Examining the Presence of Multimorbidity Clusters in Patients Evaluated for Acute Coronary Syndrome

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THESIS

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This dissertation is dedicated to my family. To my loving and supportive husband, Ryan, without whom it would have never been accomplished. Also, to my mother, Jane, without her guidance throughout my life, I would not be the person I am today.

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KB

Contribution of Authors Statement

Katherine Breen was the author of the papers included in this dissertation. She performed the analyses, calculations, and interpretation of the data. Dr. Holli DeVon was the senior author and contributed to the development, execution of the research project, critically revised the papers and supervised the work. Dr. DeVon oversaw overall direction and planning. She gave the final approval of the version to be submitted and revised versions. Dr. Lorna Finnegan contributed to the analysis and interpretation of the research data by critically revising the paper. Dr. Karen Vukovic, Dr. Anne Fink, and Dr. Wayne Rosamond contributed equally to this work through their mentorship and critiques. They participated in the critical revision of the papers. All authors provided critical feedback and helped shape the manuscript and commented on the manuscript at all stages

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
BIC	Bayesian Information Criteria
BLRT	Bootstrapped Likelihood Ratio Test
CABG	Coronary Artery Bypass Graft
CCI	Charlson Comorbidity Index
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVCM	Cardiovascular Comorbidity
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ED	Emergency Department
HF	Heart Failure
HTN	Hypertension
IQR	Interquartile Range
LCA	Latent Class Analysis
LOS	Length of Stay
MCM	Multimorbidity Conceptual Model
MM	Multimorbidity
NONCVCM	Non- Cardiovascular Comorbidity

ABBREVIATIONS (CONTINUED)

NSTEMI	Non-ST-Elevation Myocardial Infarction
ONC	Oncology
PCI	Percutaneous Coronary Intervention
SD	Standard Deviation
STEMI	ST-Elevation Myocardial Infarction
UA	Unstable Angina

SUMMARY

A study of multimorbidity (>2 chronic conditions) in patients evaluated for symptoms suggestive of acute coronary syndrome in the emergency department was conducted. This secondary data analysis was conducted using data from the prospective longitudinal "Think Symptoms" study. A latent class analysis was conducted using all available cas with complete comorbidity data (n=1003) to examine the existence of specific patterns of multiple chronic conditions (multimorbidity phenotypes). These phenotypes were then tested for association with readmission and emergency department visits at 30-days and 6-months. The association with clinic visits was also examined for at 6-months.

Four multimorbidity phenotype classes were found Class 1) High overall multimorbidity, Class 2) Low multimorbidity, Class 3) Cardiovascular multimorbidity, and Class 4) Cardiovascular- oncology multimorbidity (cardio-onc). Each of the classes varied by age, sex, functional status as measured by the Duke Activity Scale Index, family history of sudden cardiac death at age < 55 years, and whether or not they were ruled-in or out for acute coronary syndrome.

Among patients evaluated for potential ACS, preexisting chronic conditions were common and associated with increased healthcare utilization at 30-days and 6-months. Multimorbidity phenotypes offer both immediate diagnostic utility and longer-term risk-stratification potential for these high-risk patients. Further research is needed, however, to investigate additional chronic conditions, known cardiovascular risk factors, and outcomes such as mortality, pharmaceutical intervention, and types of specialist visits in patients ruled-in and ruled out for ACS to identify protective and predictive factors that help identify high-risk individuals.

Introduction

This dissertation consists of an introduction, two manuscripts, and a conclusion. The aims of the first manuscript were to determine the magnitude and impact of multimorbidity (>2 chronic conditions) on mortality, length of stay, and rates of percutaneous interventions in patients with acute coronary syndrome (ACS) and to compare the prevalence of cardiovascular versus non-cardiovascular multimorbidities. The aim of the second manuscript was to identify clusters of individuals defined by distinct multimorbidity profiles using self-reports (Charleson Comorbidity Index and ACS Patient Questionnaire) of the following conditions: obesity, coronary heart disease (prior myocardial infarction), peripheral vascular disease, cerebrovascular disease, cancer, respiratory disease (chronic obstructive pulmonary disease and asthma), renal disease, lupus, hyperlipidemia, and hypertension.

Multimorbidity is an emerging concept, different from the familiar concept of comorbidity, and is defined as the coexistence of two or more chronic conditions in the same individual.[1] Chronic conditions which may be equally important and overlapping in management strategies, and require similar intensity and simultaneous management to achieve optimal quality of life and outcomes (Figure 1). [2] Chronic conditions are accumulated as a result of lifestyle factors, environmental factors, genetics, treatment of prior conditions (e.g., heart failure [HF] as a consequence of chemotherapy regimens), and aging itself culminates in a highly heterogenic population of older adults that require management of multiple medical problems.[2] As the number (count) of chronic conditions increases, the risk of poorer outcomes increases as well. As individuals age, multimorbid dyads (2 conditions) and triads (3 conditions) emerge and include CV risk factors.[2] The proportion of adults aged 65 and over is rapidly increasing and will comprise approximately 19% of the US population by the year 2030. By age 65, over 60% of adults will have 2 or more chronic conditions, >25% will have 4 or more conditions, and almost

10% will have at least 6 conditions.[2] In Medicare beneficiaries, the burden of multimorbidity is exceptionally high. In the context of the six most frequently managed conditions (HF, stroke, hyperlipidemia, atrial fibrillation, ischemic heart disease, and hypertension) in cardiovascular medicine, there is a high prevalence (>50%) of three or more additional chronic conditions.[3] Furthermore, as individuals age and conditions accumulate, the risk for an ACS event increases, as does the risk of mortality for multimorbid patients compared to their non-multimorbid counterparts.[2]

Each year in the United States, 5.5 million patients are evaluated for ACS in emergency departments.[4] This year, approximately 720,000 Americans will have a new coronary event (defined as the first hospitalization for myocardial infarction [MI] or coronary heart disease [CHD] death), and approximately 335,000 will have a recurrent event.[5] ACS survival rates have increased, resulting in an increase in the elder population, [6-8] and these individuals are living with more chronic conditions (multimorbidity), which is associated with reduced quality of life, increased healthcare burden, and greater mortality.[9-11]

Multimorbidity places ACS patients at a higher risk for complications during hospitalization, leads to increased rates of in-hospital complications (e.g., bleeding and drug-drug interactions), and increases the length of stay.[12] In ACS patients with multimorbidity (CV-multimorbidity and/or non-CV multimorbidity), there was a 3-fold increase in all-cause 30-day readmission as compared to their non-multimorbid counterparts.[12] Patients hospitalized with ACS, baseline multimorbid patients had a two-fold higher risk of recurrent cardiovascular (CV) events after discharge, compared to patients without multimorbidity.[12] After discharge, patients with multimorbidity frequently receive care from different specialists, which may impact the achievement of secondary prevention targets.[13-15]

Multimorbidity is described at the cumulative number of chronic conditions[16-19] level, and investigators are just beginning to examine whether multimorbidity clusters (specific combinations of chronic conditions)[17,20-22] exist, and if specific clusters impact clinical outcomes. There has been some research done in HF reporting multimorbidity clusters and this provides a rationale for examining clusters within the ACS population. “Benign” and "malignant” phenotypes of multimorbidity were recently (2018) described in the HF population. Individuals with concurrent anemia, dysrhythmia and respiratory disease experienced significantly higher all-cause mortality (malignant phenotype) at 12-months than those without these conditions (36.1% vs. 3.6%, respectively; hazard ratio, 6.1).[23] Additionally, a malignant phenotype of multimorbidity was associated with a markedly increased risk of all-cause mortality and more longer inpatient stays, unplanned readmissions and the highest costs in the short and longer-term (12-months) when compared with less malignant phenotypes of multimorbidity.[23] Since ACS is often a precursor to HF, it is important to study multimorbidity clusters in the ACS population.

The Multimorbidity Conceptual Model (MCM) [2] is a novel conceptualization of risk stratification and management for ACS patients. The MCM demonstrates a more patient-centric approach to managing CVD than the traditional comorbidity model. The multimorbidity model is the inverse of the comorbidity model that considers the primary or index disease as the most important component of the model and the comorbid conditions as lesser influences of overall health than. The MCM considers the primary or index disease as the smallest component and progresses to higher levels of complexity as one moves from the center out (see Figure 1).[2] The MCM takes into consideration the identification and management of the primary disease, the presence of multimorbid conditions, geriatric syndromes, and psychosocial factors.[2] Developing

studies with a more patient-centered conceptual framework is necessary to identify salient variables for analysis and provide evidence that may lead to better patient outcomes .

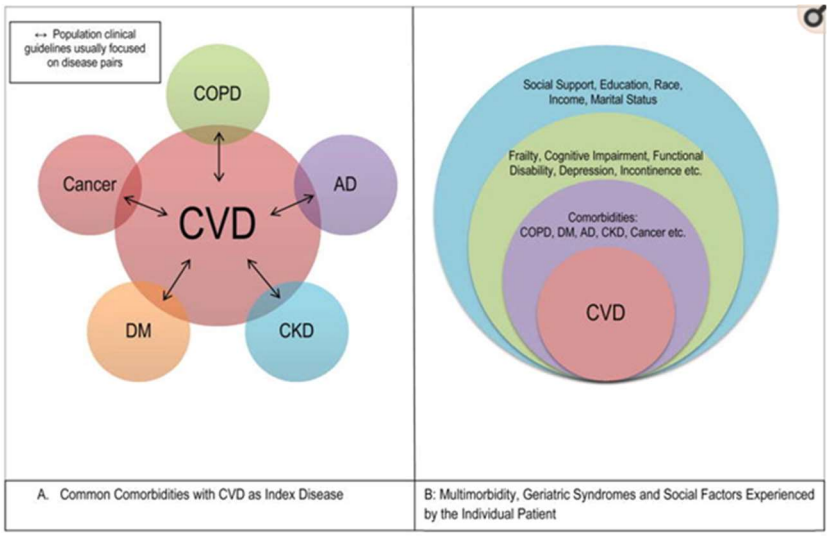

Figure 1. Comorbidity model versus MCM model

Clinical care is primarily driven by single-disease based guidelines that focus on diagnosis, therapeutics/management, and decision-making (e.g., ACS); yet the relevance and applicability of these guidelines become less useful when the diagnosis and treatment plan are complicated by multimorbidity.[13] Clinical guidelines are based on randomized clinical trials that include patients with a single disease process and exclude multimorbid patients; therefore, current guidelines have very limited applicability to multimorbid [13,16] patients. Limited applicability of guidelines greatly disadvantages multimorbid ACS patients and places them at increased risk for adverse outcomes.[13,24] The science of multimorbidity is in its infancy for the ACS population. Multimorbidity literature in the ACS population is currently sparse. To make a

significant contribution to reducing adverse outcomes such as readmission and mortality, along with improving patient-centered outcomes such as healthcare utilization, multimorbidity in the ACS population must be better understood.

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II. Manuscript #1:

Greater Mortality, Higher Readmission Rates, and Increased Length of Stay. Multimorbidity in the ACS population: A Systematic Review.

A. Background

Multimorbidity is defined by the World Health Organization (2015) as the co-occurrence of two or more chronic conditions. Multimorbidity affects every aspect of the healthcare system, and the burden of multimorbidity will increase as the aging population swells over the next 10 years.[1] Approximately 40 million individuals over the age of 65 have cardiovascular disease (CVD), which remains the leading cause of morbidity and mortality.[2,3] The proportion of adults aged 65 and over is rapidly increasing and will comprise approximately 19% of the US population by the year 2030.[2] For Medicare beneficiaries, the burden of multimorbidity is exceptionally high. As individuals age, multimorbidity dyads and triads emerge and include cardiovascular risk factors.[4,5] For the six most frequently managed conditions (heart failure, stroke, hyperlipidemia, atrial fibrillation, ischemic heart disease, and hypertension), there is a high prevalence (>50%) of three or more additional chronic conditions.[6] The number (count) of comorbid conditions increases the risk of poorer outcomes. Multimorbidity is also associated with polypharmacy, reduced quality of life, and higher mortality.[7]

In the US, 5.5 million patients are evaluated for acute coronary syndrome (ACS) in emergency departments every year.[8] Approximately 720,000 Americans will have a new coronary event this year, defined as the first hospitalization for myocardial infarction (MI) or coronary heart disease, and approximately 335,000 will have a recurrent event.[2] Mortality rates from ACS have declined in the past decade, and people are living longer; hence a highly

heterogeneous cohort of complex multimorbid patients now require care.[9] The risk for ACS increases in those with multimorbidity compared to the non-multimorbidity population.[10]

Given the frequency of multimorbidity in ACS and the rapidly aging population, it is imperative to determine the prevalence of multimorbidity in this population to better understand clinical presentation for ACS, improve chronic care management, and design pragmatic clinical trials to include patients with multimorbidity. To date, no systematic review of the prevalence of or outcomes from multimorbidity in patients with ACS has been published. Therefore, the aims of this systematic review were to (1) determine the prevalence and effect of multimorbidity in patients with ACS on clinical outcomes, including short and long-term mortality, length of stay, and readmission; and (2) to determine the prevalence of cardiovascular and non-cardiovascular multimorbidity among patients with ACS.

