Validation of Acute Outcomes Among Patients With Type 2 Diabetes Mellitus in US Medicare: A Pilot Study

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BACKGROUND

- A major limitation of administrative claims databases is the lack of detailed clinical and laboratory information, which may be necessary to correctly classify outcomes, particularly acute events.
- Outcome validation is often required in postauthorization drug safety studies conducted in medical record or insurance claims databases to evaluate and quantify possible outcome misclassification.
- In an ongoing postauthorization drug safety study, we conducted a pilot assessment in the United States (US) Medicare claims database to evaluate the positive predictive performance of algorithms to identify acute outcomes among individuals with type 2 diabetes mellitus who initiated an antidiabetic drug.

OBJECTIVE

- To estimate the positive predictive values (PPV) of claims algorithms for hospitalizations for acute kidney injury (AKI), hospitalizations for acute liver injury (ALI), and severe complications of urinary tract infection (UTI).

METHODS

- Eligible patients:
  - The study population included enrolled beneficiaries of fee-for-service US Medicare, aged ≥ 65 years, and initiating an antidiabetic drug from January 1, 2014 to December 31, 2015.
  - Patients were prescribed the study drug, dapagliflozin (a sodium-glucose co-transporter-2 [SGLT2] inhibitor), or another oral antidiabetic drug (i.e., dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, thiazolidinediones, or alpha glucosidase inhibitors).
- We used prespecified algorithms (Figure 1) to identify AKI, ALI, and UTI cases in claims data. The validation process is outlined in Figure 2, and the clinical case definitions for AKI, ALI, and UTI are outlined in Table 1.
- PPVs and 95% confidence intervals (CI) were estimated in three ways depending on assumptions about postreview provisional cases (i.e., patients with insufficient information to confirm as a case or a noncase):
  - (1) PPV 1: The proportion of confirmed cases among all cases included in the adjudication review, assuming all postreview provisional cases are noncases (worst-case scenario)

$$PPV\ 1 = \frac{Confirmed\ cases}{All\ reviewed\ cases}$$

  - (2) PPV 2: The proportion of confirmed cases among only cases where a definitive case status was assigned (i.e., confirmed cases and confirmed noncases)

$$PPV\ 2 = \frac{Confirmed\ cases}{(Confirmed\ cases + Confirmed\ noncases)}$$

  - (3) PPV 3: The proportion of confirmed cases and postreview provisional cases among all cases included in the adjudication review, assuming all postreview provisional cases are confirmed cases (best-case scenario)

$$PPV\ 3 = \frac{(Confirmed\ cases + Postreview\ provisional\ cases)}{All\ reviewed\ cases}$$

Figure 1. Claims Algorithms for Hospitalizations for Acute Kidney Injury or Acute Liver Injury, and Severe Complications of Urinary Tract Infection

Acute Kidney Injury

- An inpatient hospitalization with an ICD-9-CM[a] or ICD-10-CM[b] diagnosis code for AKI in any diagnosis position.

Acute Liver Injury

1. An inpatient hospitalization with an ICD-9-CM[c] or ICD-10-CM[b] diagnosis code for ALI in any diagnosis position.

   OR

2. An inpatient hospitalization with an ICD-9-CM[c] procedure code, ICD-10-PCS[b] code, or HCPCS[c] code for liver transplantation.

Severe Complication of Urinary Tract Infection

Pyelonephritis

An inpatient hospitalization or emergency department visit (outpatient record with revenue center code[d] values of 0450-0459 or 0981) with an ICD-9-CM[e] or ICD-10-CM[b] diagnosis code for pyelonephritis in any diagnosis position.

Urosepsis

1. Sepsis diagnosis: An inpatient hospitalization or emergency department visit (outpatient record with revenue center code[d] values of 0450-0459 or 0981) with an ICD-9-CM[f] or ICD-10-CM[b] diagnosis code for sepsis in any diagnosis position.

   AND

2. UTI diagnosis: A visit to any place of service with an ICD-9-CM[g] diagnosis code or ICD-10-CM[b] diagnosis code for UTI in any position with a visit date within 7 days before or after the sepsis date.

HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; ICD-10-PCS = International Classification of Diseases, 10th Revision, Procedure Coding System; ResDAC = Research Data Assistance Center.

[a] AKI ICD-9-CM diagnosis codes: 584.5, 584.6, 584.7, 584.8, 584.9.

[b] ICD-10-CM and ICD-10-PCS codes were used for events on or after 1 October 2015. ICD-10-CM and ICD-10-PCS code lists were generated using CMS-based mapping to the ICD-9-CM codes and clinical review.

