Multiple Chronic Conditions and Post-Stroke Functional Outcome

by

Xiaqing Jiang

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Doctoral Committee:

Professor Lynda D. Lisabeth, Chair
Associate Professor Christine T. Cigolle
Professor Lewis B. Morgenstern
Associate Professor Lu Wang

Xiaqing Jiang

jxq@umich.edu

ORCID iD: 0000-0003-3633-0688

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Abstract

Stroke is a leading cause of disability in the United States (US) and the number of disabled stroke survivors will rise with the aging population. The aging of the US population will also lead to an increase in the prevalence of multiple chronic conditions (MCC) at stroke onset, which impacts post-stroke functional outcome (FO), although current evidence is inconsistent. The goal of this dissertation was to advance the understanding of MCC in post-stroke functional outcome through a systematic literature review and data analyses using a bi-ethnic population-based stroke cohort. Specifically, this dissertation investigated the association between MCC and post-stroke FO by 1) summarizing the findings of previous studies that have investigated the relationship between MCC and FO after ischemic stroke using MCC indices, 2) developing and internally validating a new MCC index to predict post-stroke FO using machine learning techniques, and 3) investigating the contribution of MCC to ethnic disparities in post-stroke FO between Mexican American (MA) and non-Hispanic white (NHW) stroke patients using the new index.

The systematic literature review showed that hospital-based prognostic studies for post-stroke FO predominantly used the Charlson Comorbidity Index (CCI) and the Modified CCI (mCCI) to measure MCC burden. The negative association between MCC and FO was statistically significant in the meta-analysis. We identified several novel predictors of post-stroke FO and developed a new MCC index among ischemic stroke

patients. The new MCC index was validated to improve the prediction of post-stroke FO at 90 days and outperformed the mCCI. MA stroke patients have significantly greater age-adjusted MCC burden at stroke onset compared to NHWs. MCC measured by the new index was found to be an important contributor to worse FO at 90 days in MAs compared with NHWs, although effect modification of the MCC-FO outcome association by ethnicity was not statistically significant.

This dissertation research confirmed that MCC is an important predictor for post-stroke FO. External validation is needed before the application of this index in other stroke populations. Accurate measurement of the MCC burden in stroke patients is important for more precise prognosis in post-stroke FO, which could inform stroke treatment, post-acute care, and intervention efforts to mitigate post-stroke functional impairment, promote functional gain and lessen ethnic disparities in post-stroke FO.

Chapter 1: Introduction

1.1 Introduction

Stroke is a leading cause of disability in the United States (US). The number of disabled stroke survivors will rise with the aging population and the cost of stroke-related care is projected to increase substantially. The aging of the US population will also lead to an increase in the prevalence of multiple chronic conditions (MCC) at the time of stroke, which could impact stroke recovery and outcomes. To date, research on MCC in stroke has focused primarily on mortality, with limited investigation of patient-centered outcomes, such as functional outcome (FO). Also, the burden of post-stroke disability is distributed unequally among ethnic groups in the population, with Mexican Americans (MAs) at a higher risk compared to non-Hispanic whites (NHWs). Research on MCC and stroke outcomes in diverse populations is lacking though MCC may contribute to race-ethnic stroke disparities.

The goal of this dissertation research was to advance the understanding of MCC in post-stroke FO from a systematic literature review in addition to analyzing data from the bi-ethnic population-based Brain Attack Surveillance in Corpus Christi (BASIC) Project, which collected detailed data on pre-stroke health status and outcomes in validated ischemic stroke cases. First, a systematic literature review was conducted to summarize the current knowledge on the association between post-stroke FO and MCC measured by existing indices. Second, through applying statistical machine learning

methods, an MCC index was developed and validated to predict 90-day functional outcome. Third, the new index was used to investigate the contribution of MCC to poorer FO in Mexican American (MA) stroke survivors compared with non-Hispanic whites (NHWs).

1.2 Specific Aims and Hypotheses

Specific Aim 1. Systematically review the literature on the association between FO after ischemic stroke and MCC measured by different indices.

Hypothesis 1: MCC will be associated with worse FO; the impact of MCC on FO will vary by MCC index and population studied.

Specific Aim 2. Using machine learning techniques, develop an MCC index to predict FO at 90 days, measured by activities of daily living (ADLs) and instrumental activities of daily living (IADLs), in ischemic stroke patients in the BASIC Project.

Aim 2a. Investigate associations between individual comorbid conditions and FO at 90 days.

