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The impact of statin use on outcomes of Diabetic adult patients hospitalized for community acquired pneumonia.

Joel Lanceta
University of Louisville

THE IMPACT OF STATIN USE ON OUTCOMES OF DIABETIC ADULT PATIENTS HOSPITALIZED FOR COMMUNITY ACQUIRED PNEUMONIA

By

Joel Lanceta

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Joel Lanceta

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November 19, 2021

By the following Dissertation Committee

_____

Dissertation Chair

Bert Little, PhD

_____

Dissertation Co-Chair

Robert Esterhay, MD

_____

Ruth Carrico, PhD

_____

J'Aime Jennings, PhD

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ABSTRACT

THE IMPACT OF STATIN USE ON OUTCOMES OF DIABETIC ADULT PATIENTS HOSPITALIZED FOR COMMUNITY ACQUIRED PNEUMONIA

Joel Lanceta

November 19, 2021

BACKGROUND: Statins, a class of drugs that treat hyperlipidemia, may have an immunosuppressive effect for patients with community acquired pneumonia (CAP). Retrospective and in vitro studies have suggested an immunomodulatory, antioxidative and anticoagulant effects from statin use in patients with Type 2 Diabetes Mellitus (T2DM) hospitalized for CAP. Prospective studies that have tested any effect of statin therapy on patients with T2DM and CAP have not been found literature. To date, prospective studies showing of the effects statin therapy may have on T2DM patients hospitalized for CAP are not available.

METHODS: This dissertation is a secondary analysis using deidentified data collected from the HAPPI Study, a prospective CAP observational study conducted in nine adult acute-care hospitals in Louisville, Kentucky, from 2014-2017. HAPPI patients were grouped by T2DM, prior statin exposure, and age. Decision tree analyses were performed to indicate how strongly the T2DM and statin interaction is related to outcomes of mortality (after one, six, and 12 months) and CAP rehospitalization (after one, six, and 12 months). Multivariate logistic regression analyses were used to identify potential covariables. Propensity score matching (PSM) and the McNemar test were used to compare the odds ratios of outcomes on paired statin users (cases) and non-statin users (controls) based on age and T2DM.

RESULTS: From 10052 CAP patients, 1265 of 2734 T2DM patients were on statins (46.3%) and 2340 of 7318 non-T2DM patients were on statins (32.0%). The decision tree analysis, logistic regression analysis, and survival analysis indicated that statin use in T2DM patients age < 65 years was significantly associated (OR = 0.55, $p < 0.01$) with a decreased likelihood for all-cause mortality at one, six, and 12 months. Analysis after PSM found statin use in T2DM patients age < 65 was associated with non-significantly decreased odds for one, six, and 12 month mortality (OR = 0.70, $p = 0.09$). The logistic regression analysis and PSM analysis showed no significant difference in mortality likelihood between T2DM patients age ≥ 65 with statin use and those without statin use. No significant difference was seen in rehospitalization between T2DM cases and controls in either age groups.

CONCLUSIONS: Decision tree analysis, logistic regression analysis, and Cox regression analysis showed that the T2DM and statin interaction was significantly associated with decreased mortality at one, six, and 12 months for T2DM patients age <65 , but not in T2DM patients age ≥ 65. A prospective case control study with a larger sample size to account for PSM may validate these findings to be significant. This dissertation emphasized the continued study of statin therapy for the attenuation of CAP severity and improved outcomes.

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CHAPTER 1

INTRODUCTION

Background to the Study

From June 1, 2014 to March 31, 2016, the University of Louisville Division of Infectious Diseases conducted the University of Louisville Pneumonia Hospitalized Adults with Pneumococcal Pneumonia: Incidence (HAPPI) Study, a prospective cohort study of all adults hospitalized for community acquired pneumonia (CAP). The purpose of HAPPI was to define the incidence, epidemiology, and mortality of CAP in Louisville, Kentucky. To the best of the author's knowledge, HAPPI was the first population-based study evaluating data on the number of unique patients who required hospitalization after being diagnosed for CAP in the United States.[1]

One benefit from HAPPI was in collecting the diverse demographic and medical history of its patient population, including the prevalence of comorbid diseases in hospitalized CAP patients. This allows for a better illustration of how two of the most common metabolic diseases in the United States, Type 2 Diabetes Mellitus (T2DM) and dyslipidemia (DLP) affect the disease process of CAP.

Type 2 Diabetes Mellitus (T2DM) and Metabolic Disorders

T2DM is a metabolic disorder primarily caused by insulin deficiency with or without insulin resistance. Hyperglycemia associated with T2DM results in the production of glycated metabolic end-products and reactive oxygen species, impairing immunity and giving rise to proinflammatory conditions.[2-4]These metabolic disturbances contribute to multiple downstream complications, such as renal failure, retinopathy, neuropathy, and osteomyelitis. T2DM is associated with worse outcomes in patients with coronary artery disease (CAD),[5] chronic obstructive pulmonary disease (COPD),[6] and peripheral artery disease (PAD).[7] Increased frequency of morbidity and mortality results from these complications.[8]

Overweight (OW) and obesity (OB) are two interconnected metabolic disorders. The prevalence of OW and OB in the US population has been increasing since the 1950s, with an estimated 73.6% of Americans age ≥ 20 years being OW or OB.[9] OW is defined as a calculated body mass index (BMI) of 25 to 29.9 kg/m2; OB as a BMI of >30 kg/m2. The risk for impaired glucose tolerance is directly proportional to increased body adipose tissue, specifically central (abdominal) obesity. OB is a risk factor for the development of T2DM, as well. However, some studies have described the "Obesity paradox", a phenomenon which associates lower mortality and improved prognosis, for obese patients with T2DM compared to T2DM patients with normal weight in certain disease states, such as pneumonia.[9,10]

Dyslipidemia and Statin Therapy

DLP is a chronic condition with an abnormal elevated serum total cholesterol (hyperlipidemia), elevated low-density lipoprotein (LDL) and triglycerides, and decreased high-density lipoprotein (HDL). DLP is diagnosed clinically when triglycerides are considered above 150 mg/dL, LDL is above 130 mg/dL and HDL is below optimal levels at 60 mg/dL. Elevated blood cholesterol is associated with increased age, gender, genetics, and other modifiable lifestyle factors such as diet, exercise, tobacco smoking cessation, alcohol consumption, and BMI. DLP is considered a major risk factor for the development of CAD. DLP is often treated in primary and secondary prevention of cardiovascular events.[11,12]

A class of drugs known as statins are the mainstay of pharmacotherapeutic treatments for DLP. Statins belong to a class of drugs that inhibit hydroxymethylglutaryl coenzyme A reductase (HMG-CoA), the rate-limiting enzyme in the metabolic pathway of cholesterol synthesis. Their actions cause potent reductions in total cholesterol and LDL-lowering effects.[11] Importantly for this thesis, statins are known to affect major histocompatibility complex II receptors (MHC II), which play a role in initiating immune responses.[13]

CAP (Community Acquired Pneumonia)

CAP is defined as an acute infection of lung parenchyma acquired outside of a hospital or healthcare-based setting, or from other recent contact within the healthcare system.[1,14,15] Despite advances in antimicrobial therapy in the past 70

years, CAP remains the 7th leading cause of death in the United States overall, and the most common infectious cause of death.[16] Patients hospitalized for CAP are also at increased odds for developing complications during hospitalizations, including need for mechanical ventilation secondary to hypoxic respiratory failure, possible shock requiring vasopressors, and multiorgan failure.[1,17]

Proposed Models of Interaction between T2DM, Statins, and CAP

Statins also have been shown to have immunomodulatory, antioxidative and anticoagulant effects in CAP patients. Statins have been studied as a possible adjunct therapy to improve the prognosis for CAP.[18,19] T2DM is a risk factor for cardiovascular disease, even in the absence of known CAD, thus the ADA recommends statin therapy for the majority of patients with T2DM.[20]

Several aspects of immunity and inflammation are altered by T2DM. In T2DM patients with poor glycemic control, CAP hospitalization has been associated with higher morbidity and mortality.[21-23] Impairment of leukocytes and phagocytosis associated with T2DM,[24,25] and proinflammatory cytokines and chemokine induction through gene upregulation in monocytes also associated with T2DM may play a role.[26]

Prospective studies that have tested any effect of statin therapy on patients with T2DM and CAP have not been found literature. To date, prospective studies showing of the effects statin therapy may have on T2DM patients hospitalized for CAP are not available.

Problem Statement

The objective of this study is to analyze the impact of ongoing statin exposure and their health outcomes of patients with T2DM hospitalized for CAP.

Research Aims

A. Mortality of CAP Patients with T2DM and Statin Therapy

Aim 1: Analyze whether or not all-cause mortality rates at 1 month, 6 months or 12 months after CAP hospitalization, are different between statin-exposed T2DM patients and statin-exposed non-T2DM patients, with statin non-exposed T2DM and non-T2DM patients are the controls.

H0: Mortality rates at 1, 6, and 12 months after CAP hospitalization for statin-using T2DM patients (OR1) are not statistically different from statin-using non-T2DM and non-exposed statin T2DM patients (OR2).

H0: $OR1 = OR2$

HA: Mortality rates at 1, 6, 12 months after CAP hospitalization for statin-exposed T2DM patients is statistically significantly different from statin-using non-T2DM and non-exposed statin T2DM patients.

HA: $OR1 \neq OR2$

B. Morbidity of CAP Patients with T2DM and Statin Therapy

Aim 2: Analyze whether or not readmission rates for CAP at 1, 6 or 12 months after the initial CAP hospitalization are different between statin-exposed T2DM patients and statin-exposed non-T2DM patients, with statin non-exposed T2DM and non-T2DM patients are the controls.

H0: Readmission for CAP at 1, 6 or 12 months after CAP hospitalization of statin-using T2DM patients (OR1) is not statistically different from statin-using non-T2DM and non-exposed statin T2DM patients (OR2).

H0: $OR1 = OR2$

HA: Readmission for CAP at 1 month, 6 months or 12 months after CAP hospitalization of statin-using T2DM patients is statistically significantly different from statin-using non-T2DM and non-exposed statin T2DM patients.

HA: $OR1 \neq OR2$

Significance

Prior studies that analyzed the outcomes of statin therapy on patients with CAP and T2DM were retrospective/historic cohort studies. This study will be one of the first to use a prospective cohort design to analyze the effect of statin therapy on all-cause mortality from discharge to one year after hospitalization in T2DM and non-T2DM patients requiring hospitalization for CAP.

Additionally, rehospitalization for CAP up to one year after initial stay will be analyzed in this study to determine whether or not T2DM or non-T2DM populations should be targeted for a more aggressive treatment course to lower the likelihood of rehospitalizations and decrease associated costs.

Summary

Retrospective and in vitro studies have suggested an anti-inflammatory/protective effect of statin use in T2DM patients hospitalized for CAP, however no prospective cohort study has been published to date.

The present investigation will be a secondary analysis of the prospectively collected data from the University of Louisville HAPPI study to analyze whether or not statin use affects mortality and morbidity outcomes in T2DM patients hospitalized for CAP. The primary outcome is mortality after CAP hospitalization and the secondary outcome is rehospitalization for CAP after the initial hospitalization. A cost analysis of CAP rehospitalization will also be conducted in the treatment and control groups.

CHAPTER 2

LITERATURE REVIEW

Diabetes Mellitus and Related Metabolic Disorders

Insulin, one of the key main anabolic hormones of the human body, is a peptide hormone that promotes glucose absorption, glyconeogenesis, lipogenesis, and protein synthesis. After its release by the pancreas, insulin binds to its receptors on hepatic, adipocytic and skeletal muscle cells, initiating a cascade of cellular processes that promotes glycogen and fat synthesis from the absorbed glucose, while inhibiting gluconeogenesis and glycogenolysis by the liver. [27-29]

The current American Diabetes Association (ADA) guidelines no longer diagnose Type 1 diabetes mellitus (T1DM) and T2DM based on the traditional paradigm of age at onset because both diseases can occur in childhood and adulthood. Instead, the ADA now defines T1DM as insulin deficiency due to autoimmune antibody-mediated disease destruction of the pancreatic β-cells.[30] By comparison, T2DM is diagnosed by the progressive loss of insulin secreted by pancreatic β-cells frequently associated with cellular insulin resistance, causing hyperglycemia. Hyperglycemia associated with T2DM causes a proinflammatory and prothrombotic reaction. Classic symptoms of T2DM include intense thirst, increased urination, headache, blurred vision, poor wound healing, fatigue, and

numbness or tingling in the extremities. T1DM may also present with clinical symptoms similar to T2DM but with the added symptoms of weight loss and increased hunger.[31] Complications from untreated or poorly managed T2DM include atherosclerotic cardiovascular disease,[5] peripheral vascular disease,[7,32] diabetic foot ulcers,[33] chronic kidney disease,[34-36] retinopathy,[37] neuropathy,[38] and increased odds for respiratory infections (i.e CAP).[39-41]

Pathways associated with β-cell failure and dysfunction are less well defined for T2DM than in T1DM. Genetic predisposition, environmental, metabolic, and inflammatory stress, have contributed insulin resistance and T2DM onset. These patients with metabolic, environmental, and genetic determinants for T2DM are currently targeted for future clinical algorithms.[42,43]

Prediabetes (intermediate hyperglycemia) is associated with elevated serum glucose below the diagnostic threshold of T2DM. Prediabetes patients may present with the classic symptoms of hyperglycemia, and are at increased odds for OB, dyslipidemia, and hypertension. Prediabetes often leads to T2DM due to simultaneous insulin resistance, β-cell dysfunction, and other possible clinical T2DM complications without meeting the official glycemic threshold for diagnosis. Unlike T2DM, prediabetes may be reversible with dietary and lifestyle changes, although an estimated 5-10% of patients with prediabetes will progress to T2DM.[44-46]

Metabolic syndrome, also known as Syndrome X, refers to a cluster of co-occurring clinical conditions that include central (abdominal) OB, hyperglycemia, hypertriglyceridemia, and hypertension. Like T2DM, metabolic syndrome causes a

proinflammatory and prothrombotic state characterized by upregulated inflammatory cytokine production and activity. Patients with OB and metabolic syndrome have a six-to-ten-fold increased odds for developing CAD, T2DM, and stroke compared to obese patients without metabolic syndrome.[47,48]

T2DM, metabolic syndrome and prediabetes are closely related due to their overlapping clinical and pathophysiological presentation, although how their pathways intersect is still to be defined by medical research.

T2DM, Prediabetes, and Metabolic Syndrome Diagnosis

ADA screening and diagnosing criteria for T2DM differs between patients with symptomatic hyperglycemia and those with asymptomatic hyperglycemia. Patients presenting with classical hyperglycemia symptoms (i.e., thirst, polyuria, weight loss, and blurry vision) may be diagnosed with T2DM with a non-fasting blood glucose level of $\geq$ 200 mg/dL (11.1 mmol/L).

The diagnosis of T2DM in an asymptomatic patient is established with any of the following laboratory test criteria:

- Fasting plasma glucose of $\geq$126 mg/dL (7.0 mmol/L), with fasting is defined as no caloric intake for at least eight hours.
- Two-hour plasma glucose values of $\geq$200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test.
- Hemoglobin A1C (HbA1c) value $\geq$6.5 percent (48 mmol/mol).

In asymptomatic patients, if only one test is available then the diagnosis of T2DM warrants confirmation on a subsequent day with a repeated measurement. If two of the test measures are available and concordant for a positive T2DM diagnosis, then no additional testing is needed.[30]

Prediabetes screening identifies patients at high risk for the development of T2DM. These patients present with impaired glucose tolerance, high fasting glucose and HbA1c, but not at the threshold sufficient for T2DM. Prediabetes is screened for and diagnosed using the same laboratory tests as for T2DM. Diagnosis of prediabetes requires one of the following criteria to be positive:

- Fasting plasma glucose between 100 and 125 mg/dL (5.6 to 6.9 mmol/L).
- Two-hour plasma glucose value during a 75 g oral glucose tolerance test between 140 and 199 mg/dL (7.8 to 11.0 mmol/L).
- HbA1c between 5.7 to <6.5% (39 to 48 mmol/mol).

If one of the diagnostic tests is consistent with prediabetes, then annual screening with repeated testing is warranted.[30]

Metabolic syndrome does not have uniform diagnostic criteria described by any major medical organization.[49] Current practice makes the diagnosis of metabolic syndrome based on the presence of any three of the five following findings:

- Fasting blood glucose ≥ 100 mg/dL.
- Blood pressure ≥130/85 mmHg.
- Waist circumference of ≥102 cm (40 in) in males or ≥88 cm (35 in) in females.

- Triglycerides ≥150 mg/dL.
- High density lipoprotein cholesterol <40 mg/dL in males or <50 mg/dL in females.

Mechanisms of Inflammatory Cellular Damage in T2DM

Diabetics are more susceptible to infectious disease through two main pathways: (1) impairment of the immune response,[50] and (2) activation of proinflammatory cytokines.[51] How T2DM triggers the inflammatory process is still under investigation. The current accepted model links inflammation and T2DM through the activation of the c-Jun NH(2)-terminal kinase (JNK) and the inhibitor of κappa-B kinase (IKK). Insulin resistance and the release of many chemokines (cytokines of chronic inflammation), including interleukin (IL)-6, IL-10, and tumor necrosis factor alpha (TNF-α).[52,53] The role of inflammation as a common mediator is linked to both the pathogenesis of T2DM and of OB. [54] Adipocytes (fat cells) also secrete proinflammatory factors correlated with insulin resistance, including leptin and adiponectin.[55] T2DM incidence and its complications are correlated with increased levels of inflammatory biomarkers, including C-reactive protein (CRP), IL-6, plasminogen activator inhibitor 1 (PAI-1),[56] TNF-α, [57] and white blood cell count.[58,59] Intensive lifestyle interventions aimed at T2DM glycemic maintenance are known to decrease markers of inflammation.[60]

T2DM-related cellular level pathophysiology includes hyperglycemia triggering the overproduction and release of reactive oxygen species as byproducts of mitochondrial oxidative phosphorylation, contributing to cellular damage.[61]

Glucose also binds to multiple proteins through glycation, causing irreparable alteration to protein structures and function. These byproducts contribute to the accumulation of glycated proteins in diabetic microvascular diseases.[62-64]

Epidemiology and Costs of T2DM in the United States

Using self-reported data, the prevalence of U.S. adults aged 18 years or older with diagnosed diabetes was between 26.8-34.2 million cases in 2018, with an estimated 7.3 million undiagnosed diabetics.[65,66] Of the diagnosed cases, 5.8% were T1DM, 90.9% were T2DM, and 3.3% had mixed/hybrid type diabetes. Notably, self-report data are believed to underestimate the actual number of adults in the U.S. with diabetes. The incidence in the U.S. in 2020 was estimated to be 1.5 million new cases of diabetes, or 6.9 out of 1,000 persons. The number of T2DM cases are expedited to increase precipitously in the next decade because of an increase in T2DM diagnosis in youths and adolescents 10-19 years of age, paralleling an increase in adolescent obesity.[66-69]

In 2017, the ADA estimated the total economic burden for diagnosed diabetes was $327 billion in 2017, including $237 billion in direct healthcare costs, $71 billion in hospital inpatient costs and $90 billion in reduced productivity associated with diabetic complications. People with diagnosed diabetes, on average, incur medical expenditures of $9600 per year attributed to diabetes alone, approximately 2.3 times higher than expenditures incurred by non- diabetics. [70,71]

Dyslipidemia in the United States

In the U.S., approximately 94 million adults ≥ 20 years old in 2018 had total cholesterol levels higher than 200 mg/dL, which is considered borderline elevated. Over 28 million adults had total cholesterol levels ≥ 240 mg/dL, which is the cutoff for dyslipidemia diagnosis. [72] Dyslipidemia is a general term for the elevation of any form of cholesterol, including triglycerides (hypertriglyceridemia), total cholesterol (hypercholesterolemia) and low-density lipoprotein cholesterol. (LDL-C). LDL-C is one of the five major groups of protein molecules that transport cholesterol. It transfers lipid and cholesterol in extracellular fluid, making it bioavailable to cells for receptor-mediated endocytosis. LDL-C is a known risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). LDL-C accumulates in vasculature, causing vessel plaques that contribute to atherosclerosis. LDL-C also contains many oxidative reactive species that can contribute to the weaking of the cardiovascular vessels. High LDL-C indicates a high risk of atherosclerosis and serves as an estimate of the total cholesterol load.[73]

Statin Therapy for Dyslipidemia

Treatment for dyslipidemia includes lifestyle and diet modifications, and drug therapy that decreases cholesterol synthesis and/or absorption. Hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins) belong to a class of drugs given for lipid altering and reduction. Statins act as competitive inhibitors for HMG CoA- reductase, an enzyme involved in the rate-limiting step of

cholesterol biosynthesis. Statins also reduce very low-density lipoprotein (VLDL) production via an effect mediated by hepatic apolipoprotein B secretion. Patients with an LDL-C of >100 mg/dL (2.59 mmol/L) and a greater risk of ASCVD are usually started on initial statin therapy.

In 2021, more than 35 million Americans are on statin therapy. [74] T2DM is considered a risk factor for ASCVD, with most patients screened for lipid dysfunction at initial T2DM diagnosis. Among diabetic patients, statin therapy is initiated based on ASCVD risk rather than LDL-C baseline levels. Thus, statins are often given to diabetics even if LDL-C levels are lower than 100 mg/dL. [20]

Statin-mediated Anti-Inflammatory Effects

In addition to cholesterol synthesis inhibition, statins have anti-inflammatory and antioxidant effects in animal models and human. *In vitro* studies show that statins reduce the release of proinflammatory factors, suppress the induction of MHC-II molecules, and normally lead the inflammatory response to invasive infections.[13,75-77] Moreover, statins modulate and downregulate inflammatory intracellular pathways involving kinase phosphorylation and protein prenylation. [78]

Statins have a proven effect to reduce inflammation in patients with various diseases such as CAD, chronic renal disease, and T2DM. Their pleiotropic effects downregulate inflammation, and are known to significantly reduce markers of inflammation (e.g., CRP, TNF, IL-6) Normolipidemic patients suppress the transcription factor NF-κB, which controls a number of genes associated with

inflammation.[79-81] Statins increase nitric oxide bioavailability, which helps maintain endothelium homeostasis through anti-atherogenic effects.[81] Statin therapy upregulates gene expression of cellular antioxidant agents, suppress free radical oxygen species, and decrease thrombosis by inhibiting platelet activation and aggregation.[82,83]

Pneumonia Presentation and Pathophysiology

Pneumonias are defined by the location of infection acquisition. CAP is an acute infection of the lung parenchyma acquired outside a hospital or healthcare facility (i.e. rehabilitation center, hemodialysis center). Nosocomial pneumonias are pneumonias acquired through healthcare settings and can be subdivided between hospital-acquired (HAP) or ventilation-associated (VAP).

The clinical presentation of CAP can vary extensively. The most common presentations are a combination of lower respiratory symptoms (i.e. cough, productive sputum production, pleurisy, dyspnea,) with systemic infection symptoms (i.e. fever >37.8°C, leukocytosis, fatigue, malaise, chest pain) that are confirmed with radiological findings consistent with CAP. Computerized topography of the chest is the gold standard in imaging, although for convenience, cost savings, and speed, chest x-rays are usually performed first. On chest radiographs, accumulation of white blood cells and fluid within the alveoli visually appear as pulmonary opacities.[84]

Bacterial pathogens, such as *Streptococcus pneumoniae, Staphylococcus aureus, Legionella* , and *Haemophilus influenza,* and respiratory viruses are the most frequently detected microbial pathogens in CAP patients. However, an estimated 62-75% of hospitalized CAP cases do not identify the causative pathogen despite extensive microbial testing.[85,86]

Although *S. pneumoniae* is the most commonly detected bacterial pathogen in CAP, incidence of pneumococcal pneumonia has decreased in the U.S. since the late 20th century to approximately 10-15% of CAP cases annually, in part due to widespread pneumococcal vaccination of persons ≥ 65 years old.[87] Subsequently, increased recognition of CAP with high severity has occurred due to respiratory viruses, such as influenza, parainfluenza, and respiratory syncytial viruses. A novel variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named COVD-19 by the World Health Organization, is currently the most commonly detected pathogen of CAP in the U.S. since 2020, occurring four years after the close of the HAPPI study.

The pathogenesis of CAP begins with the aspirated or inhaled pathogen entering the lower respiratory tract and begins multiplication in the lung alveoli, competing with the normal respiratory flora. Detection of the pathogen by alveolar macrophages releases cytokines that initiates a host immune response that can cause inflammation and damage in the lung parenchyma. Progression into pneumonia is dependent on multiple factors, such as the inoculum of the pathogen, virulence of the pathogen, and frequency of aspirate.[88] Conditions that impair the immune host

response, such as chronic malnutrition, alcoholism, and T2DM, can increase the severity of the developing pneumonia.

CAP Epidemiology and Health Determinants in the United States

Prior to the COVID-19 pandemic, the initial HAPPI study found that 650 adults per 100,000 population in the U.S. were hospitalized for CAP annually, corresponding to more than 1.5 million unique hospitalization to CAP yearly.[89] The true incidence of CAP may be underreported as patients with mild infections may not seek medical attention.