B. Methods

1. Search Strategy and Study Selection

Articles were obtained by searching the Medline, PubMed, Medline Plus, CINAHL, OVID, and Embase databases for articles published from January 2009 through August 2019. The following search terms were used: multimorbidity, multiple chronic conditions, multiple comorbidities, concurrent chronic conditions, acute coronary syndrome, myocardial infarction, ST-elevation myocardial infarction (STEMI). Search limits were used in each database to restrict findings to the following inclusion criteria: 1) original research studies published between 2009-2019; 2) articles in English; 3) research articles which examined multimorbidity in patients with ACS; or 4) studies examining health outcomes following ACS (myocardial infarction [MI], non-ST elevation myocardial infarction [NSTEMI], ST-elevation myocardial infarction [STEMI], and unstable angina [UA]); and 5) study participants over age 18. We excluded studies that did

not analyze multimorbidities. Case reports, abstracts, reviews, conference proceedings, editorials, or opinions were also excluded. Reference lists from the selected articles were reviewed to identify additional articles that did not appear in the database search. The selection process followed PRISMA guidelines (Figure 2). Only research published in the past 10 years was selected as older studies may be less generalizable to the present-day, due to changes in the ACS patient population, anticoagulants, percutaneous treatments, and improved outcomes. Furthermore, a recent systematic review found that 79% of all studies with multimorbidity as the focus were published between 2013 and 2016.[12]

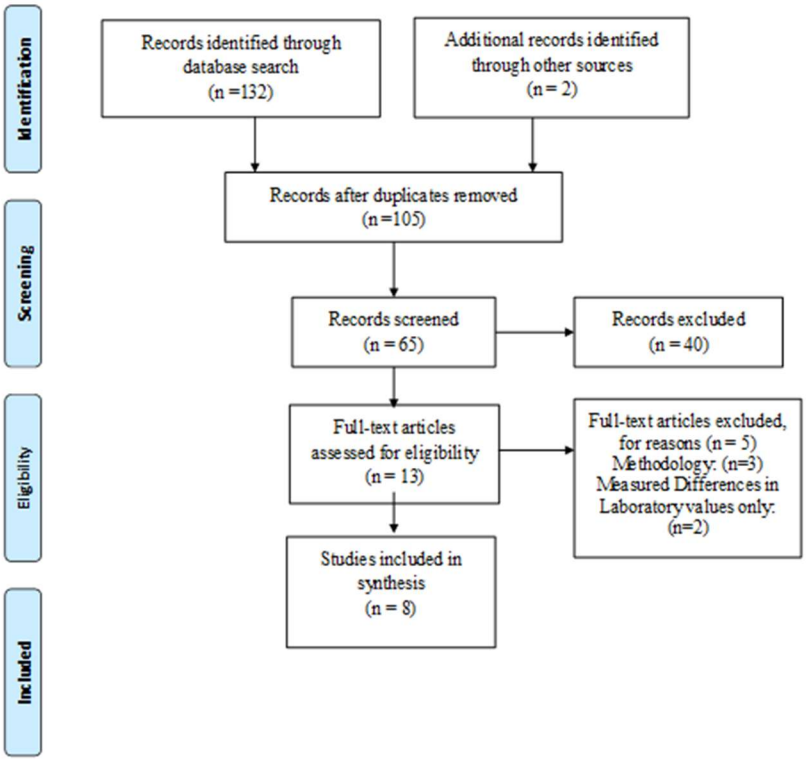

Figure 2. Prisma guidelines flow sheet.

2. Data Extraction and Synthesis

The first author independently examined the titles and abstracts to determine eligibility for inclusion. Duplicate articles were removed. If the title and abstract appeared to be relevant, it was marked for full-text review by the last author. Articles marked as questionable by the rater were also marked for full-text review. If there was a disagreement on inclusion, a 3rd reviewer examined the paper, and the paper was included or excluded based on majority opinion. A systematic analysis of all articles was completed by two reviewers who are experts in cardiovascular diseases. Data analysis and synthesis included extracting data from each article into tables that included the essential characteristics of each study.

3. Quality Appraisal

The Crowe Critical Appraisal Tool (CCAT) was used to assess the quality of research articles in this review. [13] The CCAT consists of eight categories: preliminaries, introduction, design, sampling, data collection, ethical matters, results, and discussion. Each category is scored on a 6-point scale ranging from 0 to 5. Total scores range from 0 to 40. A higher score indicates higher quality. No quality parameters have been established; however, the score is useful for comparison purposes.

4. Search Outcomes

A total of 132 articles were identified in the initial search. Duplicate articles and studies based on the title and abstract screen were removed. No qualitative studies were found that met inclusion criteria. The full texts of 13 articles were reviewed with eight articles meeting inclusion criteria (Figure 2). A review of reference lists from the eight articles resulted in the identification of one additional eligible study. The final number of research articles included was eight.

C. Results

1. Study Characteristics

Study characteristics are summarized in Table 1. One study included patients with diabetes mellitus (DM) and STEMI. The remaining seven studies included patients with either ACS or a specific clinical subcategory (MI, STEMI, or UA). Seven of the studies were multicenter, and one was a single center. Six of the studies were retrospective. Two studies were prospective cohort studies. Three of the six retrospective studies analyzed different variables and different time points from the large Worcester Heart Attack Study dataset. Four were US-based studies. The five non-US-based studies were performed in Australia (n=2), England & Wales (n=1), Switzerland (n=1), and Poland (n=1). All studies utilized medical records for data collection. Two utilized ICD-9 & ICD-10 codes. One utilized a baseline interview in addition to medical records. As determined by CCAT, the quality scores of the studies ranged from 30 to 38, indicating moderate to high quality (Table 1).

TABLE I. STUDY CHARACTERISTICS

Authors/ Country	Study Design/Time Period	Purpose	Sample/Setting/Condition	Quality Score
Canivell et al. (2018)[7], Switzerland	Prospective cohort data collected from 2009-2014	Examine the prognosis of patients with CV and non-CV MM compared to patients without prior MM following ACS	N=5,635 Mean Age: 67.7 years 79% Male 97.5% Caucasian Multiple hospitals in Switzerland, ACS	38/40
Hall et al. (2018)[14], England & Wales	Retrospective analysis of data collected in the *MINAP* database from January 2003-June 2013	Investigate MM phenotype clusters exist across a range of pre-existing long-term health conditions and study the association with long-term survival for patients hospitalized with AMI	N=693,388 Mean Age: 70.7 years 65.5% male Race not reported All hospitals in the National health service in England & Wales AMI	37/40
Chen et al. (2013)[21], USA	Retrospective analysis of the *Worcester Heart Attack Study* with data collected in 2003, 2005, & 2007	Describe the prevalence of cardiac and non-cardiac comorbidities in a community-based population of patients hospitalized w with AMI	N=2,972 Mean Age: 71 years 55% male 93% Caucasian All medical centers in Massachusetts AMI	38/40
McManus et al. (2012)[5], USA	Retrospective analysis of the *Worcester Heart Attack Study* with data collected between 1990-2007	Examine the overall and changing (1990-2007) frequency and impact on 30-day and 1-year death rates from multiple CV comorbidities	N=9,581 Mean age: 70 years 57% male 93% Caucasian All medical centers in Massachusetts AMI	35/40
Tisminetzky et al. (2019)[17], USA	Multisite prospective cohort design with data collected between 2001-2011	Describe the prevalence of, and patient characteristics associated with, CV and non-CV multimorbidities in patients discharged	N=2,174 Mean age: 67 years 67% male 81% Caucasian Medical centers in Massachusetts and Georgia ACS	38/40

Authors/ Country	Study Design/Time Period	Purpose	Sample/Setting/Condition	Quality Score
		from the hospital after ACS		
Worrall-Carter et al. (2015)[20], Australia	Retrospective cohort study of VAED) database analyzing data collected between June 2007-July 2009	Determine the impact of gender and comorbidity on use of coronary interventions in patients diagnosed with high-risk non-ST-segment elevation ACS	N=16,771 Age Range: 15-59(21%), 60-74(32%), 75+(48%) 62% male Race not reported All Victorian hospitals in Australia NSTEMI ACS	34/40
Hudzik et al. (2017) [15], Poland	Retrospective cross-sectional analysis of data collected over a 12-month period	Determine the prognostic value of multiple comorbidities on long-term outcomes in patients with type II diabetes and STEMI	N=277 Mean age: 63.5 years 58.8% male Race not reported Location not reported Patients with concurrent type II Diabetes & STEMI	31/40
Ofori-Aseno et al. (2019)[16], Australia	Retrospective cohort study of data collected between July 2013 - December 2015	Examine the prevalence and impact of non-cardiac comorbidities on the length of stay and mortality among older adults hospitalized for non-ST-segment elevation-ACS	N=1,488, Mean age: 79.4 years 62% male, Race not reported Single-center (Alfred hospital) in Melbourne NSTEMI & UA	35/40

NOTE: ACS is acute coronary syndrome. AMI is acute myocardial infarction. CV is cardiovascular. MM is multimorbidity. NSTEMI is non-ST elevation myocardial infarction. STEMI is ST-elevation myocardial infarction. UA is unstable angina. VAED is The Victorian Admitted Episodes Data Set.

2. Participant Characteristics

Study sample sizes ranged from 277 to 693,388 [14,15]; only one of the studies included <1,000 subjects.[15] The mean age ranged from 61 to 79 years.[7,16] Five of the eight studies included data on race/ethnicity, and the majority of subjects (81% to 97%) in those studies were Caucasian[7,17] and male (55%-95%).[4,7]

3. Assessment and Prevalence of Individual Comorbidities

Comorbidities were assessed in multiple ways; simple counts (n=6), a combination of the Elixhauser and Charlson Comorbidity Indices (n=1), and the Charlson Comorbidity Index alone (n=1). The prevalence of comorbidities ranged from one additional comorbidity present in 16% to 57% of study populations [4,14] to four or more comorbidities ranging from 0.02% to 36.8% across study populations.[7,17] See Figure 3 for full details on comorbidities by study. The most common comorbidities considered were DM, renal disease, chronic obstructive pulmonary disease (COPD), hypertension (HTN), heart failure (HF), anemia, cerebrovascular disease, and cancer.[5,7,14,16,18-20]

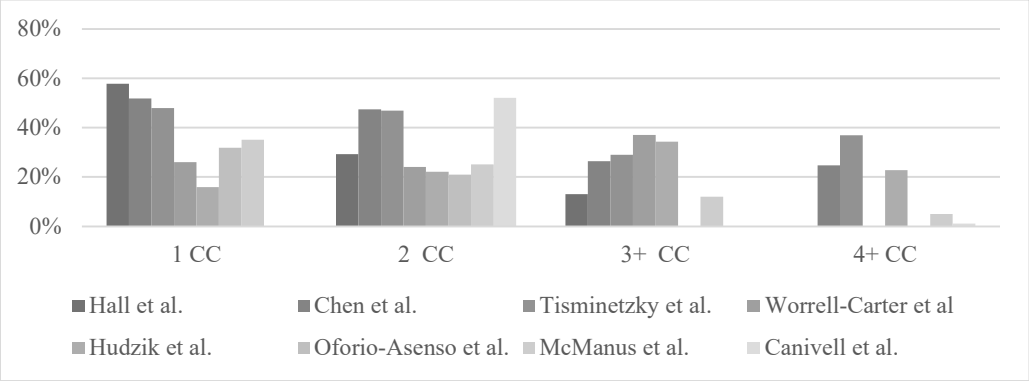

Figure 3. Individual Comorbid Conditions by Study

Six studies classified individual comorbidities as either cardiovascular or non-cardiovascular and comorbidities had slight differences in classification of comorbidities as either cardiovascular or non-cardiovascular. For example, Ofori-Asenso, Zomer, Chin, Markey, Si, Ademi, Curtis, Zoungas, Liew [16] counted DM as non-cardiovascular comorbidity. However, given that DM is a CVD equivalent and four of the six studies measured DM as cardiovascular comorbidity, it will be reported as such for clarity (see Table 2 for a complete listing of comorbidities by study). Cardiovascular comorbidities were more prevalent than non-cardiovascular comorbidities; 24% versus 11%, respectively. [10,14,15,19-21] The most prevalent cardiovascular comorbidities were HTN (46% to 76%) [19], DM (6%-35%) [20 22] and HF (1.7% to 45%) [7 15] (Figure 4). Of the non-cardiovascular comorbidities reported renal disease was most prevalent (4% to 24%) [7,16] followed by COPD (2% to 36%)[14] (Figure 5).

