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Diabetes Mellitus is Associated with Worse Outcome in Patients Hospitalized for Asthma

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Title: Diabetes Mellitus is Associated with Worse Outcome in Patients Hospitalized for Asthma

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Abstract

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Background: Asthma is a prevalent disease with high economic cost. Over 50% of its direct cost relates to asthma hospitalizations. Diabetes mellitus (DM) is a significant comorbidity in asthmatic patients, yet its impact on asthma-related hospitalizations is unknown.

Objective: To compare the outcome of asthma-related hospitalizations in patients with and without DM.

Methods: Using Healthcare Cost and Utilization Project Nationwide Readmissions Database, we analyzed data of all adults with index admission for asthma and with no other chronic pulmonary conditions, and compared outcomes between patients with and without DM. Weighted regression analysis was used to determine the impact of DM on hospitalization outcomes. All multivariate regression models were adjusted for patient demographics, socioeconomic status and chronic medical comorbidities.

Results: A total of 717,200 asthmatic patients were included, with 202,489 (28.3%) had DM. Diabetic patients were older and had more comorbidities. When hospitalized for asthma, diabetic patients had increased hospital length of stay, cost, and risk for 30-day all-cause and asthma-related readmission. They also had a higher risk for developing non-respiratory complications during their hospital stay compared to non-diabetics. The risk of mortality was similar between the two groups.

Conclusion: Patients hospitalized for asthma with coexisting DM had increased hospital length of stay, cost, and risk for readmission. Interventions are urgently needed to reduce the risk for hospital admission and readmission in patients with co-existing DM and asthma. These interventions would have profound economic and societal impact.

Highlights

What is already known about this topic?

Diabetes Mellitus and asthma frequently co-exist and are closely related. Diabetes, via augmented systemic inflammation, likely worsens asthma disease severity. Conversely, certain asthma treatments including corticosteroid negatively impact diabetic control.

What does this article add to our knowledge?

When hospitalized for asthma, patients with co-existing diabetes had longer length of stay, higher cost, and were more likely to be readmitted within 30 days of discharge when compared to patients without diabetes.

How does this study impact current management guidelines?

Patients with co-existing asthma and diabetes likely constitute a under-recognized high-risk group for asthma hospitalization and related adverse outcomes. Dedicated research and innovative management strategies for this group are urgently needed.

Key words: asthma, diabetes mellitus, length of stay, cost, readmission

Abbreviations

COPD: chronic obstructive pulmonary disease

T2DM: type 2 diabetes mellitus

AIDS: acquired immune deficiency syndrome

Introduction

Asthma, a common disease, is associated with significant morbidity and cost to society. The burden of asthma is rising both nationally and globally. In the US, asthma prevalence steadily increased from 3.6% in 1980 to 8.4% in 2010; asthma was responsible for 479,300 hospitalizations in 2009 (1) and resulted in over \$2 billion aggregate cost (2). Hospitalization is one of the major drivers of the direct economic cost in asthma (3,4).

Diabetes mellitus (DM), another significant public health concern, affects 14% of the US population (5). DM can co-exist with asthma, and cumulative evidence points towards a close, bidirectional relationship between DM and asthma. For example, patients with DM have higher asthma prevalence, severity and risk for exacerbations (6,7); conversely, patients with asthma have higher incidence of type 2 DM independent of body mass index (BMI) (8). Despite the close interaction between DM and asthma, studies are scarce on the outcomes of these patients when they are hospitalized for asthma. One study showed that, amongst patients hospitalized for asthma, concurrent DM was associated with higher hospital admission cost. However, the study did not adjust for chronic medical conditions (9). Another study showed that following an index admission for asthma, patients with uncomplicated DM had higher risk of 30-day all-cause readmission after adjusting for other chronic medical conditions (OR [95% CI] 1.13 [1.05-1.21]; $p < 0.001$); yet the study failed to show similar association between DM with diabetic complications and risk of readmission (OR [95% CI] 0.97 [0.93-1.01]; $p = 0.18$) (10). In addition, these studies are not readily generalizable to a wider US population due to limitations in study design and relatively small sample size (9,10).

In this study, we used a large, nationally representative database to characterize asthma related admissions in patients with coexisting DM. We hypothesized that, amongst adult patients hospitalized for asthma, the presence of DM is associated with longer hospital length of stay (LOS), higher hospital cost, and higher 30-day readmission risk after discharge.

Methods

Study Design and Setting

We analyzed data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Readmissions Database (NRD). The HCUP is a family of health-care databases developed through a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP includes the largest collection of longitudinal hospital care data in the United States, with all-payer, encounter-level information. As part of HCUP, NRD contains data from 18 million discharges per year in the dataset and estimates roughly 36 million discharges nationwide after weighting (11). Readmission data for all patients regardless of the expected payer at admission (e.g. Medicare, private insurance, self-pay) for the hospital stay were included (12). Data from 2012 through 2015 were used. The study period was chosen for the consistency of using the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis in the database. A data user agreement was signed with AHRQ.