The risk for CAP increases with patient age and chronic comorbidities. The annual incidence of CAP among adults ≥ 65 years old is approximately 2000 per 100,000 in the U.S., and adults ≥ 65 years old are threefold more likely to be hospitalized for CAP than the general population.[1,90] Chronic medical comorbidities that are associated with increased odds for CAP hospitalization include chronic obstructive pulmonary disease (COPD) and other chronic lung diseases (i.e. asthma, bronchiectasis), chronic heart failure, chronic kidney disease, T2DM, epilepsy, stroke, and immunocompromised conditions. Lifestyle-related factors, such as smoking, alcoholism, and chronic malnutrition are positively correlated with increased incidence of CAP hospitalization. Socioeconomic factors associated with an increased odds of CAP have included crowded living conditions (i.e. prisons, homeless shelters), residence in low-income neighborhoods, and

exposure to environmental toxins (e.g. nitrogen dioxide, sulfur dioxide, gasoline).[91-93]

Despite advances in antimicrobial therapy, CAP still remains a leading cause of hospitalization and mortality worldwide, particularly in the developing world. In 2015, CAP was the leading infectious cause of death, and the eighth leading cause of death in the U.S.[94] 30-day mortality rates vary with pneumonia severity. The CAP 30-day mortality rate was estimated to be 10%, and up to 20-25% in patients with severe CAP.[95,96] Respiratory complications and cardiovascular events (i.e. myocardial infarctions, atrial fibrillation) occur frequently among patients hospitalized for CAP, increasing the risk for mortality.[97]

CAP is associated with increased long-term mortality, although the range and time to mortality is still unclear. [98,99] The HAPPI study followed CAP patients up to one year after their initial CAP hospitalization and estimated that mortality was 23% at six months after hospitalization, and 31% at one year after hospitalization. Extrapolating this mortality rate to the total number of estimated patients hospitalized for CAP in the study year (1,581,860), the number of cumulative deaths in the U.S. population would be estimated at 370,156 at six months after CAP hospitalization, and 484,050 at one year after CAP hospitalization.[1]

30-day readmission for CAP have been estimated to be between 7 – 18% in the U.S. Risk of recurrent and/or exacerbation of CAP increases with comorbidities, such as the ones discussed above with increased odds for CAP hospitalization, and increased age. [100,101]

CAP Healthcare Utilization and Cost Burden

Americans age ≥ 65 years have higher CAP incidence rates, higher rates of hospitalization and higher mortality rates associated with CAP than any other age group in the U.S.[71] The average cost per pneumonia episode was US $10,962.5 ($10,822.8-$11,102.2) for hospitalization from 2008 to 2014 (adjusted for inflation in 2020 to be $11,896.8-12,204). The highest average pneumonia-related healthcare utilization expenditure was for adults ≥ 65 year, who had an estimated economic burden and total costs of $846.7 per 100,000 person-years from CAP-related hospitalizations in 2015.[70]

Inflammatory Response of CAP and T2DM

T2DM increases the risk for infection and is an important and known risk factor for CAP hospitalization and mortality.[21,102,103] Hyperglycemia above ≥250 mg/dl is a criteria on the Pneumonia Severity Index (PSI) that increases the likelihood of severe pneumonia in the clinical management for the patient. In studies monitoring glycemic control in T2DM patients, poor glycemic control (HbA1c ≥11%) was associated with an increased odds for CAP compared to optimal glycemic control (HbA1c 6–7%). [104]

Mechanisms by which hyperglycemia increases the risk for CAP and its severity were discussed above. T2DM alters chemotaxis, phagocytosis and cytokine secretion in cell-mediated immunity, restricting the host's ability to attack the pathogen. This in turns increases CAP severity.[24,105] Natural killer immune

cells, which are effector lymphocytes that kill infected cells, have reduced activity in T2DM. [106]

The proinflammatory state caused by T2DM can lead to an exaggerated response to pathogens by macrophages, monocytes, and T-cells in the lung. This leads to the overproduction of proinflammatory cytokines (the so-called "cytokine storm") that may eventually damage the lung parenchyma.[107,108] Additionally, T2DM is associated with alveolar impairment, resulting in permeability of the respiratory vasculature and reduced gas exchange, which may be aggravated in CAP.[109] Finally, endothelial dysfunction, commonly seen in microvascular disease of T2DM, heightens pulmonary ischemia and tissue edema in CAP.[110]

Statin Therapy in Patients with CAP and T2DM

Statins have known pleotropic effects in reducing reactive oxygen species and regulating anti-inflammatory and antioxidant processes. Statins have long been proposed as therapeutic agents in infectious diseases, such as influenza virus, psoriasis, and more recently, COVID-19.[111-113] Postulated beneficial effects of statins specific to CAP patients include a reduced influx of inflammatory cells in the lungs, prevention of T-cell activation, and improved neutrophil function, including reduction of inflammatory markers and proinflammatory cytokines as discussed above.[114,115]

The interaction between statins and T2DM is complex. Large randomized clinical trials (RCT) have shown that statins may be diabetogenic, and that the risk is slightly greater with intensive statin therapy than moderate statin therapy.[116,117] The excess risk of developing T2DM from high dose statin therapy has been estimated to be 50-100 cases per 10,000 treated individuals. The T2DM risk was associated with other high-risk factors for T2DM, including elevated body mass index (BMI), impaired fasting glucose, and high HbA1c.[118] The pathogenesis of T2DM by statins is currently unknown. Hypotheses include a causal relationship between LDL receptor-mediated transmembrane cholesterol transport upregulated by statins and T2DM, and the inhibition of the mevalonate pathway by statins promotes adipose insulin resistance.[119,120] In spite of this risk, statins are still indicated for the treatment of T2DM given evidence from RCTs such as the JUPITER trial, which found that statins reduce ASCVD events and mortality of

patients with T2DM.[121] Risk benefit analysis found that the benefit of statins is 50 times greater than the risk of T2DM.[117]

Several epidemiological studies have associated statin use with the reduced risk of CAP severity in the general population, and in patients with T2DM. Many retrospective studies have found more favorable short-term mortality and clinical outcomes for CAP patients with T2DM on statin therapy compared to those not on statins. Hypothetically, these benefits are a result of statins' anti-inflammatory effects.[122-126]

Among these studies are Douglas et al. (2011), that used propensity scores to match every patient starting a statin between 1995 and 2006 in the United Kingdom Health Improvement Network database to as many as five non-statin patients. The patients were screened for diagnosis of pneumonia in their electronic medical records and then subsequent all-cause mortality within six months of diagnosis. The study estimated that within the six-month period, 13% of statin users died compared with 19.7% of non-users, giving an adjusted hazard ratio of 0.67 (0.49 to 0.91)[122]

Mortensen et al. (2012) analyzed Department of Veterans Affairs (VA) data of elderly patients hospitalized with CAP between 2002-2007 and used propensity score matching to examine the association of statins, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) on CAP-outcomes. Statins were significantly associated with a decreased 30-day mortality, decreased need for mechanical ventilation, and reduced length of stay in CAP patients.[123]

By comparison to Mortensen, Havers et al. (2016) was a prospective observational study which used propensity score analysis to match statin users and non-statin users among 2016 patients hospitalized for CAP in five non-VA hospitals in Chicago, Illinois and Nashville, Tennessee. Havers et al. (2016) found no significant association of statin use with decreased length of stay or in-house mortality. However, they did not follow up with patient outcomes after discharge.[127]

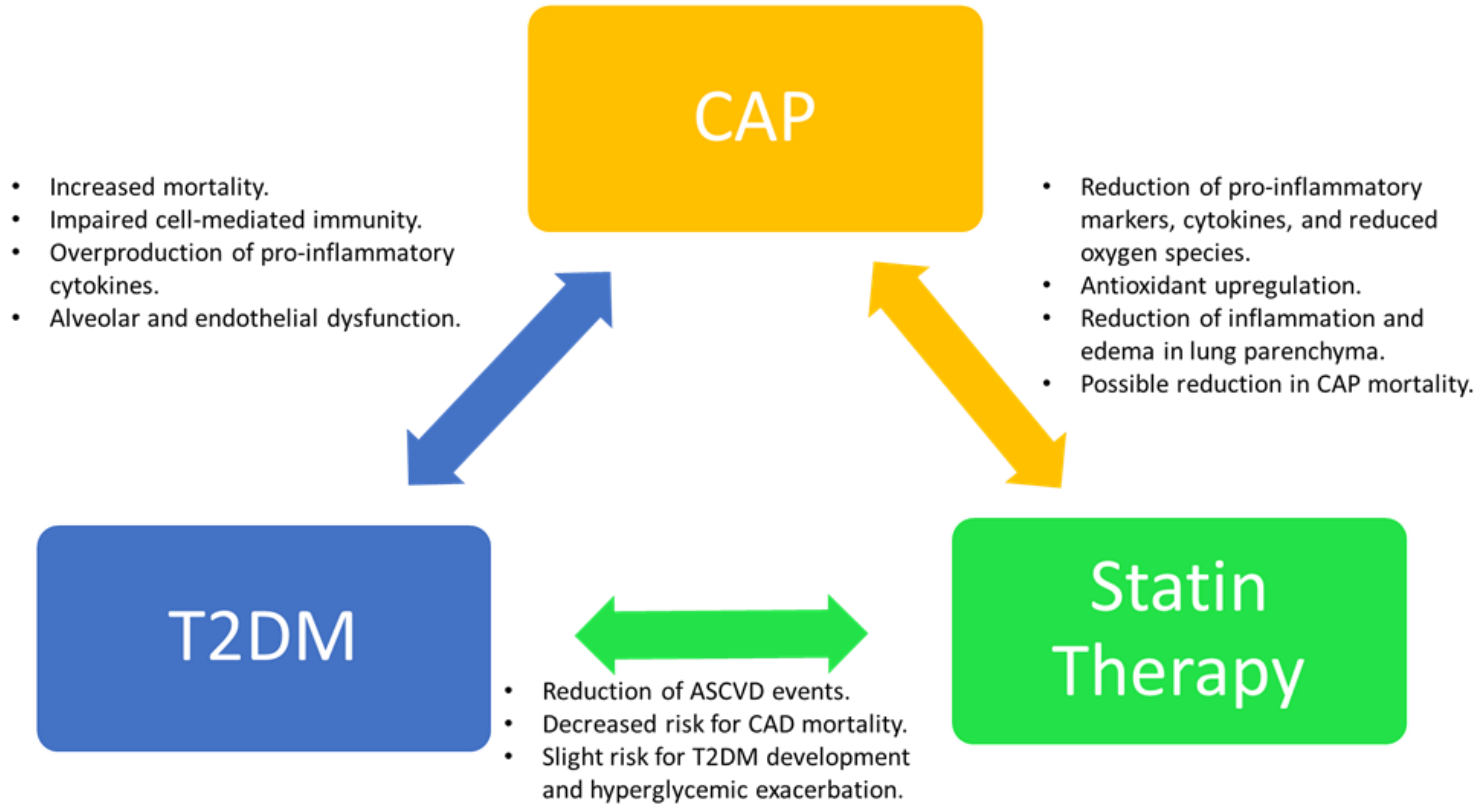
van de Garde et al. (2011) employed a matched case-control design, using ICD-9 diagnosis data and medication lists from the UK Department of Health database, to identify to CAP patients with diabetes and prior statin use. It matched one statin-treated case with four controls matched on age, gender and date of diagnosis, while co-morbidities such as cardiovascular and pulmonary diseases were controlled in the regression. van de Garde et al. found statin use reduced the risk of fatal and non-fatal cases of CAP. However, it followed patients for 10 years beginning from 1987, with a lower incidence of statin and a longer follow up period than the HAPPI study.[125]

Policardo et al. (2017) is a retrospective case-control, a model similar to van de Garde et al. (2011), using coded diagnoses and prescription filled lists of patients in the Tuscany, Italy health system. Policardo et al. (2017) matched one statin-treated case with two controls matched on age, gender and date of diagnosis, and found statin use decreased the risk for CAP hospitalization in subjects without or with diabetes.[124]

One recent observational study conducted at a single hospital in Bronx, New York compared outcomes for patients admitted for COVID-19 pneumonia, grouping them as those who did and those who did not receive prior statin therapy. Analysis after propensity score matching showed a significantly lower risk of in-house mortality for COVID-19 patients with T2DM who received statins compared to those who did not receive statins.[128]

Figure 2.1 displays the current known interactions between T2DM, CAP, and statin therapy.

Figure 2.1 Interactions between T2DM, CAP, and Statin Therapy



Gaps in the Literature

Most publications that report a positive effect of statins on CAP are retrospective observational studies with limited power. Meta-analyses aggregating RCTs that included statins among other CAP interventions or nonrandomized controlled studies were also based on retrospective data. These studies had conflicting results in the analysis of length of statin treatment and the magnitude of a preventative effect on CAP outcomes.[129-133] Additionally, RCTs did not show the positive effects of statins on outcomes that preclinical and observational studies found.[134] Only one ongoing RCT in the U.S. is evaluating statins with other pharmaceutical interventions in critically ill patients with CAP.[135] A prior RCT found no effect of simvastatin therapy on the 28 day mortality of pneumonia patients, but patients were diagnosed with VAP.[136] To the best of our knowledge, no large scale prospective cohort study showed the effect of statin therapy on the long-term mortality and morbidity of T2DM patients hospitalized for CAP.

CHAPTER 3

METHODS

Study Design

This present investigation is a secondary analysis of deidentified data collected from the HAPPI Study, a prospective cohort study. The HAPPI Study was conducted in nine adult acute-care hospitals in Louisville, Kentucky over three years, from 6/1/2014-5/31/2016 and from 10/1/2016-3/31/2017. The author worked on HAPPI as a PhD student and research coordinator from 2014-2016.

A patient was deemed eligible for HAPPI by the following criteria met:

1) Presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading,

2) At least one of the following symptoms of laboratory findings:

a) new cough or increased cough or sputum production;

b) Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F);

c) Changes in leukocyte count;

3) No alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2.

Patients admitted for CAP were deemed ineligible for enrollment in HAPPI if they did not have a permanent or valid address in the Louisville, Kentucky area based on the US Census Bureau data, did not possess a valid Social Security Number (SSN), or were incarcerated in a corrections system or mental health facility at the time of hospital admission.

Past medical history and medication treatment was verified using electronic medical records (EMR) and diagnostic coding (ICD-9 from 6/1/2014- 10/14/2015, ICD-10 after 10/15/2015).

All the data was deidentified prior to analysis, using an industry standard deidentification process, including name, address, SSN, birthdate, and medical record number. Admission date and date of discharge were retained. All participants were given declassified case IDs when their cases were entered into the Pneumonia Database, the source of this study's data.

This study is IRB approved as Exempt because de-identified data was used and further IRB approval was deemed not necessary by the IRB Office.

Study Cohort, Inclusion, and Exclusion Criteria

A total of 10,101 verified cases from HAPPI were available for use and were eligible for study. Patients were excluded from analysis if they were lost to follow up 1 year after their initial CAP hospitalization (n = 49). If a patient was unable to reach by phone call, mortality was evaluated by reviewing medical records and mortality data obtained from the Kentucky Department for Public Health Office of Vital Statistics. SSNs were checked with the Kentucky Office of Vital Statistics to see if any patient had died unreported.

Using the above criterion, 10,052 cases were included in this study cohort (n = 10,052).

Description of Study Variables and Covariates

A. Definition of T2DM

2,734 T2DM patients were identified in the study cohort using the following ADA criteria:[30]

(a) Past medical history listing T2DM and a HbA1c test value performed at admission for CAP or done within six months prior to admission for CAP.

(b) Past medical history not listing T2DM prior to admission for CAP, however, the patient was diagnosed with T2DM during their hospitalization, with HBA1c values confirmatory for T2DM ($\geq$ 6.5%).

(c) Insulin-dependent diabetes was a variable collected in the HAPPI study. 541 patients were identified as T1DM and excluded from the T2DM cohort.

B. Definition of Statin Exposure

Statin use is defined by any class of statin on the patient's home medication list recorded on admission, confirmed by the HAPPI data collection team on review of their electronic medical records (EMR) and outpatient medication list as recorded by the hospital. The frequency of statins prescribed to the patient to be at least once per day. Patients who discontinued statin therapy before CAP hospitalization were excluded. Statin dosage was not among the variables recorded in the HAPPI study.

Using this criteria, 3605 patients with prior statin exposure were identified in the study cohort.

C. Description of Covariates

Covariates for the regression model included all demographic variables, medical co-morbidities, clinical conditions, and pharmaceutical usage associated with CAP hospitalizations. Covariate data was acquired by the HAPPI study using EMR and diagnostic coding (ICD-9 from 6/1/2014- 10/14/2015, ICD-10 after 10/15/2015).

The covariates considered and analyzed for the model include age $\geq$ 65 years, race, sex, OW, OB, hospitalization in the past 90 days, direct admission to the ICU

on CAP hospitalization, mechanical ventilation on admission, nursing home residence, prior hospitalization within the past 90 days, history of renal disease, active or recently diagnosed cancer, CAD, hypertension, congestive heart failure (CHF), prior myocardial infarction (MI), and current medication usage of beta-blockers, warfarin or ACE-I.

Statistical Methods Analysis

The study design with the proposed statistical methods included decision tree analysis, logistic regression and propensity score analysis (Figure 3.1). Using propensity score matching (PSM) may reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among patients who were previously on statins versus those that did not.

Sub-Analysis: Cost Analysis

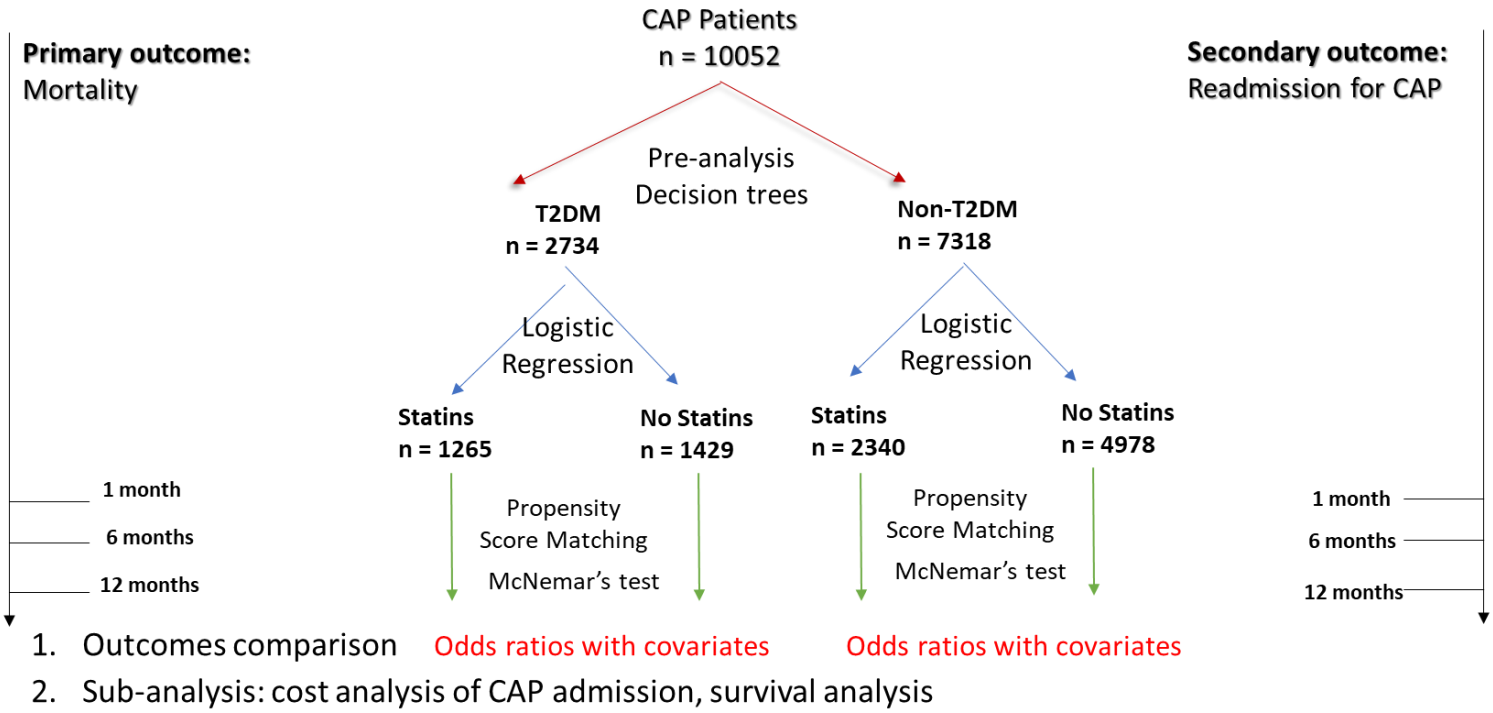
Length of stay as an inpatient was a variable collected in the HAPPI study through chart review, with dates of admission and discharge withheld. Total mean costs for hospitalizations were estimated using mean length of stay in days between patients with the T2DM/statin interaction and T2DM patients without prior statin use.

These values would then be used to calculate hospital cost estimates based on the 2014-2016 aggregate data from the Agency for Healthcare Research and Quality (AHRQ).

Statistical Tools

IBM SPSS Statistics 27 was used for all data processing and statistical analysis.

Figure 3.1. Study Design and Statistical Methodology



CHAPTER 4

RESULTS

Study Population Description

There were 10,052 CAP cases in the HAPPI study suitable for analysis after excluding those patients lost to follow up after 1 year of their CAP hospitalization and enrollment into the HAPPI study (n=49). Of these, 2734 cases were T2DM, while the remaining 7318 had no T2DM diagnosis before or during their CAP hospitalization.

Table 4.1 presents the demographic characteristics of the study population by T2DM status. At baseline, there were significantly a higher proportion of non-Caucasians in the T2DM cohort (22.8%) than in the non-T2DM cohort (19.9%) ($p < 0.01$). Hispanic ethnicity was not a category collected in the HAPPI dataset. By gender, there was a higher percentage of females in the T2DM cohort (54.7%) than in the non-T2DM cohort (53.4%), but this was not significant ($p = 0.24$). There is a significantly lower percentage of T2DM patients under the age of 34 (2.2%) than non-T2DM cases (5.5%) ($p < 0.01$). The majority of T2DM patients were in the 60-80 age range. There was a significantly higher percentage of T2DM patients age 60 to 64 (12.1%) than non-T2DM patients (10.0%) ($p < 0.01$), and a significantly

higher percentage of T2DM patients age 65-74 (24.8%) than non-T2DM cases (21.3%) ($p < 0.01$). There was a significantly higher percentage of non-T2DM age ≥ 85 years (15.5%) than the T2DM (12.5%) ($p < 0.01$), implying that the T2DM patients had a lower longevity than the non-T2DM patients.

Table 4.1. Baseline Patient Demographics

Characteristic	**T2DM (n = 2,734)**	**Non-T2DM (n= 7,318)**	**P value**
Race			
Caucasian	2108 (77.1)	5874 (80.3)	<0.01
African American	572 (21.0)	1361 (18.6)	<0.01
Other	51 (1.8)	83 (1.2)	0.02
Gender			
Male	1238 (45.3)	3410 (46.6)	0.24
Female	1496 (54.7)	3908 (53.4)	0.24
Age Groups			
18 to 24	15 (0.5)	115 (1.6%)	<0.01
25 to 34 years	46 (1.7)	288 (3.9%)	<0.01
35 to 44 years	155 (5.7)	455 (6.2%)	0.35
45 to 54 years	309 (11.3)	822 (11.2%)	0.89
55 to 59 years	283 (10.4)	709 (9.7%)	0.30
60 to 64 years	330 (12.1)	734 (10.0%)	<0.01
65 to 74 years	677 (24.8)	1557 (21.3%)	<0.01
75 to 84 years	576 (21.1)	1507 (20.6)	0.58
≥ 85 years	343 (12.5)	1131 (15.5)	<0.01

Data are represented as n (%).

A comparison of the percentage distribution of age groups between adults hospitalized CAP and the overall adult Louisville population from 2016-2019 is shown in Figure 4.1. Both T2DM and non-T2DM cohorts skew left in age compared to the city at large, with the percentage of patients 65 and older significantly higher in both cohorts than in the overall city population ($p < 0.001$).

Comparisons of CAP patients' demographics by race and gender to the adult Louisville population from 2016-2019 are shown in Figure 4.2. Both T2DM and non-T2DM cohort groups significantly have a higher percentage of Caucasians and less non-black minorities in than the city population at large ($p = 0.005$). There is no significant difference in gender between all three groups ($p = 0.24$).

Figure 4.1 Comparison of percentage distribution of HAPPI patient age to the Louisville population: (blue) T2DM patients hospitalized with CAP, (gray) non-T2DM patients hospitalized with CAP, (red) overall adult population of Louisville from 2016-2019.

