|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1. Baseline characteristics of patients.** | | | | | | | | | | | | | | |  | |  | |
|  | | | | | | | Metformin User  (n=13,396) | | | | Metformin Non-User  (n=52,736) | | | | p-value | | STD | |
| Number | | % | | Number | | % | |
| Sex | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | Male | | |  | | | 7681 | | 57.34% | | 25809 | | 48.94% | | <.001 | | 16.89% | |
|  | Female | | |  | | | 5715 | | 42.66% | | 26927 | | 51.06% | |  | | -16.89% | |
| Age 1) | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | 20-29 | | |  | | | 216 | | 1.61% | | 1375 | | 2.61% | | <.001 | | -6.93% | |
|  | 30-39 | | |  | | | 1133 | | 8.46% | | 4204 | | 7.97% | |  | | 1.77% | |
|  | 40-49 | | |  | | | 3064 | | 22.87% | | 9797 | | 18.58% | |  | | 10.61% | |
|  | 50-59 | | |  | | | 3896 | | 29.08% | | 13410 | | 25.43% | |  | | 8.21% | |
|  | 60-69 | | |  | | | 3089 | | 23.06% | | 13024 | | 24.70% | |  | | -3.84% | |
|  | 70-79 | | |  | | | 1601 | | 11.95% | | 8254 | | 15.65% | |  | | -10.74% | |
|  | ≥80 | | |  | | | 397 | | 2.96% | | 2672 | | 5.07% | |  | | -10.73% | |
| Anti-diabetic treatment 2) | | | | | | |  | |  | |  | |  | |  | |  | |
|  | Insulin therapy | | |  | | | 1585 | | 11.83% | | 2228 | | 4.22% | | <.001 | | 28.27% | |
|  | Sulfonylurea | | |  | | | 8253 | | 61.61% | | 8260 | | 15.66% | | <.001 | | 107.02% | |
|  | Other drugs(excluding Metformin) | | |  | | | 4630 | | 34.56% | | 2685 | | 5.09% | | <.001 | | 79.55% | |
| Anti-diabetic treatment 3) | | | |  | | |  | |  | |  | |  | |  | |  | |
| Insulin therapy | | | |  | | | 1439 | | 10.74% | | 3828 | | 7.26% | | <0.01 | | 12.19% | |
| Sulfonylurea | | | |  | | | 7811 | | 58.31% | | 8071 | | 15.30% | | <0.01 | | 99.62% | |
| Other drugs(exclusingMetformin) | | | |  | | | 2651 | | 19.79% | | 2013 | | 3.82% | | <0.01 | | 51.09% | |
| Other comorbidities  2) | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | Malignancy | | |  | | | 581 | | 4.34% | | 4429 | | 8.40% | | <.001 | | -16.69% | |
|  | Malabsorption | | |  | | | 11 | | 0.08% | | 118 | | 0.22% | | 0.001 | | -3.63% | |
|  | Chronic kidney disease | | |  | | | 32 | | 0.24% | | 871 | | 1.65% | | <.001 | | -14.64% | |
|  | Dialysis | | |  | | | 3 | | 0.02% | | 290 | | 0.55% | | <.001 | | -9.89% | |
|  | Gastrectomy | | |  | | | 5 | | 0.04% | | 111 | | 0.21% | | <.001 | | -4.92% | |
|  | HIV/AIDS& Organ Transplantation | | | | | | 11 | | 0.08% | | 126 | | 0.24% | | <.001 | | -3.9% | |