Study Population

We included all adult patients (age 18 years and older) in NRD with a principle admission diagnosis (DX1) of asthma (ICD-9-CM 493.xx and ICD-10-CM J45.xx on the 4th quarter of 2015), or a principle admission diagnosis of respiratory failure (HCUP Clinical

Classification Software [CCS] code: 131 (13)) and secondary diagnosis of asthma. The index admission was defined as the first admission during a particular year with the above diagnoses. Patients were excluded if they had pneumonia, or any chronic pulmonary conditions other than asthma [Table E1]. Patient with dual diagnoses of COPD and asthma were also excluded. To analyze 30-day readmissions, we excluded patients who died during index admission, or were discharged during December.

Measurements

The database contains information on patient characteristics, including demographics (age and sex), socio-economic status (estimated household income, primary insurance type), medical conditions (ICD-9-CM diagnoses, medical comorbidities at admission), hospital length of stay (LOS) and total charge of the admission. The HCUP Cost-to-Charge Ratio (CCR) Files were used to translate reported hospital admission charges into actual costs (14). Costs were then inflated to 2015 USD using the Gross Domestic Product (GDP) price index (15).

Exposure

The exposure variable was patient's status of DM at index admission. Patients with DM were further divided into DM without chronic complication (HCUP CCS code: 49) or DM with chronic complications (HCUP CCS code: 50).

Outcome Measures

The outcome variables include LOS, hospital admission cost, in-hospital mortality rate, acute complications during both index and re-admissions, and the readmission rate within 30 days of discharge from index admission. The acute complications during hospitalization included acute respiratory failure, sepsis, shock, acute kidney injury (AKI), delirium, encephalopathy and stroke.

Statistical analysis

Analytic sample weights (discharge-level weight: DISCWT) were used for the following analysis according to published HCUP-NRD guidelines (16) to create national estimates. Descriptive statistics, including medians [interquartile range] (IQR) and percentages, were computed. Unadjusted comparison of subjects with DM vs. those without was done using t-tests for continuous variables and chi-square tests for categorical variables. Weighted regression analysis was used to determine the impact of having DM on hospitalization outcomes. Weighted logistic regression was used for binary outcomes (respiratory failure, sepsis, shock, acute kidney injury [AKI], encephalopathy, stroke, in-hospital death, and 30-day readmission); weighted odds ratios with 95% confidence intervals are presented. Continuous outcomes (length of stay and costs) were analyzed using weighted linear regression. Length of stay and costs were log-transformed and the exponential of the slope parameter and corresponding 95% confidence interval are presented. When using a natural logarithmic transformation on the outcome variable in linear regression, the exponential of the slope ($\exp(\beta)$) is interpreted as a relative change in the outcome. All models included alcohol and tobacco misuse, age, gender, primary insurance type, predicted median household income per zip code, AIDS, iron deficiency anemias, rheumatoid arthritis/collagen vascular diseases, chronic blood loss anemia, congestive heart failure, coagulopathy, depression, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity (as determined by ICD-9-CM code), paralysis, peripheral vascular disorders, psychoses, renal failure, solid tumor without metastasis, peptic ulcer disease (excluding bleeding), valvular disease, weight loss, hospital size, hospital location (rural vs.

urban) and other hospital characteristics (private vs. public, teaching vs. non-teaching). Information on other risk factors for severe asthma such as allergic rhinitis, gastroesophageal reflux disease, and race were not available; therefore, these variables were not included in the analysis. All tests were two-tailed and performed at a significance level of 0.05. Analyses were performed using the SURVEY package in R (R Foundation for Statistical Computing, Vienna, Austria).

Missing data

Patients with missing median household income national quartile (missing: 1.6%), hospital location (missing: 0.29%), or primary expected payer (missing: 0.17%) were excluded from the analysis. However, patients with missing outcome variables including in-hospital death (missing: 0.03%), length of stay (missing: 0.006%) or total charges/costs (missing: 1.2%) were excluded from the analysis of that outcome variable only.

Results

Patient Characteristics at time of Index admission

There were 717,200 patients meeting our inclusion criteria. The majority (70.2%) of these patients were women, with mean (SE) age of 55.4 (0.1) years. Among them, 202,489 (28.3%) patients had diabetes, including 174,666 (24.4%) with uncomplicated DM (U-DM), and 27,823 (3.9%) with DM and diabetic complications (CX-DM). Patients with DM were older, more likely to be female, and had more chronic medical conditions such as obesity, congestive heart failure (CHF), hypertension (HTN), and depression. This comorbidity burden was reflected by the higher number of diagnosis at discharge (NDX) and higher diagnosis related group (DRG) severity and mortality risk scores in patients with DM. In contrast, DM was associated with a lower rate of alcohol or tobacco misuse ($p < 0.001$) [Table 1].