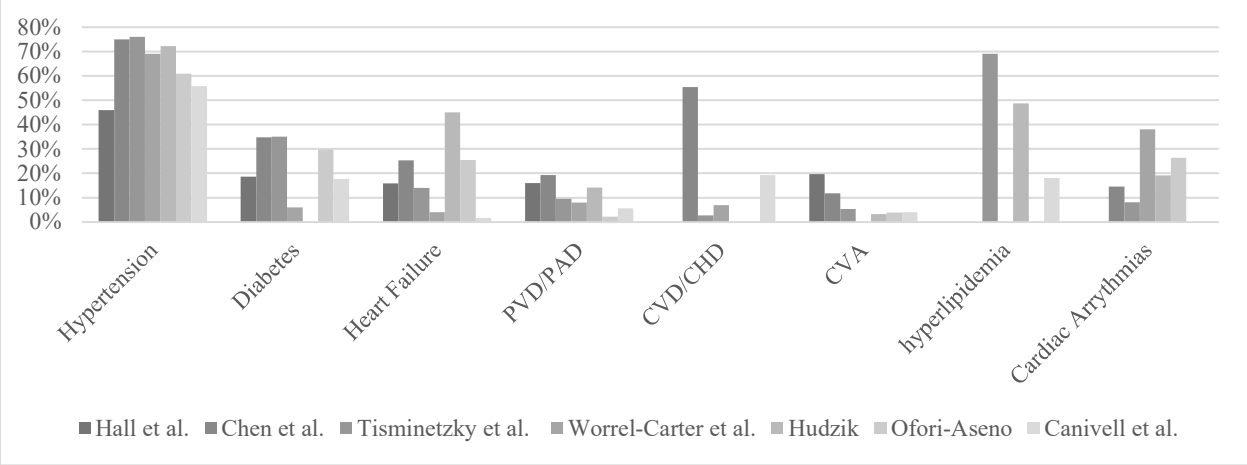

Figure 4. Prevalence of Individual Cardiovascular Comorbidities by Study

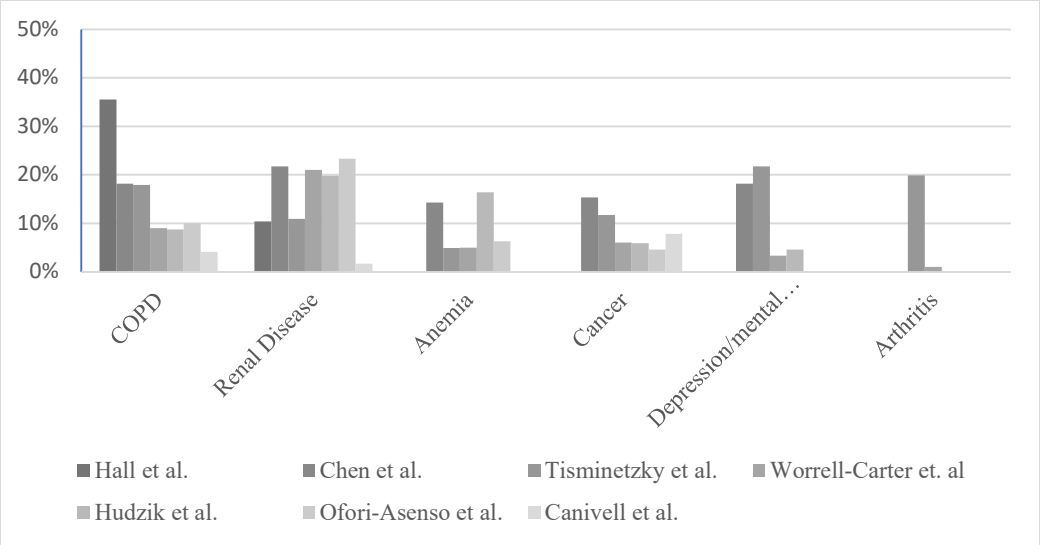

Figure 5. Prevalence of Individual Non-Cardiovascular Comorbidities

TABLE II. PREVALENCE OF MULTIMORBIDITY BY STUDY

Citation	Method	CV Comorbidities Examined	NON-CV Comorbidities Examined	Prevalence of Multimorbidity
Canivell et al. (2018)[7]	Simple counts of predetermined CV & non-CV MM	CHD (prior MI, PCI, or CABG), PAD, Cerebrovascular disease (stroke or TIA), DM, HTN, or possible familial hypercholesterolemia	Cancer, gastrointestinal bleeding, systemic inflammatory disease (defined as lupus erythematosus, polymyosite, mixed connective tissue disease, polymyalgia rheumatic, rheumatoid arthritis, or psoriasis), severe renal disease, and liver disease	No MM: 65% MM: 35% CV MM: 33% Non-CV MM:1% Both CV & non-CV MM: 1%
Hall et al. (2018)[14]	Simple counts of predetermined CV & non-CV MM	COPD or Asthma, DM, chronic heart failure, chronic renal failure (defined as creatinine chronically > 200 µmol/l), CVA, PVD, or HTN		Preexisting comorbidity count (1,2,3+,7): 59.5%, 29. 2%, 13.0%, & 0.02% No MM: 59.5% MM: 25.2%
Chen et al. (2013)[4]	Simple counts of predetermined CV & non-CV MM	AFIB, CHD (angina pectoris, CHD, MI, CABG, or PCI), DM, HF, HTN PVD, & CVA	Anemia, depression, cancer, COPD, & CKD	1+ CV preexisting comorbidity: 87% 1+ NON CV preexisting condition: 55%

Citation	Method	CV Comorbidities Examined	NON-CV Comorbidities Examined	Prevalence of Multimorbidity
				CV MM (0,1,2,3,4+): 12.9%, 19.8%, 24.2%, 18.7%, & 24.6% Non-CV MM (0,1,2,3+): 44.8%, 32.0%, 15.6%, 7.6% ≥4 CV MM and ≥3 non-CV MM:4.3% Neither CV MM nor non-CV MM:9.6%
McManus et al. (2012)[5]	Simple counts of predetermined CV MM	AF, DM, HF, hypertension, MI, & CVA	N/R	Preexisting Comorbidity count (1,2,3,4+): 35%,25%,12%, & 5% >1 preexisting comorbidity: 77% No MM: 35% MM:42%

Citation	Method	CV Comorbidities Examined	NON-CV Comorbidities Examined	Prevalence of Multimorbidity
Tisminetzky et al. (2019)[17]	Simple counts of predetermined CV & non-CV MM	HTN, HLD, type II DM, PVD, HF, AFIB, CVA, & valvular heart disease	COPD, arthritis, depression, anxiety, cancer, CKD, cirrhosis, & Anemia	CV MM (0,1,2,3,4): 12.5%, 17.7%, 31.5%, 23.8%, 14.5% Non-CV MM (0,1,2,3,4): 47.4%, 30.3%, 15.5%, 5.1%, & 1.7% ≥4 or more CV & non-CV MM: 36.8%
Worrall-Carter et al. (2015)[20]	30 predetermined conditions developed by Elixhauser et al.	HF, cardiac arrhythmia, valvular disease, pulmonary circulation disorder, PVD, HTN, paralysis, other neurological disorder, COPD, DM, hypothyroidism, renal failure, liver disease, peptic ulcer disease, AIDS, lymphoma, cancer, rheumatoid arthritis/ collagen vascular diseases, coagulopathy, obesity, weight loss, fluid-electrolyte imbalance, anemia, alcohol abuse, drug abuse, psychoses, & depression		Preexisting comorbidity count (0,1,2, 3+): 12%,26.5%, 24.2%, & 37.2% No MM: 38.6% MM: 61.4%
Hudzik et al. (2017)[15]	Simple counts of predetermined conditions	HTN, AF, HF, HLD, CVA, & PAD	COPD, asthma, cancer, anemia, peptic ulcer/GI bleeding, CKD ≥ than stage 3, thyroid disorders, depression, and connective tissue disease	Preexisting comorbidity count (1,2,3,4+): 15.9%,22.0%,34.4%, & 22.7% CV MM (1+):93%

Citation	Method	CV Comorbidities Examined	NON-CV Comorbidities Examined	Prevalence of Multimorbidity
		*All patients in sample had DM as an inclusion criterion		No non-CV MM: 46.9% Median number of concurrent chronic conditions: 3
Ofori-Aseno et al. (2019)[16]	Simple counts of a priori selected CCI comorbidities & conditions from literature	N/R	DM, renal disease, COPD, anemia, cancer, dementia, peptic ulcer disease, liver disease, HIV, obesity	Preexisting NCC comorbidity count (0,1, 2+): 47.2%, 31.9%, & 21% ≥ 1 preexisting Non-cardiac comorbidity:53% Non-CV MM: 21%

NOTE: AF is atrial fibrillation, AMI is acute myocardial infarction, CABG is coronary artery bypass graft, CCI is Charlson comorbidity index., CKD is chronic kidney disease, COPD is chronic obstructive pulmonary disease, CV is cardiovascular, DM is diabetes melitis, GI is gastrointestinal, HF is heart failure, HLD is hyperlipidemia, HTN is hypertension MI is myocardial infarction MINAP is myocardial Ischaemia National Audit Project (England & Wales). MM is multimorbidity. PAD is peripheral artery disease, PCI is percutaneous coronary intervention, PVD is peripheral vascular disease, and TIA is transient ischemic attack.

Specific comorbidities, regardless of overall prevalence, were linked to either the presence or absence of multimorbidity, as well as specific additional comorbidities. Hall, Dondo, Yan, et al.,[14] reported that specific low prevalence comorbidities such as renal disease, HF, and peripheral vascular disease (PVD) were more frequently associated with multimorbidity (27,8123[89.6%], 28,445[84.1%], and 23.201[84.0%], respectively) in the study population (n=693,388). Ofori-Asenso, Jakhu, Curtis, et al.,[23] reported the occurrence of atrial fibrillation (AF), HF, and PVD were less frequent in patients without non-cardiovascular comorbidities (25% versus 32% [p-value=0.05], 18% versus 43% [p-value<0.001], and 1% versus approximately 3% [p-value=0.038], respectively).

4. <u>Prevalence of Multimorbidity</u>

Overall, multimorbidity ranged from 25% to 95% (Figure 6). [5,7,14-19] Seven out of eight studies reported that patients with a greater multimorbidity count and burden were more likely to be older, female, non-white, and widowed, or single. Four studies examined the prevalence of multimorbidity by the categories of cardiovascular and non-cardiovascular multimorbidity (Figure 7). Two studies simply classified conditions as multimorbidity. McManus, Nguyen, Saczynski, et al.,[5] only examined cardiovascular multimorbidity while Ofori-Asenso, Zomer, Chin, et al.,[16] examined only non- cardiovascular multimorbidity. The prevalence of cardiovascular multimorbidity ranged from 33% to 69%, with a mean of 56%. [15,18,24] Non-cardiovascular multimorbidity varied widely from 1% to 53%, with a mean of 31%.[7,14]

Two studies report mixed multimorbidity, including both cardiovascular comorbidity & non-cardiovascular comorbidity. [14,19] Tisminetzky, Gurwitz, Miozzo, et al.,[17] generated groupings by the presence and combination of cardiovascular comorbidities and non-cardiovascular comorbidity and obtained four groupings: 1) ≤2 cardiovascular comorbidities and

no non-cardiovascular comorbidity (28%), 2) ≤2 cardiovascular comorbidities and ≥ 1 non-cardiovascular comorbidity (21%), 3) ≥3 cardiovascular comorbidities and no non-cardiovascular comorbidity (20%), and 4) ≥3 cardiovascular comorbidities and ≥1 non-cardiovascular comorbidity (31%). Hall, Dondo, Yan et al., [14] reported three multimorbidity classes: 1) high overall multimorbidity (class 1) with concomitant HTN, HF, and PVD was present in 7% (n=47,839) of patients; 2) moderate overall multimorbidity (class 2) with concomitant HTN and PVD was present in 13% (n=87,009) of patients, and 3) low overall multimorbidity (class 3) with high prevalence concomitant PVD was present in 62% (n=433,215) of individuals. The high multimorbidity class more often had NSTEMI (83.2%) than STEMI diagnoses compared with the moderate and low multimorbidity classes (71.6% and 57.6%, respectively).[14]

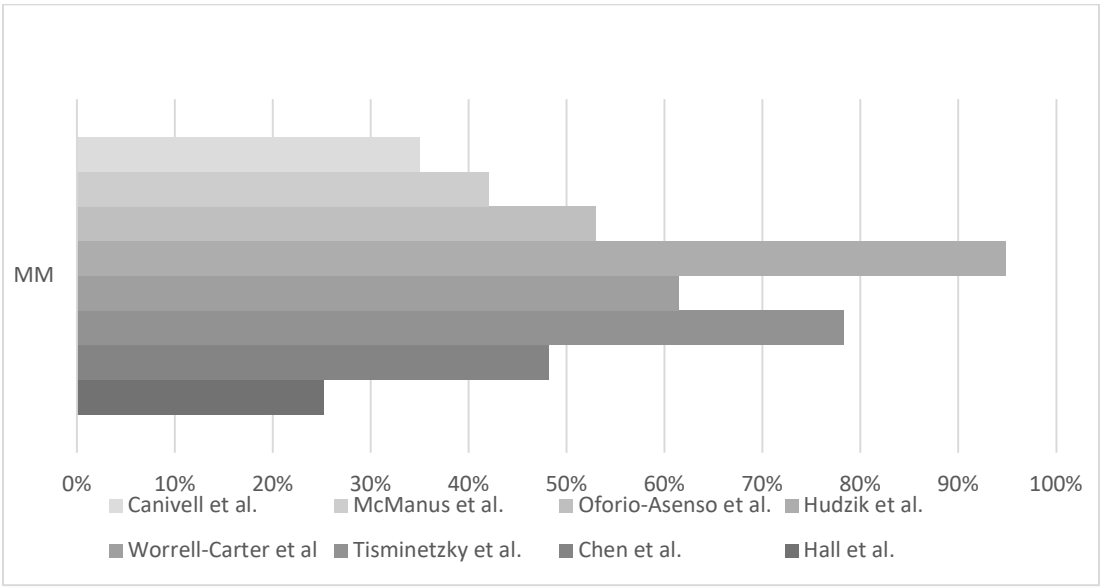

Figure 6. Prevalence of multimorbidity by study

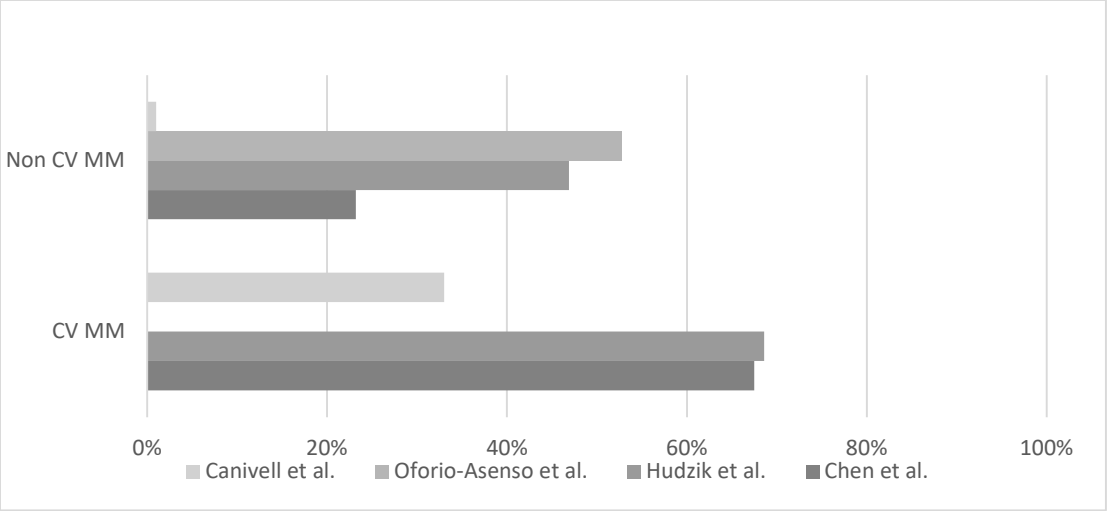

Figure 7. Prevalence of Cardiovascular and Non-Cardiovascular Multimorbidity
[1]Oforio-Asenso et al. did not report CV MM.