[c] ALI ICD-9-CM diagnosis codes: 572.2, 570, 572.4, 573.3, 573.8, 996.82, V42.7, 782.4; ALI ICD-9-CM procedure codes: 50.5, 50.51, 50.59; ALI CPT codes (HCPCS): 47133, 47135, 47136, 47143, 47144, 47145, 47146, 47147.

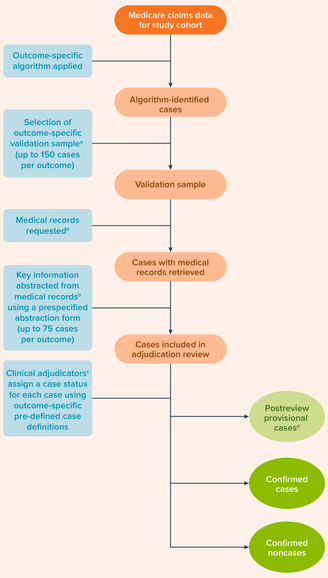
[d] Revenue center codes used by the Centers for Medicare and Medicaid Services are copyrighted by the American Hospital Association.[1]

[e] Pyelonephritis ICD-9-CM diagnosis codes: 590.10, 590.11, 590.80, 590.81.

[f] Sepsis ICD-9-CM diagnosis codes: 038.0, 038.10, 038.11, 038.12, 038.19, 038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 995.91, 995.92, 790.7, 785.52, 003.1, 020.2, 036.2.

[g] UTI ICD-9-CM diagnosis codes: 099.40, 099.41, 099.49, 595.0, 597.0, 597.8, 597.81, 597.89, 599.0, 601.0, 601.1, 601.3, 601.9, 634.7, 634.71, 634.72, 635.7, 635.71, 635.72, 636.7, 636.71, 636.72, 637.7, 637.71, 637.72, 638.7, 639.8, 646.6, 646.61, 646.62, 646.63, 646.64.

Figure 2. Validation Process: Sample Selection, Medical Record Request and Abstraction, and Adjudication Review



[a] It was planned to sample an equal number of algorithm-identified cases (≥ 75) from the dapagliflozin group and the comparator group for each outcome. However, because fewer than 75 cases for each outcome were identified by the algorithm in the dapagliflozin group, all such cases were selected into the validation sample.

[b] Medical record requests and abstractions were conducted by a third-party vendor.

[c] Two clinical adjudicators independently reviewed information on each algorithm-identified case to assign case status. Disagreements between the two clinical adjudicators were resolved through discussion among an adjudication committee consisting of three clinical adjudicators.

[d] Insufficient information to assign a case status.

Table 1. Clinical Case Definitions for Hospitalizations for Acute Kidney Injury or Acute Liver Injury, and Severe Complications of Urinary Tract Infection

Outcome	Criteria for Confirmed Cases	Source
Acute kidney injury	1. Hospital discharge diagnosis of AKI and 2. Increases in serum creatinine at or within 72 h of hospital admission and 3. No recorded diagnosis of chronic kidney disease before cohort entry	Based on prior epidemiological research and on a subset of the RIFLE[a] criteria proposed by the Acute Dialysis Quality Initiative[2]
Acute liver injury	1. Recorded hospitalization of ALI and 2. ≥ 1 elevated liver enzyme test (ALT, AP, TB) within 26 wks before or within 48 h of hospital admission and 3. No chronic liver disease, hepatic or pancreatic cancer, or alcoholism before cohort entry	Based on guidance published by the FDA[3] and criteria proposed by Navarro et al., 2006[4]
Severe complications of urinary tract infection	Hospitalization or emergency department visit for pyelonephritis or urosepsis and met the other criteria for pyelonephritis or urosepsis	
Pyelonephritis	A confirmed case met Criterion 1 and either Criterion 2 or 3: 1. ≥ 2 symptoms: fever, dysuria, flank pain or costovertebral angle tenderness, leukocytosis or WBC count > 12,000/mm^3, abnormal urine 2. ≥ 1 imaging test (CT, MRI, or ultrasonography) indicating either renal inflammation, renal abscess, or hydronephrosis 3. ≥ 1 positive blood and/or urine culture test[b]	Patkar et al., 2009[5]
Urosepsis	1. Diagnosis of UTI and/or infection of male genital organs within 1 week of hospital admission for sepsis and 2. Either proof of bacteremia or clinical suspicion of sepsis and 3. ≥ 2 symptoms: fever, tachycardia, tachypnea, respiratory alkalosis, leucocytes ≥ 12,000 per µL or ≤ 4,000 per µL or band forms > 10%	Wagenlehner et al., 2008[6]

ALT = alanine transaminase; AP = alkaline phosphatase; CT = computed tomography; h = hours; MRI = magnetic resonance imaging; TB = total bilirubin; WBC = white blood cell; wks = weeks.