Characteristics of Index Admissions

Diabetes was associated with increased hospital length of stay and cost.

Within the entire study cohort, the weighted median [IQR] of hospital LOS for the index admission was 3 [2 - 4] days, with an weighted median [IQR] cost of \$5,343 [3,501 - 8,414]. Compared to patients without DM, patients with DM had longer LOS and higher cost. Moreover, the presence of diabetic complications was associated with further increase in LOS and cost; compared to patients without DM, patients in CX-DM group had an average increase of 1 day in hospital and 41% increase in hospital cost (or \$2,075f additional) [Table 2].

Using a multivariable linear regression model adjusted for patient demographics, socioeconomic status and chronic medical comorbidities, we found that subjects with U-DM had 22% higher LOS than those without DM, corresponding to adjusted exponential of slope [95% CI] of 1.22 [1.18-1.27]). Similarly, the association between U-DM and increased cost of hospitalization was significant (adjusted exponential of slope [95% CI]: 1.07 [1.06-1.07]). Moreover, CX-DM maintained the highest risk for both LOS (adjusted exponential of slope [95% CI]: 1.56 [1.42-1.72]) and cost (adjusted exponential of slope [95% CI]: 1.14 [1.13-1.16]) [Table 3].

Diabetes was associated with higher risk for non-respiratory complications but not mortality.

During index admission, respiratory failure was the most common acute complication (16.6%), while the most common non-respiratory acute complications were AKI (5.5%), sepsis (0.4%) and encephalopathy (0.4%). Compared to patients without DM, patients with DM (especially U-DM) had lower rate of respiratory failure (15.1% vs 17.0%, $p < 0.001$). However, the risk of having non-respiratory complications, especially AKI, sepsis and encephalopathy were much higher in diabetics. Patients with CX-DM had the highest risk of developing these complications during their hospitalization [Table 4].

For the index admission, the in-hospital mortality rate for the entire cohort was 0.9% [Table 2]. DM was associated with increased risk of mortality during index admission; however, such association was no longer present after adjusting for other factors in the multivariate model. In fact, CX-DM even appeared to be associated with slightly lower mortality risk during the index admission (adjusted OR [95% CI]: 0.79 [0.63-0.98]) [Table 3].

Characteristics of 30-day readmissions

A total of 68,260 (9.5%) patients were readmitted within 30 days of hospital discharge from the index admission, including 22,719 (3.2%) patients readmitted with for asthma. The average time from discharge to the first readmission was around 13 days (SE=0.1). Compared to index admission, hospital LOS and cost were higher in both all-cause and asthma-related readmissions ($p < 0.001$); in addition, the mortality rate was higher for all-cause readmissions (2.4% vs 0.9%; $p < 0.001$) [Table 2].

Adjusting for age, gender, Median Household Income by Zip Code, diabetes without complications was associated with higher risk for all-cause readmission (adjusted OR [95% CI] = 1.68[1.59-1.77]), and asthma-related readmission (adjusted OR [95% CI] = 1.18 [1.12-1.24]). In contrast, diabetes with complications was associated with higher risk for all-cause readmission (adjusted OR [95% CI] = 1.24 [1.20-1.27]) but not for asthma-related readmission (adjusted OR [95% CI] = 0.90 [0.80-1.01]) [Table E2]. In both situations, diabetes (U-DM and CX-DM) was also associated with significantly higher LOS and cost but not mortality [Table 3]. In a subgroup analysis of patients with asthma and nicotine addiction, the association between diabetes (U-DM and CX-DM) and mortality, LOS and cost mirrored the results from the total studied population and any differences could be explained by smaller sample size caused by stratification.

The rate of respiratory failure was similar between index admission and all-cause readmission (16.6% vs 14.2%). However, the rate for non-respiratory complications - especially AKI (11.1% vs 5.5%), sepsis (5.9 % vs 0.4%), and encephalopathy (1.0% vs 0.4%) - was much higher during all-cause readmissions than in the initial admission, and diabetic patients were at increased risk. In contrast, the complication rate was similar between index admission and asthma-related readmission [Table 4].

Stratified analysis by obesity status

We performed a stratified analysis by obesity status (as indicated by reported comorbidities at the time of admission). In the subgroup of patients with no obesity, the presence of U-DM or CX-DM was associated with higher LOS and cost in index admission, 30-day all cause and asthma related readmissions comparing to patients without DM. In the

subgroup of patients with obesity, patients with U-DM or CX-DM incurred higher LOS and cost during index admission [Table E3].

