NAFLD and MAFLD as emerging causes of HCC: a populational study

MYERS, Shuna, et al.

Abstract

There are conflicting data regarding the epidemiology of hepatocellular carcinoma (HCC) arising in the context of non-alcoholic and metabolic-associated fatty liver disease (NAFLD and MAFLD). We aimed to examine the changing contribution of NAFLD and MAFLD, stratified by sex, in a well-defined geographical area and highly characterised HCC population between 1990 and 2014.

Reference

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NAFLD and MAFLD as emerging causes of HCC: A populational study

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| Variable                          | Male sex, n=52  | Female sex, n=24 | p-value |
|----------------------------------|----------------|-----------------|---------|
| **Clinical**                     |                |                 |         |
| Age (y)                          | 75 (70-79)     | 75.5 (65.5-80.5) | 0.960   |
| Diabetes (%)                     | 37/50 (74%)    | 17/24 (70.8%)   | 0.786   |
| Hypercholesterolemia (%)         | 23/48 (47.9%)  | 11/24 (45.8%)   | 1.000   |
| Weight (kg)                      | 86 (75.8-91.2) | 70.5 (64-89.2)  | 0.025   |
| BMI (kg/m²)                      | 29.8 (26.7-30.8) | 28.1 (24.5-32.3) | 0.404   |
| BMI ≥ 25kg/m² (%)                | 34/49 (69.4%)  | 14/24 (58.3%)   | 0.433   |
| **Biological**                   |                |                 |         |
| ALT (IU/L)                       | 36.5 (25-56.8) | 35 (24.8-69.8)  | 0.976   |
| AST (IU/L)                       | 53 (38.8-82.8) | 54 (33.8-126)  | 0.720   |
| Albumin (g/L)                    | 31 (27-34)     | 28 (26.8-32)    | 0.338   |
| Total bilirubin (µmol/L)         | 19 (14.8-32.8) | 20 (11.2-24.8)  | 0.386   |
| Creatinine (µmol/L)              | 91 (78-124.5)  | 77.5 (63.8-97)  | 0.052   |
| Sodium (mmol/L)                  | 137.5 (135-139) | 136.5 (133.8-140) | 0.733   |
| Platelets (10⁹/L)                | 218 (139-296.8) | 239.5 (149.2-354) | 0.624   |
| GGT (IU/L)                       | 197.5 (68.5-350) | 126 (37.5-205)  | 0.052   |
| Alk Phos (IU/L)                  | 149 (84-194)   | 113 (80.5-213.5) | 0.795   |
| Hemoglobin (g/L)                 | 148.5          | 113 (101.5-132.8) | 0.015   |
| INR                              | 1 (1-1)        | 1 (1-1)         | 0.365   |
| MELD                             | 11 (9-14)      | 9 (6-12)        | 0.018   |
| **Background liver**             |                |                 |         |
| Histological F3-F4               | 20/36 (56%)    | 9/18 (50%)      | 0.777   |
| Histological or clinical F3-F4   | 29/45 (64%)    | 12/22 (55%)     | 0.594   |
| AFP (ng/mL)                      | 10.5 (3.8-331.2) | 8.5 (4-760.8)  | 0.775   |
| Surveillance prior to diagnosis  | 4/36 (11%)     | 1/20 (5%)       | 0.645   |
| **Cancer staging**               |                |                 |         |
| T1                               | 7/46 (15%)     | 7/24 (29%)      | 0.300   |
| T2                               | 20/46 (43%)    | 6/24 (25%)      |         |
| T3                               | 17/46 (37%)    | 9/24 (38%)      |         |
| T4                               | 2/46 (4%)      | 2/24 (8%)       |         |
| N0                               | 29/33 (88%)    | 12/14 (86%)     | 1.000   |
| N1                               | 4/33 (12%)     | 2/14 (14%)      |         |
| N2                               | 0/33 (0%)      | 0/14 (0%)       |         |
| M0                               | 24/34 (71%)    | 12/16 (75%)     | 1.000   |
| M1                               | 10/34 (29%)    | 4/16 (25%)      |         |
| TNM stage                        |                |                 | 0.602   |
| 1 (T1N0M0)                       | 5/34 (15%)     | 5/16 (31%)      |         |
| 2 (T2N0M0)                       | 10/34 (29%)    | 3/16 (19%)      |         |
| 3 (T3-4N0M0)                     | 9/34 (26%)     | 4/16 (25%)      |         |
| 4 (N1 or M1)                     | 10/34 (29%)    | 4/16 (25%)      |         |
| **Treatment**                    |                |                 |         |
| Liver transplantation            | 1/49 (2%)      | 1/24 (4%)       | 1.000   |
| Resection                        | 8/49 (16%)     | 7/24 (29%)      | 0.228   |
| Treatment                                      | Female | Male  | p-value |
|-----------------------------------------------|--------|-------|---------|
| Radiofrequency ablation                       | 5/49 (10%) | 5/24 (21%) | 0.281 |
| Chemoembolization                             | 23/49 (47%) | 9/24 (38%) | 0.466 |
| Systemic therapy                              | 6/49 (12%) | 4/24 (7%) | 0.720 |
| Best supportive care / no therapy             | 14/49 (29%) | 6/24 (25%) | 1.000 |