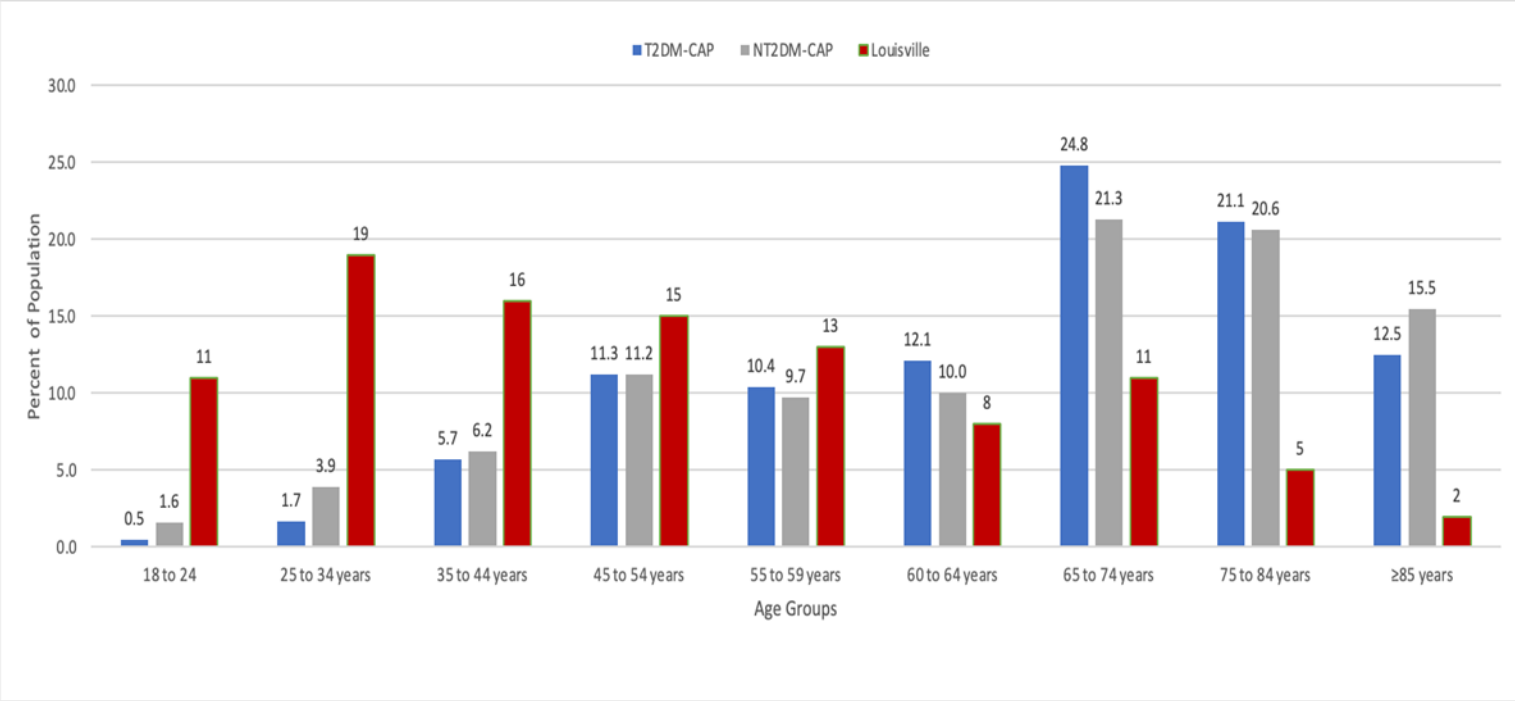


Figure 4.2. Comparison of HAPPI patient race and gender demographics to the Louisville population: (blue) T2DM patients hospitalized with CAP, (gray) non-T2DM patients hospitalized with CAP, (red) overall adult population of Louisville from 2016-2019.

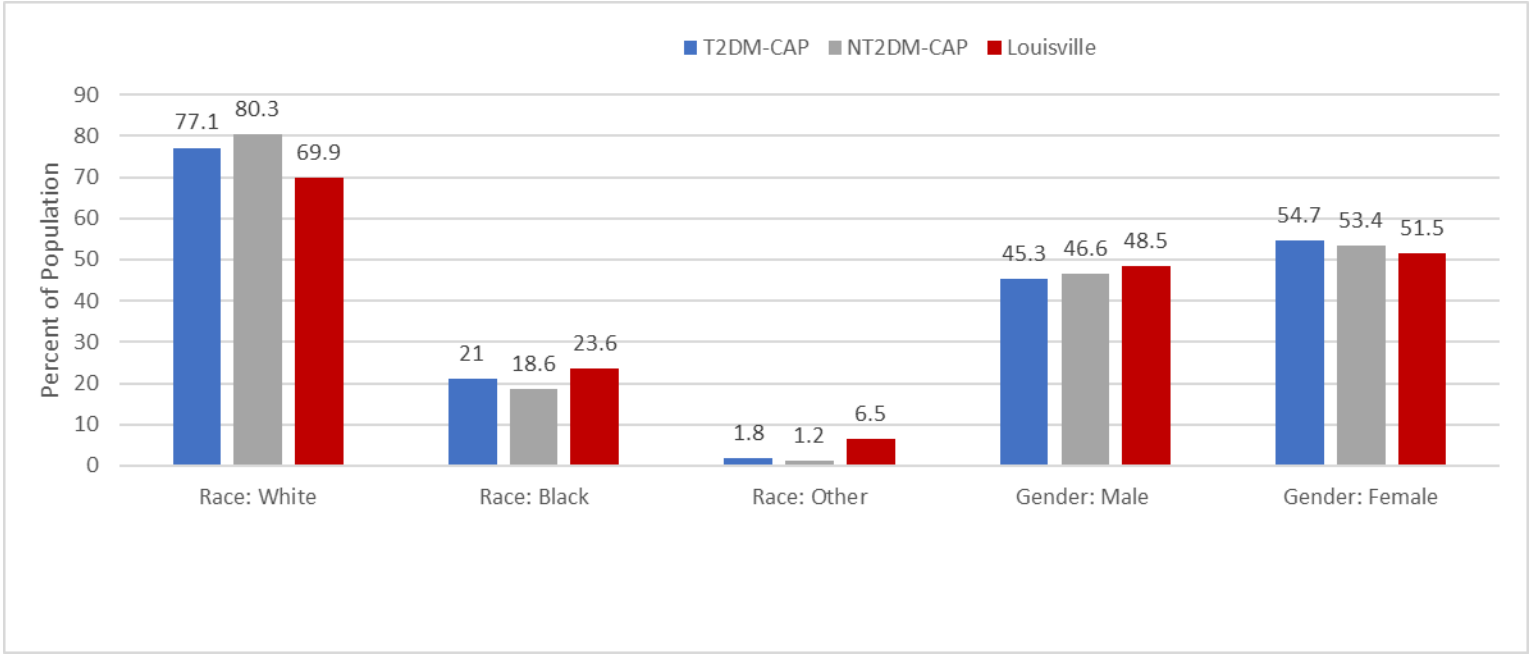


Table 4.2 shows the prior medical history characteristics of the study population. At baseline, the T2DM cohort had significantly higher prevalence of cardiovascular disease, its sequalae, and cardiovascular treatment than the non-T2DM cohort. Patients in the T2DM cohort had higher prevalence of chronic diseases such as hypertension (79.8% vs 32.6%), dyslipidemia (56.0% vs 40.0%), coronary artery disease (37.5% vs 27.4%), chronic heart failure (36.2% vs 27.4%), chronic renal disease (35.6% vs 26.1%), obesity (46.2% vs 30.7%), and prior myocardial infarction (17.8% vs 11.7%) (Table 4.2). Patients in the T2DM cohort were significantly more likely to report usage of cardiovascular drug treatments, including statins (46.3% vs. 32.0%), beta blockers (47.2% vs 36.1%), and ACE inhibitors (34.3% vs 25.5). Patients with T2DM had higher incidence of going directly to the ICU (19.9% vs 16.1) and being mechanically ventilated (16.8% vs 12.3%) within the first 24 hours of their CAP hospitalization.

Patients in the non-T2DM cohort had a significantly higher prevalence for a previous neoplastic disorder (15.0% vs 10.9%). There was no statistically significant difference in the prevalence of COPD (49.4% vs 48.1%), OW (25.9% vs 26.1%), smoking history (69.1% vs 69.6%), prior hospitalization in the past 90 days, or nursing home residence between the two groups.

Table 4.2. Patient Medical History and Hospitalization Characteristics

Characteristic	**T2DM (n = 2,734)**	**Non-T2DM (n= 7,318)**	**P value**
Past Medical History			
Renal Disease	974 (35.6)	1909 (26.1)	<0.01
Cancer, any type	299 (10.9)	2095 (15.0)	<0.01
CAD	1026 (37.5)	2008 (27.4)	<0.01
CHF	991 (36.2)	2005 (27.4)	<0.01
Hypertension	2183 (79.8)	4817 (65.8)	<0.01
COPD	1351 (49.4)	3520 (48.1)	0.25
MI	487 (17.8)	853 (11.7)	<0.01
DLP	1530 (56.0)	2926 (40.0)	<0.01
OW	709 (25.9)	1913 (26.1)	0.84
OB	1262 (46.2)	2247 (30.7)	<0.01
Current or former smoker	1890 (69.1)	5092 (69.6)	0.63
Hospitalized in the previous 90 Days	804 (29.4)	2109 (28.8)	0.56
Nursing home residence	337 (12.3)	929 (12.7)	0.59
Statin usage	1265 (46.3)	2340 (32.0)	<0.01
Beta-Blocker usage	1290 (47.2)	2639 (36.1)	<0.01
ACE-I usage	939 (34.3)	1866 (25.5)	<0.01
Hospitalization			
Direct ICU admission	544 (19.9)	1179 (16.1)	<0.01
Ventilation on admission	468 (16.8)	900 (12.3)	<0.01
Pneumonia Severity Index (mean)	107.7	100.3	0.07

Crosstabs

1265 HAPPI patients had the T2DM and statin interaction. 1469 HAPPI patients had T2DM without a history of prior statin use. Of the 6447 HAPPI patients who were non-T2DM, 2340 patients had prior statin exposure, while 4978 patients were exposed to neither variable.

Contingency tables were employed to test if there was some association between T2DM and statin use in CAP patients (Table 4.3) with the expected values in paratheses. The chi-square statistic for the table was significant ($x^2 = 176.78$, p

< 0.0001), indicating that there is some association between T2DM and statin use in CAP patients, with an odds ratio (OR) of 1.83 (95% confidence interval (CI): 1.68 – 2.00, p < 0.01). After the cross tabulations, decision tree analysis was employed to see if statin exposure and T2DM are strongly related to morbidity and mortality in CAP patients.

Table 4.3 Crosstabulation showing HAPPI patients by T2DM diagnosis and previous statin usage with expected values for each group in parentheses.

		T2DM: Positive	T2DM: Negative
Statin	Exposed	n=1265 (981)	n=1469 (1754)
	Unexposed	n=2340 (2625)	n=4978 (4694)

n=10052
X^2 = 176.78
p< 0.00001

Odds ratio for statin exposure among diabetics vs. non-T2DM:
OR = 1.83 (95% CI: 1.68 -2.00, P<0.001)

Decision Tree Analyses

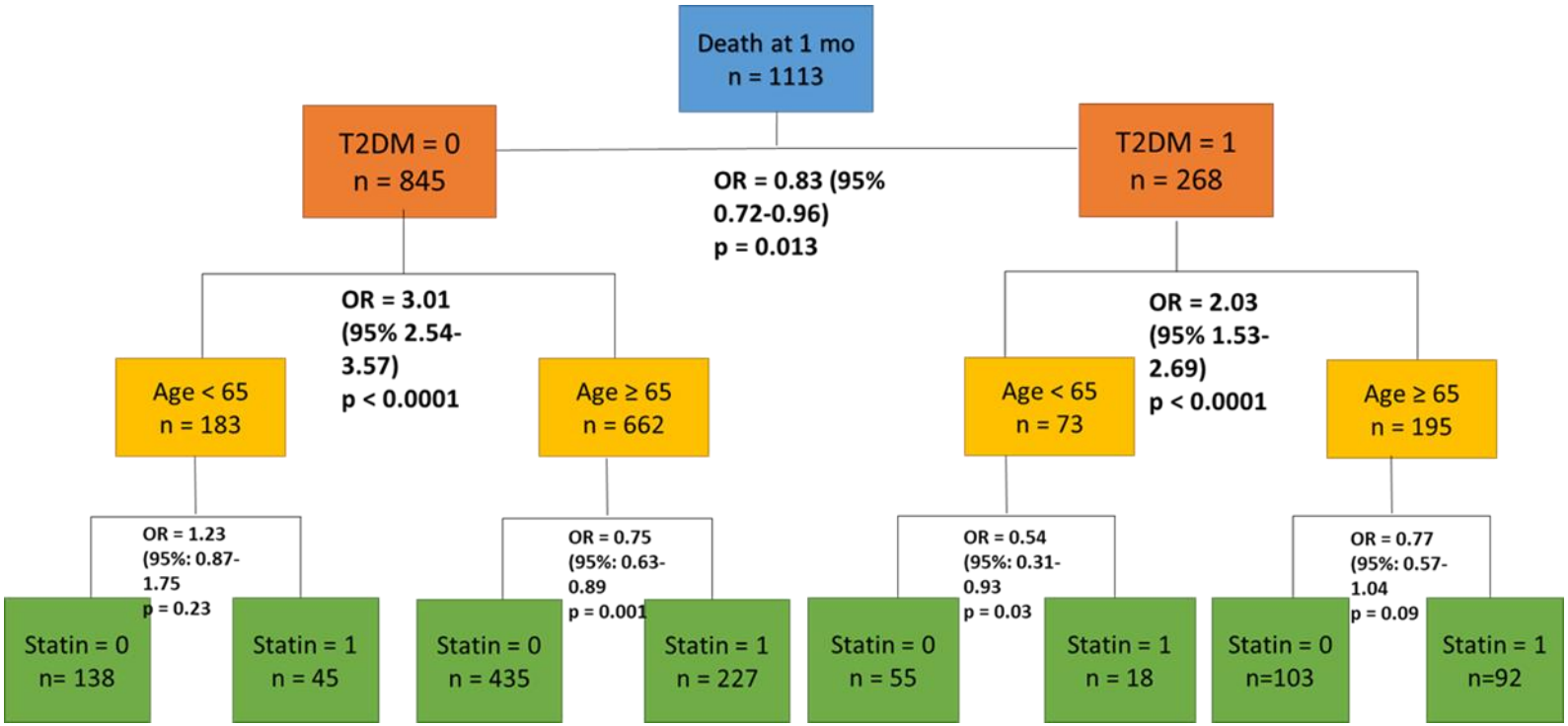
A. Decision Tree Analysis of Mortality Outcomes at One Month

The classification tree produced by decision tree analysis found the most important predictor of mortality at one month was T2DM status, followed by age ≥ 65, and then statin use. (Figure 4.3) In the decision tree analysis, T2DM was a

significant protective effect against mortality at one month (OR = 0.83: 95% CI 0.72-0.96, p = 0.01). Patients age ≥ 65 were at increased odds for death in both diabetics (OR = 2.03: 95% CI 1.53-2.69) and non-diabetics (OR = 3.01: 95% CI 2.54-3.57), and these odds was significant for both populations (p < 0.0001 and p < 0.0001, respectively).

Statin exposure had a significant protective effect against mortality at one month in patients with T2DM and age < 65 (OR = 0.54: 95% CI 0.31-0.93, p = 0.03) and in patients without T2DM and age ≥ 65 (OR = 0.75: 95% CI 0.63-0.89, p = 0.001). Patients with T2DM and age ≥ 65 had a protective effect from statins against mortality at one month (OR = 0.77: 95% CI 0.57-1.04, p = 0.09), however this was not significant. Statin exposure was associated with an increased odds for mortality at one month in patients without T2DM and age < 65 (OR = 1.23: 95% CI 0.87-1.75), but this was not significant.

Figure 4.3. Decision tree analysis for mortality after one month based around history of T2DM, statin usage, and age.

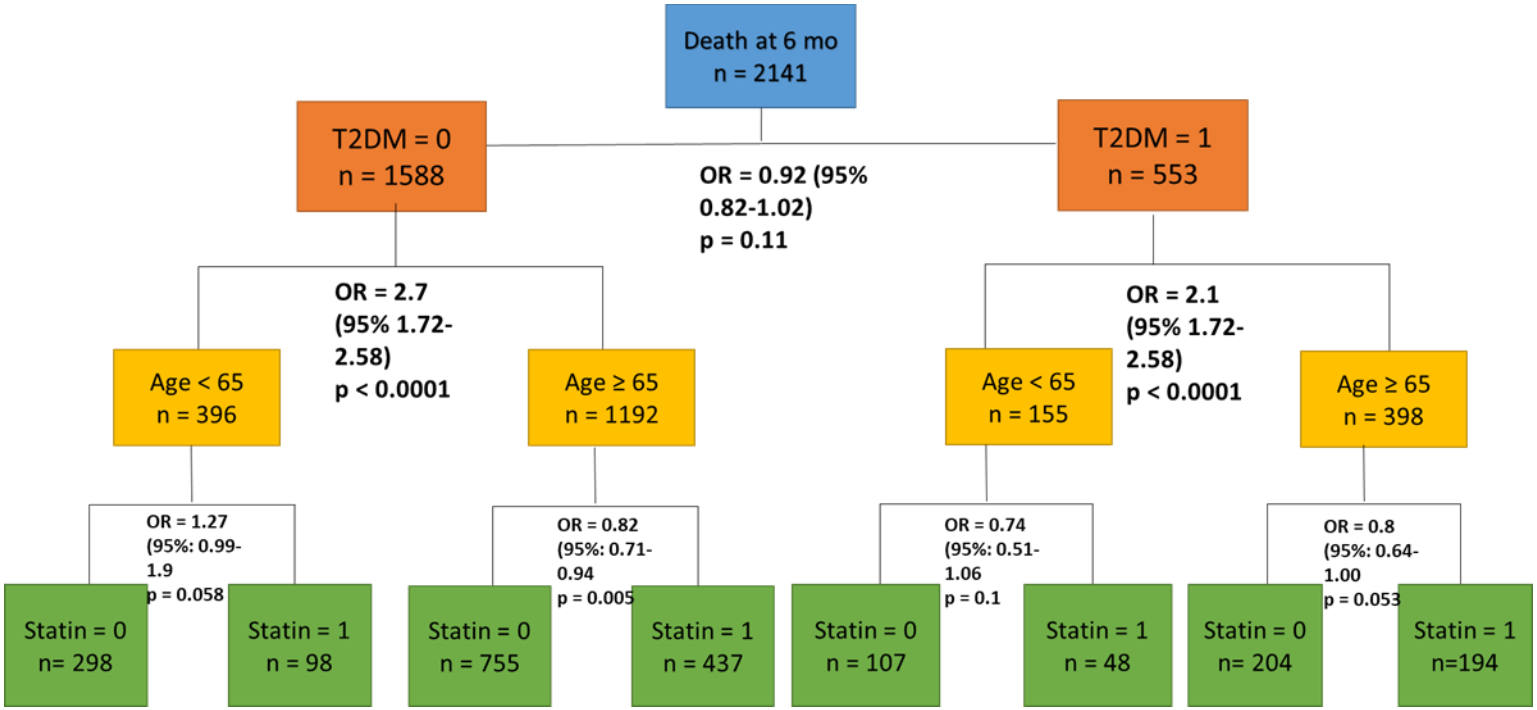


B. Decision Tree Analysis of Mortality Outcomes at Six Months

The decision tree analysis for death within six months of CAP hospitalization (Figure 4.4) found T2DM had a protective effect against mortality (OR = 0.92: 95% CI 0.82-1.02, p = 0.11), but this effect was not significant. The risk for death within six months was significantly increased for patients age ≥ 65, in diabetics (OR = 2.1: 95% CI 1.72-2.58, p < 0.0001) and non-diabetics (OR = 2.7: 95% CI 1.72-2.58, p < 0.0001).

Statin exposure was associated with a decreased odds against mortality at six months in patients without T2DM and age ≥ 65 (OR = 0.82: 95% CI 0.71-0.94, p = 0.005) that was significant, and a decreased odds in patients with T2DM and age ≥ 65 (OR = 0.8: 95% CI 0.64-1.00, p = 0.053) that approached significance. Patients with T2DM and age < 65 had a protective effect from statins against mortality at six months (OR = 0.74: 95% CI 0.51-1.06, p = 0.10), however this was not significant. Statin exposure was associated with an increased odds for mortality at six months in patients without T2DM and age < 65 (OR = 1.27: 95% CI 0.99-1.9, p = 0.058), that approached significance.

Figure 4.4. Decision tree analysis for mortality after six months based around history of T2DM, statin usage, and age.

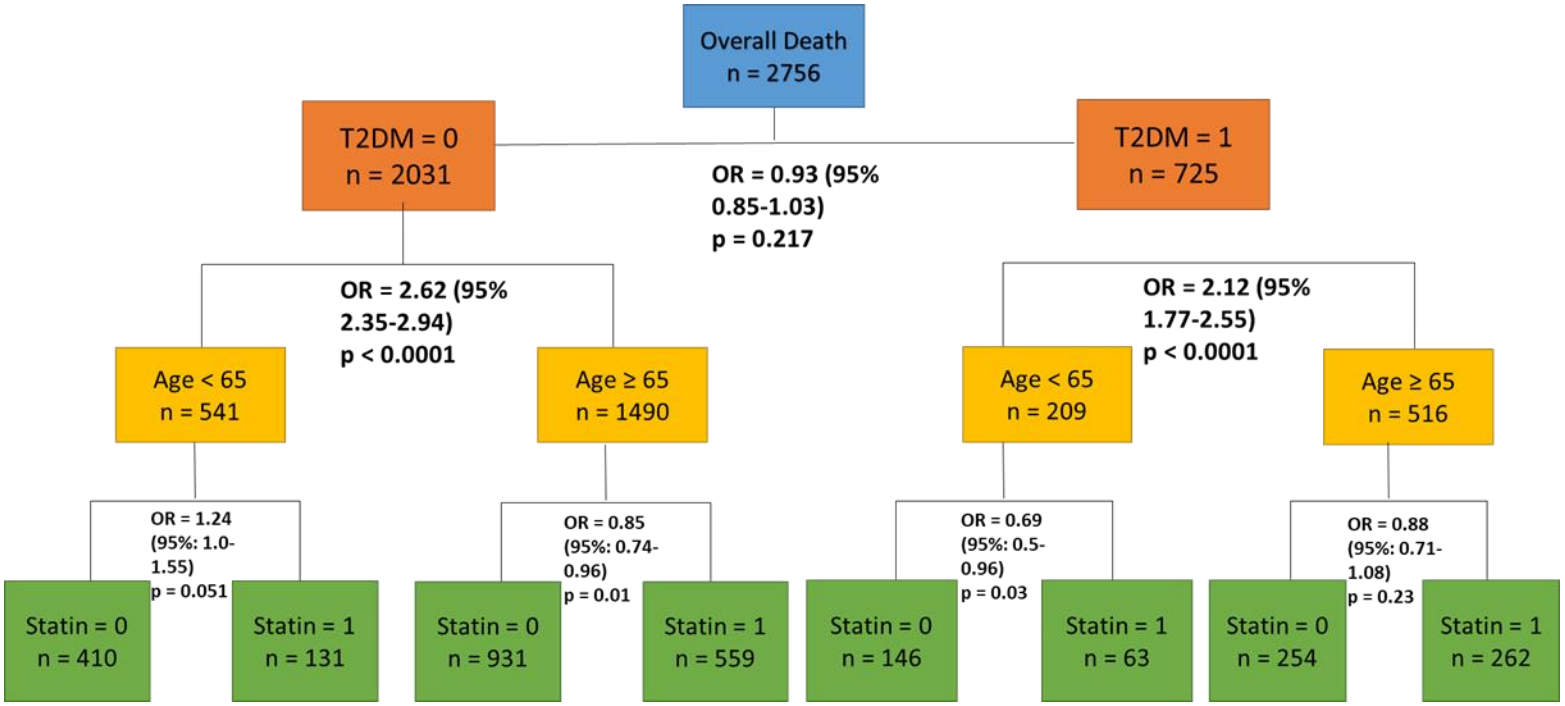


C. Decision Tree Analysis of Mortality Outcomes at 12 Months

The decision tree analysis for all-cause mortality within 12 months of CAP hospitalization (Figure 4.5) found T2DM trended toward a protective effect against mortality (OR = 0.93: 95% CI 0.85-1.03, p = 0.22), but this effect was not significant. As with mortality at one month and mortality at six months, age ≥ 65 was associated with a significant increased odds for death within 12 months in both diabetics (OR = 2.12: 95% CI 1.77-2.55, p < 0.0001) and non-diabetics (OR = 2.62: 95% CI 2.35 -2.94, p < 0.0001).

Statin exposure was significantly associated with a decreased odds against mortality at 12 months in patients with T2DM and age < 65 (OR = 0.69: 95% CI 0.50-0.96, p = 0.03) and patients without T2DM and age ≥ 65 (OR = 0.85: 95% CI 0.74-0.96, p = 0.01). Statin exposure was associated with a protective effect against mortality at 12 months in patients with T2DM and age ≥ 65 (OR = 0.88: 95% CI 0.71-1.08, p = 0.23), however this was not significant. Statin exposure was associated with an increased odds for mortality at 12 months in patients without T2DM and age < 65 (OR = 1.24: 95% CI 1.0-1.55, p = 0.051), that was significant.

Figure 4.5. Decision tree analysis for all-cause mortality after 12 months based around history of T2DM, statin usage, and age.