To assess if the effect of diabetes on mortality depends on obesity, we included an interaction term between diabetes and obesity in our models. We found no interaction between diabetes and obesity on “mortality” as an outcome in the initial admission (p for the interaction = 0.68), during the 30-days all-cause readmission (p for the interaction = 0.45) or during the 30 days asthma-related readmission (p for the interaction = 0.47).

Discussion

When hospitalized for asthma, patients with coexisting diabetes mellitus had increased hospital length of stay, cost, and risk for 30-day all-cause and asthma-related readmission. These patients also had a higher risk for developing non-respiratory complications during their hospital stay. To our knowledge, this is the first study to use a large, nationally representative database to specifically characterize hospitalized patients with concurrent asthma and DM. Compared to prior studies (9,10), our large nation-wide sample and increased statistical power makes our results more generalizable to the United States population.

Asthma consumes a significant portion of economic resources; however, this expenditure is not evenly shared among patients. Over 80% of the total cost arises from 20% of asthmatics, i.e. the “high-cost” patients. Furthermore, hospital admissions alone were responsible for over 65% of the expenditure for these “high-cost” patients, while it only accounts for 1% of the expenditure for “low-cost” patients (4). In fact, a recent study confirmed the presence of exacerbation-prone asthma phenotype – with the tendency for developing repeated asthma exacerbations over multiple years – in a subgroup of asthmatics that might benefit from targeted intervention (17). Therefore, considerable financial cost could be saved if we can minimize asthma-related hospital admissions and readmissions in high-risk patients. Our findings suggest that patients with co-existing asthma and diabetes likely belong in this high-risk patient group where targeted interventions are needed to reduce readmissions and cost of care.

There are several potential explanations for the association between DM and increased hospital LOS, cost, and risk for readmissions. First, asthma patients with DM may have different physiologic and immunologic characteristics compared to asthma patients without DM. Potential mechanisms linking DM (especially T2DM) and asthma include insulin resistance and hyperinsulinemia, which causes greater airway smooth muscle contractility via phosphoinositide 3-kinase and rho-kinase-dependent pathways (18) and increased bronchial hyper-responsiveness (19). Indeed, we showed that DM was associated with higher admission LOS and cost in subgroup of patients without obesity. This suggests a possible direct association between DM and asthma outcomes. Second, obesity and metabolic dysfunction often co-exists with DM, leading to pro-inflammatory state via adipokines, IL-6, TNF- α , and C-reactive protein (20,21) and altered immune function via suppression of natural killer cell (22) and CD8+ cytotoxic T cells (23). In asthmatics, both obesity (24,25) and systemic IL-6 inflammation (26,27) are associated with higher asthma disease severity, symptom burden and decreased response to inhaled corticosteroids. Furthermore, the presence of diabetes, obesity, and higher plasma IL-6 level appears to be able to predict the Exacerbation-Prone Asthma phenotype (17). Third, treatment for asthma exacerbations may adversely affect a patient’s diabetes. Most notably, systemic glucocorticoids (GC) substantially alter the homeostasis of glucose control, and can increase the risk of non-respiratory adverse effects like infection (28).

Acute non-respiratory complications during hospital stay, especially AKI and sepsis, pose a significant threat to asthma patients with DM. Systemic glucocorticoid is the mainstay therapy currently available for asthma exacerbation. In contrast to its known deleterious effect on DM, GC's efficacy for patients with non-T2 asthma, including a subgroup of patients with metabolic dysfunction and systemic inflammation, are less consistent (29,30). Our study highlights the impact of non-respiratory complications for asthma patients with diabetes. The optimal management of such patients requires further studies, especially regarding the association between GC-based asthma therapy and the occurrence of non-respiratory complications associated with uncontrolled diabetes. Furthermore, our study supports the urgent need to evaluate novel glucocorticoid sparing therapeutics that are both effective and safe for patients with comorbid asthma and DM.

Patients with uncomplicated DM showed a small but statistically significantly lower rate of respiratory failure when compared to patients without DM, which was a finding we cannot fully explain. It is possible that, because our study is based on diagnostic coding, there are known coding biases which may account for this finding (31). For example, it is possible that patients with uncomplicated DM and asthma were misclassified as having pneumonia and excluded from this analysis based on our strict patient selection criteria. Alternatively, retrospective observational studies suggest the protective effects of metformin (32,33) and thiazolidinediones (34) for asthma and asthma exacerbations. Unfortunately, we do not have medication-use data to evaluate the association between DM medication use and respiratory-related outcomes.

