**Supplementary file**

Table 1 ICD-10 code of bleeding and comorbidity

|  |  |
| --- | --- |
| **Disease** | **ICD-10 code** |
| **Bleeding**  | D62.X01, I60.901, I61.101, I61.102, I61.103I61.104, I61.201, I61.301, I61.302, I61.303, I61.304, I61.401, I61.601, I61.901, I61.501, I61.902, I62.001, I62.102, K29.001, K29.002, K52.903, K06.802, K08.803, K13.711, K14.801, K62.502, K92.001, K92.101, K92.201, K92.202, K92.203, K92.204, K92.205, K92.206, K92.207, K92.208, N 28.809, N 89.702, R04.001, R04.101, R04.201, R04.801, R04.802, R04.901, R23.301, R57.101, R57.803, R58.X01, R58.X02, R58.X03, R58.X05 |
| **Hematological disease** | C81-C96, D65-D69, D60-D64, D47.301 |
| **Liver disease** | K70-K77 |
| **Malignant tumor** | C00-C97 |
| **Sepsis** | A41.9, P36.1, P36.3, P36.8 |
| **Renal failure**  | N17-N19 |

Table 2 Radiotherapy-related medical texts

|  |  |
| --- | --- |
| **Field** | **Medical texts** |
| Radiotherapy | 放疗,放射治疗,放化疗 |
| Treated | 行,予以, 开始, 给予,予 |
| Untreated | 不, 不考虑, 未, 拒绝, 不行, 未行, 不予以, 未给予, 未予,未予以, 不给予, 不予 |

Table 3 Summary of adverse events among patients receiving concomitant medications

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cefoperazone/ sulbactam** | **Cefoperazone/tazobactam** | **Ceftazidime** |
| **n (%)** | **n (%)** | **n (%)** |
| **Patients receiving anticoagulants (N = 11037)** |
| Number of patients  | 6579 (43.6) | 2401 (56.1) | 1288 (36.6) |
| Coagulation disorders | 961 (14.6) | 51 (2.1) | 82 (6.4) |
| PTprolongation | 586 (8.9) | 22 (0.9) | 33 (2.6) |
| Decreased PLT | 1273 (19.3) | 414 (17.2) | 206 (16) |
| Bleeding | 338 (5.1) | 71 (3.0) | 51 (4.0) |
| **Patients receiving vitamin K, hemostatic or coagulation factors (N = 7678)** |
| Number of patients  | 4919 (32.6) | 1271 (29.7) | 1488 (21.1) |
| Coagulation disorders | 795 (16.2) | 89 (7.0) | 110 (7.4) |
| PTprolongation | 486 (9.8) | 48 (3.8) | 50 (3.4) |
| Decreased PLT | 1229 (25.0) | 407 (32.0) | 344 (23.1) |
| Bleeding | 429 (8.7) | 114 (9.0) | 120 (8.1) |
| **Patients receiving antiplatelet drugs (N = 2850)** |
| Number of patients  | 1576 (10.4) | 404 (9.4) | 870 (12.4) |
| Coagulation disorders | 181 (11.5) | 15 (3.7) | 44 (5.1) |
| PTprolongation | 96 (6.1) | 9 (2.2) | 10 (1.1) |
| Decreased PLT | 215 (13.6) | 42 (10.4) | 80 (9.2) |
| Bleeding | 81 (5.1) | 7 (1.7) | 18 (2.1) |

Table 4 Sensitivity analyses using alternative statistical model, comparing cefoperazone/sulbactam vs. cefoperazone-tazobactam

