**Supplemental Appendix: Risk Factor Analysis Methods**

*Risk Factor Measurement*

Patient comorbidities were identified using the discharge diagnosis ICD-9-CM (January 2015 – September 2015) and ICD-10-CM (October 2015 – December 2017) codes on each record. Deyo et al. (1992) and Quan et al. (2005) algorithms were adapted to identify components of the Charlson comorbidity index (CCI) score (Supplemental Table 1).1,2 Diagnosis codes for incident events (e.g. acute myocardial infarction) were removed from all component definitions.1 Peripheral vascular disease (PVD) was also excluded due to low incidence (n=201) and both malignancy (solid tumor or metastatic disease) and human immunodeficiency viruses (HIV) were incorporated into the broader classification of immunocompromised.

Immunocompromised patients were identified using the Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines, which are used to determine persons who cannot receive live-attenuated vaccinations.3 Diagnoses of immunosuppressive conditions- which included HIV, neutropenia, organ transplant, and any malignancy- were identified using discharge diagnosis codes; relevant ICD-9-CM codes were identified using the Greenberg et al. (2016)4 algorithm and ICD-10-CM codes were identified using CMS Generalized Equivalence Mappings (GEMS) (Supplemental Table 1). Patients receiving chemotherapeutic agents, corticosteroids, or immune-modulating agents within the first 2 days of their hospitalization were identified using inpatient medications (Supplemental Table 2). Neutropenia was identified using both diagnosis codes and laboratory blood test results within the first 2 hospitalization days (defined as ≥2 WBC counts <500 cells/mm3). Urinary retention was identified through inpatient medication treatment for the condition (Supplemental Table 2).

Severity of illness was captured using the Modified Early Warning Score (MEWS)5,6 and Morse Fall Scale7,8, which are captured and calculated within the UNC Hospitals EMR. The MEWS uses vital signs- specifically systolic blood pressure, heart rate, respiratory rate, temperature, level of consciousness, and hourly urine output (for two hours)- to detect patients at risk for imminent clinical deterioration. The Morse Fall Scale is a simple prediction score designed to identify patients at risk for falling in the hospital. The Morse Fall Scale includes the following variables: history of falling, number of secondary diagnoses, whether ambulatory aid is needed, intravenous therapy/heparin lock, gait, and mental status. For each patient, the first MEWS and Morse Fall Scale score within the first 2 days of admission was captured and categorized using clinically relevant cut points (MEWS: <1 [reference], 2, 3, ≥4; Morse Fall Scale: 0 [reference], 1-24, 25-45, >45). A MEWS ≥4 and a Morse Fall Scale score >45 are both considered indicators of severe illness.

All medications were identified using orders captured in the EMR and receipt was confirmed using the medication administration record (Supplemental Table 2). Urinary retention was captured through treatment for urinary dysfunction (Supplemental Table 2), and urologic procedures were identified using CPT codes 50010 – 53899.

*Inverse-Probability of Missing Weights (IPTW)*

 Due to missing values of BMI (n=15,146, 17%), MEWS (n=18,761, 21%), Morse Fall Scale (n=8,571, 10%), and location/discharge disposition (n=8,482, 10%), inverse-probability of missing weights (IPMW) were calculated.9 Weights were estimated using multivariable logistic regression, which modeled the probability of being a complete case as a function of the following variables: year and season of admission, cause of admission, patient age, sex, Charlson score comorbidities (excluding HIV and cancer), immunosuppression, TPN, target medication usage anytime during hospitalization (antibiotics, antipsychotics, local anesthetics, general anesthetics, benzodiazepines, opioids, alpha-2 agonists, non-steroid anti-inflammatory drugs [NSAIDs], calcium channel blockers, statins, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], histamine-2 agonists, proton pump inhibitors), device use (urinary catheter, ventilator, central venous catheter, peripheral venous catheter), whether they underwent any surgery (CPT 10021 – 69990), and LOS, as well as interaction terms between admission date (year and quarter) and both cause of admission and LOS. Age and LOS were modeled as restricted quadratic splines.10 Because 99% of hospitalizations from January-March 2015 were missing MEWS (28% of all the missing data), all hospitalizations in this time period were excluded from multivariable analysis.