Our study demonstrates that DM patients have higher in-hospital mortality risk during hospital stay, but that this association disappeared in multivariable analysis when adjusting for other factors. This suggests that the increased mortality risk may not entirely come from asthma. The mortality risk could also arise from other non-respiratory causes, including acute inpatient complications. Our findings are consistent with published data suggesting a relatively low mortality rate directly attributed to asthma (1.4 per 10,000 persons) (1).

Taken together, these differences between hospitalized asthma patients with and without DM represent a crucial window for intervention. Once considered "a rare coincidence" in the 1970s (35), DM is now a common and significant co-morbidity of asthma. The prevalence of DM in patients with asthma ranges from 5% to 16% (36,37), and was as high as 28% in our study. From an individual patient level, mechanistic studies on how DM and asthma interact are urgently needed. Currently, we lack guidance on the optimal strategy to care for asthma patients with DM. Our existing asthma therapy may cause serious adverse effects yet not offer maximal efficacy for our patients. From the population health perspective, we need novel tools to identify vulnerable patients, and effective protocols to mitigate their risk for complications and readmissions. From a cost-effectiveness standpoint, targeting these vulnerable populations with preventative strategies could reduce direct medical costs and indirect societal costs.

Our study has several limitations. First, given the nature of the observational study design, we were unable to establish any causal effect. However, our findings of increased hospital LOS and cost in patients with DM were consistent between index admission and readmissions, and were consistent between patient subgroups with or without obesity. In addition, our study design enabled accurate capture of readmissions and allowed direct comparison between patients with and without DM. Second, HCUP is an administrative claim-based database and does not provide detailed clinical data or information on medication use. As a result, we could not control for asthma disease phenotype, disease severity, outpatient medications, or inpatient care process; information on asthma-related comorbidities is also

limited. Nonetheless, being one of the largest administrative health care data sets, HCUP offers unique advantages in asthma research: 1) these data represents “real-world” scenario on unselected patients; 2) the number of patients included in the data sets are huge, and the patient population is nationally representative; 3) outcomes including hospital admission and length of stay are reliably reported in these data sets (38). Third, NRD database do not provide information on patients’ race and ethnicity, yet we know there is considerable racial/ethnic disparity in asthma hospitalizations (39). Fourth, we could not guarantee complete exclusion all COPD patients, as up to 20% could have COPD-asthma overlap syndrome (40). To make up for this limitation, we excluded all patients with COPD diagnosis, regardless of whether they also had asthma diagnosis. Among patients excluded from our study, 14.9% carry both COPD and asthma diagnosis. Lastly, all diagnoses and complications were determined by corresponding ICD-9/10 codes. A previous study suggested a relatively high specificity (over 90%) but fairly variable sensitivity of ICD code-based diagnosis accuracy (41); therefore, some DM patients may be mistakenly included in the “no DM” group which could dilute the observed results. Similarly, some obese individuals could be misclassified and analyzed in the “non-obese” group, which could lead to decreased inter-group difference when we tested for interaction between obesity and DM status.

Conclusion

Using stringent criteria that adjusted for age-related comorbidities and other socio-economic and demographic factors, we show that patients hospitalized for asthma with coexisting diabetes mellites had increased hospital length of stay, cost, and risk for 30-day all-cause and asthma-related readmission. These patients were also more likely to develop acute inpatient non-respiratory complications. Interventions are urgently needed to reduce the risk for hospital admission and readmission in patients with co-existing DM and asthma that would have profound economic and societal impact.

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Table 1 Baseline characteristics of study cohort at time of index admission