5. Prevalence of Multimorbidity Over Time

Multimorbidity prevalence changed over time in two studies. McManus, Nguyen, Saczynski, et al.,[5] found that the proportion of people with no comorbid conditions declined by half and the number of people with four or more comorbidities diagnosed previously more than doubled between 1990 and 2007, (3% to 7%, and 31% to 16%, $p<0.05$, respectively). Hall, Dondo, Yan, et al.,[14] reported the percentage of people in the high and moderated multimorbidity classes (classes 1 and 2) were more frequently observed in the latter years of study, as compared to the earliest time points of study (class 1: 9.0% in 2011-2013 versus 7.9% 2003-2006; class 2: 16.6% in 2011-2013 versus 13.9% in 2003-2006). There was an associated 2% (95% CI 1.9% - 2.3%) increase in the number of comorbidities per year.[14]

6. Females and Multimorbidity

Patients with higher levels of multimorbidity were more likely to be older and female, with females making up more than half of patients with greater multimorbidity across

studies.[14,17,21] Women with multimorbidity were 42-93% more likely to receive no coronary intervention compared to males with the same number (count) of comorbidities.[20] Females were overly represented in the high multimorbidity class compared to the moderate and low multimorbidity classes (40.5% versus 38.5% and 33.1%, respectively).[14] Females were also reported to have a higher representation in mixed multimorbidity (≥2 cardiovascular and ≥1 non-cardiovascular comorbidity) groups than their male counterparts.[17]

7. <u>Greater Mortality and Decreased Intervention</u>

Six out of eight studies reported a poorer prognosis and increased mortality for patients with multimorbidity (Table 3). Four studies reported a significant association with cumulative multimorbidity, and in-hospital mortality compared to non-multimorbid patients.[15,16,18,19] Please see Table 4 for in-hospital mortality by multimorbidity classification and study. Two studies reported a significant increase in 30-day mortality with an increase in the highly multimorbid patient (≥4 comorbid conditions) compared to low or non-multimorbid patients (17% versus 7.4% and 22.3% versus 9%, respectively).[5,14] This effect remained at one year across studies. The average 1-year mortality across studies for multimorbid patients versus their non-multimorbid counterparts was 37% versus 13%. [5,14,15] Hall, Dondo, Yan, et al.,[14] reported a 2.4 fold increased hazard of death for class 1 (high multimorbidity) compared with class 3 (low multimorbidity) (hazard ratio [HR] 2.40; 95% CI 2.33 - 2.47) patients over the 8.4 year study period. Increased LOS was also associated with multimorbidity with median LOS days in multimorbid patients ranging from five to nine days compared with a LOS of three to four days in non-multimorbid patients.[15,16,19] See Table 3 for outcomes by study.

Half of the studies reviewed demonstrated that as multimorbidity (count) increased, rates of revascularization (cardiac catheterization or CABG) decreased.[14,15,17,19-21] Revascularization

rates for patients with high multimorbidity were significantly lower than their non- or low levels of multimorbidity counterparts (9%-14% versus 39%-42%).[17,21] Three studies reported that multimorbid patients were less likely to receive evidence-based pharmacologic treatments.[14,17,18] For example, patients with ≥2 non-cardiovascular comorbidities (OR=0.72, 95 % CI) or ≥3 non-cardiovascular comorbidities (OR= 0.62, 95% CI) were significantly less likely to receive at least four of the six following medications: angiotensin-converting enzyme- inhibitors or angiotensin two receptor blockers , anticoagulants, aspirins, beta-blockers, lipid-lowering agents, or thrombolytics during their ACS hospitalization.[2]

TABLE III. PATIENT OUTCOMES AND LIMITATIONS

Citation	Data Source	Outcome Findings	Study limitations
Canivell et al. (2018)[7]	Medical records	Multimorbid patients have a poorer prognosis, poorer control of CV risk factors, lower use of high-dose statins, lower attendance of cardiac rehab, and an increase in the risk of CV event at 1-yr. post ACS event	Classified patients according to the presence of multimorbidity(count), and not comorbidity Patients in the no multimorbidity group could still suffer from one of the CV or/and non-CV comorbidities No information on grade or severity of the different comorbidities
Hall et al. (2018)[14]	MINAP database	The prevalence of multimorbidity was high in AMI patients and conferred an accumulative increased risk of death. Patients in Class 1 (high multimorbidity) and class 2 (moderate multimorbidity had a 2.89- and 1.52-years loss in life expectancy	MINAP database doesn't have 100% case ascertainment; missing data could have biased estimates. Limited to all-cause mortality
Chen et al. (2013)[4]	Worcester heart attack study (ICD-9, medical records)	High prevalence of multiple CV and non-CV comorbidities in patients hospitalized with AMI. Multimorbidity was associated with a higher likelihood of dying during hospitalization and being hospitalized for a more prolonged period	Study population only from a metropolitan area. Majority of the population Caucasian. No information on income, education, and psychological factors included in study

Citation	Data Source	Outcome Findings	Study limitations
McManus et al. (2012)[5]	Medical Records	In patients with AMI, the odds of having multiple CV-comorbidities increased over time. Multimorbidity was associated with poor prognosis over the period of study	Majority of the study population Caucasian. Non-randomized study design. Physician thresholds for diagnosing several of the comorbid conditions studied may have changed over time
Tisminetzky et al. (2019)[17]	Medical records & baseline interview	CV and non-CV conditions are highly prevalent in patients hospitalized with MI Patients with both CV and non-CV conditions at greatest risk for developing adverse-in-hospital and short-term outcomes Patients with 1+ non-CV condition were less likely to be prescribed evidence-based medications and/or coronary intervention than those without non-CV conditions	Limited generalizability to other ethnic/racial groups >90% of the population Caucasian. No estimation of severity or duration of chronic conditions
Worrall-Carter et al. (2015)[20]	Dataset Review derived from medical records	High prevalence of multimorbidity. Increasing multimorbidity with age. Higher rates of non-intervention in multimorbid females than their male counterparts 28/30 comorbidities recorded were more prevalent (usually significantly) amongst patients who received no intervention	Potential underreporting of comorbidity, as comorbidity was classified based on coded diagnosis in the hospital record
Hudzik et al. (2017)[15]	Medical records	A majority of patients have at least 2 other CV-comorbidities and/or two non-CV comorbidities	Limited generalizability given study population is 100% of patients

Citation	Data Source	Outcome Findings	Study limitations
		Multimorbidity associate with greater 12-month all-cause mortality and risk of ACS event. Every additional comorbidity was associated with a 15% increase in relative risk of 12-month mortality and a 41% increase in relative risk of 12-month ACS event	with type 2 DM and STEMI patients. Small sample size

TABLE IV. CLINICAL OUTCOMES DATA BY STUDY

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Canivell et al. (2018)[7]	Age-Sex adjusted HR (95% CI): NoMM: 1.00 (ref) CV-MM: 1.87(1.50-2.33) NONCVMM: 2.27(1.11-4.63) CV&NONCVMM: 3.16(1.82-5.50) *Measured as CV event	N/M	N/M	**Cardiac Rehab at 1 year:** No MM: 72%, CV-MM:56.7%, NONCVMM: 52.5%, CV& NONCVMM: 32.4%. **Polypharmcy (>5) at 1 year:** No MM: 59.1%, CV-MM:79.5%, NONCVMM: 83.9%, CV& NONCVMM: 81.4%.	**High-Dose Statins at Discharge:** No MM: 71.7%, CV-MM: 64.7 %, NONCVMM: 62.3%, CV& NONCVMM: 55.9% (p<0.001) **High-Dose Statins at 1-year:** No MM: 60.5%, CV-MM:54.7%, NONCVMM: 50.9%, CV& NONCVMM: 41.4%. (p<0.001)

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Hall et al. (2018)[14]	**30 Day:** Class 1: 17% Class 2: 10% Class 3: 7.4% (p <0.001) **1 year:** Class 1: 39.8% Class 2: 21.4% Class 3: 14.4% (p <0.001) **5 year:** Class 1: 57.4% Class 2: 34% Class 3: 22.4% (p <0.001)	**Revascularization:** Class 1: 14.8% Class 2: 26.9% Class 3: 42.7% (p <0.001) **Diuresis with Loop Diuretic** Class 1: 62.9% Class 2: 36.8% Class 3: 22% (p <0.001)	N/M	N/M	**Statins at discharge:** Class 1: 80.6% Class 2: 58.9% Class 3: 85.2% (p <0.001) **Beta-blocker at discharge:** Class 1: 74% Class 2: 80.9% Class 3: 85.2% (p <0.001)

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Chen et al. (2013)[4]	**In-Hospital** CVCM (0,1,2,3+): 3.7%,6.1%,10.6%,11.2%,14.2% (p<0.001) NONCVCM (0,1,2,3+): 6.9%,10.1%,14.7%,15.9% (p<0.001)	**PCI:** CVCM (0,1,2,3,>4): 69.6%,61.8%,46.4%,39.6%,27.3% (p<0.001) NONCVCM (0,1,2,3,>4): 60.6%,41.4%,29.2%,19.9% (p<0.001) **CABG:** CVCM (0,1,2,3,>4): 4.7%,6.8%,6.4%,6.8%,2.9% (p<0.004) NONCVCM(0,1,2,3,>4): 6.2%,6.3%,3.2%,2.7% (p<0.015)	**LOS >3 days** CVCM (0,1,2,3,4+): 39.8%,48.0%,55.7%,60.8%, 68.1%(p<0.001) NONCVCM (0,1,2,3,4+):47.8%, 58.3%, 68.6%,70.7% (p<0.001)	N/M	During hospitalization: Patients received an average of 4.2 of the 6 cardiac medications (b-blockers, ace or arbs, lipid-lowering agents, anticoagulants, aspirin, and thrombolytics)

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
McManus et al. (2012)[5]	**Mortality:** 30-day (0,1,2,3, ≥4): 9.01%, 13.03%, 17.76%, 21.32%, 22.3% 1-year (0,1,2,3, ≥4): 15.02%, 22.56%, 34.34%, 45.01%, 53.56%	N/ M	N/M	N/M	N/M
Tisminetzky et al. (2019)[17]	**In-Hospital** Group 1: 9.1%, Group 2: 14%, Group 3: 11.2%	**PCI:** Group 1: 59.9% Group 2: 41.7%, Group 3: 56.6%	**Days (median):** Group 1: 4 Group 2: 5	**Readmission** **7 days:** Group 1: 4.6% Group 2: 6.5%	**During hospitalization** **ACE-I/ARBs:** Group 1: 65.1%

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
	Group 4: 13.9%	Group 4: 42.2% (p<0.001) **CABG:** Group 1: 7.7 Group 2: 4.5%, Group 3: 7% Group 4: 4.8% (p<0.01)	Group 3: 4 Group 4: 5 (p<0.01)	Group 3: 5.9% Group 4: 6.8% **30 days:** Group 1: 14.5% Group 2: 15.8% Group 3: 17.1% Group 4: 21.5%	Group 2: 58.8% Group 3: 74.0% Group 4: 68.1% (p<0.001) **Aspirin:** Group 1: 92.8% Group 2: 90.0% Group 3: 92.6% Group 4: 90.2% (p<0.01) **Beta-Blockers:** Group 1: 90.5% Group 2: 86.1% Group 3: 90.1% Group 4: 89.6% (p<0.01) **Lipid-Lowering agents:** Group 1: 70.5% Group 2: 63.2% Group 3: 77.9% Group 4: 75.3% (p<0.001)

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Worrall-Carter et al. (2015)[20]	N/M	**Angiogram** Female with (0,1,2,3+) CM: 56%, 51%, 40%, 36% Male: 75%,71%, 61%, 50% **Stent** Female with (0,1,2,3+) CM:11%, 10%, 5%, 4% Male: 19%, 17%, 9%, 5% **CABG** Female with (0,1,2,3+) CM	N/M	N/M	N/M

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
		2%, 3%, 7%, 10% Male with (0,1,2,3+) CM: 5%,8%, 17%, 18% **No Intervention** Female with (0,1,2,3+) CM: 44%, 48%, 58%, 61% Male with (0,1,2,3+) CM: 24%, 26%, 34%, 45%			
Hudzik et al. (2017)[15]	**In-hospital:** Group 1: 5.2% Group 2: 11.4% (p<0.05) **1 year:** Group1: 8.6% Group 2: 19.9% (p<0.05)	**Successful PCI:** Group1: 89.9% Group2: 84.0% (p=0.4)	**Median days:** Group 1: 7.5 Group 2: 9 (p<0.04)	N/M	N/M

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Ofori-Asenso et al. (2019)[16]	**In-hospital mortality for** (0,1,2+) NONCVCM: 4.4%, 5.5%, 10.6% **In-hospital mortality**: the cohort 6.1%, UA 2.6%, and NSTEMI 7.1% (p=0.003)	**PCI** (0,1, 2+) NONCVCM: 30.9%,23.2%,11.9% (p<0.001) **CABG** (0,1, 2+) NONCVCM:15.8%, 11.8%, 7.4% (p=0.001)	**Median (IQR)** for (0,1,2+) NONCVCM: 3.83 (1.96-8.04), 4.40 (2.38-8.92), 5.83 (3.04-10.5)	N/M	N/M

8. Post-Discharge Outcomes

Three studies reported on post-discharge outcomes including cardiac rehab attendance, readmission, medications at discharge and at one-year post-discharge, and medication prescriptions at one-year post-discharge (Table 4). Canivell, Muller, Gencer, et al.,[7] reported that cardiac rehab attendance at one year was decreased in multimorbid patients compared to non-multimorbid patients (32.4% versus 72%; $p<0.001$). Higher readmission rates were reported in multimorbid patients compared to non-multimorbid patients at seven and thirty-days post-discharge (6.8% versus 4.6% and 21.5% versus 14.5%), respectively .[17] Two studies examined statins or lipid-lowering agents at discharge and one year following discharge and found decreased rates of usage in multimorbid patients (Table 4).[14,24] Polypharmacy (>5 medications) at one year was also significantly increased in multimorbid patients compared to their non-multimorbid counterparts (81.4% versus 59.1%, $p<0.001$).[7]

D. Discussion

Multiple critical findings were revealed in this review: 1) There is an inconsistency in the way which multimorbidity is measured and characterized in the ACS population 2) Multimorbidity is highly prevalent in the ACS population, 3) Multimorbidity has a large impact on mortality rates, LOS, and pharmacologic intervention, 4) Females have greater levels of multimorbidity, and 5) There is a sparse literature on clinical outcome measures other than mortality at one-year.