Hypothesis 2a: Comorbid conditions will be associated with worse FO; the impact of different conditions on FO will vary.

Aim 2b. Fit an FO prediction model with variable selection methods to develop a new MCC index for FO at 90 days.

Hypothesis 2b. Higher scores on the new MCC index will be associated with worse FO in validation samples after adjusting for confounding factors.

Aim 2c. Compare predictivity of the new MCC index with that of existing indices, and validate the index using the study population and another recent sample from BASIC.

Hypothesis 2c. The new MCC index will have better predictive ability than existing indices, and its ability to discriminate functional dependency will be better than other existing indices.

Specific Aim 3. Understand the contribution of MCC to ethnic disparities in FO at 90 days between MA and NHW ischemic stroke patients in BASIC.

Aim 3a. Investigate the distribution of MCC burden among MAs and NHWs ischemic stroke patients.

Hypothesis 3a. MAs will have higher scores on the MCC index than NHWs adjusting for confounders.

Aim 3b. Investigate the contribution of MCC to ethnic disparities in FO at 90 days.

Hypothesis 3b. The strength of ethnicity-FO association will be reduced after controlling for the MCC index.

Aim 3c. Investigate whether the association of MCC with FO-90 differs by ethnicity.

Hypothesis 3c. The association between MCC index and FO-90 will be stronger in MAs than NHWs.

1.3 Background

Pathophysiology of Ischemic Stroke

Stroke refers to the alteration in blood supply that leads to the rapid death of nerve cells.[1,2] The causes of stroke can be divided into hemorrhagic varieties where a ruptured blood vessel hemorrhages into the brain/onto the surface of the brain (hemorrhagic stroke), or ischemic varieties where there's a blockage in the arteries supplying blood to the brain (ischemic stroke).[1,3] Most strokes (87%) are ischemic,[4] and the most common etiology that results in cerebral ischemia is the local damage to the vessel wall from atherosclerosis.[2] The development of atherosclerosis often takes years beginning with endothelial injury and inflammation followed by plaque formation. The thickened and fibrotic plaques then adhere to the sclerotic material that fills and occludes the vessel lumen, which follows by releasing factors that initiate the coagulation-clotting cascade, and a clot or thrombus is then formed. A clot can either remain in place and affect the internal carotids, middle cerebral or basilar arteries as a thrombotic event, or break off as an embolus traveling to and blocking a distal vessel.[5] Events caused by an embolus from the thrombus in the atria or the ventricle are referred to as cardioembolic strokes. The loss of blood supply to the infarcted region is followed rapidly by inhibition of protein synthesis, depletion of intracellular energy stores, membrane depolarization and the release of extracellular potassium, resulting in cellular swelling and further elevation of intracellular calcium that activates a large number of damaging enzymatic pathways.[6] This damaging cascade eventually will lead to apoptosis of brain cells in the infarcted tissue.[6]

Disability and Functional Impairment in Stroke Survivors

In the US, over 70% of stroke survivors live with some long-term disability.[7] Stroke-related disability hinders the patients' reintegration into society by impairing their ability to perform even the simplest tasks. The types and degrees of the stroke-caused diability depend on many factors including the location of the damage and the amount of the brain tissue affected.[1-3,5,6,8,9] Five types of disability are common among stroke survivors, including 1) paralysis or problems controlling movement (motor control); 2) sensory disturbances, including pain; 3) speech or language problems (aphasia); 4) problems with thinking and memory, and 5) emotional disturbances. Paralysis is one of the most commonly seen disabilities among stroke survivors, which is often on the side of the body opposite the side of the brain damage (hemiplegia).[8,9] One in two and one in three stroke survivors has lifelong arm and leg paralysis, respectively, which impledes their ability to drive and walk independently.[10] Stroke survivors may also have difficulty with swallowing, coordinating movement or balancing depending on the functioning of the damaged part of the brain. Sensory deficits in stroke patients are also common, which inhibit their ability to feel touch, pain, temperature, or position. Numbness and chronic pain also exist in some stroke patients due to immobilization and damage to the sensation pathways in the brain. A combination of sensory and motor deficits can lead to temporary and permanent incontinence. On the other hand, more than one in five stroke survivors experiences aphasia,[10] which can be caused by the lesions in the Broca's area or Wernicke's area.[8,10] In severe cases, patients with global aphasia could lose all of their linguistic ability due to damage in multiple-areas. In addition, loss of memory, learning, and awareness in stroke patients can shorten their attention spans,

affect their short-term memory, and impair their ability to plan and accomplish more complex tasks. Many stroke survivors feel fear, anxiety, frustration, anger, sadness, and a sense of grief for their physical and mental losses, which is a combined result of the stroke-related psychological response and the physical effects. Emotional disorders also have a great impact on the individual's ability to function.[1-3,5,6,8,9]

