1 Supplementary material

2 Supplementary Table 1 Sensitivity analysis to account for immortal time bias

| Removal of | | | |
|------------------|------------------|--------------------|---------|
| events within | | | |
| 24 months of LT | | | |
| HCC- | Hazard ratio P | value Multivariate | P value |
| recurrence and | and confidence | analysis | |
| all-cause | interval | | |
| mortality | | | |
| Statins | 1.52 (95% CI 0.2 | 29 1.58 (95% CI | 0.23 |
| | 0.70-3.28) | 0.75-3.31) | |
| Aspirin | 1.38 (95% CI 0.7 | 73 1.77 (95% CI | 0.56 |
| | 0.27-8.59) | 0.26-12.17) | |
| Metformin | 0.72 (95% CI 0.5 | 0.61 (95% CI | 0.33 |
| | 0.27-1.92) | 0.23-1.64) | |
| Removal of | | | |
| events within 24 | | | |
| months of LT | | | |
| HCC-recurrence | | | |
| Statins | 0.50 (95% CI 0.1 | 0.52 (95% CI | 0.24 |
| | 0.18-1.39) | 0.17-1.56) | |
| Aspirin | N/A | N/A | |
| Metformin | 0.95 (95% CI 0.9 | 94 1.00 (95% CI | 0.99 |
| | 0.25-3.60) | 0.26-3.91) | |
| Removal of | | | |
| events within 24 | | | |
| months of LT | | | |
| HCC-related | | | |
| mortality | | | |
| Statins | N/A | N/A | |
| Aspirin | N/A | N/A | |

| Metformin | 0.44 | (95% | CI | 0.38 | N/A |
|-----------|--------|-------|----|------|-----|
| | 0.70-2 | 2.78) | | | |

- 1 Events removed within 24 months to account for immortal time bias
- 2 HCC Hepatocellular carcinoma, LT Liver transplantation
- 3 N/A unable to be calculated due to low numbers

5 Supplementary Table 2 Sensitivity analysis to account for immortal time bias

| Removal of | - | | | |
|------------------|----------------|---------|--------------|---------|
| events within | | | | |
| 12 months of LT | | | | |
| HCC- | Hazard ratio | P value | Multivariate | P value |
| recurrence and | and confidence | | analysis | |
| all-cause | interval | | | |
| mortality | | | | |
| Statins | 1.66 (95% CI | 0.23 | 1.67 (95% CI | 0.27 |
| | 0.76-3.24) | | 0.73-3.01) | |
| Aspirin | 1.35 (95% CI | 0.72 | 0.55 (95% CI | 0.55 |
| | 0.25-7.18) | | 0.34-9.81) | |
| Metformin | 0.84 (95% CI | 0.69 | 1.45 (95% CI | 0.38 |
| | 0.37-1.94) | | 0.30-1.58) | |
| Removal of | | | | |
| events within 12 | | | | |
| months of LT | | | | |
| HCC-recurrence | | | | |
| Statins | 0.63 (95% CI | 0.33 | 0.57 (95% CI | 0.26 |
| | 0.25-1.59) | | 0.21-1.53) | |
| Aspirin | 0.22 (95% CI | 0.15 | 0.28 (95% CI | 0.16 |
| | 0.027-1.70) | | 0.046-1.69) | |
| Metformin | 1.07 (95% CI | 0.91 | 1.13 (95% CI | 0.82 |
| | 0.36-3.16) | | 0.39-3.29) | |

| Removal of | | | | | | |
|------------------|----------|-------|----|-------|--------------|------|
| events within 12 | | | | | | |
| months of LT | | | | | | |
| HCC-related | | | | | | |
| mortality | | | | | | |
| Statins | 0.50 | (95% | CI | 0.51 | 0.32 (95% CI | 0.34 |
| | 0.063-3 | 3.93) | | | 0.032-3.25) | |
| Aspirin | 0.18 | (95% | CI | 0.096 | 0.24 (95% CI | 0.15 |
| | 0.025-1 | 1.35) | | | 0.036-1.68) | |
| Metformin | 1.26 | (95% | CI | 0.75 | 1.50 (95% CI | 0.45 |
| | 0.31-5.1 | 14) | | | 0.53-4.24) | |