**Table S1.** Comparison of clinical characteristics between female and male patients with NAFLD-HCC (n=76)

AFP, alpha fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End Stage Liver Disease; RFA, radiofrequency ablation; TACE, transarterial chemoembolization
| Variable                        | NAFLD (n=76) | MAFLD, no NAFLD (n=377) | no MAFLD, no NAFLD (n=467) | Overall p-value |
|--------------------------------|--------------|--------------------------|----------------------------|-----------------|
| **Clinical**                   |              |                          |                            |                 |
| Age (y)                        | 75 (70-80)   | 67 (60-74)                | 67 (58-77)                 | <0.001          |
| Female sex (%)                 | 24/76 (31.6%)| 54/377 (14.3%)            | 103/467 (22.1%)            | 0.001           |
| Diabetes (%)                   | 54/74 (73%)  | 236/356 (66.3%)           | 1/242 (0.4%)               | <0.001          |
| Hypercholesterolemia (%)       | 34/72 (47.2%)| 81/318 (25.5%)            | 19/233 (8.2%)              | <0.001          |
| Weight (kg)                    | 81 (69.8-91) | 80 (72.3-90.6)            | 66.7 (57-74)               | <0.001          |
| BMI (kg/m2)                    | 28.7 (25.6-31)| 27.4 (25.5-30)          | 21.4 (19.9-23.3)           | <0.001          |
| **Biological**                 |              |                          |                            |                 |
| ALT (IU/L)                     | 36 (25-61)   | 48 (30-78.2)              | 51.5 (33-88)               | 0.007           |
| AST (IU/L)                     | 53 (37.5-95.2)| 74 (48-124)              | 89 (60-151.5)              | <0.001          |
| Albumin (g/L)                  | 30 (27-34)   | 29 (25-34)                | 28 (23-32)                 | 0.011           |
| Total bilirubin (µmol/L)       | 19 (14-31)   | 26 (17-46)                | 32 (18-62.8)               | <0.001          |
| Creatinine (µmol/L)            | 87.5 (73-117.8)| 85 (70-112)              | 80 (65.5-100.5)            | 0.015           |
| Sodium (mmol/L)                | 137 (134.8-139)| 136 (134-139)          | 137 (134-139)              | 0.105           |
| Platelets (10⁹/L)              | 224.5 (142.2-305)| 144 (99.2-199.2)        | 129 (83-208)               | <0.001          |
| GGT (IU/L)                     | 167 (62-295) | 203 (110.8-362.2)         | 182.5 (101-357.2)          | 0.171           |
| Alk Phos (IU/L)                | 130.5 (82.8-196.8)| 123 (90-186)            | 133 (97-197)               | 0.205           |
| Hemoglobin (g/L)               | 126 (107-145.5)| 128 (111.2-142)         | 127 (109-142)              | 0.753           |
| MELD                           | 10 (8-14)    | 12 (8-15.5)               | 12 (9-17)                  | 0.075           |
| Histological or clinical F3-F4 | 41/67 (61.2%)| 294/312 (94.2%)           | 264/286 (92.3%)            | <0.001          |
| **Tumor characteristics**      |              |                          |                            |                 |
| TNM stage 3 or 4               | 27/50 (54%)  | 130/205 (63.4%)           | 204/290 (70.3%)            | 0.046           |
|AFP (ng/mL)                     | 9.5 (4-463)  | 21 (6-315.5)              | 40 (7-745)                 | 0.035           |
| **First line therapy**         |              |                          |                            |                 |
| Curative therapy (LT, Resection or RFA) | 25/71 (35.2%)| 91/340 (26.8%)          | 77/341 (22.6%)             | 0.070           |
| Palliative therapy (TACE, systemic therapy or other) | 26/71 (36.6%)| 140/340 (41.1%)        | 109/341 (32.0%)            | 0.044           |
| Best supportive care / no therapy | 20/71 (28.2%)| 109/340 (32.1%)        | 155/341 (45.4%)            | <0.001          |