	Total	No DM	Uncomplicated DM (U-DM)	Complicated DM (CX-DM)	<i>p</i>
n (% of N)	717,200 (100)	514,711 (71.8)	174,666 (24.4)	27,823 (3.9)	
Demographics					
Age in years, mean (SE)	55.4 (0.1)	53.1 (0.1)	60.9 (0.1)	62.9 (0.2)	<0.001
Female, % (SE)	71.2 (0.1)	69.5 (0.1)	75.8 (0.2)	74.2 (0.5)	<0.001
NDX ^{&} , mean (SE)	9.3 (0.04)	8.3 (0.04)	11.4 (0.05)	15.3 (0.1)	<0.001
Primary Insurance					
Type,% (SE)					<0.001
Medicare	41.7 (0.2)	36.3 (0.2)	54.0 (0.3)	62.8 (0.5)	
Medicaid	21.1 (0.2)	21.9 (0.3)	19.8 (0.3)	16.5 (0.4)	
Private	23.1 (0.2)	25.3 (0.2)	18.0 (0.2)	15.8 (0.4)	
Other	3.1 (0.1)	3.4 (0.1)	2.7 (0.1)	1.9 (0.1)	
Median Household Income by Zip Code, %(SE)					
< \$41,999	37.3 (0.6)	36.3 (0.6)	40.3 (0.6)	37.7 (0.8)	<0.001
\$42,000 - 51,999	24.5 (0.3)	24.6 (0.3)	24.4 (0.4)	24.6 (0.5)	
\$52, 000 - 67,999	20.3 (0.3)	20.7 (0.3)	19.1 (0.3)	20.3 (0.5)	
> \$68,000 , %	16.3 (0.4)	16.9 (0.4)	14.4 (0.4)	16.1 (0.6)	
Comorbidities, %(SE)					
Alcohol use	2.9 (0.1)	3.4 (0.1)	1.8 (0.1)	1.5 (0.1)	<0.001
Tobacco use	24.4 (0.2)	26.8 (0.2)	18.9 (0.2)	15.6 (0.4)	<0.001
Obesity	25.6 (0.2)	19.9 (0.1)	39.1 (0.3)	46.7 (0.5)	<0.001
CHF	12.1 (0.1)	8.8 (0.1)	19.2 (0.2)	30.3 (0.5)	<0.001
Depression	14.6 (0.1)	13.9 (0.1)	16.1 (0.2)	18.7 (0.5)	<0.001
HTN	55.2 (0.2)	46.0 (0.2)	77.8 (0.2)	83.5 (0.4)	<0.001
High Severity [#]	25.6 (0.2)	22.0 (0.2)	31.7 (0.3)	54.9 (0.6)	<0.001
High risk of Mortality [#]	17.7 (0.2)	15.8 (0.2)	20.6 (0.2)	35.1 (0.5)	<0.001

& NDX stands for Number of diagnosis at discharge.

High severity and high-risk mortality are defined as patients belonged to All Patient Refined DRGs (APR-DRGs) severity class 3 or 4 and risk of mortality class 3 or 4, respectively.

Frequencies presented are weighted counts.

Data expressed as weighted mean (SE) or weighted percent (SE).

CHF = Congestive heart failure. HTN = hypertension. SE: standard error.

Table 2 Outcomes of index admission and 30-day readmission

	Total	No DM	Uncomplicated DM (U-DM)	Complicated DM (CX-DM)	<i>p</i>
Index Admission					
n (% of N)	717,200 (100)	514,711 (71.8)	174,666 (24.4)	27,823 (3.9)	
LOS in days, median [IQR]	3 [2-5]	3 [2,4]	3 [2-5]	4 [2-6]	<0.001
Cost in \$, median [IQR]	5,343 [3,501-8,414]	5,057 [3,318-7,952]	6,002 [4,006-9,339]	7,132 [4,586-11,088]	<0.001
In-hospital Mortality, % (SE)	0.9 (0.02)	0.8 (0.02)	1.0 (0.04)	1.1 (0.1)	<0.001
30-day readmission rate					
All-cause, % (SE)	9.5 (0.1)	8.6 (0.1)	11.4 (0.1)	15.4 (0.4)	<0.001
Asthma-related, % (SE)	3.2 (0.03)	3.1 (0.03)	3.3 (0.1)	2.8 (0.2)	0.006
30-Day All-Cause Readmission					
n (% of N)	68,260 (100.0)	44,060 (64.5)	19,925 (29.2)	4,275 (6.3)	
Days to Readmission, median [IQR]	12 [5-20]	12 [5-21]	12 [5-20]	12 [5-20]	0.62
LOS in days, median [IQR]	3 [2-5]	3 [2-5]	4 [2-6]	4 [3-7]	<0.001
Cost in \$, median [IQR]	6,112 [3,900-9,956]	5,755 [3,678-9,344]	6,610 [4,281-10,596]	8,245 [5,122-13,504]	<0.001
In-hospital Mortality, % (SE)	2.4 (0.01)	2.4 (0.1)	2.4 (0.2)	2.5 (0.3)	0.96
30-Day Asthma-Related Readmission					
n (% of N)	22,719 (100.0)	16,122 (71.0)	5,814 (25.6)	783 (3.4)	
Days to Readmission, median [IQR]	12 [5-21]	13 [5-21]	13 [5-21]	11 [5-21]	0.46
LOS in days, median [IQR]	3 [2-4]	3 [2-4]	3 [2-5]	4 [2-6]	<0.001
Cost in \$, median [IQR]	5,080 [3,271-8,105]	4,794 [3,084-7,534]	5,748 [3,741-9,268]	6,700 [4,091-10,515]	<0.001
In-hospital Mortality, % (SE)	0.7 (0.01)	0.6 (0.1)	1.0 (0.2)	*** (n = 8)	0.07

Frequencies presented are weighted counts. Data expressed as weighted median [IQR] or weighted percent (SE). LOS = length of stay.