¹ Events removed within 12 months to account for immortal time bias

4 Supplementary Table 3 Sensitivity analysis to account for immortal time bias

| | Hazard ratio | P value | Multivariate | P value |
|-----------------|----------------|---------|--------------|---------|
| | and confidence | | analysis | |
| | interval | | | |
| Removal of | | | | |
| events within 6 | | | | |
| months of LT | | | | |
| HCC-recurrence | | | | |
| and all-cause | | | | |
| mortality | | | | |
| Statins | 1.49 (95% CI | 0.25 | 1.43 (95% CI | 0.29 |
| | 0.76-2.93) | | 0.74-2.74) | |
| Aspirin | 1.17 (95% CI | 0.84 | 1.47 (95% CI | 0.61 |
| | 0.25-5.34) | | 0.33-6.55) | |
| Metformin | 0.74 (95% CI | 0.47 | 0.60 (95% CI | 0.21 |
| | 0.32-1.69) | | 0.27-1.35) | |

² HCC - Hepatocellular carcinoma, LT - Liver transplantation.

| events within 6 months of LT HCC-recurrence Statins 0.75 (95% CI 0.54 0.76 (95% CI 0.56 0.31-1.88) Aspirin 0.48 (95% CI 0.33 0.75 (95% CI 0.64 0.11-2.09) Metformin 0.98 (95% CI 0.98 0.71 (95% CI 0.64 0.17-2.97) Removal of events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.32 0.33-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 0.61-4.10) 1.59 (95% CI 0.34 0.61-4.10) | Removal of | | | |
|---|-----------------|--------------|---------|-------------------|
| HCC-recurrence Statins 0.75 (95% CI 0.54 0.31-1.88) Aspirin 0.48 (95% CI 0.33 0.75 (95% CI 0.64 0.11-2.09) Metformin 0.98 (95% CI 0.98 0.17-2.97) Removal of events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.33-3.00) Aspirin 0.76 (95% CI 0.47 0.32 (95% CI 0.32 0.33-3.00) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.32-3.77) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | events within 6 | | | |
| Statins 0.75 (95% (95% CI 0.54) 0.76 (95% CI 0.56) Aspirin 0.48 (95% CI 0.33) 0.75 (95% CI 0.64) Aspirin 0.98 (95% CI 0.33) 0.75 (95% CI 0.64) Metformin 0.98 (95% CI 0.98) 0.71 (95% CI 0.64) 0.27-3.55) 0.17-2.97) Removal of events within 6 0.17-2.97) HCC-related mortality 0.47 (95% CI 0.47) 0.32 (95% CI 0.32) Statins 0.47 (95% CI 0.47) 0.033-3.90) Aspirin 0.76 (95% CI 0.74) 0.75 (95% CI 0.73) 0.15-3.77) 0.14-3.93) Metformin 1.18 (95% CI 0.85) 0.85 1.59 (95% CI 0.34) | months of LT | | | |
| Name Name | HCC-recurrence | | | |
| Aspirin 0.48 (95% CI 0.33 0.75 (95% CI 0.64 0.11 - 2.09) 0.22-2.56) Metformin 0.98 (95% CI 0.98 0.71 (95% CI 0.64 0.27-3.55) 0.17-2.97) Removal of events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.063-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | Statins | 0.75 (95% | CI 0.54 | 0.76 (95% CI 0.56 |
| Metformin 0.98 (95% CI 0.98 0.71 (95% CI 0.64 0.27-2.97) Removal of events within 6 months of LT Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.06-3.67) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 0.82-2.56) 0.71 (95% CI 0.64 0.71 (95% CI 0.64 0.71 0.72 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) 0.17-2.97) | | 0.30-1.89) | | 0.31-1.88) |
| Metformin 0.98 (95% (95% (95% (95% (95% (95% (95% (95% | Aspirin | 0.48 (95% | CI 0.33 | 0.75 (95% CI 0.64 |
| 0.27-3.55) Removal of events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.06-3.67) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | | 0.11 - 2.09) | | 0.22-2.56) |
| Removal of events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.033-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | Metformin | 0.98 (95% | CI 0.98 | 0.71 (95% CI 0.64 |
| events within 6 months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.003-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | | 0.27-3.55) | | 0.17-2.97) |
| months of LT HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.06-3-67) 0.033-3.90) 0.033-3.90) 0.75 (95% CI 0.73 Aspirin 0.15-3.77) 0.14-3.93) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | Removal of | | | |
| HCC-related mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.06-3-67) 0.033-3.90) 0.033-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.15-3-77) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | events within 6 | | | |
| mortality Statins 0.47 (95% CI 0.47 0.32 (95% CI 0.32 0.06-3.67) 0.033-3.90) 0.033-3.90) Aspirin 0.75 (95% CI 0.73 0.15-3.77) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | months of LT | | | |
| Statins 0.47 (95% CI 0.47 (95% CI 0.32 (95% CI 0.32 (95% CI 0.033-3.90)) Aspirin 0.76 (95% CI 0.74 (95% CI 0.74 (95% CI 0.14-3.93)) Metformin 1.18 (95% CI 0.85 (95% CI 0.34 (95% CI 0.32 | HCC-related | | | |
| 0.06-3.67) 0.033-3.90) Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 0.34 0.34 0.34 0.34 0.34 0.34 0.34 | mortality | | | |
| Aspirin 0.76 (95% CI 0.74 0.75 (95% CI 0.73 0.15-3.77) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | Statins | 0.47 (95% | CI 0.47 | 0.32 (95% CI 0.32 |
| 0.15-3.77) 0.14-3.93) Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | | 0.06-3.67) | | 0.033-3.90) |
| Metformin 1.18 (95% CI 0.85 1.59 (95% CI 0.34 | Aspirin | 0.76 (95% | CI 0.74 | 0.75 (95% CI 0.73 |
| | | 0.15-3.77) | | 0.14-3.93) |
| 0.20-6.92) 0.61-4.10) | Metformin | 1.18 (95% | CI 0.85 | 1.59 (95% CI 0.34 |
| | | 0.20-6.92) | | 0.61-4.10) |