*References*

1. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-619.
2. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-1139.
3. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012;61:816-819.
4. Greenberg JA, Hohmann SF, Hall JB, Kress JP, David MZ. Validation of a method to identify immunocompromised patients with severe sepsis in administrative databases. *Ann Am Thorac Soc* 2016;13:253-258.
5. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. *QJM* 2001;94:521-526.
6. Morgan RJM, Williams F, Wright MM. An early warning scoring system for detecting developing critical illness. *Clin Intensive Care* 1997;8:100.
7. Morse JM, Morse RM, Tylko SJ. Development of a scale to identify the fall-prone patient. *Can J Aging* 1989;8:366-377.
8. Morse JM, Black C, Oberle K, Donahue P. A prospective study to identify the fall-prone patient. *Soc Sci Med* 1989;28:81-86.
9. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2013;22:278-295.
10. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ, Jr. Splines for trend analysis and continuous confounder control. *Epidemiology* 2011;22:874-875.

Supplemental Table 1. Diagnosis codes used to identify comorbidities and immunosuppressive conditions.

|  |  |  |
| --- | --- | --- |
|  | ICD-9-CM code(s) | ICD-10-CM code(s) |
| Comorbiditiesa |  |  |
| History of MI | 412 | I25.2 |
| Congestive heart failure | 428.0 – 428.9 | I50.1 – I50.9 |
| Cerebrovascular disease | 438.0 – 438.9 | I69.00 – I69.998 |
| Dementia | 290.0 – 290.9 | F01.5 – F03.91 |
| Chronic pulmonary disease | 490 – 496, 500 – 505, 506.4 | J40 – J47.9, J60 – J67.9, J68.4 |
| Rheumatic disease | 710.0, 710.1, 710.4, 714.0 – 714.2, 714.81, 725 | M05.00 – M05.9, M06.00 – M06.9 |
| Peptic ulcer disease | 531.4 – 531.7, 532.4 – 532.7, 533.4 – 533.7, 534.4 – 534.7 | K25.4 – K25.7, K26.4 – K26.7, K27.4 – K27.7, K28.4 – K28.7 |
| Mild liver disease | 571.2, 571.4 – 571.6 | K70.30, K70.31, K74.0, K74.3, K74.4, K74.5, K74.60, K74.69 |
| Moderate or severe liver disease | 572.2 – 572.8 | K72.10, K72.90, K72.91, K76.6, K76.7 |
| Diabetes without chronic complications | 250.0 – 250.3, 250.7 | E10.10, E10.11, E10.61 – E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.61 – E11.69, E11.8, E11.9, E12.00, E12.01, E12.10, E12.11, E12.61 – E12.69, E12.8, E12.9, E13.00, E13.01, E13.10, E13.11, E13.61 – E13.69, E13.8, E13.9, E14.00, E14.01, E14.10, E14.11, E14.61 – E14.69, E14.8, E14.9 |