[a] The components of the RIFLE classification system for acute renal failure includes Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.

[b] A positive culture test includes any of the following: (1) blood cultures and urine cultures positive for the same organism; (2) blood cultures positive for gram-negative organisms, *Enterococcus* species, or *Staphylococcus saprophyticus*; (3) urine culture positive for > 100,000 gram-negative organisms, *Enterococcus* species, or *S. saprophytic*; (4) urine culture positive for < 100,000 any organism and patient treated for ≥ 7 days with antibiotics.

RESULTS

Table 2. Disposition of Requested Medical Records and Adjudicated Cases

	AKI	ALI	UTI[b]
Validation sample			
Medical records requested, n	150	59	150
Medical records retrieved, n (%)[b]	94 (63)	45 (76)	80 (53)
Adjudication review			
Medical records included in adjudication review, n[c]	75	38	75
Cases with sufficient information to assign case status, n (%)[d]	60 (80)	36 (95)	65 (87)
Confirmed cases, n (%)[e]	35 (58)	20 (56)	51 (79)
Confirmed noncases, n (%)[e]	25 (42)	16 (44)	14 (22)
Medical records with insufficient information to assign case status (post-review provisional cases), n (%)[d]	15 (20)	2 (5)	10 (13)

[a] Includes hospitalizations or emergency department visits for urosepsis and/or pyelonephritis after a diagnosis of UTI.

[b] Percentage among cases with medical cases requested.

[c] For this pilot assessment, up to 75 cases were included in the adjudication review for each outcome based on the number of algorithm-identified cases and the number of cases for whom medical records were retrieved. Only medical records that were retrieved prior to initiating adjudication review were included in the adjudication review (for the ALI outcome, 7 additional records were retrieved after the adjudication period initiated).

[d] Percentage among cases included in adjudication review.

[e] Percentage among cases included with definitive case status.

Table 3. Positive Predictive Values of Algorithms for Adjudicated Cases

PPV Estimation Approach	AKI	ALI	UTI[d]
PPV 1,[a] % (95% CI)	46.7 (35.1-58.6)	52.6 (35.8-69.0)	68.0 (56.2-78.3)
PPV 2,[b] % (95% CI)	58.3 (44.9-70.9)	55.6 (38.1-72.1)	78.5 (66.5-87.7)
PPV 3,[c] % (95% CI)	66.7 (54.8-77.1)	57.9 (40.8-73.7)	81.3 (70.7-89.4)

CI = confidence interval; PPV = positive predictive value.

[a] PPV 1: Numerator is confirmed cases; denominator is the sum of all algorithm-identified cases included in the adjudication review.

[b] PPV 2: Numerator is confirmed cases; denominator is the sum of confirmed cases and confirmed noncases. Postreview provisional cases (insufficient information to assign case status) are excluded from the numerator and denominator.

[c] PPV 3: Numerator is the sum of confirmed cases and postreview provisional cases; denominator is the sum of all algorithm-identified cases included in the adjudication review.

[d] Includes hospitalizations or emergency department visits for urosepsis and/or pyelonephritis after a diagnosis of UTI.

DISCUSSION

- The PPV values for AKI observed in our study are consistent with other comparable algorithms in the literature (previously reported PPVs of 44.5%-48.1%)[7,8] but are lower than stricter case definitions.[9]
- Previously published ALI algorithms yield highly variable PPV values and are not directly comparable with our algorithm because of differences in algorithm components and definitions.[9-11]
- To our knowledge, there are no published algorithms with validation results for our UTI outcomes of pyelonephritis or urosepsis.

Limitations

- Classification as a confirmed case or noncase during adjudication review required laboratory results for each outcome (e.g., serum creatinine levels for AKI, liver enzymes for ALI, and blood/urine cultures for pyelonephritis and urosepsis). A definitive case status could not be determined in some instances because of a lack of laboratory data; these cases were classified as postreview provisional cases.

CONCLUSIONS

- In this pilot validation study, claims algorithms resulted in moderate PPVs for identifying hospitalizations for AKI, ALI, or severe complications of UTI among older patients with type 2 diabetes in US Medicare, with considerable variability across outcomes in PPV estimates.

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