***: Per HCUP analysis guidelines, we presented the exact number instead of a relative percentage when n < 10.

Table 3 Unadjusted and adjusted[#] analysis of outcome during hospitalization

	Uncomplicated DM (U-DM)		Complicated DM (CX-DM)	
	Exponential of slope [†] (95% CI)	Adjusted Exponential of slope [†] (95% CI)	Exponential of slope [†] (95% CI)	Adjusted Exponential of slope [†] (95% CI)
Index admission				
LOS	1.27 (1.25-1.28)*	1.22 (1.18-1.27)*	1.44 (1.41-1.47)*	1.56 (1.42-1.72)*
Cost	1.19 (1.18-1.20)*	1.07 (1.06-1.07)*	1.40 (1.38-1.43)*	1.14 (1.13-1.16)*
30-Day All-cause readmission				
LOS	1.10 (1.07-1.12)*	1.04 (1.01-1.06)*	1.25 (1.20-1.30)*	1.12 (1.07-1.17)*
Cost	1.14 (1.11-1.17)*	1.07 (1.04-1.09)*	1.30 (1.24-1.36)*	1.13 (1.08-1.18)*
30-Day Asthma-related readmission				
LOS	1.18 (1.14-1.22)*	1.06 (1.02-1.09)*	1.35 (1.24-1.47)*	1.15 (1.05-1.26)*
Cost	1.22 (1.17-1.27)*	1.10 (1.06-1.14)*	1.39 (1.26-1.52)*	1.18 (1.07-1.30)*
	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Index admission				
In-hospital Mortality	1.15 (1.04-1.20)*	1.02 (0.92-1.14)	1.36 (1.11-1.70)*	0.79 (0.63-0.98)*
30-Day All-cause readmission				
In-hospital Mortality	0.94 (0.79-1.12)	0.89 (0.74-1.10)	0.97 (0.71-1.31)	0.82 (0.59-1.14)
30-Day Asthma-related readmission				
In-hospital Mortality	1.68 (1.01-2.77)*	1.47 (0.89-2.43)	1.69 (0.66-4.32)	1.00 (0.31-3.12)

Adjusted for demographic features, insurance and income status, and all known chronic comorbidities including obesity.

†LOS and Cost were analyzed using linear regression with a natural log transformation. When using a natural logarithmic transformation on the outcome variable in linear regression, the exponential of the slope ($\exp(\beta)$) is interpreted as a relative change in the outcome. For example, an exponential slope of 1.27 means that subjects with U-DM had 27% higher LOS than those without DM.

Mortality was analyzed with logistic regression.

LOS = length of stay. CI: confidence interval.

* $p < 0.05$

Table 4 Respiratory and non-respiratory complications during hospitalization

	Total	No DM	Uncomplicated DM (U-DM)	Complicated DM (CX-DM)	<i>p</i>
Index admission					
n (% of N)	717,200 (100.0)	514,711 (71.8)	174,666 (24.4)	27,823 (3.9)	
Respiratory failure, %	16.6 (0.2)	17.0 (0.2)	15.1 (0.2)	18.8 (0.5)	<0.001
Sepsis, %	0.4 (0.01)	0.4 (0.0)	0.5 (0.0)	0.8 (0.1)	<0.001
Shock, %	0.3 (0.01)	0.3 (0.01)	0.4 (0.02)	0.5 (0.1)	<0.001
AKI, %	5.5 (0.01)	4.1 (0.1)	7.9 (0.1)	15.8 (0.4)	<0.001
Delirium, %	0.2 (0.01)	0.2 (0.01)	0.2 (0.02)	0.3 (0.1)	0.018
Encephalopathy, %	0.4 (0.01)	0.4 (0.02)	0.4 (0.03)	0.6 (0.1)	<0.001
Stroke, %	0.1 (0.01)	0.1 (0.01)	0.1 (0.01)	0.2 (0.01)	0.002
30-day All-cause readmission					
n (% of N)	68,260 (100.0)	44,060 (64.5)	19,925 (29.2)	4,275 (6.3)	
Respiratory failure, %	14.2 (0.3)	14.7 (0.3)	13.2 (0.4)	13.7 (0.9)	0.006
Sepsis, %	5.9 (0.2)	5.6 (0.2)	6.2 (0.3)	7.5 (0.6)	0.002
Shock, %	1.7 (0.01)	1.6 (0.1)	1.9 (0.1)	1.8 (0.3)	0.16
AKI, %	11.1 (0.2)	8.7 (0.2)	14.4 (0.5)	20.0 (1.0)	<0.001
Delirium, %	0.4 (0.01)	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.92
Encephalopathy, %	1.0 (0.01)	1.0 (0.1)	1.0 (0.1)	1.5 (0.3)	0.13
Stroke, %	0.8 (0.01)	0.7 (0.1)	1.1 (0.1)	0.8 (0.2)	0.006
30-Day Asthma-Related Readmission					
n (% of N)	22,719 (100.0)	16,122 (71.0)	5,814 (25.6)	783 (3.4)	
Respiratory failure, %	17.6 (0.5)	17.9 (0.5)	16.7 (1.0)	19.5 (2.4)	0.34
Sepsis, %	0.4 (0.01)	0.4 (0.1)	0.5 (0.1)	*** (n = 4)	0.62
Shock, %	0.2 (0.01)	0.1 (0.03)	0.5 (0.1)	*** (n = 2)	<0.001
AKI, %	5.0 (0.2)	3.8 (0.2)	7.2 (0.6)	13.9 (2.0)	<0.001
Delirium, %	0.1 (0.01)	0.1 (0.03)	*** (n = 3)	*** (n = 2)	0.45
Encephalopathy, %	0.2 (0.03)	0.2 (0.04)	0.3 (0.1)	*** (n = 3)	0.59
Stroke, %	0.1 (0.01)	*** (n = 6)	*** (n = 6)	*** (n = 0)	0.45