| Diabetes with chronic complication | 250.4 –250.6 | E10.21 – E10.29, E10.31 – E10.39, E10.40 – E10.49, E10.51 – E10.59, E10.71 – E10.79, E11.21 – E11.29, E11.31 – E11.39, E11.40 – E11.49, E11.51 – E11.59, E11.71 – E11.79, E12.21 – E12.29, E12.31 – E12.39, E12.40 – E12.49, E12.51 – E12.59, E12.71 – E13.79, E13.21 – E13.29, E13.31 – E13.39, E13.40 – E13.49, E13.51 – E13.59, E13.71 – E13.79, E14.21 – E14.29, E14.31 – E14.39, E14.40 – E14.49, E14.51 – E14.59, E14.71 – E14.79 |
| Hemiplegia or paraplegia | 342.0 – 342.9, 344.1 | G81.0 – G82.54 |
| Renal disease | 582.0 – 582.9, 583.0 – 583.7, 585.1 – 585.9, 586, 588.0 – 588.9 | N03.0 – N03.9, N05.0 – N05.9, N18.1 – N18.9, N19, N25.0 – N25.9 |
| Immunosuppressive conditions |  |  |
| HIV/AIDS | 042, 079.53 | B20 |
| Neutropenia | 288.00 – 288.9 | D70.0 – D70.9 |
| Organ transplant | 996.80 – 996.99, V42.0 – V42.9 | T86.00 – T86.99, Z94.0 – Z94.9 |
| Hematological malignancy | 200.0 – 208.92 | C81. 00 – C96.9 |
| Solid malignancy | 140.0 – 199.2, 209.0 – 209.79, 235.0 – 239.9 | C00.0 – C80.2, C7A, C7B, D37.01 – D49.9 |
| Rheumatologic/inflammatory condition | 135, 277.30 – 277.39, 340, 341.0 – 341.9, 357.0 – 357.9, 422.0 – 422.99, 446.0 – 446.7, 495.9, 516.0 – 516.9, 555.0 – 558.9, 695.4, 710.0 – 712.99, 714.0 – 714.9, 720.0 – 720.9 | D86.0 – D86.9, E10.40, E10.42, E11.40, E11.42, E12.40, E12.42, E13.40, E13.42, E14.40, E14.42, E85.0 – E85.9, G35, G36.0 – G36.9, G61.0 – G65.2, I40.0 – I40.9, I41, J67.9, J84.01 – J84.09, K50.00 – K52.9, K55.0 – K55.9, L93.0, L93.2, M00.00 – M00.9, M01.X0 0 M01.X9, M02.10 – M02.19, M02.30 – M02.39, M04.1, M05.00 – M05.9, M06.00 – M06.9, M08.00 – M08.99,M11.00 – M11.9, M12.00 – M12.09, M30.0 – M30.8, M32.0 – M34.9, M35.00 – M35.3, M35.8, M35.9, M45.0 – M46.1, M46.50 – M46.59, M46.80 – M46.99, M49.80 – M49.89 |
| Other immune conditions | 279.0 – 279.9, 288.0 – 288.2, 288.50 – 279.59, 288.8, 288.9, 288.00 – 288.9, 289.83, 289.89, 289.9, 795.71, 795.79 | D47.4, D71, D72.0, D72.810 – D72.819, D72.89, D72.9, D75.81, D75.89, D75.9, D80.0 – D80.9, D89.2, R75, R76.0, R76.8, R76.9 |
| Cause of admission |  |  |
| Trauma | 800.0 – 959.9 | S00.00XA – T34.99XS, T79.0XXA – T79.9XXS |
| Urologic diseaseb | 590.0 – 599.9, 996.64, 997.5 | N10 – N13.9, N16, N20.0 – N22, N28.0 – N37, N39.0 – N39.9, N99.0 – N99.89, T83.510 – T83.598SR80.2 |
| Abbreviations; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical modification; ICD-10-CM, International Classification of Diseases, 10th edition, Clinical modification; CCI, Charlson Comorbidity Index; MI, myocardial infarction: HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndromea Only codes which could be applied to the index hospitalization were used; e.g. history of MI (ICD-9-CM 412) was included, but acute MI (ICD-9-CM 410-410.92) was excludedb Captured by assessing admitting diagnoses (DX1) only |