and ceftazidime

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | PT prolongationOR (95%CI) | Coagulation disordersOR (95%CI) | Decreased PLTOR (95%CI) | BleedingOR (95%CI) |
| Cefoperazone/sulbactam vs Cefoperazone/tazobactam (N = 19,377) |
| Traditional logistic regression  |
|  Unadjusted | 2.89 (2.29 to 3.64) | 2.76 (2.32 to 3.27) | 0.81 (0.74 to 0.88) | 1.18 (0.99 to 1.42) |
|  Model 1 | 2.08 (1.63 to 2.66)a | 2.00 (1.67 to 2.41)a | 0.91 (0.82 to 1.00)b | 1.20 (0.99 to 1.46)c |
|  Model 2 | 2.06 (1.61 to 2.64)d | 2.00 (1.66 to 2.40)d | 0.89 (0.80 to 0.98)e | 1.21 (1.00 to 1.48)f |
| Propensity Score Weighting |
|  Model 1 | 1.51 (1.08 to 2.11)a | 1.49 (1.14 to 1.94)a | 0.87 (0.75 to 1.00)b | 0.83 (0.64 to 1.09)c |
| Model 2 | 1.51 (1.08 to 2.11)d | 1.48 (1.13 to 1.94)d | 0.87 (0.76 to 1.01)e | 0.82 (0.63 to 1.08)f |
| Cefoperazone/sulbactam vs Ceftazidime (N =18,613) |
| Traditional logistic regression |
|  Unadjusted | 3.51 (2.66 to 4.62) | 2.62 (2.18 to 3.15) | 1.40 (1.26 to 1.58) | 1.38 (1.12 to 1.71) |
|  Model 1 | 2.36 (1.78 to 3.16)**g** | 1.83 (1.51 to 2.22)**g** | 1.32 (1.17 to 1.50)h | 1.07 (0.85 to 1.34)i |
| Propensity Score Weighting |
|  Model 1 | 2.16 (1.50 to 3.13)**g** | 1.44 (1.13 to 1.82)**g** | 1.08 (0.93 to 1.26)h | 0.81 (0.61 to 1.06)i |

aAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, drugs for treatment of coagulation disorders, anticoagulant drugs, other antibiotics, duration of antibiotics use

bAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy

cAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, anticoagulant drugs, drugs caused bleeding, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy

dAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, anticoagulant drugs, other antibiotics, average daily dose of cefoperazone

eAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, other antibiotics, average daily dose of cefoperazone, chemotherapy or radiotherapy

fAdjusted for sex, age, departments, hospital stays, discharged year, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, anticoagulant drugs, drugs caused bleeding, other antibiotics, average daily dose of cefoperazone, chemotherapy or radiotherapy

gAdjusted for sex, age, departments, hospital stays, discharged year, AKD,CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, anticoagulant drugs, other antibiotics, duration of antibiotics use

hAdjusted for sex, age, departments, hospital stays, discharged year, AKD,CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy

iAdjusted for sex, age, departments, hospital stays, discharged year, AKD,CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, anticoagulant drugs, drugs caused bleeding, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy

Table 5 Baseline characteristics of patients treated with cefoperazone/ tazobactam versus ceftazidime