1. Assessment of Multimorbidity

Despite the high prevalence of multimorbidity in the ACS population, our findings suggest that there is a lack of consistency in the way multimorbidity is measured and characterized. Currently, there is no “gold standard” for measuring the rather complex

phenomenon of multimorbidity. Multiple methods for assessing multimorbidity, ranging from simple counts to psychometrically sound indices, have been employed in health research. Simple counts of comorbidities are the most straightforward approach; however, it lacks the ability to account for the severity of a condition or impact across conditions. Similar challenges are faced with the use of administrative data (i.e., claims databases) given that the data do not account for the severity of diseases at the time of initial diagnosis and prevent investigators from assessing outcomes such as symptom burden, functional status, and quality of life. Comorbidity indices vary across studies and are widely utilized, given the ease of application. The summary scores derived from the various indices, however, can pose a challenge to apply in clinical decision-making in the care of the ACS patient.[22] A relatively recent systematic review comparing measures of multimorbidity used with administrative data found that the most frequently employed measure is the Charlson Comorbidity Index, followed by the Elixhauser Index.[25] The authors concluded that the performance of a given comorbidity measure is dependent on the patient population and the outcome of interest.[25] Future studies, utilizing both administrative data and supplemental data sources such as electronic health records and self-report measures, may improve our understanding of multimorbidity burden in adults with ACS.

2. <u>Prevalence of Multimorbidity</u>

The accumulation of chronic conditions is the result of genetics, lifestyle factors, environmental factors, treatment of prior conditions (e.g., heart failure as a consequence of chemotherapy regimens), and aging itself resulting in a heterogeneous population of older adults that requires management of multiple medical problems.[10] Multiple pathologies are prevalent among older adults; a recent systematic review revealed that 66% of older adults in ambulatory settings had multimorbidity.[23] One study in this review reported that in patients with

multimorbidity (cardiovascular multimorbidity and/or non-cardiovascular multimorbidity), 92% were found to have one or more concordant conditions (i.e., HF, HTN, arrhythmias, and/or DM) related to their ACS diagnosis.[20] This helps explains the finding of this review regarding the high prevalence of certain comorbidities in the ACS population, such as HTN and DM, which are known ACS risk factors.

3. **Females Have a Higher Prevalence of Multimorbidity**

Our review found that sex is associated with multimorbidity. While a majority of study populations in this review were predominantly male, females had a higher multimorbidity burden and were overly represented in both high and moderate multimorbidity groups across studies [5,14,15,24]. Why women carry an added burden of multimorbidity is complex and warrants further study. Future studies should focus on the influence of multimorbidity on sex differences in diagnostic testing, treatments, and outcomes.

4. **Multimorbidity Negatively Impacts Inpatient Treatment**

This is the first review to address the effect of multimorbidity on clinical outcomes in patients with ACS. Patients with greater multimorbidity and burden have been shown to be at risk for increased risk of poor outcomes.[20] Clinically, patients with multimorbidity are more susceptible to increased rates of complications from ACS treatment, such as bleeding, owing to factors such as drug interactions and drug-disease interactions.[16] Patients with multimorbidity are less likely to receive guideline indicated treatments.[14,21,26] During inpatient treatment, the studies reviewed revealed lower rates of revascularization, less frequent high-dose statin use, and decreased cardiac rehab referrals for patients as comorbidities increase. [14,21,27] We also found that females were less likely than their multimorbidity matched male counterparts to receive any

invasive treatments for ACS. This disparity warrants further investigation to determine the extent of the disparity and the impact on outcomes following ACS hospitalization.

5. Multimorbidity and Post-Discharge Outcomes at 1-year

The increased risk of adverse outcomes continues as treatment progresses from the acute setting to post-discharge care. [24] After discharge, patients with multimorbidity frequently receive care from different specialists, which may impact the medical optimization and achievement of secondary prevention targets. [1,24,28,29] Unfortunately, no studies reviewed measured healthcare utilization (emergency department visits and specialist visits), following discharge, and only Canivell, Muller, Gencer, et al.,[7] measured polypharmacy (>5 medications), medications at one-year, and cardiac rehab attendance. The benefits and risks of treatments and preventive drugs are unknown among patients with multimorbidity. This is frequently due to clinical guidelines that are based on scientific studies that focus on the primary/index disease and exclude or underrepresent multimorbid patients. [1,12,22,28,30-33] Future studies should employ a pragmatic design and focus on healthcare utilization following discharge in multimorbid ACS patients.

E. Limitations

Only studies published in English were included in this review. The impact of multimorbidity on patients with ACS published in non-English journals remains unknown. The majority of studies limited their outcomes to in-hospital, 30-day, and 1-year all-cause mortality, making it difficult to determine cardiovascular mortality and draw critical conclusions about overall versus cardiovascular mortality. Few studies measured healthcare utilization post-discharge, which limits the ability to make conclusions about the impact of multimorbidity on secondary prevention measures such as cardiac rehab referrals, statin use, and follow-up of care (ED, specialist visits, clinic visits, and primary care visits).

F. Conclusion

While multimorbidity is associated with a poorer prognosis and higher mortality (in-hospital, 30-day, 1-year, and 5-year), there is limited data on healthcare utilization such as cardiac rehab, primary care versus specialist care, and emergency department visits post-discharge. Our review also suggests there is a lack of consistency in the measurement and characterization of multimorbidity making critical comparisons across studies difficult. Additionally, capturing the complexity of multimorbidity in the ACS population remains a challenge yet to be adequately addressed in clinical trials. Finally, further research is needed to identify and determine the impact of specific combinations of multimorbidity "phenotypes" on both inpatient and outpatient healthcare utilization.

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III. Manuscript #2:

Multimorbidity and Healthcare Utilization in Patients Presenting to the Emergency Department with Possible Acute Coronary Syndrome: A Latent Class Analysis.

A. Background

1. Introduction

This year, approximately 720,000 Americans will have a new coronary event, defined as the first hospitalization for myocardial infarction (MI) or coronary heart disease (CHD) death, and approximately 335,000 will have a recurrent event. Acute coronary syndrome (ACS), an acute form of CHD[1], consists of three clinical conditions: unstable angina (UA), non-ST segment MI (NSTEMI), and ST-segment MI (STEMI).[2] Approximately 40 million individuals over the age of 65 have CHD, which remains the leading cause of morbidity and mortality [2,3], and of those, nearly two-thirds have at least 1 additional chronic condition.[3] The increasing prevalence of chronic conditions and the growing prevalence of multimorbidity (>2 chronic conditions), is a major challenge facing healthcare systems globally since multimorbidity (count) increases the risk for adverse outcomes. [4,5] Compounding the problem is the aging population; the proportion of adults aged 65 and over is rapidly increasing and is projected to comprise 19% of the US population by the year 2030.[2] For Medicare beneficiaries, the burden of multimorbidity is exceptionally high. As individuals age, multimorbidity dyads and triads emerge and include cardiovascular risk factors.[4,5] Multimorbidity is not only a problem for the aged; nearly half of all middle-aged adults in the United States will develop some manifestation of CHD, and frequently, the first clinically recognized manifestation of CHD is ACS.[1]

2. Multimorbidity and Current ACS Clinical Care

The current clinical care approach in ACS is driven in large by single-disease based clinical practice guidelines that are aimed at diagnosis, management, and decision-making; these guidelines are less relevant when care and diagnosis are complicated by multimorbidity.[6] Clinical guidelines are primarily based on randomized clinical trials that exclude multimorbid patients and, therefore, limit their applicability to these complex patients.[7] Multimorbid patients with ACS are at a higher risk for sub-optimal care, as they frequently receive lower rates of revascularization [8,9] and evidence-based pharmacologic treatments. [8-10] The implications of multimorbidity extend past the ED, through hospitalization, and continue on after discharge. Multimorbidity can increase the rate of in-hospital complications such as mortality, length of stay, and procedural bleeding.[10-13] After discharge for ACS, both cardiovascular-multimorbidity and/or non-cardiovascular multimorbidity was associated with a 3-fold increase in all-cause 30-day readmission as compared to their non-multimorbid counterparts.[11] Determining whether these findings are similar when multimorbidity is no longer simply count-based, but rather comprised of specific conditions is the first step to identifying and improving risk stratification of these highly complex high-risk patients. Regardless of ACS diagnosis, patients with cardiovascular disease (CVD) and increased multimorbidity (count of conditions) burden are at risk for poorer outcomes.[20]

3. Multimorbidity Research in ACS

A multitude of studies have assessed the association between ACS and individual chronic conditions, including chronic obstructive pulmonary disease (COPD)[14,15], diabetes[2,8,9,16,17], and heart failure (HF)[18-20] with mortality and readmission rates post ACS diagnosis. Few, however, have assessed the burden of multimorbidity in terms of complex patterns of multimorbidity

(multimorbidity phenotype classes), which are comprised of specific combinations of chronic conditions, and their association with ACS diagnosis.[10] The prognostic role of multimorbidity in evaluation for ACS has been poorly studied and it remains unknown if conditions associated with CVD, such as diabetes or hypertension (HTN), have a similar impact as non-cardiovascular conditions such as pulmonary disease or cancer.[5] Multimorbidity clustering is an emerging concept within the ACS population. Previous studies concerning multimorbidity clusters have relied on basic analytical techniques that use simple composite additive [5,8,9] comorbidity index scores or examine all possible combinations of conditions.[21,22] One prior study by Hall, Dondo, Yan, et al.,[10] utilized latent class analysis and found three multimorbidity phenotype clusters in the ACS population.

4. <u>Multimorbidity a Latent Class Approach</u>

Advanced statistical methods, such as latent class analysis, which is data-driven, provide insights into multidimensional disease patterns based on probabilistic modeling of specific conditions.[23] These probabilistic patterns have been previously described as "computational phenotypes", through which the sum of the components making up the phenotype may offer a deeper understanding of the patient's clinical picture on both the individual and population-level.[24,25] The prevalence of MI as the first manifestation of ischemic heart disease is approximately 50%-70%.[26] Patients ruled-out for ACS remain understudied with studies focusing only on patients that were ruled-in for ACS. Despite the fact that patients ruled-in comprise only 13.5% of the 5.5 million patients evaluated for ACS in the emergency department (ED) every year in the United States.[27] Additionally, patients admitted for suspected ACS, but later ruled-out may be at higher risk of adverse outcomes than ruled-in patients. Barrabes, Bardaji, Jimenez-Candil, et al.,[28] in a multicenter registry study, reported that 9% of patients

hospitalized for suspected ACS were discharged with a non-ACS diagnosis. Of that 9%, one-third had a worse prognosis (death or readmission for cardiovascular causes at six months) than patients who were ruled-in for ACS, despite similar clinical characteristics at presentation.[28] Furthermore, a large proportion of patients ruled-out for ACS have ischemic heart disease and are at risk for future ACS events.[7,29,30] In previous work from our dataset, it was found that in patients ruled-out, a majority had ischemic heart disease, and therefore at high risk for a future ACS event.[31] Prompt identification and early risk stratification of these patients is critical for appropriate clinical management decisions.

Identification and analysis of multimorbidity phenotype classes in patients who present with suspected ACS potentially could assist clinicians with the treatment and management of these highly complex patients and will contribute to the design of more pragmatic trials leading to enhanced precision health strategies. Therefore, the aims of this study were to investigate and examine the presence of multimorbidity phenotype classes across a range of pre-existing chronic conditions and to determine whether these classes differed by diagnosis (ruled-in or out for ACS). We hypothesized that: 1) subgroups of patients with similar multimorbidity phenotype classes (latent classes), could be identified and that these classes would differ by diagnosis and 2) class membership would be associated with increased healthcare utilization (readmission, clinic visits, and ED) at 30-days and 6-months following discharge.

B. Methods

1. Study Design

This is a secondary data analysis of de-identified data from the *Think Symptoms* study.[32] The parent study was approved by the Institutional Review Boards (IRB) at the sponsoring institution, and the five clinical sites and the IRB approved an exemption for this analysis. All

human subject involvement, characteristics, potential risks, benefits, and strategies to minimize risks and benefits were addressed in the parent study (R01NR012012) and all participants gave written consent.

2. Sample and Setting

The main aim of the parent *Think Symptoms* study was to characterize the influence of sex on symptoms during ACS.[32] Data were collected at five academic medical centers and a large community hospital located in the Midwest, Southwest, Pacific Northwest, and Western regions of the United States. Data were collected between January 2011 and December 2014. Patients were included if they were high risk for ACS (abnormal electrocardiogram (ECG) or positive troponin), English speaking, ≥21 years of age, had telephone access, and intact cognition. A positive troponin was defined as any value exceeding the institutional reference norm. Cognitive capacity was considered acceptable if the patient understood the purpose of this study and could provide written informed consent. Patients were excluded if they had a history of heart failure or were diagnosed during initial evaluation for heart failure exacerbation (B-type natriuretic peptide> 500ng/mL), were admitted from a hemodialysis center or were referred for cardiac dysrhythmia evaluation. A total of 1064 patients presenting to the ED with symptoms suggestive of ACS were enrolled. Nine hundred thirty-five patients had complete data for clustering and covariate analysis. For healthcare utilization outcomes, 674 patients had complete data for 30-days. At 6-months, 523 patients with complete data were included in the analysis.