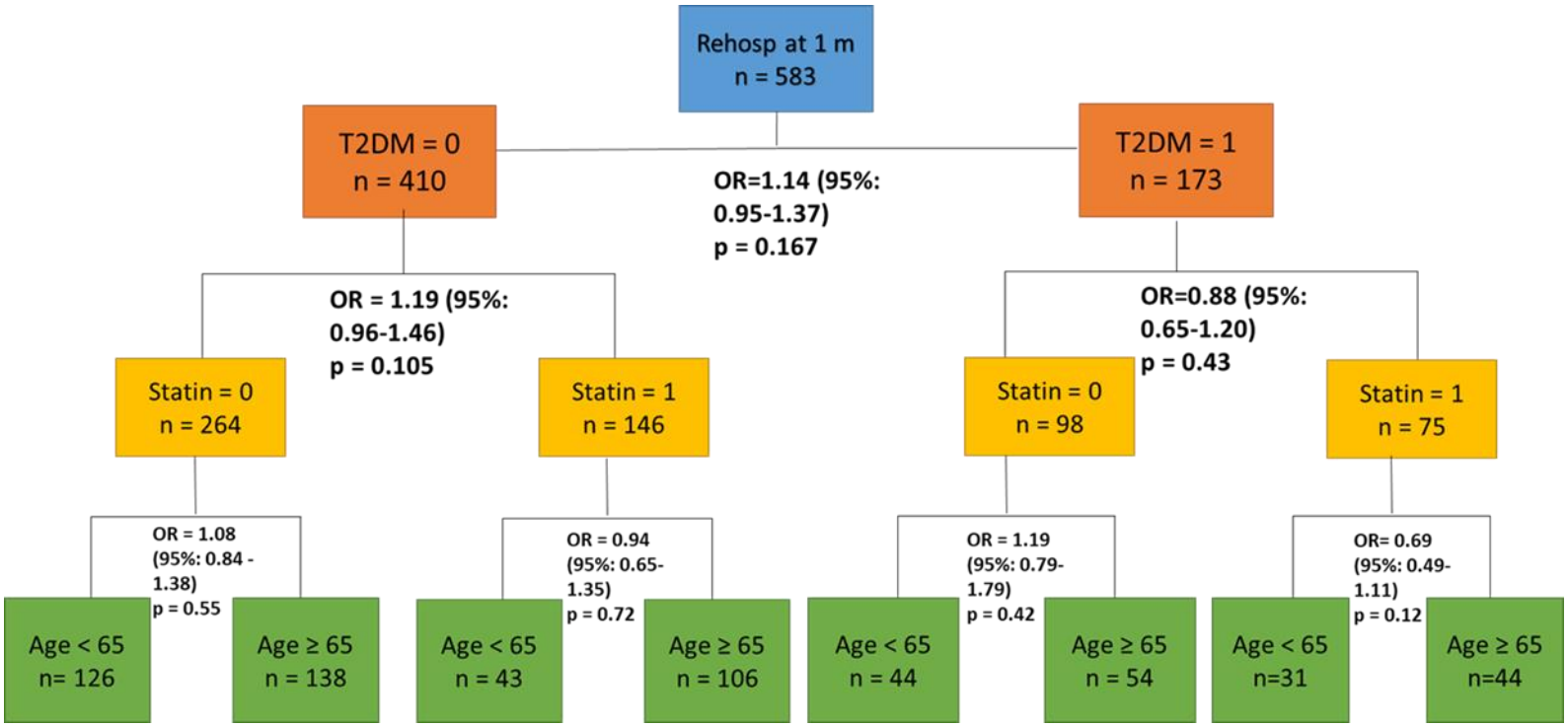


D. Decision Tree Analysis of Morbidity Outcomes at One Month

The decision tree analysis for morbidity (Figure 4.6) found T2DM increased the risk for CAP rehospitalization within one month of the initial admission (OR = 1.14: 95% CI 0.95-1.37, p = 0.17), but this effect was not significant. Statin exposure had a protective effect against CAP rehospitalization within one month in diabetics (OR = 0.88: 95% CI 0.65-1.2), whereas in non-diabetics, statin exposure was associated with an increased odds for CAP rehospitalization (OR = 1.19: 95% CI 0.96-1.46). Neither effect was significant (p = 0.43 and p = 0.11, respectively).

Age ≥ 65 was associated with a decreased odds of CAP rehospitalization in patients with both the T2DM and statin interaction (OR = 0.69: 95% CI 0.49-1.11) and in non-T2DM patients with statin exposure (OR = 0.94: 95% CI 0.65-1.35), however neither effect was significant (p = 0.12 and p = 0.72, respectively). Age ≥ 65 was associated with a non-significant tendency toward an increased odds for CAP rehospitalization in T2DM patients without statin exposure (OR = 1.19: 95% CI 0.79-1.79, p = 0.42) and non-T2DM patients without statin exposure (OR = 1.08: 95% CI 0.84-1.38, p = 0.55).

Figure 4.6. Decision tree analysis for morbidity (CAP rehospitalization) within one month based around history of T2DM, statin usage, and age.

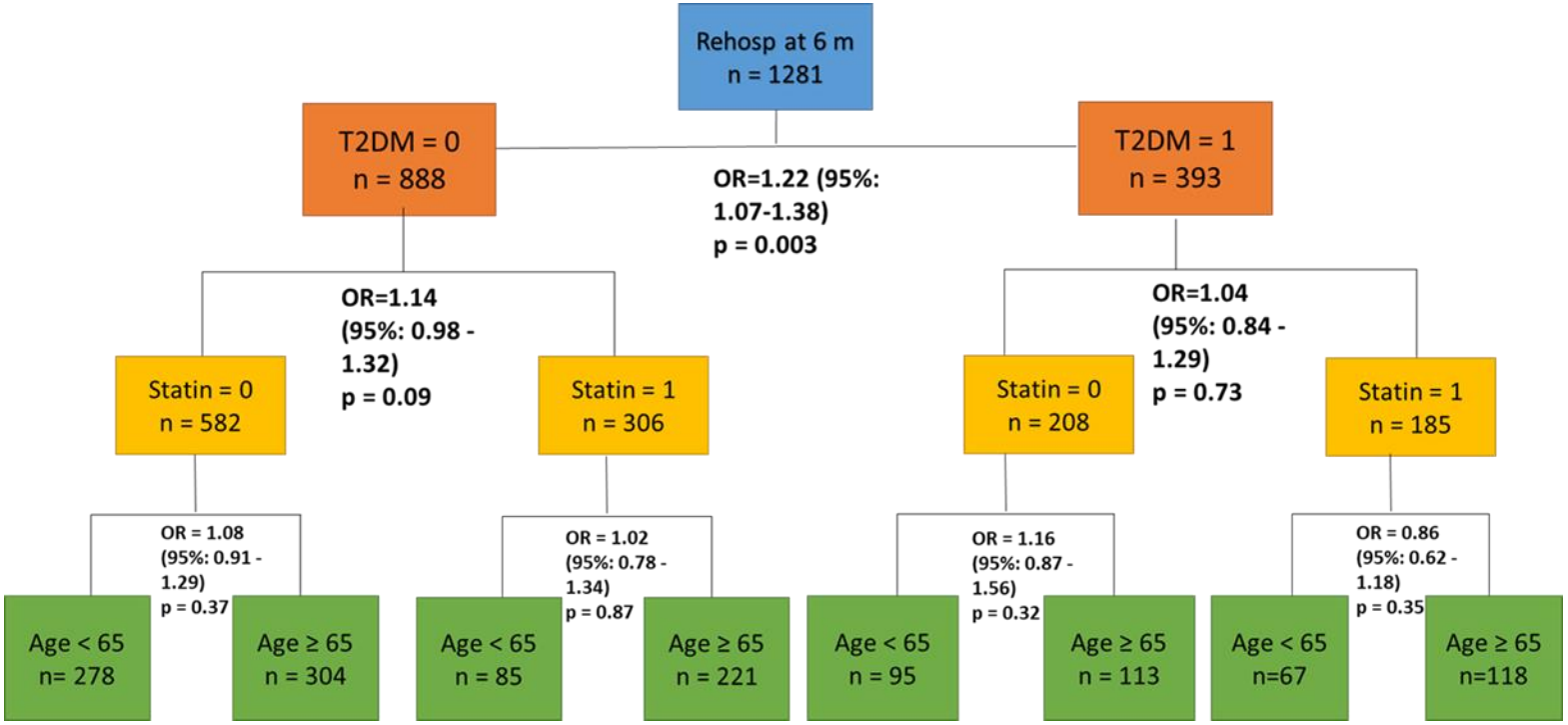


E. Decision Tree Analysis of Morbidity Outcomes at Six Months

Decision tree analysis for CAP rehospitalization within six months (Figure 4.7) found T2DM was associated with a significantly increased odds (OR = 1.22: 95% CI 1.07-1.38, p = 0.003). Further down in the decision tree, the risk for CAP rehospitalization was increased for both T2DM patients exposed to statins (OR = 1.04: 95% CI 0.84-1.29) and non-T2DM and statin exposed patients (OR = 1.14: 95% 0.98-1.32), but neither effect was significant (p = 0.73 and p = 0.09, respectively).

Age ≥ 65 had a protective effect from CAP rehospitalization in patients with the T2DM and statin interaction (OR = 0.86: 95% CI 0.62-1.18, p = 0.35), however not significantly. Interestingly, age ≥ 65 was associated with a non-significant increased odds for CAP hospitalization in diabetic patients without prior statin exposure (OR = 1.16: 95% CI 0.87-1.56, p = 0.32), in statin-exposed non-diabetic patients (OR = 1.02: 95% CI 0.78-1.34, p = 0.87), and non-diabetic patients without statin exposure (OR = 1.08: 95% CI 0.91-1.29, p = 0.37).

Figure 4.7. Decision tree analysis for morbidity within six months based around history of T2DM, statin usage, and age.

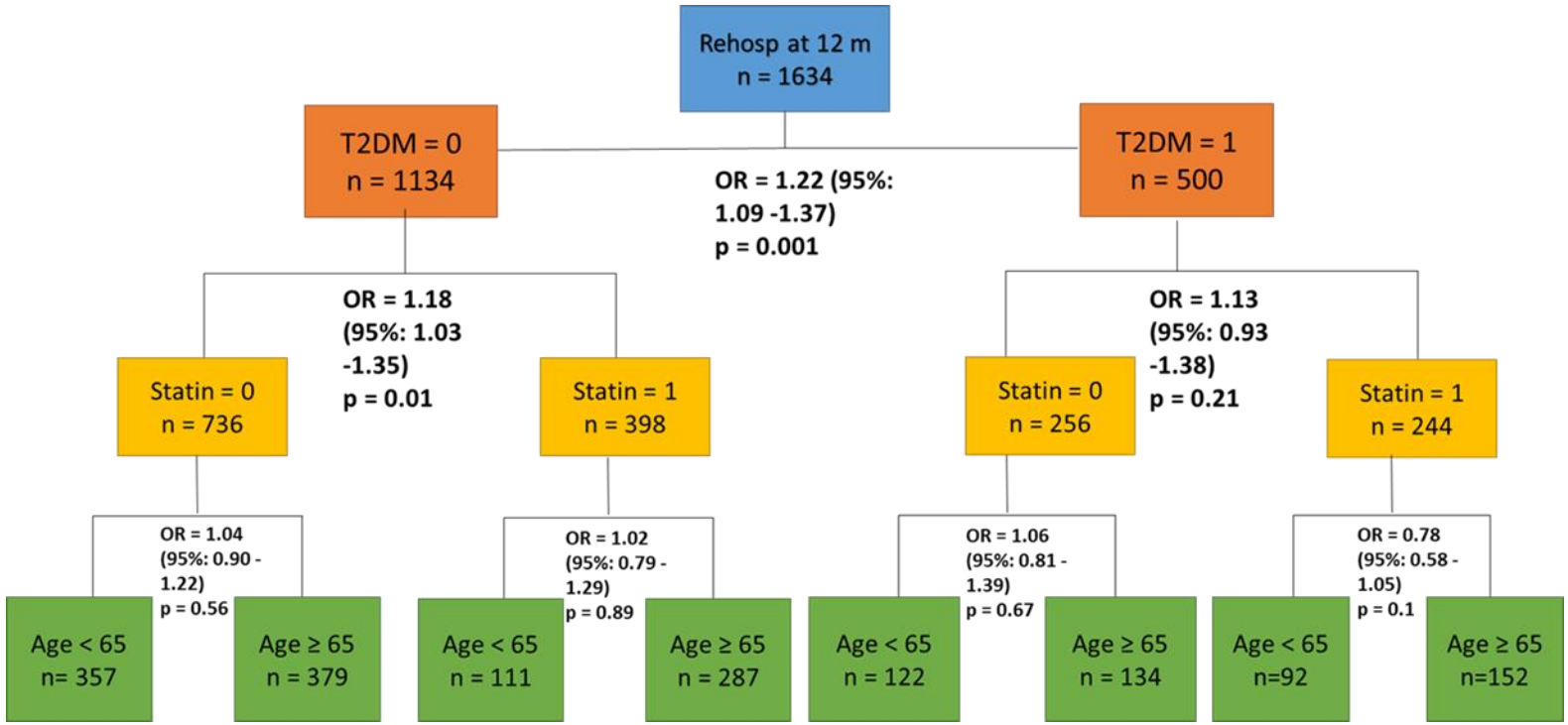


F. Decision Tree Analysis of Mortality Outcomes at 12 Months

The decision tree analysis for morbidity (Figure 4.8) found T2DM patients had a significantly increased odds for CAP rehospitalization within 12 months (OR = 1.22: 95% CI 1.09 -1.37, p = 0.001). Statin exposure was significantly associated with an increased odds for CAP rehospitalization patients without T2DM (OR = 1.18: 95% CI 1.03-1.35, p = 0.01). Statin exposure was associated with a non-significant increased odds for CAP rehospitalization in T2DM patients (OR = 1.13: 95% CI 0.93 -1.38, p =0.21).

Age ≥ 65 had a non-significant trend toward a protective effect from CAP rehospitalization in patients with the T2DM and statin interaction (OR = 0.78: 95% CI 0.58-1.05, p = 0.10). Age ≥ 65 was associated with a non-significant risk for CAP hospitalization in T2DM patients without prior statin exposure (OR = 1.06: 95% CI 0.81-1.39, p = 0.67), in statin-exposed non-T2DM patients (OR = 1.02: 95% CI 0.79-1.29, p = 0.89), and in non-T2DM patients without statin exposure (OR = 1.04: 95% CI 0.90-1.22, p = 0.56).

Figure 4.8. Decision tree analysis for morbidity within 12 months based on T2DM, statin usage, and age.



G. Summary of the Decision Tree Analysis Results

This present study found that statin use was significantly protective from mortality at one month ($p = 0.03$) and at 12 months ($p = 0.03$) after CAP hospitalization in T2DM cases under the age of 65 in the decision tree analysis. Additionally, a protective effect from mortality at six months was also seen in T2DM cases with statin exposure that was not significant ($p = 0.10$). For T2DM cases age $\geq$ 65, the decision tree analysis found statin usage also was protective from mortality at one month, six months, and 12 months, but none were significant or only approached significance.

For non-T2DM cases, statin usage was significantly protective from mortality at all three times for patients age $\geq$ 65. Interestingly, statin use was associated with increased mortality in non-T2DM patients at all three times but were not significant or approached significance ($p > 0.05$).

The decision tree analysis for morbidity outcomes showed a trend for T2DM cases age $\geq$ 65 on statins to have lower odds for CAP rehospitalization one month, six months, and 12 months after their first hospitalization compared to T2DM cases under 65 years old. However, these trends were not significant at all three time frames ($p > 0.05$). Patients with T2DM and no prior statin usage age $\geq$ 65 showed a trend for higher odds for CAP rehospitalization one month, six months, and 12 months after their first hospitalization compared to T2DM cases < 65 years old, but these trends also were not significant ($p > 0.05$).

In summary, the decision tree analysis showed that statin use was associated with significantly lower odds ratios in T2DM patients age > 65 years for mortality at one month (OR = 0.82: 95% CI 0.71-0.94, p = 0.005) and at 12 months (OR = 0.69: 95% CI 0.50-0.96, p = 0.03). In T2DM patients age ≥ 65, non-significantly lower odds for mortality were observed. Statin use was associated with significantly lower odds for mortality at one, six, and 12 months in non-T2DM patients age ≥ 65 but was associated with a higher odds for mortality in non-T2DM patients age < 65. The decision tree analysis found that statin use was associated with non-significant lower odds for CAP rehospitalization one, six, and 12 months after admission for T2DM patients age ≥ 65. This association was not seen in the other three groups (T2DM patients age < 65, non-T2DM patients age ≥ 65, and non-T2DM patients age < 65) for morbidity at one, six, and 12 months.

Binary Logistic Regression Analysis: Mortality Outcomes

A. Logistic Regression for Mortality at One Month Overall

Binary logistic regressions analyses of mortality outcomes at one month, six months and 12 months (dependent variables), using all independent study variables for the regression model for mortality at one month were done (Table 4.4). Originally, the model included the two study variables of interest (T2DM and prior statin exposure), and an interaction variable (combined T2DM X statin use) that indicated the effect of neither (non-T2DM with no statins), either (T2DM or statins), or both T2DM and statins if the case had dual exposure, and all the covariates as listed.

Through backwards stepwise elimination regression variable selection, the significant covariates that were significant for mortality in all at three time frames (one month, six, months and 12 months) were identified: as race, gender, age ≥ 65, OW, OB, history of neoplastic disease, history of a prior MI, direct admission to an ICU, mechanical ventilation on day of admission, nursing home residence, and being hospitalized within the past 90 days. These above covariates were used in the final logistic regression model. Additional subgroup regression models were stratified by age, gender, and race. (Supplementary Tables 4.1 – 4.8)

Table 4.4. Regression Equation for Mortality at One Month

Variables in Equation	**OR**	**SE**	***p***	**95% CI**	
				Lower	**Higher**
Overall Mortality					
T2DM	0.95	0.10	0.60	0.78	1.16
Statin	0.85	0.09	0.07	0.72	1.01
T2DM_Statin	0.87	0.16	0.39	0.63	1.20
Race: White	1.43	0.36	<0.01	1.19	1.73
Sex: Male	1.17	0.07	0.02	1.02	1.34
Age ≥ 65	2.23	0.08	<0.01	1.90	2.615
OW	0.65	0.09	<0.01	0.55	0.77
Obese	0.57	0.09	<0.01	0.48	0.68
Cancer	3.03	0.08	<0.01	2.59	3.54
MI	1.26	0.10	0.02	1.04	1.52
Nursing home	2.97	0.07	<0.01	2.53	3.48
Hospitalized in past 90 days	1.38	0.07	<0.01	1.20	1.58
ICU on Admit	2.54	0.09	<0.01	2.11	3.00
Intubation on Admit	1.80	0.10	<0.01	1.49	2.18
Mortality Age < 65 Years					
T2DM	1.41	0.18	0.06	0.99	2.02
Statin	1.11	0.20	0.59	0.76	1.63
T2DM x Statin	0.70	0.16	0.03	0.52	0.96
Race: White	1.20	0.16	0.25	0.88	1.64
Sex: Male	1.23	0.14	0.13	0.94	1.62
OW	0.71	0.18	0.06	0.49	1.01
Obese	0.70	0.16	0.03	0.52	0.96
Cancer	7.02	0.16	<0.01	5.17	9.53
MI	1.73	0.22	0.01	1.13	2.65
Nursing home	2.90	0.20	<0.01	1.95	4.33
Hospitalized in past 90 days	1.23	0.14	0.15	0.93	1.63
ICU on Admit	2.88	0.18	<0.01	2.04	4.08
Intubation on Admit	2.29	0.19	<0.01	1.58	3.31
Mortality Age ≥ 65 Years					
T2DM	0.80	0.13	0.08	0.63	1.03
Statin	0.79	0.10	0.01	0.65	0.95
T2DM x Statin	1.09	0.19	0.65	0.76	1.57
Race: White	1.57	0.12	<0.01	1.24	2.00
Sex: Male	1.19	0.08	0.03	1.02	1.39
OW	0.65	0.10	<0.01	0.54	0.78
Obese	0.54	0.10	<0.01	0.44	0.66
Cancer	2.30	0.09	<0.01	1.91	2.76
MI	1.18	0.11	0.13	0.95	1.45
Nursing home	2.92	0.09	<0.01	2.45	3.47
Hospitalized in past 90 days	1.42	0.08	<0.01	1.21	1.67
ICU on Admit	2.32	0.11	<0.01	1.89	2.86
Intubation on Admit	1.68	0.12	<0.01	1.34	2.11

Of 10,052 CAP patients, 1,113 patients had expired one month by after their initial hospitalization (11.1%). The odds for mortality at one month was significantly increased for patients age ≥ 65 years (OR = 2.23: 95% CI 1.9 – 2.62, p <0.001), which was seen in the decision tree analysis for mortality at one month. A history of statin use was protective against death at one month (OR = 0.85: 95% CI 0.72-1.01), approaching significance (p = 0.06). T2DM (OR = 0.95: 95% CI 0.77-1.16, p = 0.6) and the T2DM-statin interaction (OR = 0.87: 95% CI 0.63-1.2, p = 0.87) both tended toward protective effects against death at one month, but not significantly. OW (OR = 0.65: 95% CI 0.55 – 0.77, p <0.0001) and OB patients (OR = 0.57: 95% CI 0.48 – 0.68, p <0.0001) were at significantly decreased odds for death at one month (p < 0.0001 and p < <0.0001, respectively). Notably, OB was slightly more protective than OW, but not significantly.

Increased odds for death after one month was also significantly associated with Caucasian race (OR = 1.43: 95% CI 1.19– 1.73, p <0.0001), male gender (OR = 1.17: 95% CI 1.02 – 1.34, p = 0.02), a history of neoplastic disease (OR = 3.02: 95% CI 2.59 – 3.54, p <0.0001), a prior MI (OR = 1.26: 95% CI 1.04-1.52, p = 0.02), direct admission to an ICU (OR = 2.5: 95% CI 2.11 – 3.00, p <0.0001), mechanical ventilation on admission (OR = 1.8: 95% CI 1.49– 2.18, p <0.0001), nursing home residence (OR = 2.97: 95% CI 2.53– 3.48, p <0.0001) and being hospitalized in the past 90 days (OR = 1.38: 95% CI 1.2 – 1.58, p <0.0001).

B. Logistic Regression for Mortality at One Month Age < 65 Years

Regression analysis of mortality at one month were done comparing separately age < 65 vs age ≥ 65 years (Table 4.4). 256 out of 4261 patients < 65 years old expired by at one month after CAP hospitalization (6.0%). In this population, the T2DM and statin interaction was significantly associated with a decreased odds of death at after one month (OR = 0.45: 95%CI 0.23-0.9, p = 0.02). This protective association for cases < 65 years was seen in the corresponding decision tree, as previously discussed above.

T2DM increased the odds for death in patients age < 65 (OR = 1.41: 95% CI 0.99-2.02) that approached significance (p = 0.056). Statin exposure (OR = 1.11: 95% CI 0.76-1.63, p = 0.59), male gender (OR = 1.23: 95% CI 0.94 – 1.62, p = 0.13), Caucasian race (OR = 1.2: 95% CI 0.88– 1.64, p = 0.25) and being hospitalized in the past 90 days (OR = 1.23: 95% CI 0.92 – 1.63, p = 0.15) were statistically non-significant, but also tended towards an increased odds for death.

Obesity had a significantly protective effect against mortality at one month (OR = 0.7: 95% CI 0.52 – 0.96, p =0.03) while overweight cases had a protective effect, also approaching significance (OR = 0.71: 95% CI 0.49 – 1.01, p = 0.058). An increased odds for death at one month was significantly associated with a history of neoplastic disease (OR = 7.02: 95% CI 0.5.17 – 9.53, p <0.0001), a prior MI (OR = 1.73: 95% CI 1.13-12.65, p = 0.01), direct admission to an ICU (OR = 2.88: 95% CI 2.03 – 4.08 p <0.0001), mechanical ventilation on admission (OR = 2.29: 95% CI 1.58– 3.31, p <0.0001), and nursing home residence (OR = 2.90: 95% CI 1.95– 4.33, p <0.0001).

C. Logistic Regression for Mortality at One Month Age ≥ 65 Years

Among patients ≥ 65 years old (Table 4.4), 857 of 5791 expired at one month after CAP hospitalization (14.8%). The T2DM and statin interaction was associated with a non-significant increased odds of death at one month (OR = 1.09: 95% CI 0.76-1.57, p = 0.65). Statin exposure alone was significantly associated with a decreased odds of death after one month (OR = 0.79: 95%CI 0.65-0.95, p = 0.01). T2DM was protective against mortality at one month in this subgroup (OR = 0.80: 95% CI 0.63-1.03) approaching significance (p = 0.078). OW (OR = 0.65: 95% CI 0.54-0.78, p <0.0001) and OB (OR = 0.54: 95% CI 0.44-0.66 p <0.0001) had a significantly protective effect against death at one month.

Risk for death at one month was significantly associated with Caucasian race (OR = 1.57: 95% CI 1.24– 2.00, p <0.0001), male gender (OR = 1.19: 95% CI 1.02 – 1.39, p = 0.03), a history of neoplastic disease (OR = 2.30: 95% CI 1.91 – 2.76, p <0.0001), direct admission to an ICU (OR = 2.32: 95% CI 1.89 – 2.86, p <0.0001), mechanical ventilation on admission (OR = 1.68: 95% CI 1.34– 2.11, p <0.0001), nursing home residence (OR = 2.92: 95% CI 2.45– 3.47, p <0.0001) and being hospitalized in the past 90 days (OR = 1.42: 95% CI 1.2 – 1.67, p <0.0001). History of a prior MI (OR = 1.18: 95% CI 0.95-1.45, p = 0.13) was not significant.

D. Logistic Regression for Mortality of Mortality at Six Months Overall

Of 10,052 HAPPI Study CAP patients, 2141 patients (21.1%) expired by six months after their CAP hospitalization. (Table 4.5). The mortality rate is cumulative, including 1113 patients who died by one month after hospitalization.

T2DM was associated with a non-significant increased likelihood of death at six months, (OR = 1.08: 95% 0.92 - 1.26, p = 0.35). But T2DM was associated with a non-significant decreased odds for death in the decision tree analysis, pointing to a non-significant effect. Odds for death at six months was significantly increased for patients age ≥ 65 years (OR = 2.08: 95% CI 1.84 – 2.34, p <0.0001), as shown in decision tree analysis.