- 1 Events removed within 6 months to account for immortal time bias
- 2 HCC Hepatocellular carcinoma, LT Liver transplantation
- 3 MTOR Mammalian Target of Rapamycin

5 Supplementary Table 4 Sensitivity analysis to account for immortal time bias

| Hazard | ratio | P value | Multivariate | P value |
|----------------|-------|---------|--------------|---------|
| and confidence | | | analysis | |
| interval | | | | |

| Removal of | | |
|-----------------|-------------------|-------------------|
| events within 3 | | |
| months of LT | | |
| HCC-recurrence | | |
| and all-cause | | |
| mortality | | |
| Statins | 1.29 (95% CI 0.48 | 1.40 (95% CI 0.33 |
| | 0.64-2.61) | 0.72-2.73) |
| Aspirin | 1.09 (95% CI 0.91 | 1.42 (95% CI 0.66 |
| | 0.24-5.00) | 0.31-6.52) |
| Metformin | 0.74 (95% CI 0.45 | 0.60 (95% CI 0.21 |
| | 0.33-1.62) | 0.26-1.34) |
| Removal of | | |
| events within 3 | | |
| months of LT | | |
| HCC-recurrence | | |
| Statins | 0.55 (95% CI 0.20 | 0.52 (95% CI 0.15 |
| | 0.22-1.38) | 0.21-1.26) |
| Aspirin | 0.37 (95% CI 0.18 | 0.48 (95% CI 0.32 |
| | 0.08-1.60) | 0.12-2.00) |
| Metformin | 1.02 (95% CI 0.97 | 0.94 (95% 0.91 |
| | 0.37-2.28) | 0.34-2.63) |
| Removal of | | |
| events within 3 | | |
| months of LT | | |
| HCC-related | | |
| mortality | | |
| Statins | 0.46 (95% CI 0.46 | 0.31 (95% CI 0.31 |
| | 0.059-3.55) | 0.033-2.97) |
| Aspirin | 0.51 (95% CI 0.40 | 0.68 (95% CI 0.64 |
| | 0.11-2.45) | 0.13-3.48) |