| Immunosuppresives 2) | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | Systemic corticosteroids | | |  | | | 4796 | | 35.80% | | 24924 | | 47.26% | | <.001 | | -23.42% | |
|  | Other immunosuppressants | | | | | | 280 | | 2.09% | | 2015 | | 3.82% | | <.001 | | -10.23% | |
| Immunosuppresives 3) | | | |  | | |  | |  | |  | |  | |  | |  | |
| Systemic corticosteroids | | | |  | | | 6605 | | 49.31% | | 31187 | | 59.14% | | <.001 | | -19.83% | |
| Other immunosuppressants | | | |  | | | 475 | | 3.55% | | 2839 | | 5.38% | | <.001 | | -8.91% | |
| Charlson comorbidity index2) | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | Mean±SD | | |  | | | 2.36 | | 1.71 | | 2.56 | | 1.96 | | <.001 | |  | |
|  | Median(Q1, Q3) | | |  | | | 2 | | (1, 3) | | 2 | | (1, 3) | |  | |  | |
|  | 0-1 | | |  | | | 4645 | | 34.67% | | 17367 | | 32.93% | | <.001 | | 3.68% | |
|  | 2-3 | | |  | | | 5926 | | 44.24% | | 22428 | | 42.53% | |  | | 3.45% | |
|  | ≥4 | | |  | | | 2825 | | 21.09% | | 12941 | | 24.54% | |  | | -8.23% | |
| Healthcare utilization 2) | | | |  | | |  | |  | |  | |  | |  | |  | |
|  | Hospitalization, days | | |  | | |  | |  | |  | |  | |  | |  | |
|  | | Mean±SD | |  | | | 0.340 | | 0.949 | | 0.495 | | 1.263 | |  | |  | |
|  | | Median(Q1, Q3) | |  | | | 0 | | (0, 0) | | 0 | | (0, 1) | |  | |  | |
|  | | 0 | |  | | | 10593 | | 79.08% | | 39000 | | 73.95% | | <.001 | | 12.11% | |
|  | | 1 | |  | | | 1905 | | 14.22% | | 8160 | | 15.47% | |  | | -3.52% | |
|  | | 2~3 | |  | | | 733 | | 5.47% | | 4296 | | 8.15% | |  | | -10.63% | |
|  | | ≥ 4 | |  | | | 165 | | 1.23% | | 1280 | | 2.43% | |  | | -8.93% | |
|  | Outpatient visit, days | | |  | | |  | |  | |  | |  | |  | |  | |
|  | | Mean±SD | |  | | | 17.448 | | 20.793 | | 22.670 | | 24.343 | | <.001 | |  | |
|  | | Median(Q1, Q3) | |  | | | 11 | | (5, 22) | | 16 | | (8, 29) | |  | |  | |
|  | | < 15 | |  | | | 8327 | | 62.16% | | 25994 | | 49.29% | | <.001 | | 26.13% | |
|  | | 16-30 | |  | | | 3065 | | 22.88% | | 14562 | | 27.61% | |  | | -10.91% | |
|  | | 31-50 | |  | | | 1249 | | 9.32% | | 7296 | | 13.83% | |  | | -14.13% | |
|  | | > 50 | |  | | | 755 | | 5.64% | | 4884 | | 9.26% | |  | | -13.84% | |
| Healthcare utilization 3) | | | |  | | |  | |  | |  | |  | |  | |  | |
| Hospitalization, days | | |  | |  | | |  | |  | |  | |  | |  | |
|  | | Mean±SD | |  | | | 0.714 | | 2.243 | | 0.954 | | 2.766 | |  | |  | |
|  | | Median(Q1, Q3) | |  | | | 0 | | (0, 1) | | 0 | | (0, 1) | |  | |  | |
|  | | 0 | |  | | | 9718 | | 72.54% | | 35745 | | 67.78% | | <.001 | | 10.42% | |
|  | | 1 | |  | | | 1967 | | 14.68% | | 8568 | | 16.25% | |  | | -4.33% | |
