report, review articles will also be excluded. Studies will be excluded if they included patients with HCC secondary to ‘cryptogenic’ causes.

Analysis:

A meta-analysis of proportions will be conducted using a generalized linear mixed model with Clopper-Pearson intervals to determine the prevalence of HCC secondary to NAFLD. Subgroup analysis will be conducted to determine the proportion of HCC secondary to NAFLD by geographical region according to the WHO regions, and by time period.

Comparative meta-analysis will be conducted in odds ratio and weighted mean difference to compare between patient characteristics, tumor characteristics, and treatment allocation between NAFLD HCC versus other etiologies. Subgroup analysis will be conducted for comparative outcomes stratified by individual etiology of HCC (i.e. HBV, HCV, ALD). Survival outcomes between NAFLD HCC and other etiologies will be performed via pooled analysis of hazard ratios. Subgroup analysis for survival outcomes will be stratified by presence of cirrhosis, and by type of treatment received. All comparative analysis will be conducted using the DerSimonian-Laird random effects model. All analysis will be conducted in R Studio using the ‘meta’ package. Quality assessment of included articles will be done via the Joanna Briggs Institute (JBI) Critical Appraisal Tool.
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