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Before PS Matching** |  | **After PS Matching** |
|  | **Cefoperazone/ tazobactam** **(N =4,283)** | **Ceftazidime** **(N =3,519)** | **SD** |  | **Cefoperazone/ tazobactam (N =2,451)** | **Ceftazidime** **(N =2,451)** | **SD** |
| **Characteristic** |  |  |  |  |  |  |  |
| Age |  |  |  |  |  |  |  |
| 18-44  | 26.1% | 26.9% | -0.019 |  | 21.5% | 22.9% | -0.033 |
| 45-64 | 31.8 %  | 34.7% | -0.060 |  | 33.5% | 32.7% | 0.016 |
| ≥65 | 42.0% | 38.4% | 0.075 |  | 45.0% | 44.4% | 0.012 |
| Sex |  |  |  |  |  |  |  |
|  Male | 59.7% | 65.8% | -0.127 |  | 61.9% | 62.9% | -0.020 |
|  Female | 40.3% | 34.2% | 0.127 |  | 38.1% | 37.1% | 0.020 |
| **Comorbidities**  |  |  |  |  |  |  |  |
| Hematological disease | 28.9% | 17.1% | 0.283 |  | 19.6% | 19.3% | 0.008 |
| Liver disease | 12.9% | 10.3% | 0.080 |  | 9.0% | 9.8% | -0.028 |
| Malignant tumor | 31.9% | 23.9% | 0.178 |  | 26.6% | 25.4% | 0.026 |
| Chronic kidney disease | 17.5% | 14.2% | 0.090 |  | 15.0% | 14.3% | 0.020 |
| Acute kidney injury | 1.4% | 1.2% | 0.023 |  | 0.8% | 0.7% | 0.015 |
| **Baseline laboratory examination and diagnosis** |
| Coagulation disorders | 14.0% | 14.5% | -0.015 |  | 10.7% | 11.5% | -0.025 |
| Diagnosed bleeding | 2.2% | 2.6% | -0.024 |  | 1.8% | 1.6% | 0.009 |
| **Others** |  |  |  |  |  |  |  |
| Hospital stays≥17 days | 53.0% | 50.3% | 0.054 |  | 55.1% | 52.1% | 0.060 |
| Surgery | 17.0% | 30.2% | -0.315 |  | 15.7% | 14.6% | 0.032 |
| Departments |  |  |  |  |  |  |  |
| Internal medicine | 92.3% | 77.0% | 0.436 |  | 92.9% | 93.1% | -0.006 |
| Surgical department | 6.5% | 21.6% | -0.444 |  | 6.6% | 6.6% | 0.026 |
| ICU | 1.1% | 1.4% | -0.024 |  | 0.5% | 0.3% | 0.026 |
| Duration of antibiotics use |  |  |  |  |  |  |  |
| <7 days | 29.5% | 33.5% | -0.085 |  | 29.9% | 30.0% | -0.001 |
| 7-14 days | 50.7% | 52.0% | -0.025 |  | 52.4% | 53.1% | -0.015 |
| >14 | 19.8% | 14.5% | 0.139 |  | 17.7% | 16.9% | 0.021 |

PS matching variable lists: age, sex, hematological disease, liver disease, malignant tumor, acute kidney disease, chronic kidney disease, coagulation disorders, diagnosed bleeding, departments, hospital stays, surgery, duration of antibiotics use

Table 6 Summary results of unadjusted and adjusted odds ratios (95% CIs) comparing cefoperazone/tazobactam vs ceftazidime

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | PT prolongationOR (95%CI) | Coagulation disordersOR (95%CI) | Decreased PLTOR (95%CI) | BleedingOR (95%CI) |
| Propensity Score–Matched Sample (N =4,902) |
|  Unadjusted | 1.12 (0.70 to 1.80) | 0.93 (0.66 to 1.30) | 1.50 (1.28 to 1.77) | 1.45 (1.05 to 2.01) |
|  Adjusted | 1.09 (0.67 to 1.78)a | 0.76 (0.53 to 1.08)a | 1.34 (1.08 to 1.65)b | 1.14 (0.78 to 1.67)c |
| Propensity Score Weighting (N =7,802) |
| Adjusted | 0.93 (0.62 to 1.40)a | 0.75 (0.57 to 1.01)a | 1.18 (0.98 to 1.42)b | 1.06 (0.77 to 1.45)c |
| Traditional logistic regression (N =7,802) |
|  Unadjusted | 1.21 (0.86 to 1.72) | 0.95 (0.75 to 1.21) | 1.75 (1.54 to 1.99) | 1.17 (0.91 to 1.50) |
|  Adjusted | 0.98 (0.66 to 1.47)a | 0.77 (0.59 to 1.03)a | 1.31 (1.11 to 1.54)b | 1.12 (0.82 to 1.51)c |

aAdjusted for sex, age, departments, hospital stays, AKD, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, anticoagulant drugs, other antibiotics, duration of antibiotics use, discharged year

bAdjusted for sex, age, departments, hospital stays, AKD, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, antiplatelet drugs, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy, discharged year

cAdjusted for sex, age, departments, hospital stays, AKD, CKD, liver disease, malignant tumor, hematological disease, sepsis, sepsis, drugs for treatment of coagulation disorders, drugs, antiplatelet drugs, anticoagulant drugs, drugs caused bleeding, other antibiotics, duration of antibiotics use, chemotherapy or radiotherapy, discharged year