|  | | 2~3 | |  | | | 1121 | | 8.37% | | 5017 | | 9.51% | |  | | -4.01% | |
|  | | ≥ 4 | |  | | | 590 | | 4.40% | | 3406 | | 6.46% | |  | | -9.07% | |
| Outpatient visit, days | | |  | |  | | |  | |  | |  | |  | |  | |
|  | | Mean±SD | |  | | | 43.556 | | 43.298 | | 47.169 | | 50.329 | | <.001 | |  | |
|  | | Median(Q1, Q3) | |  | | | 33 | | (19, 54) | | 34 | | (17, 60) | |  | |  | |
|  | | < 15 | |  | | | 2620 | | 19.56% | | 12103 | | 22.95% | | <.001 | | -8.30% | |
|  | | 16-30 | |  | | | 3492 | | 26.07% | | 11740 | | 22.26% | |  | | 8.90% | |
|  | | 31-50 | |  | | | 3550 | | 26.50% | | 11836 | | 22.44% | |  | | 9.45% | |
|  | | > 50 | |  | | | 3734 | | 27.87% | | 17057 | | 32.34% | |  | | -9.76% | |
| 1) Age at cohort entry date | | | |  | |  | | |  | |  | |  | |  | |  | |
| 2) Within 1-year prior to index date | | | | | | | | | | | | |  | |  | |  | |
| 3) Within follow-up period (During 2-year from index date or until TB development) | | | | | | | | | | | | |  | |  | |  | |
|  | | | | | | | | | | | | |  | |  | |  | |

**Table 2. Comparison of baseline characteristics in 1:1 matched cohort between metformin user and non-user**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Metformin User**  **(n=12,916)** | | **Metformin Non-User**  **(n=12,916)** | | **P-value** | **STD** |
| **Number** | **%** | **Number** | **%** |
| Sex | |  |  |  |  |  |  |
|  | Male | 7377 | 57.12 | 7378 | 57.12 | 0.990 | -0.02% |
|  | Female | 5539 | 42.88 | 5538 | 42.88 |  | 0.02% |
| Age1) | |  |  |  |  |  |  |
|  | 20-29 | 210 | 1.63 | 174 | 1.35 | <0.001 | 2.30% |
|  | 30-39 | 1086 | 8.41 | 913 | 7.07 |  | 5.01% |
|  | 40-49 | 2932 | 22.70 | 2694 | 20.86 |  | 4.47% |
|  | 50-59 | 3750 | 29.03 | 3611 | 27.96 |  | 2.38% |
|  | 60-69 | 2986 | 23.12 | 3156 | 24.43 |  | -3.09% |
|  | 70-79 | 1559 | 12.07 | 1854 | 14.35 |  | -6.75% |
|  |  | 393 | 3.04 | 514 | 3.98 |  | -5.09% |
| Anti-diabetic treatment2) | |  |  |  |  |  |  |
|  | Insulin therapy | 1319 | 10.21 | 1078 | 8.35 | <0.001 | 6.43% |
|  | Sulfonylureas | 7331 | 56.76 | 7650 | 59.23 | <0.001 | -5.01% |
|  | Other drugs (excluding metformin) | 2190 | 16.96 | 1797 | 13.91 | <0.001 | 8.43% |
| Other comorbidities2) | |  |  |  |  |  |  |
|  | Malignancy | 565 | 4.37 | 615 | 4.76 | 0.136 | -1.85% |
|  | Malabsorption | 11 | 0.09 | 7 | 0.05 | 0.346 | 1.17% |
|  | Chronic kidney disease | 32 | 0.25 | 36 | 0.28 | 0.627 | -0.60% |
|  | Dialysis | 3 | 0.02 | 1 | 0.01 | 0.625 | 1.24% |
|  | Gastrectomy | 4 | 0.04 | 5 | 0.03 | 1.000 | -0.41% |