Table S2. Clinical characteristics of NAFLD subjects (all were also MAFLD), MAFLD without NAFLD and subjects without NAFLD or MAFLD
| Variable                      | NAFLD (n=76) | HCV, MAFLD (n=82) | HCV, no MAFLD (n=109) | p-value | ALD, MAFLD (n=220) | ALD, no MAFLD (n=177) | p-value |
|-------------------------------|-------------|-------------------|-----------------------|---------|-------------------|-----------------------|---------|
| **Clinical**                  |             |                   |                       |         |                   |                       |         |
| Age (y)                       | 75 (70-80)  | 62 (53-69)        | 59 (52-71)            | 0.871   | 68 (61.8-74)      | 67 (61-73)            | 0.380   |
| Female sex (%)                | 24/76 (31.6%) | 25/82 (30.5%)    | 35/109 (32.1%)       | 0.875   | 17/220 (7.7%)     | 18/177 (10.2%)        | 0.477   |
| Diabetes (%)                  | 54/74 (73%) | 51/77 (66.2%)    | 0/71 (0%)             | <0.001  | 141/212 (66.5%)   | 0/99 (0%)             | <0.001  |
| Hypercholesterolemia (%)      | 34/72 (47.2%) | 17/72 (23.6%)    | 5/68 (7.4%)           | 0.010   | 55/193 (28.5%)    | 6/95 (6.3%)           | <0.001  |
| Weight (kg)                   | 81 (69.8-91)| 75.5 (66-85.8)   | 64.5 (55-71.2)       | <0.001  | 82 (75-91.9)      | 68.2 (61-77)          | <0.001  |
| BMI (kg/m²)                   | 28.7 (25.6-31)| 26.1 (24.8-28)  | 21.2 (19.9-23.2)     | <0.001  | 28.4 (25.9-30.7) | 22.4 (20.3-23.4)      | <0.001  |
| **Biological**                |             |                   |                       |         |                   |                       |         |
| ALT (IU/L)                    | 36 (25-61)  | 66 (41-113)       | 69 (43-113)           | 0.773   | 40 (28-62.5)      | 41 (28-63.8)          | 0.938   |
| AST (IU/L)                    | 53 (37.5-95.2) | 95 (59.8-126.5)  | 102 (72.5-158.5)     | 0.010   | 68 (45-119.2)     | 81 (55-129)           | 0.037   |
| Albumin (g/L)                 | 30 (27-34)  | 29 (24-33)        | 28 (24.8-32)         | 0.800   | 28.5 (25-34)      | 26.5 (23-30.8)        | 0.003   |
| Total bilirubin (µmol/L)      | 19 (14-31)  | 24 (16-45)        | 24 (18-48)           | 0.439   | 27 (17-46.8)      | 41 (22-75)            | 0.002   |
| Creatinine (µmol/L)           | 87.5 (73-117.8) | 75.5 (66-104)    | 73 (61-88.5)         | 0.257   | 85 (72-110)       | 83 (67-114)           | 0.667   |
| Sodium (mmol/L)               | 137 (134.8-139) | 137 (134-139)    | 136 (135-139)        | 0.612   | 136 (133-139)     | 136 (133-139)         | 0.452   |
| Platelets (10^9/L)            | 224.5 (142.2-305) | 110.5 (79.2-173) | 96 (69-137.8)        | 0.099   | 149 (111.8-197.8) | 136.5 (87.8-205.2)    | 0.152   |
| GGT (IU/L)                    | 167 (62-295) | 125.5 (74.2-253.2) | 142 (75.2-242.5)     | 0.664   | 264 (134.8-390.2) | 209 (146.5-428)       | 0.660   |
| Alk Phos (IU/L)               | 130.5 (82.8-196.8) | 116 (86.5-164)   | 125 (94.5-153)       | 0.461   | 127 (94.5-189.5)  | 143 (105-212)         | 0.038   |
| Hemoglobin (g/L)              | 126 (107-145.5) | 125 (113-139)    | 128 (114.8-143.2)    | 0.186   | 128 (109-142)     | 123 (104-138)         | 0.059   |
| MELD                          | 10 (8-14)   | 12 (8-15)         | 10 (8-16)            | 0.787   | 12 (8-16)         | 13 (10-18)            | 0.020   |
| Histological or clinical F3-F4| 41/67 (61.2%) | 72/75 (96%)      | 91/92 (98.9%)        | 0.327   | 174/185 (94.1%)   | 118/127 (92.9%)       | 0.815   |
| **Tumor characteristics**     |             |                   |                       |         |                   |                       |         |
| TNM stage 3 or 4              | 27/50 (54%) | 23/48 (47.9%)    | 42/75 (56%)          | 0.460   | 76/113 (67.3%)    | 75/107 (70.1%)        | 0.666   |
| AFP (ng/mL)                   | 9.5 (4-463) | 24.5 (8-225.5)   | 42 (10-413.5)        | 0.436   | 15 (5-318)        | 28 (6-824)            | 0.152   |
| **First line HCC therapy**    |             |                   |                       |         |                   |                       |         |
| Aetiology                        | MAFLD | No MAFLD | P-value | MAFLD | No MAFLD | P-value |
|---------------------------------|-------|----------|---------|-------|----------|---------|
| Curative therapy (LT, Resection or RFA) | 25/71 (35.2%) | 31/78 (39.7%) | 0.204 | 43/202 (21.3%) | 22/141 (15.6%) | 0.209 |
| Palliative therapy (TACE, systemic therapy or other) | 26/71 (36.6%) | 34/78 (43.6%) | 0.649 | 84/202 (41.6%) | 43/141 (30.5%) | 0.041 |
| Best supportive care / no therapy | 20/71 (28.2%) | 13/78 (16.7%) | 0.052 | 75/202 (37.1%) | 76/141 (53.9%) | 0.003 |