| Metformin | 1.28 (95% CI 0.70 | 1.54 (95% CI 0.38 |
|-----------|-------------------|-------------------|
| | 0.36-4.53) | 0.59-3.99) |

- 1 Events removed within 3 months to account for immortal time bias
- 2 HCC Hepatocellular carcinoma, LT Liver transplantation
- 3 MTOR Mammalian Target of Rapamycin

- 5 Supplementary Table 5 Sensitivity analysis to account for immortal time bias -
- 6 mammalian target of rapamycin inhibitor use

| | Univariate | P value | Multivariate | P value |
|----------------|--------------|---------|--------------|---------|
| | analysis | | analysis | |
| HCC- | | | | |
| recurrence | | | | |
| and all-cause | | | | |
| mortality | | | | |
| Removal of | 1.43 (95% CI | 0.33 | 0.94 (95% CI | 0.86 |
| events within | 0.70-2.91) | | 0.47-1.86) | |
| 12 months of | | | | |
| LT | | | | |
| HCC- | | | | |
| recurrence | | | | |
| Removal of | 1.11 (95% CI | 0.21 | 0.80 (95% CI | 0.50 |
| events within | 0.52-2.37) | | 0.42-1.53) | |
| 12 months of | | | | |
| LT | | | | |
| HCC-related | | | | |
| mortality | | | | |
| Removal of all | 0.26 (95% CI | 0.15 | N/A | |
| events within | 0.042-1.63) | | | |
| 24 months of | | | | |
| LT | | | | |

| Removal of | 0.88 (95% CI | 0.83 | 0.57 (95% CI 0.27 |
|----------------|--------------|------|-------------------|
| events within | 0.27-2.84) | | 0.21-1.54) |
| 12 months of | | | |
| LT | | | |
| Removal of all | 0.96 (95% CI | 0.94 | 0.61 (95% CI 0.27 |
| events within | 0.34-2.71) | | 0.25-1.47) |
| 6 months of | | | |
| LT | | | |
| Removal of all | 0.99 (95% CI | 0.94 | 0.61 (95% CI 0.27 |
| events within | 0.35-2.65) | | 0.26-1.45) |
| 3 months of | | | |
| LT | | | |

Sensitivity analysis for immortal time bias, with removal of evens within 3, 6, 12, 24

Supplementary Table 6 Summary characteristics and sensitivity analysis for obesity and overweight status

| | Summary | Summary o | Summary characteristics | | |
|----------------------|-----------------|-------------|-------------------------|---------|--|
| | characteristics | | | | |
| Variable | Total | For HCC | No HCC | | |
| | | recurrence | recurrence | | |
| Overweight | 201 (65.90%) | 26 (76.47%) | 175 (64.58%) | 0.17 | |
| pre-LT | | | | | |
| (BMI>25) | | | | | |
| Post-LT | 137 (44.92%) | 16 (47.06%) | 121 (44.65%) | 0.79 | |
| Obesity | | | | | |
| HCC-related | Univariate | P value | Multivariate | P value | |
| mortality | analysis | | analysis | | |
| Overweight | HR 1.65 (95% | 0.46 | HR 1.01 | 0.98 | |
| pre-LT | CI 0.44-6.24) | | (95% CI 0.43- | | |
| (BMI <u>></u> 25) | | | 2.35) | | |