|  | HIV & Organ transplantation | 14 | 0.11 | 11 | 0.09 | 0.548 | 0.75% |
| Immunosuppresives2) | |  |  |  |  |  |  |
|  | Systemic corticosteroids | 4659 | 36.07 | 4690 | 36.31 | 0.688 | -0.5% |
|  | TNF alpha + Other immunosuppressant | 275 | 2.13 | 268 | 2.07 | 0.761 | 0.38% |
| Charlson comorbidity index2) | |  |  |  |  |  |  |
|  | Mean | 2.34 | 1.70 | 2.24 | 1.75 | <0.001 |  |
|  | Median (Q1,Q3) | 2 | (1,3) | 2 | (1,3) |  |  |
|  | 0-1 | 4511 | 34.93 | 4903 | 37.96 | <0.001 | -6.31% |
|  | 2-3 | 5719 | 44.28 | 5489 | 42.50 |  | 3.59% |
|  |  | 2686 | 20.80 | 2524 | 19.54 |  | 3.13% |
| Healthcare utilization2) | |  |  |  |  |  |  |
|  | Hospitalization, days |  |  |  |  |  |  |
|  | Mean | 0.34 | 0.95 | 0.32 | 0.91 | 0.169 |  |
|  | Median (Q1,Q3) | 0 | (0,0) | 0 | (0,0) |  |  |
|  | 0 | 10237 | 79.26 | 10327 | 79.96 | 0.458 | -1.73% |
|  | 1 | 1818 | 14.08 | 1780 | 13.78 |  | 0.85% |
|  | 2-3 | 701 | 5.43 | 652 | 5.05 |  | 1.70% |
|  |  | 160 | 1.24 | 157 | 1.22 |  | 0.21% |
|  | Outpatient visit, days |  |  |  |  |  |  |
|  | Mean | 17.59 | 20.93 | 16.98 | 20.17 | 0.018 |  |
|  | Median (Q1,Q3) | 11 | (5,22) | 11 | (5,22) |  |  |
|  | 0 | 7986 | 61.83 | 8164 | 63.21 | 0.147 | -2.85% |
|  | 1 | 2968 | 22.98 | 2858 | 22.13 |  | 2.04% |
|  | 2-3 | 1223 | 9.47 | 1191 | 9.22 |  | 0.85% |
|  |  | 739 | 5.72 | 703 | 5.44 |  | 1.21% |

STD: standardized difference;

1) age at cohort entry,

|  |
| --- |
| 2) Within 1-year prior to index date |
| 3) Within follow-up period (During 2-year from index date or until TB development) |

**Table 3. Association between metformin use and the risk of TB development in 1:1 matched cohort**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Tb development** | | | **Univariate** | | | **Adjusted\*** | | |
| **n** | **N** | **%** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| Any Metformin (≥28d within 6mo) |  |  |  |  |  |  |  |  |  |
| Non-user | 40 | 12,916 | 0.31% | ref |  |  | ref |  |  |
| User | 44 | 12916 | 0.34% | 1.10 | 0.72-1.69 | 0.663 | 1.17 | 0.75-1.83 | 0.482 |
| Age1) |  |  |  |  |  |  |  |  |  |
| 20-29 | 1 | 384 | 0.26% | 1 |  |  | 1 |  |  |
| 30-39 | 6 | 1,999 | 0.30% | 1.15 | 0.14-9.59 | 0.894 | 0.81 | 0.26-2.55 | 0.722 |
| 40-49 | 11 | 5,626 | 0.20% | 0.75 | 0.10-5.82 | 0.785 | 0.79 | 0.28-2.29 | 0.669 |
| 50-59 | 23 | 7,361 | 0.31% | 1.20 | 0.16-8.90 | 0.857 | 1.46 | 0.53-4.06 | 0.466 |
| 60-69 | 17 | 6,142 | 0.28% | 1.06 | 0.14-8.00 | 0.952 | 1.77 | 0.64-4.92 | 0.271 |
| 70-79 | 19 | 3,413 | 0.56% | 2.14 | 0.29-16.01 | 0.458 | 2.22 | 0.80-6.18 | 0.126 |