Statin exposure alone (OR = 0.95: 95% CI 0.83-1.08, p = 0.4) and the T2DM/statin interaction (OR = 0.86: 95% CI 0.67-1.09, p = 0.20) had a non-significant decrease likelihood for mortality at six months.

OW (OR = 0.65: 95% CI 0.57 – 0.74, p <0.0001) and OB (OR = 0.51: 95% CI 0.45 – 0.58, p <0.0001) patients had a significantly decreased odds for death at six months. An increased odds for death at six months was significantly associated with Caucasian race (OR = 1.31: 95% CI 1.14– 1.51, p <0.0001), male gender (OR = 1.16: 95% CI 1.05 – 1.29, p = 0.01), a history of neoplastic disease (OR = 3.49: 95% CI 3.07– 3.98, p <0.0001), a prior MI (OR = 1.35: 95% CI 1.17-1.57, p <0.0001), direct admission to an ICU (OR = 1.8: 95% CI 1.51 – 2.09, p <0.0001), mechanical ventilation on admission (OR = 1.78: 95% CI 1.51– 2.09, p <0.0001),

nursing home residence (OR = 2.77: 95% CI 2.42– 3.18, p <0.0001) and hospitalization in the past 90 days (OR = 1.70: 95% CI 1.52 – 1.90, p <0.0001).

Table 4.5. Regression Equation for Mortality at Six Months

Variables in Equation	**OR**	**SE**	***p***	**95% CI**	
				Lower	**Higher**
Overall Mortality					
T2DM	1.08	0.08	0.35	0.92	1.26
Statin	0.95	0.07	0.40	0.83	1.08
T2DM x Statin	0.86	0.12	0.20	0.67	1.09
Race: White	1.37	0.07	<0.01	1.14	1.51
Sex: Male	1.16	0.05	0.01	1.05	1.29
Age ≥ 65	2.08	0.06	<0.01	1.84	2.34
OW	0.65	0.07	<0.01	0.57	0.74
Obese	0.51	0.07	<0.01	0.45	0.58
Cancer	3.49	0.07	<0.01	3.07	3.98
MI	1.35	0.08	<0.01	1.17	1.57
Nursing home	2.77	0.07	<0.01	2.42	3.18
Hospitalized in past 90 days	1.70	0.06	<0.01	1.52	1.90
ICU on Admit	1.80	0.08	<0.01	1.55	2.09
Intubation on Admit	1.78	0.08	<0.01	1.51	2.09
Mortality Age < 65 Years					
T2DM	1.39	0.14	0.01	1.07	1.82
Statin	1.15	0.14	0.34	0.87	1.51
T2DM x Statin	0.59	0.24	0.03	0.37	0.95
Race: White	1.46	0.12	0.001	1.16	1.84
Sex: Male	1.23	0.10	0.04	1.01	1.50
OW	0.70	0.13	0.01	0.54	0.90
Obese	0.64	0.12	<0.01	0.51	0.81
Cancer	7.98	0.12	<0.01	6.30	10.10
MI	1.82	0.16	<0.01	1.34	2.46
Nursing home	2.33	0.17	<0.01	1.69	3.22
Hospitalized in past 90 days	1.89	0.10	<0.01	1.55	2.31
ICU on Admit	1.70	0.14	<0.01	1.30	2.23
Intubation on Admit	2.11	0.15	<0.01	1.58	2.83
Mortality Age ≥ 65 Years					
T2DM	0.96	0.10	0.69	0.79	1.17
Statin	0.88	0.08	0.11	0.76	1.03
T2DM x Statin	0.99	0.15	0.93	0.74	1.31
Race: White	1.23	0.09	0.03	1.02	1.47
Sex: Male	1.18	0.06	0.01	1.04	1.34
OW	0.63	0.08	<0.01	0.55	0.73
Obese	0.46	0.08	<0.01	0.39	0.54
Cancer	2.49	0.08	<0.01	2.13	2.91
MI	1.26	0.09	0.01	1.06	1.48
Nursing home	2.79	0.08	<0.01	2.40	3.24
Hospitalized in past 90 days	1.62	0.07	<0.01	1.42	1.84
ICU on Admit	1.79	0.09	<0.01	1.49	2.15
Intubation on Admit	1.71	0.10	<0.01	1.40	2.08

E. Logistic Regression for Mortality at Six Months Age < 65 Years

Regression analyses of mortality at six months were done comparing separately < age 65 vs age ≥ 65 years (Table 4.5). 551 of 4261 patients were < 65 years and expired at six months after CAP hospitalization (12.9%). The T2DM and statin interaction (OR = 0.59: 95% CI 0.37-0.95, p = 0.03) was associated with a significant decreased odds of death after six months. Notably, the T2DM and statin interaction was not significant in the decision tree analysis. Risk for death at six months was significantly associated with T2DM (OR = 1.39: 95% CI 1.07 – 1.81 p = 0.01) as found in the decision tree analysis.

OW (OR = 0.65: 95% CI 0.54-0.78, p <0.0001) and obese (OR = 0.54: 95% CI 0.44-0.66 p <0.0001) patients had a significantly protective effect against death at six months. Interestingly, statin exposure was associated a non-significant risk of death at six months in patients < 65 (OR = 1.15: 95% CI 0.87 – 1.51, p = 0.34).

A significantly increased odds for death at six months was associated with T2DM alone (OR = 1.39: 95% CI 1.07 – 1.81 p = 0.01), Caucasian race (OR = 1.46: 95% CI 1.16 – 1.84, p = 0.001), male gender (OR = 1.23: 95% CI 1.01 – 1.5, p = 0.037), a history of neoplastic disease (OR = 7.98: 95% CI 6.30 – 10.09, p <0.0001), direct admission to an ICU (OR = 1.7: 95% CI 1.30– 2.23, p <0.0001), mechanical ventilation on admission (OR = 2.11: 95% CI 1.58– 2.83, p <0.0001), nursing home residence (OR = 2.33: 95% CI 1.69– 3.22, p <0.0001), prior MI (OR = 1.82: 95% CI 1.34– 2.46, p <0.0001), and hospitalization in the past 90 days (OR = 1.89: 95% CI 1.55 – 2.31, p <0.0001).

F. Logistic Regression for Mortality at Six Months Age ≥ 65 Years

1590 of 5791 patients age ≥ 65 (27.5%) expired at 6 months after CAP hospitalization (Table 4.5). T2DM alone (OR = 0.96: 95% CI 0.79-1.17, p = 0.69), statin exposure alone (OR = 0.88: 95% CI 0.76-1.03, p = 0.11), and the T2DM and statin interaction (OR = 0.99: 95% CI 0.74-1.31, p = 0.93) were not significantly associated with a decreased odds for mortality. The decision tree analysis also found a statistically non-significant lower odds for death in patients ≥ 65 years for the T2DM and statin interaction.

OW (OR = 0.65: 95% CI 0.54-0.78, p <0.001) or OB (OR = 0.54: 95% CI 0.44-0.66 p <0.001) patients age ≥ 65 had a significant protective effect against death at six months.

Odds for death at six months was significantly associated with Caucasian race (OR = 1.23: 95% CI 1.02 – 1.47, p = 0.03), male gender (OR = 1.18: 95% CI 1.04 – 1.34, p = 0.01), a history of neoplastic disease (OR = 2.49: 95% CI 2.13 – 2.91, p <0.0001), direct admission to an ICU (OR = 1.79: 95% CI 1.49– 2.15, p <0.0001), mechanical ventilation on admission (OR = 1.71: 95% CI 1.41– 2.08, p <0.0001), nursing home residence (OR = 2.79: 95% CI 2.40– 3.24, p <0.0001), prior MI (OR = 1.26: 95% CI 1.06–1.48, p <0.0001), and hospitalization in the past 90 days (OR = 1.62: 95% CI 1.42 – 1.84, p <0.0001).

G. Logistic Regression for Mortality of Mortality at 12 Months Overall

2756 of 10052 patients (27.4%) expired within 12 months after CAP hospitalization (Table 4.6). This number is cumulative, including all deaths at one month and six months after hospitalization. An increased odds for death at 12 months was significantly associated with age ≥ 65 years (OR = 2.05: 95% CI 1.84 – 2.28, p <0.001), while T2DM was associated with a non-significant increased odds of death after 12 months (OR = 1.10: 95% 0.95 - 1.27, p = 0.22), similar to the decision tree analysis. Statin exposure alone (OR = 0.96: 95% CI 0.85-1.09, p = 0.53), and the T2DM and statin interaction (OR = 0.87: 95% CI 0.70-1.09, p = 0.23) were associated with a non-significant decreased odds for mortality.

Table 4.6. Regression Equation for All-Cause Mortality at 12 Months

Variables in Equation	OR	SE	*p*	95% CI	
				Lower	Higher
Overall Mortality					
T2DM	1.10	0.07	0.22	0.95	1.27
Statin	0.96	0.06	0.53	0.85	1.09
T2DM x Statin	0.87	0.11	0.23	0.70	1.09
Race: White	1.30	0.07	<0.001	1.14	1.48
Sex: Male	1.18	0.05	0.001	1.07	1.30
Age ≥ 65	2.05	0.06	<0.001	1.84	2.28
OW	0.64	0.06	<0.001	0.56	0.72
Obese	0.53	0.06	<0.001	0.47	0.59
Cancer	3.57	0.06	<0.001	3.15	4.04
MI	1.41	0.07	<0.001	1.23	1.62
Nursing home	2.62	0.07	<0.001	2.30	2.99
Hospitalized in past 90 days	1.81	0.05	<0.001	1.64	2.01
ICU on Admit	1.70	0.07	<0.001	1.48	1.96
Intubation on Admit	1.71	0.08	<0.001	1.46	1.99
Mortality Age < 65 Years					
T2DM	1.42	0.12	0.004	1.12	1.80
Statin	1.09	0.13	0.50	0.85	1.40
T2DM x Statin	0.55	0.22	0.006	0.36	0.85
Race: White	1.40	0.10	0.001	1.14	1.72
Sex: Male	1.16	0.09	0.10	0.97	1.39
OW	0.61	0.12	<0.001	0.49	0.78
Obese	0.62	0.10	<0.001	0.50	0.76
Cancer	8.49	0.12	<0.001	6.78	10.64
MI	2.03	0.14	<0.001	1.54	2.67
Nursing home	2.38	0.15	<0.001	1.77	3.21
Hospitalized in past 90 days	2.08	0.09	<0.001	1.74	2.49
ICU on Admit	1.62	0.13	<0.001	1.26	2.08
Intubation on Admit	1.91	0.14	<0.001	1.46	2.51
Mortality Age ≥ 65 Years					
T2DM	0.96	0.09	0.63	0.79	1.15
Statin	0.90	0.07	0.16	0.79	1.04
T2DM x Statin	1.06	0.14	0.67	0.81	1.38
Race: White	1.24	0.09	0.01	1.05	1.47
Sex: Male	1.23	0.06	0.001	1.09	1.38
OW	0.64	0.07	<0.001	0.55	0.73
Obese	0.48	0.08	<0.001	0.42	0.56
Cancer	2.41	0.08	<0.001	2.08	2.81
MI	1.27	0.08	0.003	1.08	1.49
Nursing home	2.60	0.08	<0.001	2.25	3.02
Hospitalized in past 90 days	1.68	0.06	<0.001	1.49	1.91
ICU on Admit	1.68	0.09	<0.001	1.42	2.02
Intubation on Admit	1.69	0.10	<0.001	1.39	2.04

OW (OR = 0.64: 95% CI 0.56 – 0.72, p <0.0001) or OB (OR = 0.53: 95% CI 0.47– 0.59, p <0.0001) patients had a significantly decreased odds for death at 12 months. An increased odds for death at 12 months was significantly associated with Caucasian race (OR = 1.299: 95% CI 1.14– 1.48, p <0.0001), male gender (OR = 1.18: 95% CI 1.07– 1.30, p = 0.01), a history of neoplastic disease (OR = 3.57: 95% CI 3.15-4.04, p <0.0001), a prior MI (OR = 1.41: 95% CI 1.23-1.62, p <0.0001), direct admission to an ICU (OR = 1.70: 95% CI 1.48 – 1.96, p <0.0001), mechanical ventilation on admission (OR = 1.71: 95% CI 1.46– 1.99, p <0.0001), nursing home residence (OR = 2.62: 95% CI 2.30– 2.99, p <0.0001) and hospitalization in the past 90 days (OR = 1.81: 95% CI 1.64 – 2.01, p <0.0001).

H. Logistic Regression for Mortality at 12 Months Age < 65 Years

Regression analysis of mortality at 12 months were done comparing separately age < 65 vs age ≥ 65 years (Table 4.6). 750 of 4261 patients age < 65 (17.6%) expired at 12 months after CAP hospitalization. As with the age <65 population at one month and six months, the T2DM and statin interaction (OR = 0.55: 95% CI 0.36-0.85, p = 0.01) was significantly associated with a decreased odds of death after 12 months. This significant relationship was also identified in the decision tree analysis. Statin exposure alone was associated with an increased odds of death within 12 months, but this was not significant (OR = 1.09: 95% CI 0.85 – 1.41, p = 0.50), while a significant increased odds for death within 12 months was associated with T2DM alone (OR = 1.42 95% CI 1.12 – 1.80, p = 0.004).

OW (OR = 0.61: 95% CI 0.49-0.78, p <0.0001) or obese (OR = 0.62: 95% CI 0.50-0.76 p <0.0001) patients had a significant protective effect against death within 12 months. A significantly increased mortality risk at 12 months was associated with Caucasian race (OR = 1.40: 95% CI 1.14– 1.72, p = 0.001), a history of neoplastic disease (OR = 8.49: 95% CI 6.78 – 10.64, p <0.0001), direct admission to an ICU (OR = 1.62: 95% CI 1.26– 2.08, p <0.0001), mechanical ventilation on admission (OR = 1.91: 95% CI 1.46– 2.51, p <0.0001), nursing home residence (OR = 2.38: 95% CI 1.77– 3.21, p <0.0001), prior MI (OR = 2.03: 95% CI 1.54– 2.67, p <0.0001), and hospitalization in the past 90 days (OR = 2.08: 95% CI 1.74 – 2.49, p <0.0001). Male gender was associated with a non-significant increased odds for death within 12 months (OR = 1.16: 95% CI 0.97 - 1.39, p = 0.095).

I. Logistic Regression for Mortality at 12 Months Age ≥ 65 Years

2006 of 5791 patients ≥ 65 years (34.6%) had expired at 12 months after CAP hospitalization (Table 4.6). The T2DM and statin interaction (OR = 0.99: 95% CI 0.74-1.31, p = 0.93) suggested a non-significant increased odds of mortality at 12 months (OR = 1.06: 95% CI 0.81-1.39, p = 0.67), which agrees with the decision tree analysis. T2DM (OR = 0.96: 95% CI 0.79-1.15, p = 0.63) and statin exposure (OR = 0.904: 95% CI 0.79-1.04, p = 0.16), were not significantly associated with a decreased odds for mortality.

OW (OR = 0.64: 95% CI 0.55-0.73, p <0.0001) or obese (OR = 0.48: 95% CI 0.42-0.60 p <0.0001) patients were significantly protected against death within 12 months. An increased odds for death within 12 months was significantly associated Caucasian race (OR = 1.24: 95% CI 1.05 – 1.47, p = 0.01), male gender (OR = 1.23: 95% CI 1.09 – 1.38, p = 0.001), a history of neoplastic disease (OR = 2.41: 95% CI 2.08 – 2.81, p <0.0001), direct admission to an ICU (OR = 1.69: 95% CI 1.42– 2.02, p <0.0001), mechanical ventilation on admission (OR = 1.68: 95% CI 1.39– 2.04, p <0.0001), nursing home residence (OR = 2.60: 95% CI 2.25 – 3.02, p <0.0001), prior MI (OR = 1.27: 95% CI 1.08–1.49, p = 0.003) and hospitalization in the past 90 days (OR = 1.68: 95% CI 1.49 – 1.91, p <0.0001).

J. Summary of the Regression Analysis for Mortality Outcomes

Binary regression analyses conducted showed that the T2DM and statin interaction had a significant protective effect against mortality in CAP when stratified for age and concurs with the decision tree analyses that the interaction is protective against mortality in the age < 65 subgroup but not in the age ≥ 65 subgroup. T2DM was significantly associated with increased odds for mortality at six months and 12 months for cases age > 65, but not the older age group. OW and OB were significantly protective against mortality at one, six, and 12 months, regardless of age.

Prior history of cardiovascular disease (i.e. prior MI), neoplastic disease, or conditions that indicated frailty (i.e. nursing home residence), or increased CAP severity (i.e. direct ICU admission or direct mechanical ventilation on admission) were significantly associated with increased odds for mortality at one, six, and 12 months, regardless of age. Male sex and Caucasian race also were significantly associated with increased odds for mortality at one, six, and 12 months, regardless of age.

Binary Logistic Regression Analysis: Morbidity Outcomes

A. Logistic Regression for Morbidity at One Month Overall

Binary logistic regression analyses of morbidity outcomes at one, six, and 12 months with all covariates used in the mortality regression models, except the variable "hospitalized within the past 90 days," because of redundancy with readmittance for CAP hospitalization. 583 of 10052 patients (5.8 %) were readmitted for CAP one month after their initial hospitalization (Table 4.7.)

The T2DM/statin interaction was not significantly but tended towards a protective effect against rehospitalization for CAP within one month (OR = 0.74: 95% CI 0.51-1.07). The decision tree analysis indicated a similar non-significant protective effect with the T2DM/statin interaction.

OW (OR = 0.95: 95% CI 0.77-1.17, p = 0.65) and age ≥ 65 (OR = 0.94: 95% CI 0.78– 1.13, p = 0.50) were not significantly protective, but direct admission to an ICU (OR = 0.79: 95% CI 0.60 – 1.04, p = 0.09) tended toward a protective effect against CAP rehospitalization within one month. OB patients (OR = 0.80: 95% CI 0.65 – 0.98, p = 0.03) had a significantly decreased odds for CAP rehospitalization within one month. Odds of CAP rehospitalization within one month was random with respect to male gender (OR = 0.98: 95% CI 0.85 – 1.19, p = 1.00). CAP rehospitalization risk within one month was significantly increased for patients with T2DM (OR = 1.31: 95% CI 1.03 – 1.67, p = 0.03), a history of neoplastic disease (OR = 1.29: 95% CI 1.031 – 1.62, p = 0.03), mechanical ventilation on admission (OR = 1.35: 95% CI 1.02– 1.80, p = 0.036), and a prior MI (OR = 1.31: 95% CI

1.04-1.66, p = 0.02). Statin exposure alone (OR = 1.17: 95% CI 0.94 – 1.45, p = 0.17) had a non-significantly increased odds for CAP rehospitalization.

Table 4.7 Regression Equation for CAP Rehospitalization by One Month

Variables in Equation	**OR**	**SE**	***p***	**95% CI**	
				Lower	**Higher**
Overall Morbidity					
T2DM	1.31	0.12	0.03	1.03	1.67
Statin	1.17	0.11	0.17	0.94	1.45
T2DM x Statin	0.74	0.19	0.11	0.51	1.07
Race: White	0.98	0.11	0.85	0.79	1.21
Sex: Male	0.99	0.09	0.97	0.84	1.18
Age ≥ 65	0.94	0.09	0.50	0.78	1.13
OW	0.95	0.11	0.65	0.77	1.17
Obese	0.80	0.11	0.03	0.65	0.98
Cancer	1.29	0.12	0.03	1.03	1.62
MI	1.31	0.12	0.02	1.04	1.66
Nursing home	1.04	0.13	0.76	0.81	1.34
ICU on Admit	0.79	0.14	0.09	0.60	1.04
Intubation on Admit	1.35	0.15	0.04	1.02	1.80
Morbidity Age < 65 Years					
T2DM	1.28	0.18	0.18	0.89	1.83
Statin	1.31	0.19	0.16	0.90	1.90
T2DM x Statin	0.96	0.31	0.88	0.53	1.74
Race: White	1.13	0.15	0.41	0.84	1.52
Sex: Male	0.95	0.13	0.70	0.73	1.23
OW	0.75	0.17	0.09	0.53	1.05
Obese	0.59	0.16	0.001	0.43	0.80
Cancer	1.07	0.21	0.74	0.71	1.23
MI	1.22	0.21	0.34	0.80	1.85
Nursing home	1.24	0.25	0.40	0.76	2.02
ICU on Admit	0.70	0.22	0.10	0.46	1.07
Intubation on Admit	1.79	0.22	0.01	1.17	2.73
Morbidity Age ≥ 65 Years					
T2DM	1.34	0.17	0.08	0.96	1.87
Statin	1.09	0.14	0.55	0.83	1.42
T2DM x Statin	0.62	0.25	0.05	0.38	1.00
Race: White	0.84	0.15	0.25	0.62	1.13
Sex: Male	1.03	0.11	0.83	0.82	1.28
OW	1.12	0.14	0.42	0.56	1.45
Obese	0.99	0.14	0.98	0.76	1.31
Cancer	1.43	0.14	0.02	1.07	1.85
MI	1.35	0.14	0.04	1.02	1.79
Nursing home	0.98	0.15	0.87	0.73	1.32
ICU on Admit	0.82	0.19	0.30	0.57	1.19
Intubation on Admit	1.07	0.20	0.74	0.73	1.57

B. Logistic Regression for Morbidity at One Month Age < 65 Years

Morbidity within one month < age 65 years and those age ≥ 65 years was analyzed in separate logistic regressions (Table 4.7). 244 of the 4261 patients age < 65 years (5.7%) were readmitted for CAP by one month after initial CAP hospitalization. In this population, the T2DM/statin interaction (OR = 0.95: 95%CI 0.53-1.74, p = 0.88), being overweight (OR = 0.75: 95%CI 0.53 – 1.05, p = 0.09), male gender (OR = 0.95: 95% CI 0.73 – 1.23, p = 0.70), and direct admission to an ICU (OR = 0.70: 95% CI 0.46 – 1.07, p = 0.10) were not significantly associated with a decreased odds of CAP rehospitalization after one month.

T2DM (OR = 1.28: 95% CI 0.89-1.83, p = 0.18), statin exposure (OR = 1.31: 95% CI 0.90-1.90, p = 0.16), Caucasian race (OR = 1.13: 95% CI 0.84-1.52, p = 0.41), nursing home residence (OR = 1.24: 95% CI 0.76 – 2.02, p = 0.40) and prior MI (OR = 1.22: 95% CI 0.80 – 1.85, p = 0.36) were not associated with a significant increased odds of rehospitalization. OB was significantly protective against CAP rehospitalization within one month (OR = 0.59: 95% CI 0.43 – 0.80, p =0.001). ODDS for CAP readmission by one month was significantly associated with mechanical ventilation on admission (OR = 1.79: 95% CI 1.17 – 2.73, p = 0.007) (Table 4.7).

C. Logistic Regression for Morbidity at One Month Age ≥ 65 Years

Among 5791 patients ≥ 65 years old, 339 (5.9%) were readmitted for CAP by one month after their initial hospitalization. The T2DM/statin interaction had a protective effect against CAP rehospitalization by one month (OR = 0.62: 95% CI

0.38-1.01, p = 0.05). OB (OR = 1.00: 95% CI 0.76-1.31, p = 0.98), Caucasian race (OR = 0.84: 95% CI 0.62 – 1.13, p = 0.25), direct admission to an ICU (OR = 0.82: 95% CI 0.57 – 1.19, p = 0.30) and nursing home residence (OR = 0.98: 95% CI 0.73 – 1.32, p = 0.87) were not significantly associated with CAP rehospitalization by one month (Table 4.7).

Increased odds for rehospitalization by one month was significantly associated with a history of neoplastic disease (OR = 1.40: 95% CI 1.07 – 1.85, p = 0.02) and prior MI (OR = 1.35: 95% CI 1.02-1.79, p = 0.04). T2DM (OR = 1.34: 95% CI 0.96-1.87) associated with CAP rehospitalization within one month that approached significance (p = 0.08). Statin exposure (OR = 1.09: 95% CI 0.83-1.421, p = 0.55), being overweight (OR = 1.12: 95% CI 0.86 – 1.45, p = 0.42), male gender (OR = 1.03: 95% CI 0.82 – 1.28, p = 0.83), and mechanical ventilation on admission (OR = 1.07: 95% CI 0.73– 1.57, p = 0.74) were not significantly associated with a risk for CAP rehospitalization by one month (Table 4.7).

D. Logistic Regression for Morbidity at Six Months Overall

1281 patients (12.7%) were readmitted for CAP within six months after their initial hospitalization (Table 4.8). OW (OR = 0.91: 95% CI 0.79 – 1.06, p = 0.23), the T2DM/statin interaction (OR = 0.91: 95% CI 0.70-1.18, p = 0.48), Caucasian race (OR = 0.95: 95% CI 0.82– 1.10, p = 0.50), and male gender (OR = 0.95: 95% CI 0.84 – 1.07, p = 0.40) were associated with a non-significant decreased odds for CAP rehospitalization by six months. OB had a protective effect against CAP rehospitalization by six months that approached significance (OR = 0.88: 95% CI 0.76 – 1.02, p = 0.08).

CAP rehospitalization by six months was significantly associated with T2DM (OR = 1.26: 95% CI 1.06 – 1.50, p = 0.008), a prior MI (OR = 1.26: 95% CI 1.06-1.48, p = 0.008), mechanical ventilation on admission (OR = 1.25: 95% CI 1.02 – 1.53, p = 0.03), a history of neoplastic disease (OR = 1.12: 95% CI 1.03 – 1.43, p = 0.02) and direct admission to an ICU (OR = 0.82: 95% CI 0.68 – 0.999, p = 0.05). Statin exposure alone (OR = 1.10: 95% CI 0.95-1.30, p = 0.18), age ≥ 65 years (OR = 1.01: 95% CI 0.89 – 1.14, p = 0.92), and nursing home residence (OR = 1.05: 95% CI 0.88 – 1.25, p = 0.63) were not significantly associated with CAP rehospitalization by six months (Table 4.8).