Frequencies presented are weighted counts. Data expressed as weighted percent $\pm$ SE. AKI = acute kidney injury.

***: Per HCUP analysis guidelines, we presented the exact number instead of a relative percentage when $n < 10$.

Table E1 Chronic pulmonary conditions excluded from study

Cancer of bronchus; lung
Cancer; other respiratory and intrathoracic
Secondary malignancy of lung
Respiratory infections
Chronic obstructive pulmonary disease and bronchiectasis
Aspiration pneumonitis; food/vomitus
Pleurisy; pneumothorax; pulmonary collapse
Lung disease due to external agents
Other lower respiratory disease

Table E2: Unadjusted and adjusted analysis of the association between diabetes and all-cause- and asthma-related re-hospitalization.

	Diabetes without complication		Diabetes with complication		All Diabetics combined	
	Unadj OR[95%CI]	Adj OR[95%CI]	Unadj OR[95%CI]	Adj OR[95%CI]	Unadj OR[95%CI]	Adj OR[95%CI]
All-Cause 30 days Readmission	1.36 [1.33-1.42]	1.24 [1.20-1.27]	1.94 [1.84-2.05]	1.68 [1.59-1.77]	1.45 [1.41-1.49]	1.35 [1.31-1.38]
Asthma-Related 30 days Readmission	1.07 [1.01-1.12]	1.18 [1.12-1.24]	0.90 [0.80-1.01]	1.02 [0.90-1.14]	1.04 [0.99-1.09]	1.16 [1.10-1.21]

Analysis adjusted to age, gender, Median Household Income by Zip Code.

OR [95%CI] compared to patients with diabetes without or without complications as compared to non-diabetics.

Table E3 Adjusted[#] analysis of outcome during hospitalization, stratified by obesity

	Non-Obese (N = 533,374)			Obese (N = 183,826)		
	No-DM	Uncomplicated DM (U-DM)	Complicated DM (CX-DM)	No-DM	Uncomplicated DM (U-DM)	Complicated DM (CX-DM)
n (% of N)	412,187 (77.3)	106,365 (19.9)	14,822 (2.8)	102,524 (55.8)	68,301 (37.1)	13,001 (7.1)
Adjusted Exponential of slope (95% CI)						
<i>Index admission</i>						
LOS	1.00	1.20 (1.15, 1.25)*	1.52 (1.36, 1.70)*	1.00	1.31 (1.26,1.36)*	1.72 (1.57, 1.89)*
Cost	1.00	1.06 (1.05, 1.07)*	1.14 (1.12, 1.16)*	1.00	1.09 (1.08, 1.10)*	1.18 (1.16, 1.20)*
<i>30-Day All-cause readmission</i>						
LOS	1.00	1.05 (1.02, 1.08)*	1.13 (1.07, 1.20)*	1.00	1.00 (0.96, 1.04)	1.10 (1.03,1.17)*
Cost	1.00	1.08 (1.05, 1.11)*	1.14 (1.07, 1.22)*	1.00	1.04 (1.01, 1.08)*	1.12 (1.05,1.20)*
<i>30-Day Asthma-related readmission</i>						
LOS	1.00	1.06 (1.01, 1.11)*	1.24 (1.09, 1.40)*	1.00	1.04 (0.98, 1.10)	1.04 (0.92, 1.19)
Cost	1.00	1.11 (1.06, 1.16)*	1.27 (1.11, 1.45)*	1.00	1.07 (1.01,1.14) *	1.08 (0.94, 1.24)

Adjusted for demographic features, insurance and income status, and all known chronic comorbidities excluding obesity. LOS and Cost were analyzed using linear regression with a log transformation. LOS = length of stay. CI: confidence interval. * $p < 0.05$