3. Measures

a) Charlson Comorbidities Index (CCI)

This 19-item, weighted index is the most extensively studied method of quantifying risk associated with comorbid conditions.[33,34] Higher scores represent a greater burden of disease.

Studies have demonstrated that the CCI is a valid measure for predicting disability and death following ischemic stroke and heart disease,[34] as well as hospital readmission, and length of stay with correlations ranging from 0.35-0.93 ($p<0.001$).[35,36] Retest reliability was confirmed with correlations of 0.92-0.94.[37] Hall reported excellent content validity and reliability in a review of four comorbidity tools. [38] The following 10 conditions were extracted from the CCI including prior history of MI (CCI-1), vascular disease (CCI-3), stroke/ transient ischemic attack (CCI-4), lupus (CCI-7), dyspnea (CCI-2) and asthma (CCI-6) were combined to form a new variable of respiratory disorders, and all cancer-related items (CCI 14, 15, 16, and 18) were combined to form the cancer variable in the analysis.

b) ACS Patient Information Questionnaire

The demographic and clinical questionnaire was designed using the standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential ACS. [10] The criteria were established by the Multi-disciplinary Standardized Reporting Criteria Task Force and are supported by the Society for Academic Medicine, the American College of Emergency Physicians, the AHA, and the ACC.[39] Four conditions were extracted from the ACS patient information questionnaire for analysis, including hypertension, hyperlipidemia, and kidney disease.

c) The Duke Activity Status Index

The DASI is a brief 12-item instrument that measures functional capacity. Scores range from 0-58.2, with higher scores representing better physical functioning. The items on the scale are weighted to reflect metabolic energy expenditure and correlate highly with peak VO^2 ($r=.80$, $p<0.0001$) [40] in patients with ACS [41], ischemic heart disease [42], heart failure [41], and revascularization procedures.[43] Concurrent validity was supported by correlations with measures

of physical functioning (r=0.69, p<0.05 & r=0.61, p<0.05).[44] Cronbach's alpha reliability has ranged from 0.76-0.85.[40,43] The tool was responsive to change in patients recovering from cardiac surgery (p<0.001).[45]

d) Medical Records Review Form

The diagnosis of ACS and body mass index were retrieved from the patient's medical record. Body mass index was the basis for the condition variable obesity.

e) Froelicher's Health Services Utilization Questionnaire-Revised. The tool measures subsequent visits to the ED, readmission, and clinic visits, and calls to healthcare providers. This instrument demonstrated initial reliability and validity in Froelicher, Shoen, Max, et al.'s [46] follow-up survey of health care utilization in women with cardiovascular disease. Clinical outcomes were measured at 30-days and 6-months included 1) readmission was all-cause readmission to a hospital as an inpatient, 2) clinic visits were all visits to an outpatient healthcare provider, and 3) ED visits were all-cause visits to an ED for an acute problem.

4. <u>Statistical Analysis</u>

Demographic and baseline characteristics were described according to class membership using numbers and percentages for categorical variables. While means and standard deviations, and medians and interquartile ranges were reported for normally and non-normally distributed continuous variables. All tests were 2-sided, and statistical significance was considered as P<0.05. Statistical analyses were performed in STATA version 15 (STATA Corp., College Station, TX) and LatentGOLD version 5.1 (Statistical Innovations Inc., Belmont, MA).

The objective of this analysis was to identify patient groups (latent classes) with similar multimorbidity patterns based on 10 comorbid conditions extracted from the Charlson Comorbidity Index, ACS patient questionnaire, and the patient's medical record including prior

history of MI, vascular disease, stroke/ transient ischemic attack, cancer, Lupus, respiratory disease, obesity, hypertension, kidney disease, and hyperlipidemia. Using Latent Gold (version 5.1), a latent class analysis was used to classify individuals into groups with similar combinations of conditions. Next, covariates were added. Finally, the latent class model probabilities were exported to Stata to determine if class membership predicted 30-day and 6-month outcomes (readmission, clinic visits, and ED visits).

A three-step analytic framework was used. First, a latent class analysis approach was used to classify individuals into groups with similar combinations of conditions. Several class solutions were explored, starting with a one-class model and subsequently increasing the number of classes up to five. The best-fitting model was selected based on an assessment of fit indices, specifically, minimization of the Bayesian information criteria (BIC) and the Bootstrap likelihood ratio test (BLRT). The BIC is based on the log-likelihood of a fitted model and includes a penalty for the number of model parameters and sample size. The BLRT test has been demonstrated to be superior to other indices of fit; in simulation studies, the BLRT and BIC performed well.[47] However, The BLRT has been found to be the most consistent indicator for selecting the correct number of classes.[47] The BLRT uses p-values to identify if there is a significant improvement between the specified model and models with one less class, the model is identified based on the occurrence of the first nonsignificant p-value ($p>0.05$) indicating that the model with more classes does not improve the model.[47] Classification quality was evaluated using the entropy statistic. The entropy statistic is calculated from the posterior probabilities ranging from zero to one. Higher values indicate that the latent class is more distinct.[48] The theoretical interpretability of the emerging classes was used in combination with the BIC and BLRT to determine the final number of classes.

Next, covariates that likely influence the probability of class membership were tested. Using Stata, between-cluster differences were explored using a one-way analysis of variance for continuous variables and Chi-square for categorical variables. Covariates examined for significance were age, sex, educational level, household income, race, functional capacity, tobacco use, and ACS status (ruled-in/out). Statistically significant covariates were included in the final analysis within Latent Gold through a multinomial logistic regression of the categorical latent variable on the covariates.

Finally, the classification based on the covariate-adjusted LCA model was exported to Stata (version 15) to determine the extent to which healthcare utilization outcomes (readmission, clinic visits, and ED visits) at 30-days and 6-months varied by class membership. Linear regressions were used for continuous outcome variables and logistic regressions for the categorical outcomes.

C. Results

1. Demographic and Clinical Characteristics

Table 5 shows the demographic and clinical information for the 935 patients with complete covariate data in the final analysis. The sample was 38% female with a mean age of 59.9(±14.0) years. Forty-four percent were ruled-in for ACS, and NSTEMI (24.2%) was the most common ACS diagnosis compared with STEMI and UA (10.7% and 9.5%). Approximately 85% were admitted for observation or full admission. The majority of patients had decreased functional capacity as measured by the DASI (mean score 34.2, ± 19.3). The most prevalent chronic conditions were HTN, hyperlipidemia, CHD, and obesity (64.9%, 55.2%, 44.7%, and 43.2%, respectively). Figure 1 shows the prevalence of conditions by class membership (Figure 8).

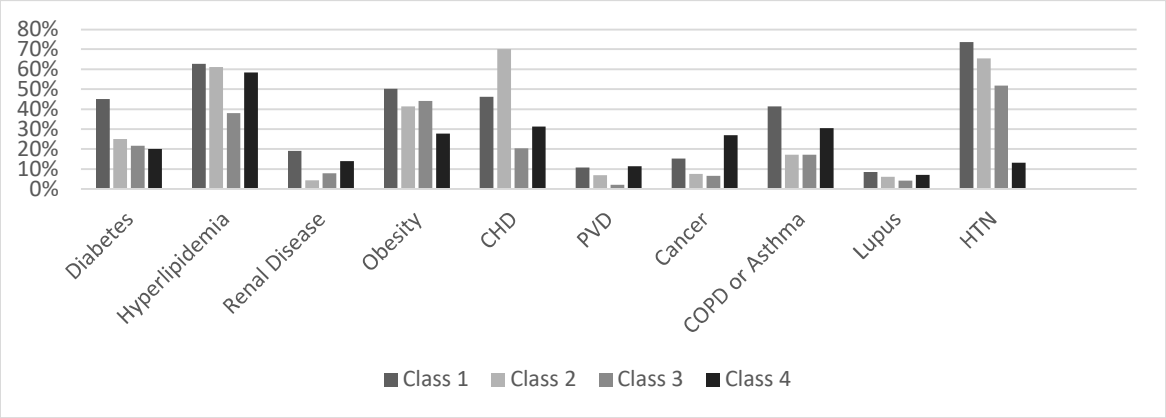

Figure 8. Prevalence of Condition by Class

TABLE V. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	n = 935
ACS ruled-in (n, %)	415 (44.4)
ACS diagnosis (n, %)	
NSTEMI	226 (24.2)
STEMI	100 (10.7)
Unstable Angina	89 (9.5)
Female (n, %)	355 (38.0)
Age (mean, SD)	59.9 (14.0)
BMI (mean, SD)	30.1 (7.1)
Duke Activity Status Index (n, %)	
58.2 (no limitation)	240 (25.6)
30-58.2	279 (29.8)
<30	416 (44.5)
Family history of SCD <55 years old (n, %)	436 (46.6)
Current Smoker (n, %)	194 (21.2)
Disposition of patient(n, %)	
Full admission	628 (67.2)
Observation	162 (17.3)
Discharge	135(14.5)

2. Latent Class Model Selection

Latent class models were derived from all available cases (n=1003) to assess relative fit indices for class enumeration (Table 2). To determine class enumeration, the classes were formed from the conditions being investigated only, and covariates were not included to fit the model. Models with 1, 2, 3, 4, and 5 classes were systematically evaluated to determine the best fit. The 2-class model had the lowest BIC; however, the 3-class and 4-class models were most theoretically and clinically interpretable. Given that the 2, 3, 4, and 5-class models were candidates for the best fitting model with p-values of 1.00, and it was difficult to determine the best model based on BIC and theoretical and clinical interpretability, further analysis was conducted. A BLRT analysis was run to test the different class solutions. The results from the BLRT comparison indicated that the 3-class model was better than the 2-class model, the 4-class was better than the 3-class model, but the 5-class model was not better than the 4-class model. A 4-class model was selected as the final class solution for further analysis based on the fit indices, BLRT testing, and theoretical and clinical interpretability. Statistically significant covariates were then added to the 4-class model for further analysis. Models were adjusted for age, sex, ACS status, family history of sudden cardiac death at less than 55 years old, and total weighted DASI score as a measure of functional capacity (Table 3).

TABLE VI. MODEL FIT EVALUATION INFORMATION (n=1003).

	LL	BIC(LL)	Npar	df	Entropy	BLRT
1-Class	-5390.5707	10857.1596	11	992	1.00	0.00
2-Class	-5203.7200	10566.3874	23	980	0.62	0.00
3-Class	-5178.1890	10598.2544	35	968	0.52	0.00
4-Class	-5154.3749	10633.5552	47	956	0.52	0.00
5-Class	-5140.9376	10689.6095	59	944	0.57	0.12

Note: When assessing BLRT values you look for the first non-significant p-value (>0.05) to determine optimal class solution

There were 935 patients with complete covariate data used for further clustering. Covariates were empirically selected for testing from previous literature differentiating multimorbid patient groups (sex, age, functional capacity, family history of sudden cardiac death at less than 55 years old) and ACS status (ruled-in versus out).[5,8,22,49-52] Table 7 shows the covariates that were found to be significant and the between class differences. Condition only models were then compared to covariate-adjusted models. The 4-class covariate-adjusted model was found to be superior to the condition-only 4-class model with a lower BIC (9710.36 versus 10633.55), increased the amount of variance in the data explained by the model (R^2=0.65 versus 0.52), and decreased classification errors (0.18 versus 0.26). The adjusted models were then evaluated against each other. The 4-class covariate-adjusted model had the lowest BIC (9710.37) of the 2, 3, and 5-class covariate-adjusted models (9787.35, 9723.57, and 9734.33, respectively). Additionally, the adjusted 4-class model provided the most meaningful theoretical and clinical interpretation. Finally, the 4-class covariate-adjusted model had the best class separation of the adjusted models and was, therefore, selected as the final model.

TABLE VII. COVARIATES AND LATENT CLASS MEMBERSHIP

Covariate	Class1: High Multimorbidity (n=294, 31.5%)	Class 2: Low Multimorbidity (n=264, 27.8%)	Class 3: Cardiovascular Multimorbidity (n=248, 26.2%)	Class 4: Cardio-Onc Multimorbidity (n=129, 14.5%)_
Age (Mean, SD)	61.9(9.5)[c,d]	48.7(12.2)[a,c,d]	58.5(9.9)[a,b,d]	82.3(5.7)[a,b,c]
Female (n, %)	119(39.8)[b,c,d]	127(51.6)[a,c]	57(21.2)[a,b,d]	52(43.0)[a,c]
DASI Weighted Score (Mean, SD)	15.6(10.0) [b,c]	46.6(14.1) [a,d]	48.4(10.8) [a,d]	23.1(15.7)[a,b,c]
Family History of Sudden Cardiac death before age 55 (n,%)	185(62.7) [b,c,d]	101(41.2)[a]	114(40.7) [a]	36(31.3)[a]
ACS ruled-in (n,%)	105(35.6) [b,c]	3(1.2) [a,c,d]	280(100) [a,bd]	30(26.0)[b,c]

[a] Significant difference from class 1
[b] Significant difference from class 2
[c] Significant difference from class 3
[d] Significant difference from class 4

3. Multimorbidity Phenotype Classes

The probability of a specific condition being present in a class was defined as high (≥0.60-1.0), moderate (≥0.30-<0.60), and low (<0.30), Figure 9 shows condition probabilities by class. Class 1 had the greatest number of patients (n=295) and was labeled as *high multimorbidity* class since it had the greatest number of high probability conditions (Table 8). Conditions included in Class 1 were hyperlipidemia, HTN, obesity, diabetes, and respiratory disorders (COPD or asthma). Class 2 contained no high probability conditions and was labeled *low multimorbidity*. Class 2 did have a moderate probability of obesity. Class 3 was labeled

cardiovascular multimorbidity and included a high probability of CHD, HTN, and hyperlipidemia. Class 4 was labeled as *cardiovascular-oncologic (cardio-onc) multimorbidity* and included hyperlipidemia, hypertension, and cancer. Table 4 includes a full description of the probability of condition occurrence by class. Class 1 was the largest with 294 patients, and Class 4 was the smallest with 129 patients. Patients with four or more individual conditions mainly clustered in Classes 1 and 3 (43.2% and 27.2%) compared with patients in Classes 2 and 4 (15.2% and 14.4%). From this point forward, the classes shall be referred to as Class 1 (high multimorbidity), Class 2 (cardiovascular multimorbidity), Class 3 (low multimorbidity), and Class 4 (cardio-onc multimorbidity).