² months of LT; MTORi – Mammalian Target of Rapamycin Inhibitor

| Post-LT | HR 1.75 (95% 0.37 | HR | 0.66 | 0.33 |
|---------|-------------------|---------------|------|------|
| Obesity | CI 0.51-5.98) | (95% CI 0.29- | | |
| | | 1.51) | | |

- 1 Mann-Whitney U test used to compare groups. HCC Hepatocellular carcinoma, LT
- 2 Liver transplantation, BMI body mass index. Multivariate analysis performed with
- 3 variables p<0.1 and pre-defined a-priori variables, please see Table 6. Pre-LT Obesity,
- 4 Post-LT obesity and overweight pre-LT status not included in the same multivariate
- 5 analysis to avoid co-linearity bias.

7 Supplementary Table 7 Sensitivity analysis for defined daily doses, accounting for

8 immortal time bias

| Excluding events | | | Events excluded | | |
|-------------------------|----------------------|---------|------------------------|--|--|
| within 12 months | | | | | |
| HCC-recurrence | Adjusting for | P value | | | |
| and all cause | immortality/time | | | | |
| mortality | bias | | | | |
| cDDD within 24 | 1.08 (95% CI 0.37- | 0.89 | Excluding events | | |
| months | 3.18) | | within 24 months | | |
| cDDD within 12 | 1.12 (95% CI 0.36- | 0.84 | Excluding events | | |
| months | 3.46) | | within 12 months | | |
| cDDD within 6 | 1.34 (95% CI 0.44- | 0.61 | Excluding events | | |
| months | 4.03) | | within 6 months | | |
| cDDD within 3 | 1.20 (95% CI 0.36- | 0.77 | Excluding events | | |
| months | 3.95) | | within 3 months | | |
| cDDD (no events | 0.91 (9% CI 0.36- | 0.84 | No events | | |
| excluded) | 2.29) | | excluded | | |
| HCC-recurrence | | | | | |
| cDDD within 24 | 0.48 (95% CI 0.0.06- | 0.48 | Excluding events | | |
| months | 3.63) | | within 24 months | | |
| cDDD within 12 | 0.82 (95% CI 0.17- | 0.81 | Excluding events | | |
| months | 4.08) | | within 12 months | | |
| months | 4.08) | | within 12 months | | |

| cDDD within 6 | 0.95 (95% CI 0.19- | 0.95 | Excluding | events | | |
|-----------------|---------------------|------|------------------|--------|--|--|
| months | 4.62) | | within 6 months | | | |
| cDDD within 3 | 1.58 (95% CI 0.37- | 0.58 | Excluding | events | | |
| months | 6.74) | | within 3 months | | | |
| cDDD (no events | 0.59 (95% CI 0.16- | 0.42 | No | events | | |
| excluded) | 2.14) | | excluded | | | |
| HCC-related | | | | | | |
| mortality | | | | | | |
| cDDD within 24 | N/A | N/A | Excluding | events | | |
| months | | | within 24 months | | | |
| cDDD within 12 | 0.90 (95% CI 0.11- | 0.92 | Excluding | events | | |
| months | 7.18) | | within 12 months | | | |
| cDDD within 6 | 1.07 (95% CI 0.14- | 0.95 | Excluding | events | | |
| months | 8.38) | | within 6 months | | | |
| cDDD within 3 | 1.56 (95% CI 0.20- | 0.67 | Excluding | events | | |
| months | 12.09) | | within 3 months | | | |
| cDDD (no events | 0.57 (95% CI 0.073- | 0.59 | No | events | | |
| excluded) | 4.44) | | excluded | | | |

¹ cDDD of statins initiated within 3, 6, 12, 24 months of LT, with the events in the

² corresponding 3,6,12,24 months removed to account of immortal time bias, HCC -

³ Hepatocellular carcinoma. cDDD - Defined daily doses.