Table S3. Comparison of HCV and ALD subjects with and without MAFLD. P-values refer to comparisons between MAFLD vs no MAFLD across aetiology.
| Variable                        | NAFLD-HCC (definition 1), n=76 | NAFLD (definition 2), n=101 |
|--------------------------------|--------------------------------|-----------------------------|
| **Clinical**                   |                                |                             |
| Age (y)                        | 75 (70-80)                     | 76 (71-82)                  |
| Female sex (%)                 | 24/76 (31.6%)                  | 32/101 (31.7%)              |
| Diabetes (%)                   | 54/74 (73%)                    | 54/95 (56.8%)               |
| Hypercholesterolemia (%)       | 34/72 (47.2%)                  | 36/93 (38.7%)               |
| Weight (kg)                    | 81 (69.8-91)                   | 76 (66.7-90)                |
| BMI (kg/m2)                    | 28.7 (25.6-31)                 | 28.5 (24.9-30.8)            |
| BMI ≥ 25kg/m2 (%)              | 48/73 (65.8%)                  | 51/95 (53.7%)               |
| **Biological**                 |                                |                             |
| ALT (IU/L)                     | 36 (25-61)                     | 36 (24.8-59.2)              |
| AST (IU/L)                     | 53 (37.5-95.2)                 | 54 (36-101.5)               |
| Albumin (g/L)                  | 30 (27-34)                     | 29 (27-34)                  |
| Total bilirubin (μmol/L)       | 19 (14-31)                     | 20 (14-32)                  |
| Creatinine (μmol/L)            | 87.5 (73-117.8)                | 86 (73-116.2)               |
| Sodium (mmol/L)                | 137 (134.8-139)                | 137.5 (135-140)             |
| Platelets (109/L)              | 224.5 (142.2-305)              | 225 (141-294)               |
| GGT (IU/L)                     | 167 (62-295)                   | 167 (64-342)                |
| Alk Phos (IU/L)                | 130.5 (82.8-196.8)             | 147 (82.2-208)              |
| Hemoglobin (g/L)               | 126 (107-145.5)                | 126.5 (107.8-141.8)         |
| INR                            | 1.19 (1.03-1.64)               | 1.20 (1.00-1.50)            |
| MELD                           | 10 (8-14)                      | 10 (8-14)                   |
| **Background liver**           |                                |                             |
| Histological F3-F4             | 29/54 (53.7%)                  | 30/60 (50%)                 |
| Histological or clinical F3-F4 | 41/67 (61.2%)                  | 54/85 (64%)                 |
| AFP (ng/mL)                    | 9.5 (4-463)                    | 12 (4-510.2)                |
| Surveillance prior to diagnosis| 5/56 (9%)                      | 5/63 (8%)                   |
| **Median survival** (weeks)    | 101 (46-160)                   | 72 (39-122)                 |
| **Cancer TNM stage**           |                                |                             |
| 1 (T1N0M0)                     | 10/50 (20%)                    | 12/61 (20%)                 |
| 2 (T2N0M0)                     | 13/50 (26%)                    | 16/61 (26%)                 |
| 3 (T3-4N0M0)                   | 13/50 (26%)                    | 15/61 (25%)                 |
| 4 (N1 or M1)                   | 14/50 (28%)                    | 18/61 (30%)                 |
| **Therapy**                    |                                |                             |
| Curative therapy (LT, Resection or RFA) | 25/73 (34%)   | 26/93 (28%)                 |
| Palliative therapy (TACE, systemic therapy or other) | 44/73 (60%) | 49/93 (53%)                 |
| Best supportive care / no therapy | 20/73 (27%)            | 34/93 (37%)                 |