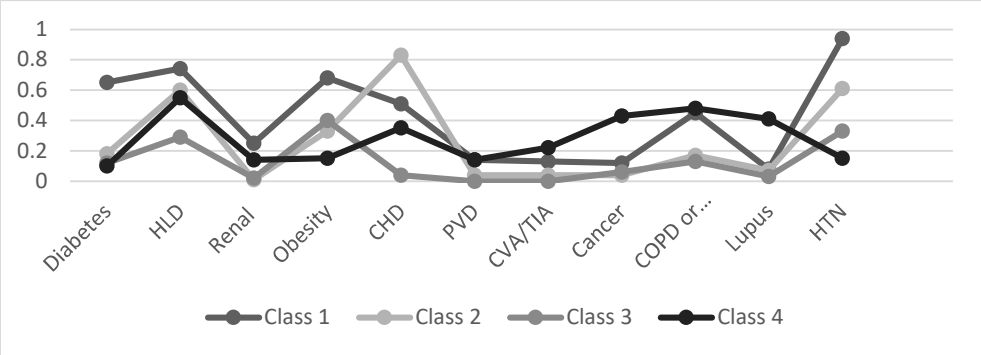

Figure 9. Condition Probabilities for Latent Classes

TABLE VIII. PROBABILITY OF CONDITION OCCURRENCE BY CLASS

Chronic Condition N=935	**Class 1 High Multimorbidity N=294 (31.5%)**	**Class 2 Low Multimorbidity N=264 (27.8%)**	**Class 3 Cardiovascular Multimorbidity N=248 (26.2%)**	**Class 4 Cardio-Onc Multimorbidity N=129 (14.5%)**
Diabetes (%)	**68.6****	10.4	15.2	6.0
Hyperlipidemia (%)	**42.1****	15.3*	**27.9****	14.7*
Renal (%)	72.4	5.4	3.1	19.1
Obese (%)	**50.3****	24.4*	20.2*	5.1
Coronary Heart Disease (%)	35.4*	2.2	**50.6****	11.9*
Peripheral vascular disease (%)	56.6	0	14.8	28.6
Cerebrovascular disease (%)	49.1	2.0	12.3	36.7
Cancer (%)	29.3	12.6	7.3	50.8*
Respiratory Disorders (COPD or Asthma) (%)	53.6*	13.6	17.8	15.1
Lupus (%)	39.5	12.0	27.3	21.1
HTN (%)	**45.9****	14.3*	**25.0****	**14.9****

Bold** indicates high probability conditions (.6-1) and * indicates moderate probability conditions (0.3 to <.60). Models are adjusted for- Age, Duke Activity Score Index weighted total score, Family history of sudden cardiac death <55 years, and ACS status (rule-in/out)

Results showed class membership varied by sex, with females most often in Class 2(35.7%) compared to Class 1, Class 3, and Class 4 members (33.5%, 16.1%, and 14.7%, respectively). When examining individual class membership, however, females comprised 51.6% of Class 2, followed by Classes 4, 1, and 3 (43%, 40%, and 21%, respectively). Classes also differed by age, ACS diagnosis (ruled-in/out), functional status, and family history of sudden cardiac death less than 55 years. Patients in Class 4 were the oldest with a mean age of 82± 5.6 years, while patients in Class 2 were the youngest (mean 48.7± 12.2 years, p=0.00). 100% of patients in Class 3 were ruled-in for ACS compared with Class 1, Class 2, and Class 4 (35.8%, 1.2%, and 29.8%, p=0.00, respectively). Patients in Classes 1 and 4 had lower functional capacity (mean DASI scores 15.6 and 23.0) compared to patients in Classes 2 and 3 (mean DASI scores 46.6 and 48.4, p<0.001). A majority of patients in Class 1 had a family history of sudden cardiac death under 55 years (63%). Patients in Class 4 had a lower prevalence of a family history of sudden cardiac death than Classes 2 and 3 (33% versus 40% and 41%, p=0.00).

4. <u>30-Day Readmission, Clinic Visits, and Emergency Department Visits</u>

Health care utilization outcomes were analyzed for 674 patients who had complete data (Table 9). Healthcare utilization at 30-days was associated with class membership. Readmission was higher for those in Classes 1 and 4 than in Classes 2 and 3 (17.5% and 11.8% versus 7.1% and 7.4%, respectively, p=0.00). Having a clinic visit (primary care or specialty) at 30-days post-discharge was associated with class membership. Those in Class 3 had the highest rates of clinic visits within 30 days (89.5%) versus classes 1, 2, and 4 (80%, 77%, and 81%, respectively, p=0.01). The average number of visits was approximately 2 at 30-days for all classes, and the total number of visits did was not associated with class membership (p=0.22). Emergency

department visit utilization at 30-days was also not associated with class membership, with the average number of visits being less than one for all classes ($p=0.18$).

TABLE IX. VARIATION IN HEALTHCARE UTILIZATION OUTCOMES BY LATENT CLASS

	Class 1 High Multimorbidity N=295 (31.7%)	**Class 2 Low Multimorbidity N=280 (29.9%)**	**Class 3 Cardiovascular Multimorbidity N=245 (26.2%)**	**Class 4 Cardio-Onc Multimorbidity N=115 (12.3%)**	**P-value**
Readmission					
30-Days (n, %)	37(49.3)	13(17.3)	14(18.7)	11(14.7)	0.00
6-months (n, %)	31(39.2)	14(17.7)	16(20.3)	18(22.8)	0.01
Health care utilization					
30-day Clinic visit (n, %)	168(30.3)	142(25.6)	169(30.5)	75(13.5)	0.00
Total number clinic visits (mean, SD)	2.1(2.0)	1.9(2.4)	2 (1.5)	2.4 (2.7)	0.20
30- day ED visit (n, %)	46(40.4)	25(21.9)	28(24.6)	15(13.2)	0.13
Total number ED visits (mean, SD)	0.28 (0.6)	0.22 (0.77)	0.18 (0.48)	0.22 (0.55)	0.43
6-month clinic visit (n, %)	147(32.5)	124(27.4)	116(25.7)	65(14.4)	0.54
Total number clinic visits (mean, SD)	6.6(9)	3.7(4.9)	4.5(7.3)	5.1 (9.3)	0.01
6- month ED visit (n, %)	71(42.8)	34(20.5)	34(20.5)	27(16.3)	0.00
Total number ED visit (mean, SD)	1.1(3.3)	0.73(2.2)	0.34(0.74)	0.64(1.1)	0.00

5. 6-Month Readmission, Clinic Visits, and Emergency Department Visits

Healthcare utilization outcomes were analyzed for 523 patients with complete data at 6-months following discharge (Table 9). Readmission at 6-months varied by class membership and was highest for patients in Class 4 (23.4%) as compared to Classes 1, 2, and 3 (18.9 %, 9.6%, and 11.8%, p=0.01). However, class membership was associated with all classes, but Class 4. The median number of clinic visits was highest for class 1 (4, IQR 2-6) compared with Class 2 (3, IQR 1-5), Class 3 (2, IQR 1-4), and Class 4 (3, IQR 2-5) at 6-months. Emergency department utilization at 6-months was associated with class membership. Patients in Classes 1 and 4 had the greatest amount of recurrent ED visits compared to Classes 2 and 3 (43.3% and 35% versus 23% and 25%, p=0.00).

D. Discussion

There were several key findings from our analysis: (1) there were four multimorbidity phenotype classes including Class 1, High Multimorbidity, Class 2 Low Multimorbidity, Class 3 Cardiovascular Multimorbidity, and Class 4 Cardio-Onc Multimorbidity, (2) specific multimorbidity phenotype classes were associated with being ruled-in or out for ACS, (3) Readmission at both 30-days and 6-months was associated with class membership, and (4) clinic visits at 30-days and 6-months were associated with class membership, while recurrent ED visits were only associated with class membership at 6-months.

1. Multimorbidity Phenotype Classes

Four multimorbidity classes were identified through latent class analysis (computational phenotypes).[24,25] Class membership differed by age, sex, functional capacity, family history of sudden cardiac death less than 55 years of age, and ACS diagnosis (ruled-in/out for ACS). The average age of our population was slightly younger (59 years) than previous studies examining

multimorbidity in the ACS population, where average ages ranged from 67.7 to 79.4 years.[5,18,22,51,53] This difference could be explained by the inclusion of patients ruled-out for ACS. The average age of Low Multimorbidity Class members who had the highest number of patients ruled-out for ACS being 48.7 years. Prior studies have focused on patients ruled-in for ACS, who tend to be older.[5,10,53,54] Females were more likely to cluster in the Low and High Multimorbidity Classes. This finding is slightly different fromwith prior literature in which females frequently exhibit a greater multimorbidity burden than their male counterparts.[5,10] However, the increased amount of females in the Low Multimorbidity Class could be partially due to the fact we also included ruled-out patients. Patients with lower functional capacity clustered in the High and Cardio-Onc Classes, which aligns with previous findings that multimorbidity was associated with lower functional capacity.[5,8,22,49] Finally, a majority of patients in the High Multimorbidity Class and nearly half of the patients in the Cardiovascular Multimorbidity Class had a family history of sudden cardiac death before age 55. Family history of sudden cardiac death at less than age 55 has been a documented risk factor in the development of CHD [43] and an earlier onset of CHD [44] along with other cardiovascular diseases such as HTN, cardiomyopathies, and arrhythmias such as atrial fibrillation.[55,56] Familial history of early cardiac death could partially explain why patients in the High and Cardiovascular Multimorbidity Classes had multiple cardiovascular conditions present.

Our 4-class solution varied from a prior study by Hall, Dondo, Yan, et al., the only prior study that utilized latent class analysis to examine multimorbidity in the ACS population. The authors found a 3-class solution was optimal.[10] However, their sample was larger (n=693,388), only included acute MI patients, and was conducted in England and Wales over a decade.[10] Our analysis included more conditions (obesity, cancer, lupus, and hyperlipidemia) than Hall, Dondo,

Yan, et al., study.[10] Our analysis is the first to include obesity as a chronic condition. Obesity has been understudied in chronic disease clustering[57]; prior studies have either included obesity as a risk-factor (covariate) or simply left it out of their analysis, as in Hall, Dondo, Yan, et al.,'s study.[10] Obesity was first declared a chronic disease in 2008[58] by the Obesity Society, followed by the American Medical Association in 2013.[59] Finally, our classification of patients into phenotypes was different from the high, medium, and low multimorbidity phenotypes in Hall, Dondo, Yan, et al.,'s study.[10] Like Hall, Dondo, Yan, et al.,[10] our analysis found high and low multimorbidity phenotype classes; however, we described additional phenotypes that included a Cardiovascular Multimorbidity Class phenotype and a Cardio-Onc Multimorbidity Class phenotype.

The Cardiovascular Multimorbidity Class phenotype and the Cardio-Onc Multimorbidity Class phenotypes identified in our study are novel additions to previous classifications of high and low multimorbidity phenotypes. Each had a distinct clinical profile and pattern of healthcare utilization post-discharge. Cardiovascular Multimorbidity Class patients represented 26.2% of our sample, were younger with an average age of 58.8 years, more often female (51.6% of total Cardiovascular Multimorbidity Class membership), reported higher functional capacity with no significant difference in DASI scores compared to Low Multimorbidity Class members, and nearly half had a positive family history of sudden cardiac death at less than 55 years. The presence of the Cardiovascular Multimorbidity Class in our study is consistent with prior literature involving risk factors for ACS, including HTN, hyperlipidemia, and CHD[5,12,50,60], which were the three conditions that were highly associated with Cardiovascular Multimorbidity Class membership. The Cardio-Onc Multimorbidity Class phenotype was the smallest class representing only 14.5% of our population. Cardio-Onc Multimorbidity Class patients were

older, male, had the lowest amount of family history of sudden cardiac death at less than 55 years, and reported lower functional capacity than the Cardiovascular Multimorbidity and Low Multimorbidity Classes. The presence of the Cardio-Onc Multimorbidity Class in our sample potentially reflects the increasing cancer survivorship rates[61-63], coupled with the unfavorable cardiovascular risk and cardiovascular disease profile present at diagnosis or developed as a result of cancer itself or treatment regimens [62], and places these patients at high-risk for adverse outcomes.

2. Multimorbidity and the Diagnosis of ACS

Patients in the Cardiovascular Multimorbidity Class were ruled-in for ACS 100% of the time and were seven times more likely to have an ACS event than the Cardio-Onc Multimorbidity Class, and three times more likely than the High Multimorbidity Class patients. Conversely, Low Multimorbidity Class patients were ruled-in only 1.2% of the time. This finding suggests multimorbidity phenotype classes may be superior to count-based multimorbidity measures, given that certain individual conditions have been associated with a worse prognosis. Merely counting all individual chronic conditions with equal weight may underestimate the true burden multimorbidity in patients evaluated for ACS.