Supplemental Table 2. Generic medication names used to classify medications of interest.

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| --- | --- |
|  | Generic medication name(s) |
| Antibiotics, systemic |  |
| β-lactams | Amoxicillin, Ampicillin, Benzathine penicillin, Dicloxacillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, PiperacillinCefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefepime, Cefixime, Cefotetan, Cefoxatime, Cefoxitin, Cefpodoxime, Ceftriaxone, Ceftaroline, Ceftazidime, Cefuroxime, Cephalexin, Cepodoxime proxetilAztreonam Ertapenem, Imipenem, MeropenemAvibactam, Clavulanic acid, Sulbactam Ampicillin/Sulbactam, Amoxicillin/Clavulanate, Ceftolozane/tazobactam, Piperacillin/TazobactamColistin (colistamethate sodium), Daptomycin, Ethambutol, Isoniazid, Polymyxin B, Pyrazinamide, Metronidazole  |
| Aminoglycosides | Amikacin, Gentamicin, Neomycin, Paromomycin, Tobramycin |
| Chloramphenicol | Chloramphenicol |
| Glycopeptides | Telavancin, Vancomycin |
| Macrolides | Azithromycin, Clarithromycin, Erythromycin, Fidaxomicin, Telithromycin |
| Oxazolidinones | Linezolid, Tedizolid  |
| Quinolones | Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin |
| Rifaximin | Rifaximin |
| Sulfonamides | Sulfadiazine, Sulfamethoxazole, Trimethoprim  |
| Tetracyclines | Doxycycline, Minocycline, Rifampin, Tetracycline, Tigecycline |
| Lincosamides | Clindamycin |
| Lipopeptides | Daptomycin |
| Nitrofurans | Nitrofuratoin |
| Anesthetics |  |
| General | Etomidate, Ketamine, Midazolam, Propofol |
| Local | Benzocaine, Bupivacaine, Chloroprocaine, Lidocaine, Ropivacaine, Tetracaine |
| Anticholinergics  |  |
| Antipsychotics/neuroleptics | Amitriptyline, Aripiprazole, Chlorpromazine, Clozapine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lurasidone, Nortriptyline, Olanzapine, Paliperidone, Paroxetine, Perphenazine, Prochlorperazine, Promazine, Promethazine, Protriptyline, Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone |
| Other | Amantadine, Atropine, Baclofen, Benztropine, Carisoprodol, Cetirizine, Chlorpheniramine, Colchicine, Cyclobenzaprine, Cyproheptadine, Dexchlorpheniramine, Dicyclomine, Digoxin, Diphenhydramine, Diphenoxylate, Darifenacin, Fesoterodine, Hydroxyzine, Hyoscyamine, Loperamide, Loratadine, Meclizine, Pseudoephedrine, Ranitidine, Scopolamine, Solifenacin, Tizanidine, Tolterodine, Trospium |
| Benzodiazepines | Alprazolam, Chlordiazepoxide, Clobazam, Clomipramine, Clonazepam, Clorazepate, Diazepam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Temazepam |
| Opioids | Buprenorphine, Codeine, Fentanyl, Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Sufentanil, Tapentadol, Tramadol |
| Urinary dysfunction medication | Doxazosin, Tadalafil, Tamsulosin, Tarazosin |
| Immunosuppressive medications |  |
| Chemotherapeutic agents (alkylating) | Bendamustine hydrochloride, Busulfan, Carmustine, Cyclophosphamide, Darabazine, Ifosfamide, Melphalan, Thiotepa |
| Chemotherapeutic agents (antibiotics) |  Bleomycin sulfate, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin |
| Chemotherapeutic agents (antimetabolites) | Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Pentostatin |
| Chemotherapeutic agents (antimitotics) |  Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine |
| Chemotherapeutic agents (monoclonal antibodies) | Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab,  Ofatumumab, Rituximab |
| Chemotherapeutic agents(other) | Aldesleukin, Arsenic trioxide, Asparaginase, Azacitidine, Brentuximab vedotin, Bortezomib, Carboplatin, Carfilzomib, Cisplatin, Dasatinib, Decitabine, Erlotinib, Etoposide, Everolimus, Imatinib, Irinotecan, Lapatinib, Mitoxantrone, Nelarabine, Nilotinib, Oxaliplatin, Pazopanib, Pegaspargase, Pralatrexate, Procarbazine, Romidepsin, Sorafenib, Sunitinib, Temozolomide, Temsirolimus, Topotecan, Tretinoin, Vorinostat |
| Immune-modulating agents | Abatacept, Adalimumab, Alefacept, Anakinra, Azathioprine, Basiliximab, Belatacept, Belimumab, Certolizumab pegol, Cyclosporine, Daclizumab, Denosumab, Eculizumab, Efalizumab, Etanercept, Fingolimod, Glatiramer, Golimumab, Infliximab, Interferon alfa-2a, Interferon alfa-2b, Interferon alfa-n3, Interferon alfacon-1, Interferon beta-1a, Interferon beta-1b, Interferon gamma-1b, Leflunomide, Lenalidomide, Muromonab-CD3, Mycophenolate acid, Mycophenolate mofetil, Natalizumab, Palifermin, Palivizumab, Pomalidomide, Pegademase bovine, Peginterferon alfa-2a, Peginterferon alfa-2b, Sirolimus, Tacrolimus, Tocilizumab, Ustekinumab |
| Systemic corticosteroids | Betamethasone, Budesonide, Dexamethasone, Methylprednisolone, Prednisolone, Triamcinolone |