Table 4.8. Regression Equation for CAP Rehospitalization by Six Months

Variables in Equation	B	SE	*p*	95% CI	
				Lower	Higher
Overall Morbidity					
T2DM	1.26	0.09	0.01	1.06	1.50
Statin	1.11	0.08	0.18	0.95	1.30
T2DM x Statin	0.91	0.13	0.48	0.70	1.18
Race: White	0.95	0.08	0.50	0.82	1.10
Sex: Male	0.95	0.06	0.40	0.84	1.07
Age ≥ 65	1.01	0.07	0.92	0.89	1.14
OW	0.91	0.08	0.23	0.79	1.06
Obese	0.88	0.07	0.08	0.76	1.02
Cancer	1.21	0.08	0.02	1.03	1.43
MI	1.26	0.09	0.01	1.06	1.48
Nursing home	1.05	0.09	0.63	0.88	1.25
ICU on Admit	0.82	0.10	0.05	0.68	0.99
Intubation on Admit	1.25	0.10	0.03	1.02	1.53
Morbidity Age < 65 Years					
T2DM	1.24	0.09	0.63	0.79	1.15
Statin	1.14	0.14	0.34	0.87	1.49
T2DM x Statin	1.07	0.22	0.77	0.70	1.64
Race: White	0.93	0.10	0.48	0.76	1.14
Sex: Male	0.90	0.10	0.24	0.74	1.08
OW	0.74	0.13	0.02	0.57	0.95
Obese	0.75	0.11	0.01	0.60	0.93
Cancer	1.31	0.14	0.06	0.99	1.74
MI	1.32	0.15	0.07	0.98	1.77
Nursing home	1.31	0.18	0.14	0.92	1.86
ICU on Admit	0.75	0.16	0.06	0.55	1.01
Intubation on Admit	1.49	0.16	0.01	1.09	2.03
Morbidity Age ≥ 65 Years					
T2DM	1.29	0.12	0.04	1.02	1.63
Statin	1.07	0.10	0.47	0.89	1.30
T2DM x Statin	0.83	0.17	0.27	0.59	1.16
Race: White	0.97	0.11	0.80	0.78	1.21
Sex: Male	0.99	0.08	0.92	0.85	1.16
OW	1.03	0.09	0.73	0.86	1.25
Obese	0.99	0.10	0.92	0.82	1.20
Cancer	1.16	0.10	0.15	0.95	1.42
MI	1.23	0.10	0.05	1.00	1.50
Nursing home	0.98	0.11	0.82	0.79	1.20
ICU on Admit	0.86	0.13	0.24	0.67	1.11
Intubation on Admit	1.10	0.14	0.50	0.84	1.43

E. Logistic Regression for Morbidity at Six Months Age < 65 Years

525 of 4261 patients (12.3 %) age < 65 years were readmitted for CAP by six months (Table 4.8) The T2DM/statin interaction (OR = 1.07: 95% CI 0.70 – 1.64, p = 0.78), T2DM alone (OR = 1.24: 95% CI 0.96 – 1.59, p = 0.10), statin exposure alone (OR = 1.14: 95% CI 0.87 – 1.49, p = 0.34), and nursing home residence (OR = 1.31: 95% CI 0.92 – 1.86, p = 0.14) did not have a significantly increased odds for CAP rehospitalization by six months. Odds for CAP rehospitalization by six months was significantly associated with mechanical ventilation on admission (OR = 1.49: 95% CI 1.09 – 2.03, p = 0.01), while history of neoplastic disease (OR = 1.31: 95% CI 0.99 – 1.74, P=0.06) and a prior MI (OR = 1.32: 95% CI 0.98 – 1.77, P = 0.07) approached significance.

OW (OR = 0.74: 95% CI 0.57-0.95, p = 0.02) or obese (OR = 0.75: 95% CI 0.60 – 0.93, p = 0.008) was significantly protective against CAP rehospitalization by six months, and direct admission to an ICU (OR = 0.75: 95% CI 0.55 – 1.01, p = 0.058) had a protective effect that approached significance. Caucasian race (OR = 0.93: 95% CI 0.76 – 1.14, p = 0.48) and male gender (OR = 0.90: 95% CI 0.74 – 1.08, p = 0.24) were not significant (Table 4.8).

F. Logistic Regression for Morbidity at Six Months Age ≥ 65 Years

756 of 5791 patients (13.1%) age ≥ 65 years were readmitted for CAP by six months after their initial hospitalization. T2DM (OR = 1.29: 95% CI 1.02-1.63, p = 0.04) and prior MI (OR = 1.23: 95% CI 1.00–1.50, p = 0.05) were associated with

a significant increased odds of CAP rehospitalization by six months. Statin exposure alone (OR = 1.07: 95% CI 0.89-1.30, p = 0.47), OW (OR = 1.03: 95% CI 0.86-1.25, p = 0.73), a history of neoplastic disease (OR = 1.16: 95% CI 0.95–1.42, p = 0.15), and mechanical ventilation on admission (OR = 1.10: 95% CI 0.84 – 1.43, p = 0.5) were not significantly associated with CAP rehospitalization by six months.

OB (OR = 0.99: 95% CI 0.82-1.12, p = 0.92), the T2DM/statin interaction (OR = 0.83: 95% CI 0.59 – 1.16, p = 0.27), Caucasian race (OR = 0.97: 95% CI 0.78 – 1.21, p = 0.80), male gender (OR = 0.99: 95% CI 0.85 – 1.16, p = 0.92), direct admission to an ICU (OR = 0.86: 95% CI 0.67 – 1.11, p = 0.24), and nursing home residence (OR = 0.98: 95% CI 0.79 – 1.20, p = 0.82) had a protective effect against CAP rehospitalization within six months but none of them were significant.

G. Logistic Regression for Morbidity at 12 Months Overall

1634 of 10052 patients (16.3%) were readmitted for CAP by 12 months after their initial CAP hospitalization (Table 4.9). T2DM (OR = 1.23: 95% CI 1.05-1.44, p = 0.01), statin use (OR = 1.17: 95% CI 1.02 -1.34, p = 0.03), a history of neoplastic disease (OR = 1.17: 95% CI 1.01-1.36, p = 0.04), and a prior MI (OR = 1.25: 95% CI 1.07-1.45, p = 0.005), were associated with a significant increased odds for morbidity. Mechanical ventilation on admission was also associated with a non-significant increased odds for CAP rehospitalization by 12 months (OR = 1.13: 95% CI 0.94 – 1.37, p = 0.19). Male sex (OR = 0.88: 95% CI 0.79 – 0.98, p = 0.024) or direct admission to an ICU (OR = 0.81: 95% CI 0.68 – 0.97, p = 0.022) had a significant protective effect against CAP rehospitalization by 12 months, while Caucasian race (OR = 0.88: 95% CI 0.77 – 1.00, p = 0.058) had a protective effect that approached significance.

The T2DM and statin interaction (OR = 0.94: 95% CI 0.75 – 1.20, p = 0.63), OW (OR = 0.91: 95% CI 0.79 – 1.04, p = 0.15), OB (OR = 0.92: 95% CI 0.81 – 1.05, p = 0.21), age ≥ 65 years (OR = 0.995: 95% CI 0.89 – 1.12, p = 0.93), and nursing home residence (OR = 0.92: 95% CI 0.78 – 1.09, p = 0.33) were not significantly associated with CAP rehospitalization by 12 months.

Table 4.9. Regression Equation for CAP Rehospitalization by 12 Months

Variables in Equation	OR	SE	*p*	95% CI	
				Lower	Higher
Overall Morbidity					
T2DM	1.23	0.08	0.01	1.05	1.44
Statin	1.17	0.07	0.03	1.02	1.34
T2DM x Statin	0.94	0.12	0.63	0.75	1.20
Race: White	0.88	0.07	0.06	0.77	1.00
Sex: Male	0.88	0.06	0.02	0.79	0.98
Age ≥ 65	0.99	0.06	0.93	0.89	1.12
OW	0.91	0.07	0.15	0.79	1.04
Obese	0.92	0.07	0.21	0.81	1.05
Cancer	1.18	0.08	0.04	1.01	1.36
MI	1.25	0.08	0.01	1.07	1.45
Nursing home	0.92	0.09	0.33	0.94	1.37
ICU on Admit	0.81	0.09	0.02	0.78	1.09
Intubation on Admit	1.13	0.10	0.19	0.94	1.37
Morbidity Age < 65 Years					
T2DM	1.24	0.12	0.06	0.99	1.56
Statin	1.18	0.12	0.18	0.93	1.50
T2DM x Statin	1.14	0.20	0.51	0.78	1.67
Race: White	0.85	0.09	0.06	0.71	1.01
Sex: Male	0.80	0.09	0.01	0.68	0.95
OW	0.77	0.12	0.02	0.61	0.96
Obese	0.77	0.10	0.01	0.63	0.93
Cancer	1.21	0.13	0.15	0.93	1.57
MI	1.30	0.14	0.06	0.99	1.70
Nursing home	1.28	0.17	0.14	0.93	1.77
ICU on Admit	0.80	0.14	0.11	0.61	1.05
Intubation on Admit	1.24	0.15	0.15	0.93	1.65
Morbidity Age ≥ 65 Years					
T2DM	1.21	0.11	0.08	0.98	1.51
Statin	1.13	0.09	0.18	0.95	1.34
T2DM x Statin	0.86	0.16	0.34	0.63	1.17
Race: White	0.92	0.10	0.39	0.76	1.12
Sex: Male	0.95	0.07	0.45	0.82	1.09
OW	0.99	0.09	0.99	0.84	1.19
Obese	1.05	0.09	0.55	0.89	1.25
Cancer	1.14	0.09	0.16	0.95	1.37
MI	1.22	0.09	0.04	1.01	1.46
Nursing home	0.83	0.10	0.07	0.68	1.01
ICU on Admit	0.81	0.12	0.07	0.64	1.02
Intubation on Admit	1.06	0.13	0.67	0.82	1.35

H. Logistic Regression for Morbidity at 12 Months Age < 65 Years

682 of 4261 patients age < 65 years old (16%) were rehospitalized for CAP by 12 months (Table 4.9). T2DM (OR = 1.24: 95% CI 0.99 – 1.60, p = 0.06) and prior MI (OR = 1.30: 95% CI 0.99– 1.70, p = 0.06) were associated with CAP rehospitalization by 12 months, and both approached significance. OW (OR = 0.77: 95% CI 0.61-0.96, p = 0.02), OB (OR = 0.77: 95% CI 0.63-0.93 p = 0.01), and male (OR = 0.80: 95% CI 0.68 - 0.95, p = 0.01) were significantly protective against rehospitalization by 12 months. Caucasian race (OR = 0.85: 95% CI 0.71 – 1.01, p = 0.06) was suggestive of a protective effect as it approached significance.

Statin use (OR = 1.18: 95% CI 0.93 – 1.50, p = 0.18), the T2DM/statin interaction (OR = 1.14: 95% CI 0.78 – 1.67, p = 0.51), a history of neoplastic disease (OR = 1.21: 95% CI 0.93 – 1.57, p = 0.15), mechanical ventilation on admission (OR = 1.24: 95% CI 0.93 – 1.65, p = 0.15) and nursing home residence (OR = 1.28: 95% CI 0.93 – 1.78, p = 0.14) were not significantly associated with an increased odds of CAP rehospitalization by 12 months. Direct admission to an ICU was associated with a non-significant decreased odds for CAP rehospitalization by 12 months (OR = 0.80: 95% CI 0.61 - 1.05, p = 0.11).

I. Logistic Regression for Morbidity at 12 Months Age ≥ 65 Years

952 of 5791 patients age ≥ 65 years (16.4%) were readmitted for CAP by 12 months after their initial CAP hospitalization (Table 4.9). CAP rehospitalization by

12 months was significantly associated with prior MI (OR = 1.22: 95% CI 1.01 – 1.46, p = 0.04) and T2DM approached significance (OR = 1.21: 95% CI 0.98-1.51, p = 0.08). Both direct admission to an ICU (OR = 0.81: 95% CI 0.64 – 1.02, p= 0.07) and nursing home residence (OR = 0.83: 95% CI 0.68 – 1.01, p = 0.065) were not significantly protective against CAP rehospitalization by 12 months but approached significance. CAP rehospitalization by 12 months was not significantly associated with the T2DM/statin interaction (OR = 0.86: 95% CI 0.63 – 1.17, p = 0.34), OW (OR = 0.99: 95% CI 0.84 – 1.19, p = 0.99), male gender (OR = 0.95: 95% CI 0.82 – 1.09, p = 0.45), and Caucasian race (OR = 0.92: 95% CI 0.76 – 1.12, p = 0.4).

Statin use (OR = 1.13: 95% CI 0.95-1.34, p = 0.18), OB (OR = 1.05: 95% CI 0.89-1.25, p = 0.55), a history of neoplastic disease (OR = 1.14: 95% CI 0.95 – 1.37, p = 0.16), and mechanical ventilation on admission (OR = 1.06: 95% CI 0.82 – 1.35, p = 0.67) were not statistically significantly associated with an increased odds for CAP rehospitalization by 12 months.

J. Summary of the Regression Analysis for Morbidity Outcomes

Binary regression analyses of morbidity outcomes found a significant protective effect against rehospitalization by one, six, and 12 months in OW and OB patients age < 65 but not among those age ≥ 65. These findings agree with the decision tree analyses that indicated the risk for rehospitalization increased with

age, although the results from decision trees at one, six, and 12 months were not significant ($p > 0.05$).

T2DM was associated with a significantly increased odds for CAP rehospitalization at one month and six months for all patients and for those aged ≥ 65 years. In addition, T2DM was associated with an increased odds for CAP rehospitalization by 12 months for all patients that approached significance, as was also found in the decision tree analyses. Statin use was associated with a significantly increased odds for CAP rehospitalization by 12 months for all patients, but was not significant at one month or six months.

The T2DM and statin interaction was associated with a significantly decreased odds for CAP rehospitalization by one month in patients age ≥ 65, but this effect not significant for CAP rehospitalization six months or 12 months.

MI was associated with an increased odds for rehospitalization by one, six, and 12 months. MI was a significant risk factor in patients age ≥ 65 years at one and six months, and was a significant risk factor for CAP rehospitalization at 12 months for patients of all ages. A history of cancer was associated with a significantly increased odds for CAP rehospitalization by 12 months for all patients, but was not significant when the analyses were subdivided by age. Nursing home residence and admission to the ICU were associated with a significant decreased odds for CAP readmission at 12 months for patients age ≥ 65 years. Male sex and Caucasian race did not have a consistent effect on morbidity; they were only significant for a decreased odds of rehospitalization at 12 months for patients age < 65.

Decision tree analyses discovered a stronger association than the logistic regression analyses between T2DM, age, and statin exposure for mortality outcomes than for morbidity outcomes. The demographic analysis of the T2DM cohort found high prevalence of cardiovascular diseases and increased CAP severity on admission in this group, as shown in published literature. The effects need to be balanced, indicating the need for matched propensity score analysis adjusting for any potential confounding effects.

Mortality Comparison using the Methodology of *Mortensen et al.* (2012)

For comparative purposes, this study compared the HAPPI data set compared to published analyses. Statin use was associated with a significant protective effect against mortality for CAP patients in Mortensen et al. (2012).[123] In this present study, the Mortensen et al (2012). methodology was used. Mortensen et al (2012) matched 11,498 cases exposed to either statins, angiotensin II- receptor blockers or angiotensin-converting enzyme inhibitors, with 11,498 non- exposed controls, all hospitalized for CAP and their data available in the Department of Veteran Affairs VISN 17 database. Mortensen et al (2012). Reported that prior statin use was associated with a significantly decreased 30-day mortality (OR = 0.74; 95% CI: 0.68–0.82, $p < 0.05$) in patients hospitalized for CAP.

In this replication study, only patients $\geq$ 65 years old were included. Cases were still defined by ongoing statin exposure. However, Mortensen did not subdivide cases and controls by T2DM status. Instead, T2DM was included as a covariate into

the PSM model, and several other variables included in the Mortensen model: Caucasian race, male gender, ICU admission, current tobacco use, alcohol use, IV drug use, prior MI, CHF, COPD, liver disease, renal disease, history of neoplastic disease, HIV, prior usage of cardiovascular medications (aspirin, beta blockers, and antiplatelet drugs), and prior usage of corticosteroids. In the Mortensen model, race, gender, ICU admission, neoplastic disease and prior MI were covariates in the replication PSM model. Other variables were dropped from the regression analysis for lack of statistical significance.

Of the 5791 HAPPI patients ≥ 65 years old, 2010 statin-exposed cases were matched with 2010 non-statin exposed controls using the Mortensen model. McNemar test of mortality outcomes (Table 4.10) found a significantly decreased odds for one month mortality (OR = 0.80, 95% CI: 0.68 – 0.96, $\chi^2 = 6.1$, p = 0.01), which Mortensen et al. (2012). The statin exposed cases also had a decreased odds for six month mortality (OR = 0.87, 95% CI: 0.76 – 1.00, $\chi^2 = 3.5$, p = 0.06) which approached significance. This aligns with the decision tree analysis for mortality at six months in T2DM patients age ≥ 65 years and on statins (Figure 4.4). At 12 months, statin-exposed cases had a tended to have a non-significant decreased odds for 12 month mortality compared to controls (OR = 0.91, 95% CI: 0.79 – 1.04, $\chi^2 = 2$, p = 0.15).

Given the shortcomings of the replicated Mortensen methodology, this study went further by subdividing the CAP patients by T2DM, statin use, and age in the PSM analysis to provide greater insight in these interactions in the CAP patients.

Table 4.10. PSM Analysis Replicating Mortensen et al. (2012)

Outcome	Mantel-Haenszel OR	95% CI	McNemar Test Statistic	p-value
Mortality				
Death at 1 month	0.80	0.68-0.96	6.1	0.01
Death at 6 months	0.87	0.76-1.00	3.5	0.06
Death at 12 months	0.91	0.79-1.04	2	0.15

Propensity Score Test Analysis of Hypothesis

A. Mortality Comparison Between Matched T2DM Cases and Controls

In the PSM analysis, cases (statin exposure) were matched to the controls (no statin exposure) in the two age groups on their respective propensity scores (i.e., probabilities from logistic regression). The cases and controls were matched on propensity scores with a match tolerance of 0.05 and controlled for the following covariates: race, gender, OW OB, history of neoplastic disease, history of a prior MI, direct admission to an ICU, mechanical ventilation on day of admission, nursing home residence, and being hospitalized within the past 90 days. The McNemar test with simple sampling bootstrapping was done to compare the mortality rates of statin-exposed to statin-unexposed matched pairs at one, six, and 12 months.

The T2DM cohort was stratified by age (<65 years versus ≥ 65) prior to PSM analysis, because the decision tree and regression analyses indicated different patterns of outcomes by age cohort. Out of 2734 T2DM patients, 1138 (41.6%) were age < 65 years (41.6%) and 1596 (58.4%) were age ≥ 65 years. 754 out of

1138 T2DM patients were matched in the age < 65 group (66.3%) while 1354 out of 1596 T2DM patients were matched in the age ≥ 65 group (84.8%).

The McNemar test of mortality outcomes in matched T2DM cases and controls (Table 4.9) showed T2DM statin-exposed cases age < 65 on statins had a decreased odds for mortality by one month (OR = 0.61, 95% CI: 0.32-1.15, $\chi^2 = 2.22$) and by six months (OR = 0.69, 95% CI: 0.43-1.08, $\chi^2 = 2.61$) than similarly aged T2DM non-statin exposed controls. Unlike the decision tree analysis or logistic regressions, the propensity score results were not significant. T2DM cases age < 65 had a non-significantly decreased odds for mortality by 12 months (OR = 0.70, 95% CI 0.46-1.06, $\chi^2 = 2.83$, p = 0.09).

The odds for mortality were not significantly different between T2DM cases age ≥ 65 and T2DM controls age ≥ 65 by one month (OR = 0.91, 95% CI: 0.70-1.34, $\chi^2 = 0.02$), six months (OR = 0.97, 95% CI: 0.76-1.24, $\chi^2 = 0.03$), and 12 months (OR = 1.07, 95% CI: 0.8-1.27, $\chi^2 = 0.001$).

Table 4.11. PSM Analysis for Mortality Outcomes in T2DM Patients

Outcome	Mantel-Haenszel OR	95% CI	McNemar Test Statistic	p-value
Mortality in Age < 65 years				
Death at 1 months	0.61	0.32-1.15	2.22	0.14
Death at 6 months	0.69	0.43-1.08	2.61	0.11
Death at 12 months	0.70	0.46-1.06	2.83	0.09
Mortality in Age ≥ 65 years				
Death at 1 months	0.91	0.70-1.34	0.02	0.87
Death at 6 months	0.97	0.76-1.24	0.03	0.85
Death at 12 months	1.07	0.80-1.27	0.001	0.99

B. Morbidity Comparison Between Matched T2DM Cases and Controls

The McNemar found no association of statin use with morbidity outcomes in outcomes in matched T2DM cases and controls (Table 4.12). In patients age < 65 years, the odds for CAP rehospitalization by one month for T2DM statin-exposed cases was 1.18 (95% CI: 0.64-2.19, $\chi^2 = 0.19$, p = 0.67) compared to T2DM non-statin controls. A non-significant increased odds for CAP rehospitalization was found for six months (OR = 1.13, 95% CI: 0.74-1.71, $\chi^2 = 0.25$, p = 0.62) and 12 months (OR = 1.35, 95% CI: 0.91-1.91, $\chi^2 = 2.05$, p = 0.15), post-hospitalization, respectively.

In patients age ≥ 65, the odds for CAP rehospitalization within one month for T2DM cases was not significant. (OR = 0.69, 95% CI: 0.42-1.11, $\chi^2 = 2.22$, p = 0.14). CAP rehospitalization was not significantly increased in frequency at six months (OR = 0.86, 95% CI: 0.63-1.17, $\chi^2 = 0.84$, p = 0.36) or 12 months (OR = 0.91, 95% CI: 0.69-1.22, $\chi^2 = 0.32$, p = 0.57). These findings of a non-significant increased odds for morbidity outcomes on in T2DM cases < 65 years and a non-

significant decreased odds for morbidity outcomes in T2DM cases ≥ 65 concur with the regression analyses previously discussed in this chapter.

Table 4.12. PSM Analysis for Morbidity Outcomes in T2DM Patients

Outcome	Mantel-Haenszel OR	95% CI	McNemar Test Statistic	p-value
Morbidity in Age < 65 years				
Rehospitalization within 1 mo.	1.18	0.64-2.19	0.19	0.67
Rehospitalization within 6 mo.	1.13	0.74-1.71	0.25	0.62
Rehospitalization within 12 mo.	1.35	0.91-1.91	2.05	0.15
Morbidity in Age ≥ 65 years				
Rehospitalization within 1 mo.	0.69	0.42-1.11	2.22	0.14
Rehospitalization within 6 mo.	0.86	0.63-1.17	0.84	0.36
Rehospitalization within 12 mo.	0.91	0.69-1.22	0.32	0.57

C. Mortality Comparison Between Matched Non-T2DM Cases and Controls

The non-T2DM cohort was stratified by age (<65 years versus ≥ 65). Out of the 7318 non-T2DM patients, 3123 (42.7%) were age < 65 years and 4195 (57.3%) were age ≥ 65. As in the T2DM cohort, the PSM analysis matched statin-exposed cases to statin-unexposed controls on the propensity score that controlled for race, gender, OW, OB, history of neoplastic disease, history of a prior MI, direct admission to an ICU, mechanical ventilation on day of admission, nursing home residence, and being hospitalized within the past 90 days. 1218 out of 3123 patients were matched on propensity scores in the age < 65 group (39%) and 3082 out of 4195 patients were matched in the age ≥ 65 group (73.5%).

The McNemar test of mortality outcomes in matched non-T2DM cases and controls (Table 4.13) showed cases age < 65 had a non-significant increased odds

for mortality by one month (OR = 1.19, 95% CI: 0.72-1.99, χ^2 = 0.36, p = 0.55) compared to non-statin exposed controls, similar to the result in the decision tree analysis. By PSM analysis, cases age < 65 had a non-significantly increased odds for mortality by six months (OR = 1.29, 95% CI: 0.91-1.84, χ^2 = 1.90, p = 0.17), that may indicate a tendency. The decision tree analysis also found an increased odds for mortality by six months in non-T2DM cases < 65 years that approached significance. PSM analysis showed a non-significant increased odds for mortality by 12 months in non-T2DM cases < 65 years (OR = 1.22, 95% CI: 0.89-1.67, χ^2 = 1.48, p = 0.22), whereas in the decision tree analysis, non-T2DM cases age < 65 had a significant increased odds for mortality by 12 months (Figure 4.5, OR = 1.24, 95% CI 1.0-1.55, p = 0.05).