3. Multimorbidity is Associated with Readmission, Clinic Visits, and Recurrent ED Visits

Class membership was associated with readmission at both 30-days and 6-months post ACS evaluation. Regardless of ACS diagnosis, patients in the High Multimorbidity Class had the highest rate of readmission, followed by the Cardio-Onc Multimorbidity Class at 30-days. However, at 6-months this finding changed, and readmissions for the Cardio-Onc Multimorbidity Class were more than two times the rate of the High, Low, and Cardiovascular

Multimorbidity Classes. This finding could be related to the older age or prior diagnosis of cancer for Cardio-Onc Multimorbidity Class patients. Class membership was associated with having a clinic visit—specialty or primary care—at 30-days and with the total number of clinic visits at 6-months. The likelihood of having a clinic visit at 30-days and the total number of clinic visits had at 6-months was highest for the High Multimorbidity Class. The high probability of having a clinic visit at 30 days is consistent with current clinical care in which a majority of patients evaluated for ACS are discharged with a referral to an outpatient clinic.[64] The higher rates of readmission and clinic utilization at 30-days and 6-months for the High Multimorbidity Class is expected, given that greater multimorbidity burden is associated with increased healthcare utilization and costs.[8,18,49,65,66] Additionally, post-discharge patients with multimorbidity frequently receive care from a variety of specialists, thus increasing their use of healthcare services.[5]

In our study, recurrent ED utilization at 6-months was associated with multimorbidity class membership. Patients in the High Multimorbidity Class and the Cardio-Onc Class were nearly twice as likely to have a recurrent ED visit as patients in the Low and Cardiovascular Multimorbidity Classes at 6-months. This finding suggests that multimorbidity classes could have potential utility in identifying patients at high risk for increased short-term (30-day and 6-month) readmission, clinic visits, and recurrent ED utilization. Possible explanations for these findings are: (1) Patients may be seeking care for other conditions that may or may not be cardiovascular in nature and; (2) Underlying preexisting psychological conditions such as depression and anxiety are associated with higher rates of ED recidivism and healthcare utilization after ACS evaluation and discharge. Furthermore, psychological conditions are frequently a consequence of admission to the ED for evaluation of ACS. Kronish, Edmondson,

Moise, et al.,[67] found that at 1-month post-discharge, there were no differences in rates of patients (ACS ruled-in versus ACS ruled-out) who developed posttraumatic stress disorder (18.9% versus 16.8%, p=0.47).

E. Strengths and Limitations

Our study had several strengths. We sampled a large geographically and racially diverse group of patients presenting to the ED with suspected ACS. Patients ruled-in and ruled-out for ACS were included. Most prior research has enrolled only patients with ACS. Since the majority of patients with chest pain and associated symptoms are ruled-out for ACS, it is important to determine similarities and differences between groups to improve diagnostic testing and safe discharge. We utilized an advanced analytic technique (latent class analysis) to provide insight into how chronic conditions cluster using a data-driven probabilistic modeling approach. Previous studies have relied on basic analytical techniques such as correlations and regression modeling that may not have fully captured the impact of multimorbidity in the ACS population. These simpler analytical techniques suffer from low statistical power and high rates of false positives (type I errors) as conditions are considered independently, additively, or use all possible combinations of conditions.[10]

There were some limitations to the study. First, data were self-reported (collected through interviews by trained research assistants) and collected through the medical record. Chiu, Huang, and Lu [68], however, found a high linkage between self-reported conditions and national health data (96.6%), and that consistency between self-reports and medical data was satisfactory to very good (Kappa = 0.8 and 0.67 for diabetes and hypertension). Healthcare utilization outcomes (readmission, clinic visits, and ED utilization) were limited to all-cause and all-specialty encounters with no indication of the type (specialty or primary care) of clinic visits. Finally,

multimorbidity was determined by the presence or absence of a specific chronic condition, and therefore, we were unable to account for differences in the severity of the chronic conditions used in the cluster analysis.

F. Conclusion

Four classes of multimorbidity phenotypes were identified in patients evaluated in the ED for potential ACS. Cluster phenotypes may contribute to improved risk-stratification in the ED for patients with symptoms suggestive of ACS and may be useful for predicting healthcare utilization following discharge. Future research should focus on the development of interventions to improve clinical outcomes such as morbidity, healthcare utilization, and patient-centered outcomes (quality of life and functional capacity).

G. Conclusion

The present study described the prevalence of multimorbidity and its impact on readmission, length of stay, and mortality in patients evaluated for symptoms suggestive of ACS. Similar to published findings, multimorbidity is highly prevalent in the ACS population and increases readmission, length of stay, and mortality. However, multimorbidity in patients ruled-out for ACS remains understudied. In our study, the ACS ruled-out patients also had a relatively high burden of multimorbidity. Similar to previous findings, diabetes, hypertension, and hyperlipidemia were the most highly prevalent chronic conditions in our population.

This study also identified four multimorbidity phenotype classes (specific combinations of >2 chronic conditions) and their impact on readmission, clinic visitation, and ED utilization at 30-days and 6-months. The four multimorbidity phenotypes identified in our study included a High Multimorbidity Class (Class 1), a Low Multimorbidity Class (Class 2), a Cardiovascular Multimorbidity Class (Class 3), and a Cardiovascular-Oncology "Cardio-Onc" Class (Class 4). We found that Cardiovascular Multimorbidity Class patients were always ruled-in for ACS and were more likely to be ruled-in than the High Multimorbidity Class patients. We also found that High and Cardio-Onc Multimorbidy Classes had a higher likelihood of readmission at 30-days and 6-months. Furthermore, High and Cardio-Onc Multimorbidity Classes had higher rates of clinic visits and ED utilization at 6-months. These findings are important and indicate cluster phenotypes may contribute to improved risk-stratification in the ED for patients with symptoms suggestive of ACS and may be useful for predicting healthcare utilization following discharge. Future research should focus on the development of interventions to improve clinical outcomes such as morbidity, healthcare utilization, and patient-centered outcomes (quality of life and functional capacity).

H. Integrative Summary of Findings

Multimorbidity (>2 chronic conditions) is highly prevalent in the acute coronary syndrome (ACS) population. Despite the high prevalence of multimorbidity, evidence-based guidelines that guide clinical decision-making and care are primarily developed utilizing randomized control trials that only focus on a single-disease process and frequently exclude multimorbid patients. Thus, current diagnostic and treatment protocols lose relevance and may cause harm when diagnosis and care are complicated by multimorbidity. Presently, multimorbidity is a count-based measure (3 chronic conditions versus 4 chronic conditions), regardless of specific chronic conditions or counts of predetermined lists of chronic conditions and, therefore, loses some of the granularity of these complex interactions between different chronic conditions. Count-based multimorbidity may have resulted in the true impact of multimorbidity to be underestimated.

The purpose of this secondary data analysis, using the *Think Symptoms* study data, was to examine the presence of preexisting chronic conditions patterns (multimorbidity clusters) reported by patients being evaluated for acute coronary syndrome (ACS) in the emergency department (ED), and to (1) determine if class membership varied by age, sex, functional capacity, family history of sudden cardiac death at age less than 55 years, and ACS status (ruled-in/out), and (2) if there was an association between multimorbidity cluster (specific combinations of chronic conditions) and readmission, clinic visits, and ED visits at 30-day and 6-months.

In the present study, the most prevalent chronic conditions were hypertension, hyperlipidemia, coronary heart disease, and obesity (64.9%, 55.2%, 44.7%, and 43.2%, respectively). Four classes of patients emerged (n=935), Class 1 which was labeled *high overall multimorbidity* with HTN, obesity, hyperlipidemia, and diabetes, Class 2 which labeled was *low*

overall multimorbidity with obesity, Class 3 which was labeled *cardiovascular multimorbidity* with CHD, HTN, and hyperlipidemia, and Class 4 which was labeled *cardio-onc multimorbidity* with HTN, hyperlipidemia, and cancer. Class 2 was the youngest (mean age 48.7 years, SD 12.2), while Class 4 was the oldest (mean age 82.3 years, SD 5.7 years, p=0.00). There were twice as many females in Classes 1 and 2 (33.5% and 35.7%) compared with Classes 3 and 4 (16.1% and 14.7%, p=0.00). Patients in Classes 2 and 3 had the higher functional capacity as measured by the Duke Activity Scale Index weighted total score with mean scores of (48.4, SD 11.6 and 47.2, SD 13.6) compared to Classes 1 and 4 which had lower functional capacity mean scores (15.6, SD 10.0 and 23.0, SD 15.7, p=0.00). Family history of sudden cardiac death at an age less than 55 years was present in almost half of Class 1 (43.1%), approximately a quarter of patients in Classes 2 and 3 (22.5% and 25.2%), and only minimally present in Class 4 (9.2%, p=0.00). Of total patients ruled in for ACS (n= 415), patients in Classes 1 and 3 (25.8% and 64.8%) were more likely to receive ACS diagnosis compared to patients in Classes 2 and 4 (0.7% and 8.7%, p= 0.00). Of note, regarding total class membership, all patients in Class 3 were ruled- in for an ACS event while patients in Class 2 were only ruled-in 1.2% of the time.

Class membership was associated with readmission, Classes 1 and 4 reported the highest rates of readmission at 30-days (17.0% and 11.8%, p=0.00) and 6-months (18.9% and 23.4%, p=0.02). While Classes 2 and 3 had nearly half the rates of readmission at 30-days (7.2% and 7.7%, p=0.00) and 6-months (9.6% and 11.7%, p=0.02). Class membership was also associated with having a clinic visit at 30-days (p=0.00). However, it was not associated with the number of clinic visits at 30-days, with the average number of visits for all classes being approximately 2 (p=0.20). At 6 months, the total number of clinic visits was associated with class membership, with Classes 1 and 4 having an average of 5 or more visits (6.6 visits and 5.1 visits, p=0.01)

compared with Classes 2 and 3 who averaged 3.7 visits and 4.5 visits (p=0.01). Recurrent ED visits were not significantly associated with class membership at 30-days (p=0.14), with all classes having an average of less than one recurrent ED visit (p=0.43). However, recurrent ED visits at 6-months were associated with class membership with class 1 having nearly twice the rate of ED utilization as Classes 2 and 3, while only slightly higher than Class 4 (44.7% versus 24.3%, 23.0%, and 34.2%, respectively, p=0.00).

Among patients evaluated for potential ACS, preexisting chronic conditions were common and associated with increased healthcare utilization at 30-days and 6-months. Four novel classes of multimorbidity were identified, which may direct future research into the health care utilization interventions for this vulnerable population. Multimorbidity clusters offer both immediate diagnostic utility and longer-term risk-stratification potential for these high-risk patients. Further research is needed, however, to investigate additional chronic conditions, known cardiovascular risk factors, and outcomes such as mortality, pharmaceutical intervention, and types of specialist visits in patients ruled-in and ruled out for ACS to identify protective and predictive factors that help identify high-risk individuals.

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APPENDIX A **Determination**

Notice of Determination – Claim of Exemption

Activity Does Not Represent Human Subjects Research

June 26, 2019

20190682-124652-1

Katherine Breen

Biobehavioral Health Science

RE: **Protocol # 2019-0682**
"Examining the Role of Multimorbidity in Patients Evaluated for Symptoms Suggestive of Acute Coronary Syndrome in the Emergency Department"

Funding Source/Sponsor: None

Dear Katherine Breen:

The UIC Office for the Protection of Research Subjects received your Claim of Exemption application and has determined that this activity **DOES NOT meet the definition of human subject research** as defined by 45 CFR 46.102(e)/ 21 CFR 50.3(g) and 21 CFR 56.102(e).

Specifically, this is a secondary analysis of de-identified data. The de-identified dataset was initially collected under UIC Research Protocol #2012-0661, which was closed by UIC IRB #3 on February 18, 2016.

You may conduct your activity without further submission to the IRB.

Please note:

- If this activity is used in conjunction with any other research involving human subjects, prospective IRB approval or a Claim of Exemption is required.
- If this activity is altered in such a manner that may result in the activity representing human subject research, a NEW Determination application must be submitted.

cc: Holli A. Devon

Appendix B **Copy Right Permission License**

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Jan 29, 2020

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TEACHING EXPERIENCE

The University of Illinois at Chicago
Clinical Teaching Associate 2019-2020
Pathophysiology, Pharmacology, and Medical/Surgical clinical instructor

Teaching Assistant 2017-2019
Management of the complex patient I and II- in the Adult Gerontology Nurse practitioner program

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Memorial Medical Center
Clinical Nurse 3, Cardiac Recovery/ Cardiac ICU 2013 –

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Staff Nurse, Cardiac- Step down/ telemetry Unit 2012-2014

Southern Illinois University
Research Assistant: Neuroscience Laboratory 2008-2010

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PUBLICATIONS AND PAPERS

DeVon, H. A., Vuckovic, K., Burke, L. A., Mirzaei, S., **Breen, K**., Robinson, N., & Zegre-Hemsey, J. (2018). What's the Risk? Older Women Report Fewer Symptoms for Suspected Acute Coronary Syndrome than Younger Women. *Biores Open Access, 7*(1), 131-138. doi:10.1089/biores.2018.0020 Journal

PODIUM PRESENTATIONS

Breen K. Ph.D. in Three; The Lived Experience: Secondary Data Analysis a Viable if Not Favorable Dissertation Methodology. Presented at the 44th Annual Midwest Nursing Research Society. April 2020; Schaumburg, IL.

POSTER PRESENTATIONS

Breen,K., Mirzaei,S., Dungan,J., Burke, L., Anne G. Rosenfeld, A.G., DeVon, H.A. Symptoms suggesting of acute coronary syndrome and associations with cytokine gene polymorphisms..Poster presented at: National Institute of Health Symptom Science Center Opening. June 2019; Bethesda, MD.

Breen,K. and Wendler, M.C. Simulation training of intermediate care nurses in the care or the post carotid endarterectomy patient. Poster presented at: Memorial Medical Center 25th annual Nursing Research Conference. April 2017; Springfield, IL.