|  |  |  |
| --- | --- | --- |
| **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% |
|  | $$\geq 80$$ | 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 $\pm SD$ | 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% |
|  | $$\geq 4$$ | 2686 | 20.80 | 2524 | 19.54 |  | 3.13% |
| Healthcare utilization2) |  |  |  |  |  |  |
|  | Hospitalization, days |  |  |  |  |  |  |
|  | Mean $\pm SD$ | 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% |
|  | $$\geq 4$$ | 160 | 1.24 | 157 | 1.22 |  | 0.21% |
|  | Outpatient visit, days |  |  |  |  |  |  |
|  | Mean $\pm SD$ | 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% |
|  | $$\geq 4$$ | 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 |

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| \* Adjusted for all variables in the table1) 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) |