For non-T2DM statin-exposed cases age ≥ 65 years, the PSM results found the risk of mortality by one month (OR = 0.86, 95% CI: 0.91-1.84, χ^2 = 1.48, p = 0.22) was non-significantly decreased compared to non-T2DM controls. However, the decision tree analysis found a decreased odds for mortality by one month in non-T2DM statin-exposed cases was significant (Figure 4.3, OR = 0.75, 95% CI 0.63 - 0.89, p = 0.001). PSM analysis also found a non-significant decreased odds for mortality by six months (OR = 0.98, 95% CI: 0.83-1.16, χ^2 = 0.04, p = 0.83), but the decision tree analysis had found a significantly decreased odds for mortality by six months in non-T2DM statin-exposed cases (Figure 4.4, OR = 0.82, 95% CI 0.71 - 0.94, p = 0.005). PSM results found non-T2DM statin-exposed cases had a non-significant increased odds for mortality by 12 months (OR = 1.04, 95% CI: 0.89-1.22, χ^2 = 0.26, p = 0.61). This finding was different from the decision tree analysis,

which found a significantly decreased odds for mortality by 12 months in non-T2DM cases (Figure 4.5, OR = 0.85, 95% CI 0.74 – 0.96, p = 0.01).

Table 4.13. PSM Analysis for Mortality Outcomes in Non-T2DM Patients

Outcome	**Mantel-Haenszel OR**	**95% CI**	**McNemar Test Statistic**	**p-value**
Mortality in Age < 65 years				
Death at 1 months	1.19	0.72-1.99	0.36	0.55
Death at 6 months	1.29	0.91-1.84	1.90	0.17
Death at 12 months	1.22	0.89-1.67	1.48	0.22
Mortality in Age ≥ 65 years				
Death at 1 months	0.86	0.70-1.06	1.90	0.17
Death at 6 months	0.98	0.83-1.16	0.04	0.83
Death at 12 months	1.04	0.89-1.22	0.26	0.61

D. Morbidity Comparison Between Matched Non-T2DM Cases and Controls

McNemar test of morbidity outcomes in matched non-T2DM statin-exposed cases and statin-unexposed controls (Table 4.14) in patients age < 65 years found non-T2DM cases had a non-significant protective effect for CAP rehospitalization by one month (OR = 0.83, 95% CI: 0.50-1.39, $\chi 2 = 0.38$, p = 0.54), by six months (OR = 0.96, 95% CI: 0.67-1.37, $\chi 2 = 0.03$, p = 0.86), and by 12 months (OR = 0.85, 95% CI: 0.62-1.19, $\chi 2 = 0.77$, p = 0.38), respectively.

Among non-T2DM patients age ≥ 65, the risk for CAP rehospitalization for T2DM cases was statistically non-significant at one month, (OR = 0.69, 95% CI: 0.42-1.11, $\chi^2 = 2.22$, p = 0.14), at six months (OR = 0.86, 95% CI: 0.63-1.17, $\chi^2 = 0.84$, p = 0.36), and by 12 months (OR = 0.91, 95% CI: 0.69-1.22, $\chi^2 = 0.32$, p = 0.57), respectively. These PSM results reflect what had been previously explored

in the regression analysis (a non-significant increased odds for morbidity outcomes in T2DM cases age < 65 years and a non-significant decreased odds for morbidity outcomes in T2DM cases age ≥ 65).

Table 4.14. PSM Analysis for Morbidity Outcomes in Non-T2DM Patients

Outcome	**Mantel-Haenszel OR**	**95% CI**	**McNemar Test Statistic**	**p-value**
Morbidity in Age < 65 years				
Rehospitalization within 1 mo.	0.83	0.50-1.39	0.38	0.54
Rehospitalization within 6 mo.	0.96	0.67-1.37	0.03	0.86
Rehospitalization within 12 mo.	0.85	0.62-1.19	0.77	0.38
Morbidity in Age ≥ 65 years				
Rehospitalization within 1 mo.	0.86	0.62-1.19	0.76	0.39
Rehospitalization within 6 mo.	0.86	0.69-1.08	1.6	0.20
Rehospitalization within 12 mo.	0.85	0.70-1.04	2.4	0.12

Survival Analysis

Cox proportional hazard regression and Kaplan-Meier analysis estimated and modeled the survival and mortality as best as possible, because mortality outcomes were only collected at three time frames (one, six, and 12 months) in the HAPPI study. After adjusting for the propensity score analysis, survival estimates were generated with patients stratified by T2DM status and age.

In T2DM patients age < 65, statin use was associated with a significantly ($p = 0.02$) lower hazard ratio (Figure 4.9) and significantly higher survival at one, six, and 12 months (Figure 4.10). T2DM patients age ≥ 65 on statins had a non-significantly ($p = 0.17$) lower hazard ratio (Figure 4.11) and non-significantly higher survival at one, six, and 12 months (Figure 4.12) compared to non-statin users.

Statin use was found to be associated with a significantly ($p = 0.05$) higher hazard ratio (Figure 4.13) and increased mortality (Figure 4.14) at one, six, and 12 months in non-T2DM patients age < 65. The opposite findings were seen in non-T2DM patients ≥ 65, where statin use was associated with a significantly ($p = 0.01$) higher hazard ratio (Figure 4.15) and lower mortality at one, six, and 12 months (Figure 4.16).

Figure 4.9. Kaplan-Meier Plot for T2DM patients age < 65 years one year after CAP Hospitalization by Statin Exposure

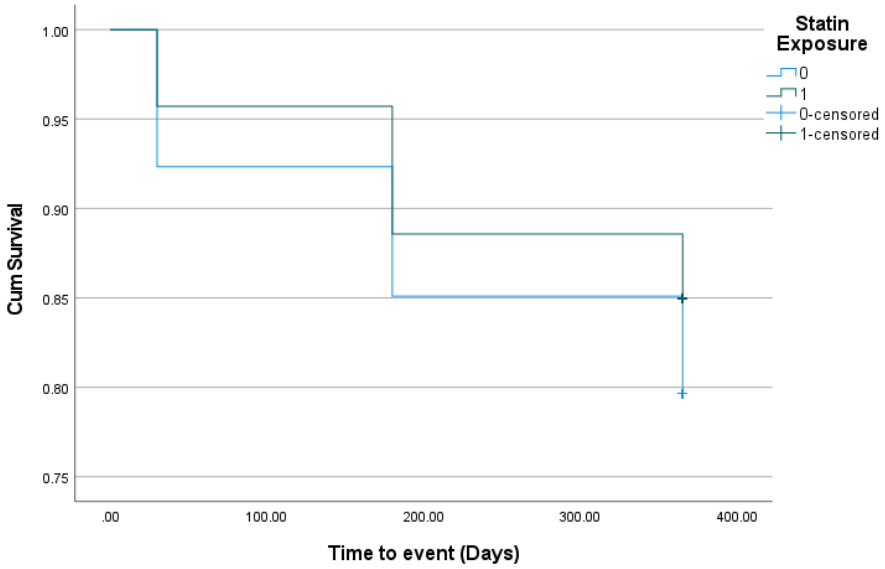


Figure 4.10. Cumulative Mortality for T2DM patients age < 65 years one year after CAP Hospitalization by Statin Exposure

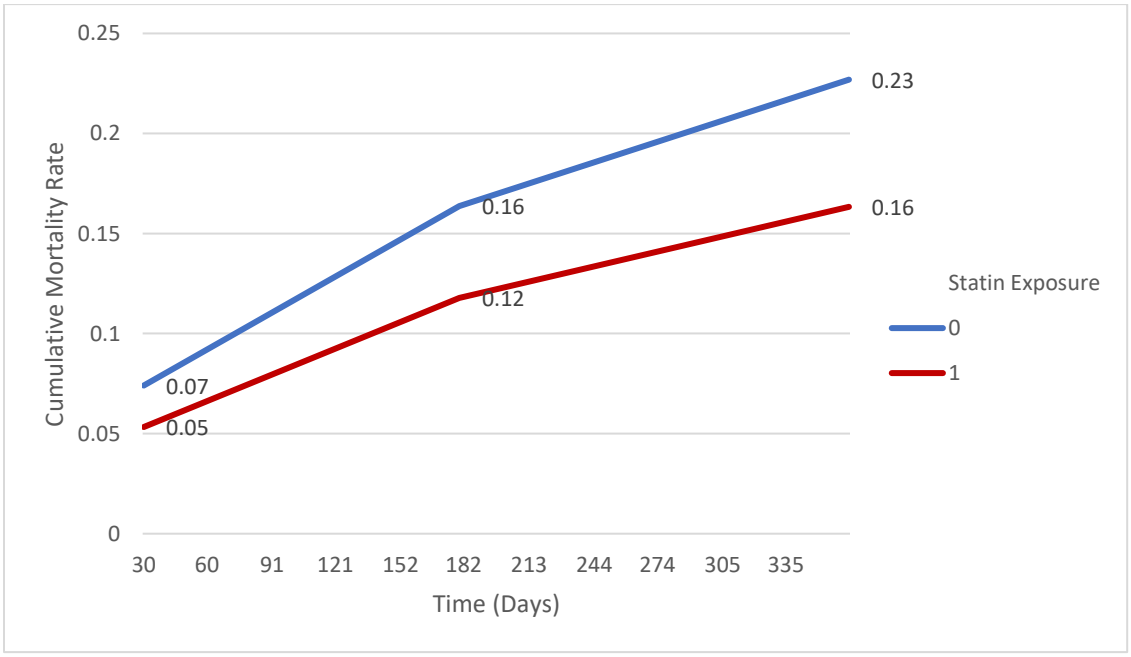


Figure 4.11. Kaplan-Meier Plot for T2DM patients age ≥ 65 years one year after CAP Hospitalization by Statin Exposure

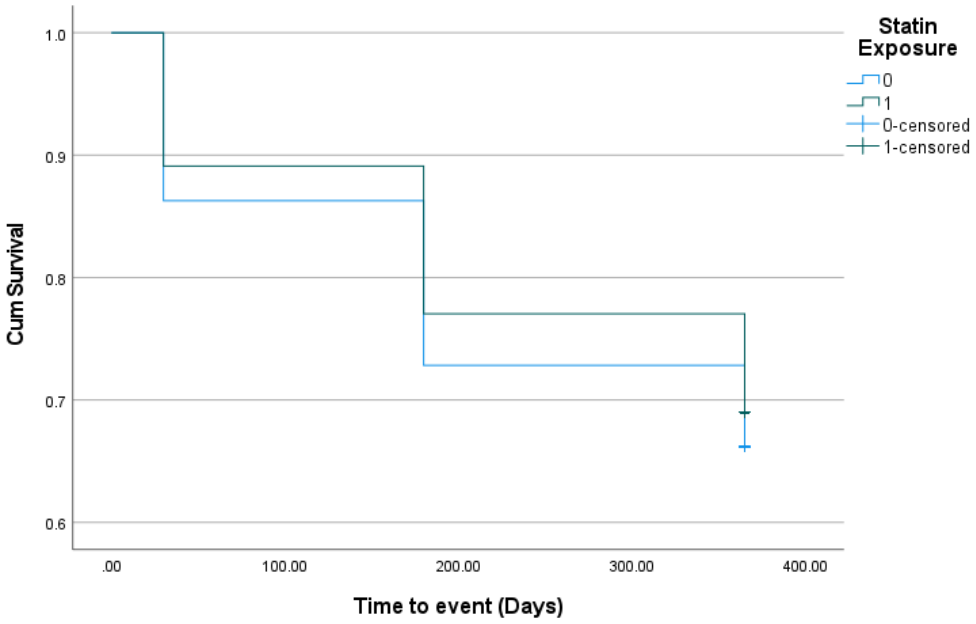


Figure 4.12. Cumulative Mortality for T2DM patients age ≥ 65 years one year after CAP Hospitalization by Statin Exposure

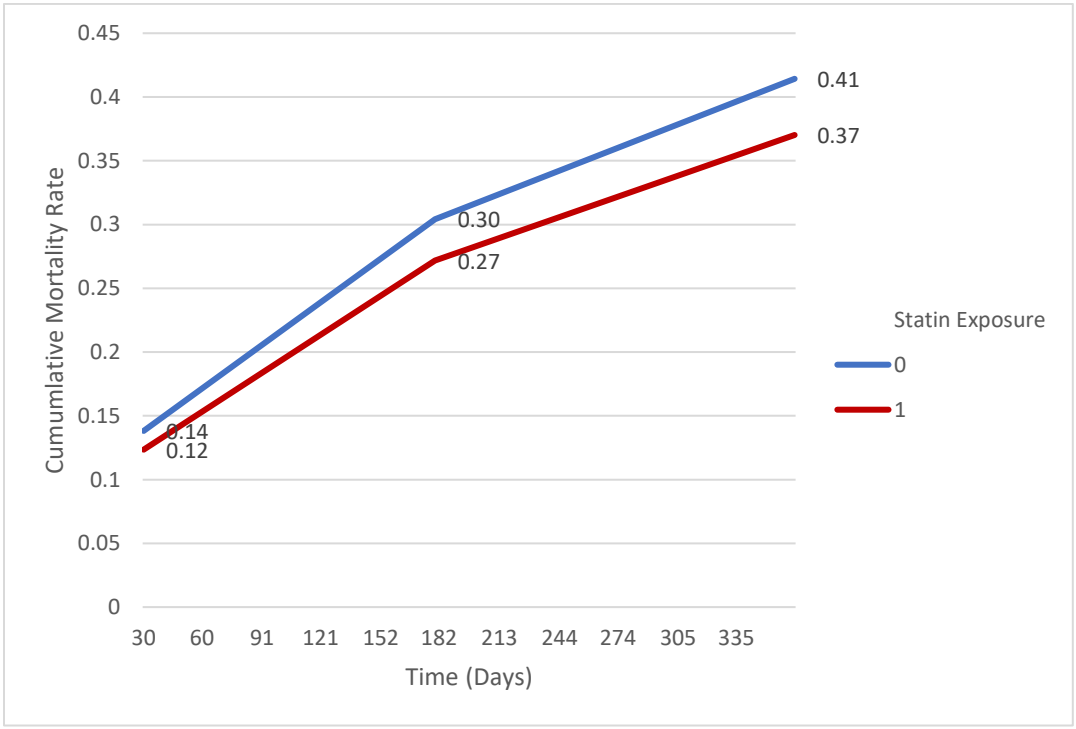


Figure 4.13. Kaplan-Meier Plot for non-T2DM patients age < 65 years one year after CAP Hospitalization by Statin Exposure

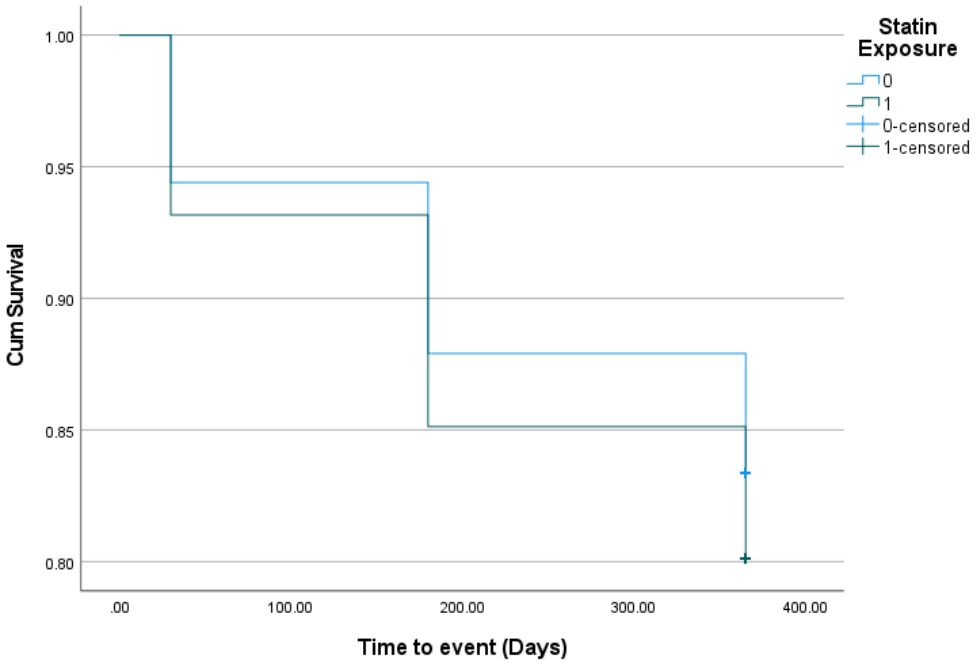


Figure 4.14. Cumulative Mortality for non-T2DM patients age < 65 years one year after CAP Hospitalization by Statin Exposure

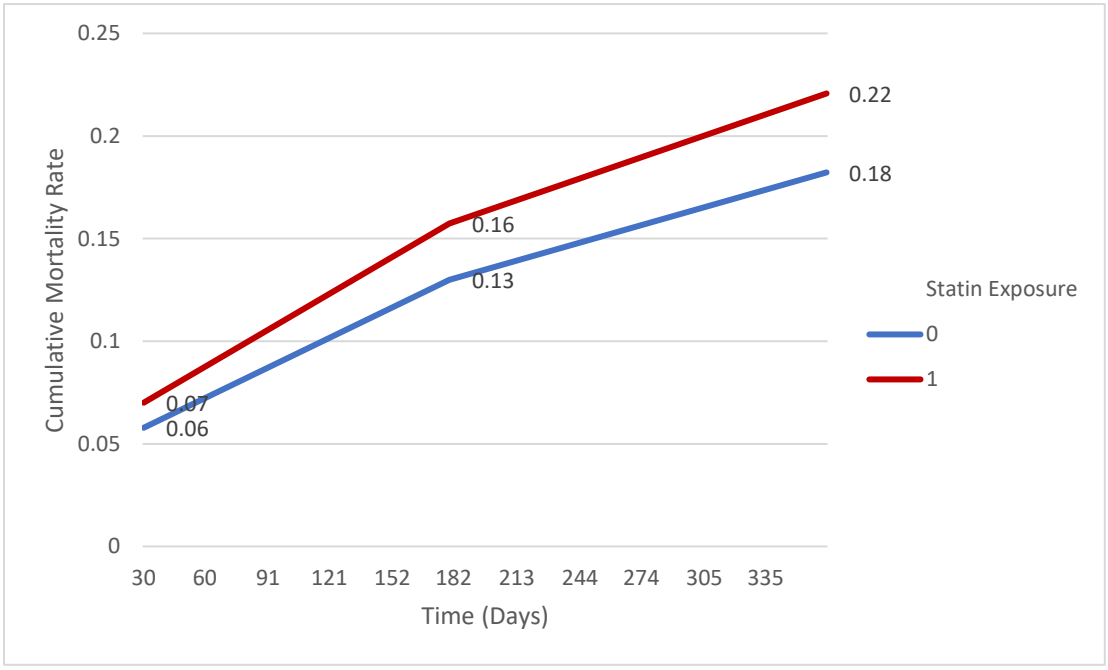


Figure 4.15. Kaplan-Meier Plot for non-T2DM patients age ≥ 65 years one year after CAP Hospitalization by Statin Exposure

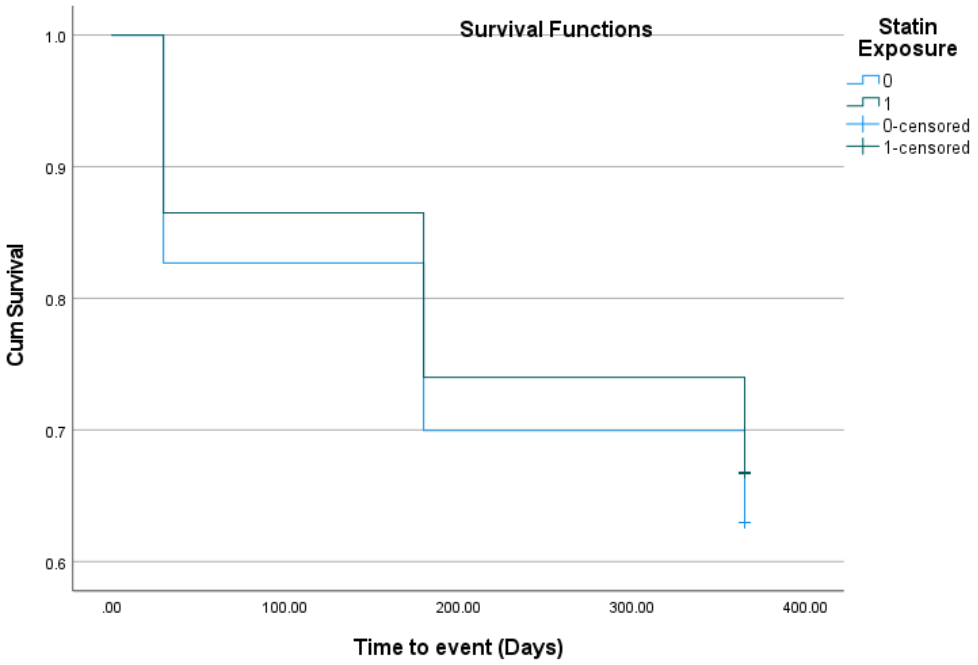
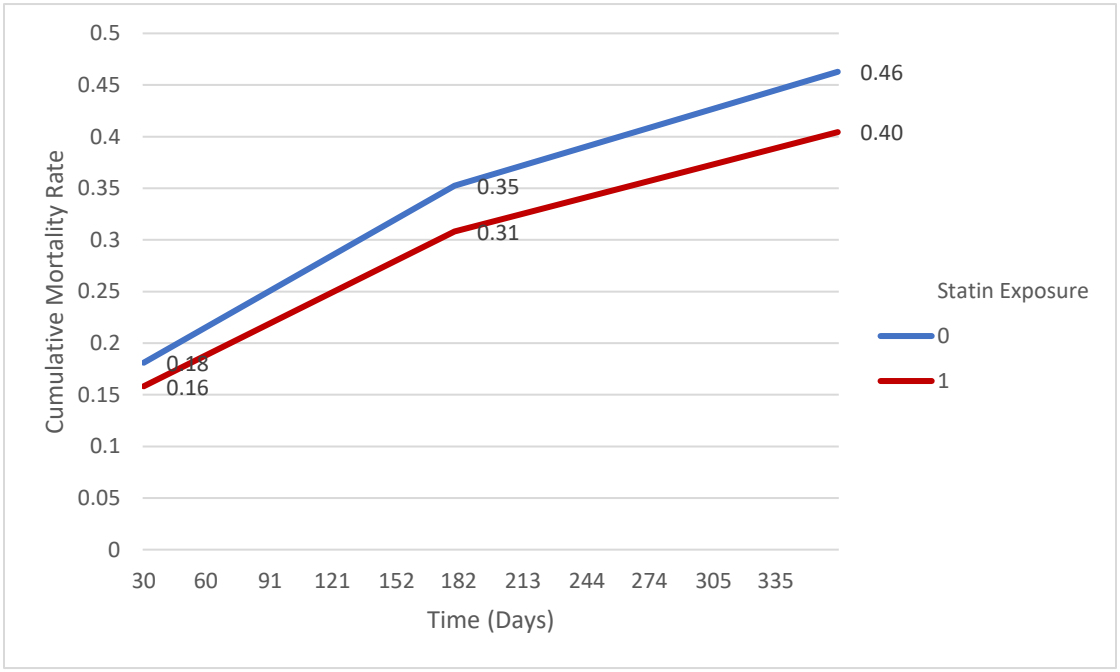


Figure 4.16. Cumulative Mortality for non-T2DM patients age ≥ 65 years one year after CAP Hospitalization by Statin Exposure



Cost Analysis

The mean (± SD) length of hospital stay (LOS) for all HAPPI patients was 6.32 ± 5.1. Using data from the 2014 National Readmission Database (NRD) – a part of a family of databases developed for the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality in the United States, the average unadjusted cost of each episode of CAP hospitalization was $11774 (mean) ± $9501 (SD) in 2014, the year the HAPPI study began.[137]

Estimates for the LOS and costs (Table 4.14) show that T2DM patients age < 65 who were on statins had a shorter LOS (6.42 ± 5.21) and incurred less costs ($11960 ± 9706) than patients who were not previously on statins (LOS 6.42 ± 5.21, costs $12836 ± $10989), but this difference was not significant (p = 0.10). T2DM patients age ≥ 65 had the mean cost per hospitalization was not significantly (p = 0.45) higher for patients without statin exposure ($13842 ± $11215) compared to the patients with prior statin exposure ($12948 ± $10526). Non-T2DM patients age ≥ 65 taking statins had a non-significant (p = 0.39) higher average cost per hospitalization ($12091 ± $9222) than those without statins ($11774 ± $9036).

Table 4.15. Cost Analysis

Length of hospital stay (LOS), costs for CAP patients by T2DM, age, and statin status.

Cohort			**LOS (Days) Mean ± SD**	**Total Costs (Dollars) Mean ± SD**	**p-value**
T2DM	Age < 65	Statin	6.42 ± 5.21	$11960 ± 9706	0.10*
		Non-Statin	6.89 ± 5.85	$12836 ± 10989	
	Age ≥ 65	Statin	6.95 ± 5.65	$12948 ± 10526	0.45
		Non-Statin	7.43 ± 6.02	$13842 ± 11215	
Non-T2DM	Age < 65	Statin	5.88 ± 4.55	$10954 ± 8477	0.48
		Non-Statin	5.58 ± 4.71	$10396 ± 8775	
	Age ≥ 65	Statin	6.49 ± 4.95	$12091 ± 9222	0.39
		Non-Statin	6.32 ± 4.85	$11774 ± 9036	
P-value for unpaired two-tailed unpaired t-test.					

CHAPTER 5

DISCUSSION

A summary of the primary outcome analysis (mortality) results is listed in Figure 5.1 and the results from the secondary outcome analysis (morbidity) is listed in Figure 5.2.