| ≥80 | 8 | 907 | 0.88% | 3.40 | 0.43-27.21 | 0.248 | 2.47 | 0.86-7.09 | 0.093 |
| Sex1) |  |  |  |  |  |  |  |  |  |
| Male | 57 | 14,755 | 0.39% | 1 |  |  | 1 |  |  |
| Female | 27 | 11077 | 0.24% | 0.63 | 0.40-1.00 | 0.048 | 0.77 | 0.59-1.00 | 0.053 |
| Comorbidities3) |  |  |  |  |  |  |  |  |  |
| Malignancy | 11 | 1798 | 0.61% | 2.02 | 1.07-3.80 | 0.030 | 1.24 | 0.61-2.52 | 0.556 |
| HIV/AIDS & Organ Transplantation | 1 | 37 | 2.70% | 8.60 | 1.20-61.77 | 0.032 | 9.36 | 1.16-75.72 | 0.036 |
| Malabsorption | 0 | 51 | 0.00% | 0 | 0 | 0.978 | 0 | 0 | 0.987 |
| Chronic kidney disease | 2 | 243 | 0.82% | 2.57 | 0.63-10.44 | 0.188 | 1.53 | 0.37-6.35 | 0.562 |
| Gastrectomy | 0 | 20 | 0.00% | 0 | 0 | 0.983 | 0 | 0 | 0.995 |
| Immunosuppresives3) |  |  |  |  |  |  |  |  |  |
| Systemic corticosteroids | 42 | 12929 | 0.32% | 1.0 | 0.65-1.53 | 0.990 | 1.31 | 0.81-2.10 | 0.272 |
| Other immunosuppressants | 4 | 938 | 0.43% | 1.33 | 0.49-3.62 | 0.580 | 0.7 | 0.25-2.00 | 0.508 |
| Charlson comorbidity index 3) |  |  |  |  |  |  |  |  |  |
| 0-1 | 26 | 9414 | 0.28 | 1 |  |  | 1 |  |  |
| 2-3 | 32 | 11,208 | 0.29% | 1.03 | 0.62-1.74 | 0.900 | 1.48 | 1.03-2.12 | 0.032 |
| ≥4 | 26 | 5,210 | 0.50% | 1.81 | 1.05-3.12 | 0.033 | 1.60 | 1.07-2.39 | 0.023 |
| Anti-diabetic treatment3) |  |  |  |  |  |  |  |  |  |
| Insulin therapy | 24 | 2,384 | 1.01% | 3.95 | 2.46-6.34 | <.001 | 1.69 | 0.97-2.94 | 0.06 |
| Sulfonylurea | 48 | 13,924 | 0.34% | 1.14 | 0.74-1.76 | 0.552 | 1.19 | 0.75-1.87 | 0.46 |
| Other drugs | 25 | 6,224 | 0.40% | 1.34 | 0.84-2.13 | 0.225 | 1.27 | 0.77-2.08 | 0.34 |
| Healthcare utilization 3) |  |  |  |  |  |  |  |  |  |
| Hospitalization, days |  |  |  |  |  |  |  |  |  |
| 0 | 32 | 18,900 | 0.17% | 1 |  |  | 1 | 1 |  |
| 1 | 26 | 3,713 | 0.70% | 4.15 | 2.47-6.96 | <.001 | 4.59 | 2.63-7.99 | <.001 |
| 2~3 | 18 | 2,069 | 0.87% | 5.16 | 2.89-9.18 | <.001 | 5.51 | 2.85-10.67 | <.001 |
| ≥ 4 | 8 | 1,150 | 0.70% | 4.12 | 1.90-8.93 | <.001 | 3.18 | 1.34-7.56 | 0.001 |
| Outpatient visit, days |  |  |  |  |  |  |  |  |  |
| <15 | 41 | 6,142 | 0.67% | 1 |  |  | 1 | 1 |  |
| 16-30 | 17 | 6,551 | 0.26% | 0.39 | 0.22-0.68 | <.001 | 0.33 | 0.18-0.58 | <.001 |
| 31-50 | 10 | 6,290 | 0.16% | 0.24 | 0.12-0.47 | <.001 | 0.16 | 0.08-0.32 | <.001 |
| > 50 | 16 | 6,849 | 0.23% | 0.35 | 0.20-0.62 | <.001 | 0.17 | 0.09-0.32 | <.001 |

|  |
| --- |
| \* Adjusted for all variables in the table  1) Age at cohort entry date |
| 2) Within 1-year prior to index date |
| 3) Within follow-up period (During 2-year from index date or until TB development) |