Table S4. Comparison of different definitions of NAFLD-HCC. **Definition 1** corresponds to exclusion of other causes of liver disease and histological / clinical documentation of NAFLD or presence of metabolic syndrome / diabetes or obesity. **Definition 2** additionally includes patients with cryptogenic liver disease (see Methods for details).
Supplementary Figures

Fig. S1. Flowchart of the study population.
Fig. S2. Age-standardised incidence of HCC by etiology and according to male and female sex in the canton of Geneva in 5-year periods from 1990 to 2014.
Fig. S3. Prevalence of overweight or obesity (body mass index [BMI] ≥ 25 kg/m$^2$), obesity (BMI ≥ 30 kg/m$^2$) and at risk alcohol consumption in the canton of Geneva from 1992 to 2012 in men and women. At risk alcohol consumption is defined as 4 standard units or more for men and 2 standard units or more for women a day.

Data from: Enquête suisse sur la santé 2017. Office fédéral de la statistique; 2018. 
https://www.ge.ch/statistique/ofis/sante2017/files/fr/02.xml accessed April 10th 2020.
Fig. S4. Age-standardised incidence of HCC according to NAFLD-HCC diagnostic criteria. Definition 1 (dx 1) corresponds to exclusion of other causes of liver disease and histological / clinical documentation of NAFLD or presence of metabolic syndrome / diabetes or obesity. Definition 2 (dx 2) additionally includes patients with cryptogenic liver disease (see Methods for details).