The decision tree analysis, logistic regression analysis, and survival analysis indicate that the T2DM and statin interaction in patients age < 65 years hospitalized for CAP was significantly associated with a decreased odds in one, six, and all-cause 12 month mortality. However, these protective effects were not significant after matched propensity score analysis. The logistic regression analysis and PSM analysis showed no significant difference in mortality odds between T2DM patients ≥ 65 years with statins use and those without statin use. The decision tree analysis and survival analysis suggest that T2DM patients ≥ 65 years on statins have a non-significant decreased odds for overall mortality compared to non-statin users (Figure 5.1).

Among non-T2DM patients hospitalized for CAP, the decision tree analysis, logistic regression analysis, and survival analysis found statin users ≥ 65 years had a significantly decreased odds for one, six, and 12 month mortality. In contrast, statin users < 65 years had a significantly increased odds for mortality compared to non-statin users. However, these effects were not significant after PSM analysis

(Figure 5.1). As was found for the T2DM group, this implies that mortality differences were due to covariate effects (i.e., the variables used in the propensity score), and not due to an effect from statins.

The decision tree analysis, logistic regression analysis, and PSM analysis also did not find a significant difference in one, six, and 12 month CAP readmission rates between statin and non-statin users in T2DM patients age < 65. However, the odds of rehospitalization at one, six, and 12 months for T2DM patients age ≥ 65 year were non-significantly decreased compared to non-T2DM patients (Figure 5.2). Lastly, the cost analysis demonstrated that statin use was associated with a non-significant decreased LOS and less incurred cost of CAP hospitalization for T2DM patients, in both age groups.

This present investigation's results do not agree with prior published analyses of statin exposure and CAP in a series of papers by Mortensen.[123,133,138-140] Mortensen et al. (2005A, 2005B, 2006, 2008, and 2012) used large EMR databases to conduct retrospective observational studies with PSM to compare CAP outcomes in patients on statins versus those not on statins. A direct comparison of the HAPPI data to the data sets used by Mortensen et al. (2012) was made using PSM analysis methodology. Multiple covariates were dropped from this study during the logistic

Figure 5.1. Summary of Results for Mortality Analysis

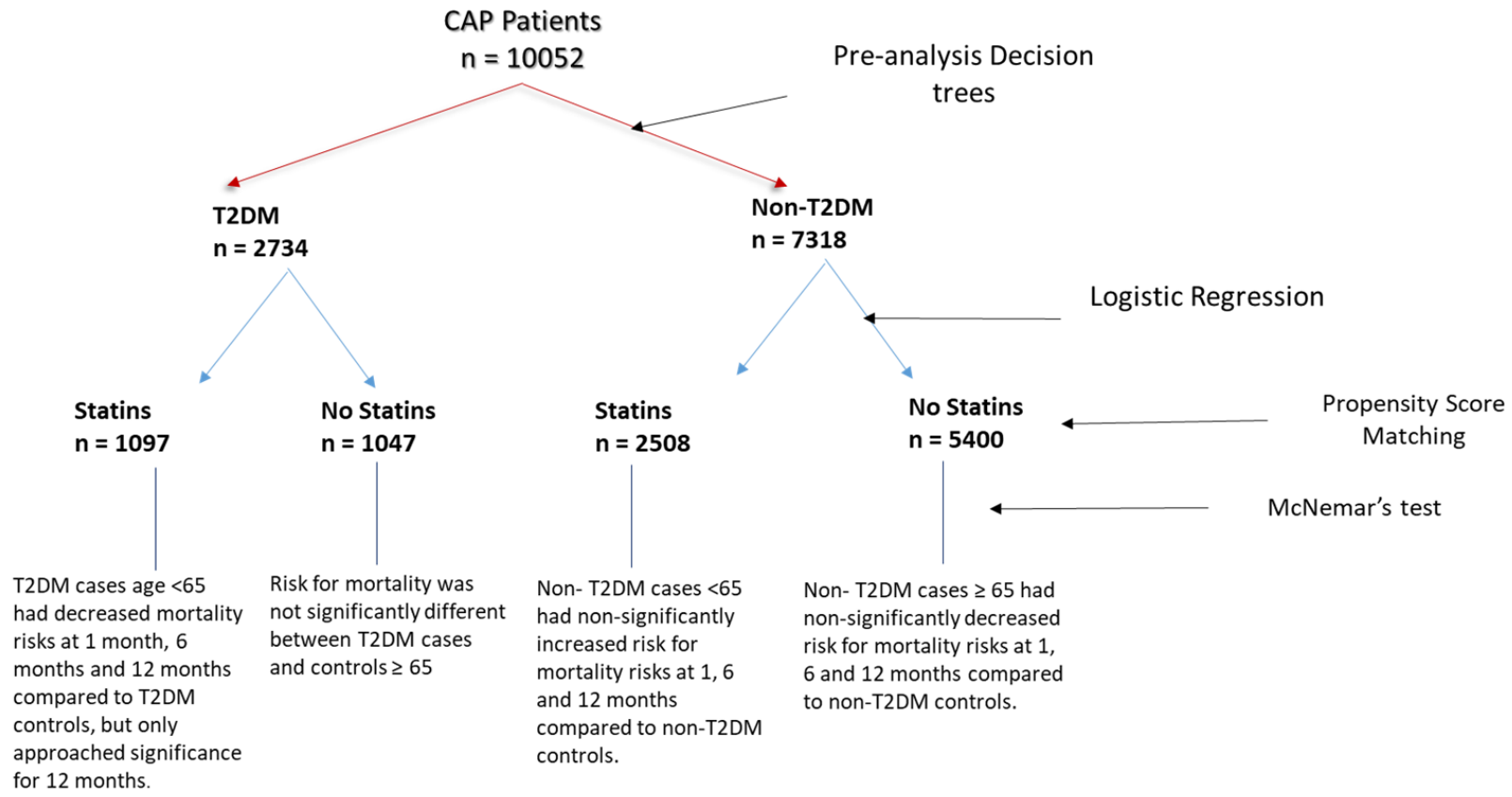
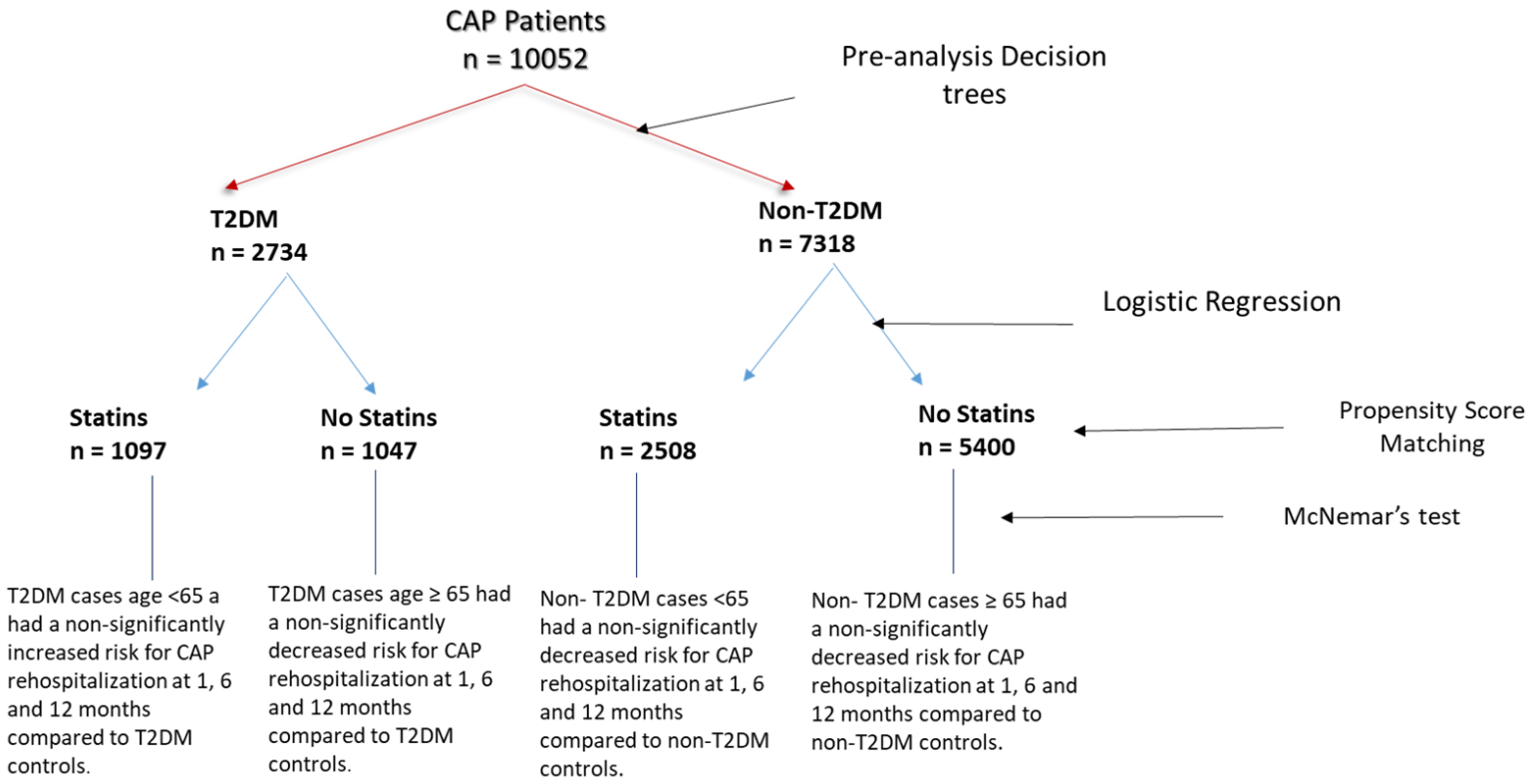


Figure 5.2. Summary of Results for Morbidity Analysis.



regression analysis (i.e., current tobacco use, alcohol use, IV drug use, CHF, COPD, chronic kidney disease, HIV and T2DM) but were included in the propensity score replicating Mortensen et al. (2012) as analyses. The covariates I used in the PSM analysis (i.e., race, gender, OW OB, history of neoplastic disease, prior MI, direct admission to an ICU, mechanical ventilation on day of admission, nursing home residence, and being hospitalized within the past 90 days) were also included in the Mortensen replication. Mortensen's data was restricted to patients age ≥ 65 years. Using this methodology, the present study found a significant decreased odds for 1 month mortality among statin users in the HAPPI study (OR = 0.74; 95% CI: 0.68–0.82, $p < 0.05$), similar to Mortensen (2012), and a decreased odds for 6 month mortality that approached significance (OR = 0.87, 95% CI: 0.76 – 1.00, $\chi^2 = 3.5$, $p = 0.06$).

Analysis of the HAPPI data into four sub-groups stratified by age (< 65 years and ≥ 65 years) and T2DM status reduced the sample size as well as statistical power. The entire HAPPI dataset, the non-T2DM subgroup ≥ 65 years, and the non-T2DM subgroup < 65 years had 100% statistical power, calculated by power analysis after the PSM analysis. But the power of the T2DM subgroup < 65 years was 80%, and the power of the T2DM subgroup ≥ 65 years was 40%. Low statistical power decreases the chances of detecting a true effect and its reproducibility, making the chances of finding an effect that is genuinely true are low.[141] Low power also negatively affects the likelihood that a statistically significant finding is a true effect, or a Type II statistical error. In this present study,

the null hypothesis was not rejected for the primary and secondary outcomes, which indicates a probable Type II statistical error, a false negative.[142]

Using the Mortensen methodology, the power of the PSM analysis was 1.0. However, the tradeoff in dividing the CAP patients by T2DM and age group in the present results are more granular than the analyses by Mortensen and his team.[123,143] Using the subgroup analyses controlled for T2DM and age heterogeneity in the cohorts rather than adding those covariates (i.e., T2DM, age) into the PSM analysis. The results show the granular details of how T2DM and age interact with statin exposure in these CAP patients, focusing on outcomes in homogenous groups which was lacking in Mortensen's previous results. Should a follow up study have a larger sample size to enhance the statistical power, then the subdivisions of the CAP patients by age group and T2DM status may exhibit a more pronounced and statistically significant effect because of homogeneity of within group variance by age group and T2DM.

The PSM analysis with McNemar test for matched data detected statin use was associated with non-significant odds for 1-month mortality ($p = 0.14$ and $p = 0.87$), 6-month mortality ($p = 0.11$ and $p = 0.85$), and 12-month mortality ($p = 0.09$ and $p = 0.99$) in T2DM patients < 65 years and ≥ 65 years, respectively. This suggests that T2DM patients < 65 may be the cohort most likely to benefit from the pleotropic effects of statins on anti-inflammation. A significant effect at 12-month mortality may be seen with higher statistical power (i.e., larger sample size).

This study's results were more in agreement with a smaller-scale observational study done in five different hospitals in Chicago, Illinois and Nashville, Tennessee.

Havers et al. (2016) used PSM to match statin users and non-statin users based on age, race, gender, education, chronic pulmonary disease, CAD, liver disease, renal disease, T2DM, OB, smoking history, home oxygen use, ACE-I use, and influenza vaccination, among patients hospitalized for CAP. They found no significant association with statin use, length of stay or in-house mortality, or in-patient costs. However, Havers et al. (2016) did not divide patients by T2DM status and did follow up with patient outcomes after discharge.[127]

Figure 4.1 shows that the HAPPI study patients study skewed significantly older than the total population of Louisville, with significantly higher proportions in age group 65-74 years, 75-84 years, and ≥ 85 years. This finding is similar to published CAP literature where the risk of worse outcomes increases with age. Compared to the non-T2DM patients, the T2DM patients were significantly more likely to have cardiac and renal comorbidities, be on cardiovascular drug treatment, and were more likely to be admitted directly to the ICU. Previously published literature indicated T2DM is associated with increased CVD risk and higher severity of CAP hospitalization. Controlling for these variables in the PSM analysis may explain the decreased effect of statin use on mortality and morbidity, as ASCVD also worsens with CAP outcomes.[91] The percent of patients age ≥ 85 was significantly higher in non-T2DM patients than in T2DM, indicating that fewer patients with T2DM survive to 85 years old in the HAPPI study, as T2DM is associated with decreased life expectancies.[144]

Thus, the T2DM patients hospitalized for CAP in this study may have comorbidities that blunt any anti-inflammatory effect of statins. Comparatively,

non-T2DM patients age < 65 years with statins had worse mortality outcomes by logistic regression and survival analysis than those not on statins. This suggests that even among the non-T2DM patients, earlier onset of DLP and ASCVD indicates greater comorbidity disease burdens.

The T2DM subgroups were comprised of significantly higher proportions of African Americans than the non-T2DM subgroups (Table 4.1). Non-Hispanic African Americans have been shown to have one of the highest prevalence rates of T2DM among demographic groups, second only to Hispanics.[145-147] Additionally, CAP hospitalization is apparently higher for non-Hispanic African Americans than other racial ethnicities.[148,149] The initial HAPPI study used geospatial epidemiology to map the home addresses of the CAP patients and found that Louisville areas with a high CAP incidence are zip codes with a high proportion of impoverished individuals and African Americans. The specific neighborhoods with higher-than-average CAP rates include Smoketown, West Louisville, Russell, and Portland. However, the incidence of CAP among whites and African Americans in Louisville were similar, and black ethnicity was not a significant risk factor for mortality or rehospitalization according to the analyses conducted in this study. Socioeconomic and environmental disparities (e.g., poor air quality, poor nutrition, suboptimal housing conditions, limited healthcare access) are more influential determinants of T2DM and CAP in Louisville than race inequalities. Racial and socioeconomic disparities may increase the risk of CAP and T2DM,[150-154] but further study is needed to better delineate the role of health inequities in T2DM and CAP.

Nursing home residence was one of the few variables in the logistic regression analysis associated with an increased odds for CAP hospital readmission that approached significance ($p = 0.07$) in patients $\geq$ 65. Nursing home residents may be particularly susceptible to infectious diseases because of proximity to other residents. The general health and advanced age of nursing home residents, and their interaction with medical staff are opportunities for infection. If the present study were able to track patients for more than one year, a pattern of CAP hospital readmission and an increase in mortality may be observed.

Results in the logistic regression analysis found that OB and OW were associated with a decreased odds for mortality at all three time points, and a decreased odds for rehospitalization in patients age < 65 years with high BMIs. This finding aligns with various studies that have described a phenomenon referred to as the "OB paradox." Although increased BMI correlates positively with the risk for developing T2DM and ASCVD, OW or obese subjects may have better prognosis when compared to those with BMI of < 25. The OB paradox was reported in ASCVD, T2DM, and in CAP, where the survival rates improve with an elevated survival.[9,10,155,156] Hypothesized explanations for the obesity paradox include reverse causality (thinner patients are sicker than obese patients) and the potential for adipose tissue to be protective during acute severe illnesses, when caloric intake is inhibited.

With the ongoing COVID-19 pandemic, these results give credence to examine the health policy recommendation of statins as an adjunctive therapy for CAP. The American College of Cardiology guidelines recommend statins for T2DM adults

age 40-75 years old for reduced risk of ASCVD mortality, however these agents still remain underused.[157] Among the T2DM patients in the HAPPI study, less than a majority (46.3%) were reported to be on statins, and 52.9% of T2DM patients age ≥ 65 were on statins. This is consistent with previously reported literature, where usage of statins in T2DM patients to be in the 40-50% range, with lower rates of underusage in minority populations.[158] This study's findings, if validated, could strengthen policy recommendations for prophylactic statin administration in populations most at-risk for CAP (i.e. T2DM, age ≥ 65).

Another health policy recommendation to emerge from this dissertation would be the replication of a large-scale epidemiological study similar to HAPPI, to conduct research on the impact of COVID-19. The University of Louisville Division of Infectious Diseases created its own large-scale database and transposed patient data from multiple healthcare EMR systems in order to better analyze the Louisville population at large. Further health policies could enable and facilitate the creation of similar large-scale data collection of COVID-19 in other cities or metropolitan areas through interoperable EMR and common registries.

This would help analyze and disseminate data more efficiently and have a more complete epidemiological picture of CAP health burden, rather than the data be compartmentalized by different healthcare systems. It could also identify beneficial interventions against COVID-19 that can inform future evidence-based policy making in each region or state.

Limitations

Several limitations exist in both the University of Louisville Pneumonia study and this present secondary analysis of the HAPPI data. As mentioned above, low statistical power is a primary limitation of the present investigation. The HAPPI study did not recruit CAP patients based on statin status. Thus, matching cases and controls was imperfect, and limited the sample size. T2DM patients could have been analyzed by glycemic control, but again the sample size would have been too small to analyze statin cases and controls with acceptable power. Sample size calculation is not straightforward in a prospective observational study as this. It is not expected to find a matching control for all statin controlled case patients, and this is a drawback of PSM. Although PSM reduces the treatment assignment bias, it is very sensitive and usually requires large sample sizes. As seen here, the use of PSM for subgroup analyses lost a large number of observations and meant any effect in the unmatched patients went unrecorded. There may have also been an imbalance of the covariates in subdividing the groups.

Exclusions of patients from the HAPPI study included: (1) those who did not have a permanent or valid address in the Louisville, Kentucky area based on the US Census Bureau data, (2) without a valid Social Security Number, or (3) were incarcerated in a corrections system or mental health facility at the time of hospital admission limits the generalizability of this study to the U.S. population overall.

The most famous limitation of the propensity score is the inability to account for unobserved variables that affect assignment to treatment and outcome in the matching procedure. The uncertainty of T2DM diagnosis and statin use are another

issue. The “unobserved” variables are unknowns that may bias the analyses. The decision tree and logistic regression analyses were done to identify covariates available in the HAPPI study that significantly correlated with T2DM, statin exposure and CAP outcomes. The PSM analysis use these covariates to conduct the final effect balancing during matching. It is very possible that unknown variables were not recorded by the HAPPI study that may have biased the PSM procedure.

Another limitation of this study, and implicitly the HAPPI study, is the method of data collection via EMR records. One example is statin use, which was obtained through medical records via ICD coding and prescription lists. No patient interaction was attempted to ascertain the true statin status or the specific statin used by the patient. CAP patients listed in EMR with prior statin use could have misreported compliance or stopped statin use after their CAP hospitalization. This would have biased outcome follow-up, and possibly affect long-term outcomes. These are unknown confounders that may affect analyses.

HAPPI was a multi-center observational study that used laboratory values analyzed by different healthcare system laboratories. Samples drawn for CAP patients on admission may vary as each of the nine hospitals may have had their own protocols. Between-group differences may have been seen in patients admitted to one hospital may have had a more complete workup compared to another hospital. One of the challenges in conducting this study was blood glucose was drawn without respect for fasting status for almost every CAP patient. HbA1c was not regularly done, even for every diabetic patient. The HAPPI study had 3301 (32.8%) patients reported to have T2DM according to their EMR, but only 2734

had a confirmatory HbA1c. Apparently, HbA1c was only tested on admission for CAP patients with a history of T2DM or suspected of having T2DM. Outcomes in prediabetics versus patients with T2DM could not be tested with a low sample size. A possible large number of undiagnosed or underdiagnosed diabetics could have been categorized as non-T2DM in the HAPPI study because no HbA1c was ordered or recorded in the EMR.

Furthermore, there were many laboratory values and past medical history data missing from the HAPPI dataset that may have been valuable to explore. Inflammatory markers such as CRP was only collected in 192 (2%). Insulin-dependence was a variable collected in the medical history, but T1DM was not. T1DM's relationship to statin therapy and CAP could not be evaluated, and it is likely that 5-10% of those labelled as T2DM were actually T1DM. The causative microbe was detected in only 991 of the 2734 CAP patients (36.2%). HDL and triglycerides were collected in 2201 CAP patients (21.9%) while waist circumference was not recorded. Therefore, it was not possible to analyze any possible relationship between statin exposure and metabolic syndrome.

The EMR contained no information on the length of time the patient had used statins. The HAPPI study did not record the type of statin, dosage or frequency of use. Therefore, a dose response relationship or statin potency differences could not be evaluated. In addition, statins may have been prescribed by either a hospitalist or outpatient physician. The hospital EMR systems are not continuous between outpatient and inpatient facilities, and information about the cases' primary care may be missing. Between-group residual variance can be large if the large numbers

of the cases and controls see outpatient physicians whose information is not linked to the hospital EMR.

A number of health policies proposal can be suggested from these limitations dealing with the EMRs of different healthcare systems and data generation from hospital admission. One health policy could allow for greater coordination of between outpatient and inpatient EMRs, to share laboratory and clinical data relevant to generate diagnoses such as T2DM and dyslipidemia. This same policy recommendation could be augmented for medications listed in outpatient and inpatient EMRs, to enable public health officials to follow dosage and scheduling and observe a dose-response relationship. One final policy could be agreed-upon protocols across the community or regions for data generation consistency regarding CAP and COVID-19, blunting some of the problems in data collection encountered in the original HAPPI study.

Strengths

The HAPPI study was able to prospectively evaluate and attempt to enroll a majority of CAP adult hospitalizations in the city of Louisville for three consecutive years. HAPPI investigators were able to define the number of unique patients in Louisville hospitalized with CAP using SSNs and home addresses from the US Census Bureau. The HAPPI investigators defined guidelines for data collection and verification for all patient medical history, hospitalization data, and outcomes.

The PSM analysis performed removed individuals in the control group who were a poor match to the cases. Among other medical observational studies, PSM

analysis reduced selection bias due to removing case control through matching. PSM analysis improved internal validity better than stratification methods.[159]

Conclusions

Prior retrospective observational studies have found statin therapy might affect mortality and morbidity outcomes in patients with T2DM and CAP. The present study used data from the HAPPI study, a prospective cohort-based study of adult patients hospitalized for CAP in Louisville, Kentucky. The objective of this dissertation was to observe in real time the effect of prior statin therapy on CAP patient outcomes at one, six, and 12 months.

Decision tree analysis, logistic regression analysis, and Cox regression analysis showed that the T2DM and statin interaction was significantly associated with decreased mortality at one, six, and 12 months for T2DM patients age <65 , but not in T2DM patients age ≥ 65. The results of PSM analysis with McNemar test analysis, controlling for covariates including neoplastic disease, MI, OB, gender, and race, showed non-significant association of the T2DM and statin interaction with decreased odds for mortality at one, six, and 12 months for patients age <65. No significant differences in CAP readmission at one, six, and 12 months were found between T2DM patients on statins versus those not on statins. The cost analysis found that statin therapy was associated with non-significant decreased LOS and incurred costs for T2DM patients in both age groups.

This dissertation provides empirical evidence from decision tree analysis, logistic regression, and survival analysis of a protective effect from mortality of

statin therapy and may be most beneficial for T2DM patients hospitalized for CAP age < 65 years. However, the sample size was reduced by the PSM analysis that lowered the statistical power of the analysis. The results indicate that future research, such as a potential randomized controlled trial, should recruit patients using a power analysis to increase the probability of matching and retain an adequate sample size. The possibility that statins may be used as adjunctive therapy for CAP treatment remains a relevant public health question to explore, particularly with the ongoing COVID-19 pandemic.

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CURRICULUM VITAE

Name: Joel Lanceta, MD.

Address: 134 Fremont Ave. Apt #1
New York, NY 10306
Tel: (C) 773-484-0293
(Pager) 917-218-5056

EDUCATION AND TRAINING

Resident, Department of Pathology
Hofstra/Northwell Health– Staten Island University Hospital
July 2018- Current

Postdoctoral Research Intern
University of Louisville, Louisville, KY
Department of Internal Medicine, Division of Infectious Disease
July 2015-March 2018

M.S., Clinical Research Methods
Tulane University, New Orleans, LA
Graduated May 2014

M.D., Doctor of Medicine
University of Louisville School of Medicine
Graduated May 2013

M.A., Medical Sciences with Honors
Boston University School of Medicine
Graduated May 2008

BA, Biological Sciences
University of Chicago
Graduated June 2006