The neurological impact of stroke is often multifaceted and depends on the brain area affected by the occluded artery and its collateral circulation.[2,3] The middle cerebral artery (MCA) supplies the mid-portion of one brain hemisphere, which is the most common site of infarction accounting for two-thirds of first ischemic strokes.[11,12] For instance, left MCA blockage can cause the lesion in the Wernicke's speech comprehension area, Broca's motor area for word formation, and neural motor control areas in the left hemisphere. A patient is likely to become demented and has dysphasia and spastic paralysis of most muscles on the right due to these lesions.[3]

Following a stroke, most patients with stroke-caused functional impairments experience some degree of recovery.[13] Thus, the level of stroke-related functional impairment is often highest immediately after the stroke and decreases significantly thereafter.[13] Most of the functional recovery occurs in the first month, and by the end of the three-month period, most people reach their maximum recovery in activities of daily living (ADLs).[14] Population-based studies report that approximately 75-88% of ischemic stroke patients are functionally dependent immediately after a stroke, and 53% at 6 months.[13,15,16] In the last two decades, functional outcome in stroke survivors has been improved due to thrombolytic treatments such as intravavenous tissue plasminogen activator and endovascular therapy. However, only about 10% of the ischemic stroke

patients in the US actually receive thrombolytic treatment,[17] mainly due to arrival outside the treatment window.[18] The prevelence of functional dependence at 3 months has been largely unchanged in non-thrombolysed stroke survivors.[19] Inpatient rehabilitation also plays an important role in functional recovery but less than one-third of the total stroke population are able to participate.[20]

Growing Public Health Importance of Stroke-Related Disability

Each year, roughly 800,000 people experience a new or recurrent stroke.[4,21] Stroke is the fifth leading cause of death, and a leading cause of serious long-term disability in the US.[22,23] From 2003 to 2013, the age-adjusted stroke death rate decreased by 33.7%, and the number of stroke deaths declined by 18.2%.[22,23] With declining stroke mortality rates in combination with the aging US population, it is projected that the prevalence of disabled stroke survivors will increase substantially in the coming decades.[24,25] It is projected that by 2030, 10 million adults will have had a stroke, a 20.5% increase from 2012.[26] Consequently, the total direct medical stroke-related costs are expected to increase between 2012 and 2030, from $71.6 billion to $184.1billion.[26] There is an urgent need to understand drivers of post-stroke disability to inform interventions for improving outcomes in the rapidly growing population of stroke survivors.

Post-Stroke Functional Outcome and Known Predictors

With the declining stroke mortality and projected increase in the number of disabled stroke survivors,[24,25] it is crucial to understand the pre-existing and co-existing factors that are associated with worse FO and how to predict functional status

accounting for these factors. Previously established pre-stroke predictors of FO from population-based and hospital-based cohort studies are summarized in Figure 1.1.

Timely and appropriate care for stroke, such as thrombolytic therapy and inpatient rehabilitation, improves functional recovery at three months, and beyond.[19,27-29] Initial stroke severity is a major predictor of both short and long-term FO [29-37] and explains the greatest variance in FO among stroke patients.[34,35,38] Established pre-stroke predictors of FO from population-based studies include older age, female sex, minority race/ethnicity, and lower socio-economic status.[29,30,32,33,35,36] Additionally, patients' baseline status, including pre-stroke physical activity and nursing home residency, as well as functional, cognitive and psychosocial status, predicts FO in hospital-based studies and a few population-based studies.[29,33,39,40] Presence of baseline comorbid conditions, such as diabetes and chronic kidney disease, are also associated with worse FO in hospital-based studies.[41,42] In studies conducted in rehabilitation settings, hypertension, coronary heart disease (CHD), atrial fibrillation, and dementia are associated with FO at 90 days or at rehabilitation discharge.[32,43-46] However, as the population at-risk for stroke ages, patients with MCC at stroke onset will become more prevalent, and the pre-stroke status of patients in this population will be more heterogeneous. In order to address this emerging complexity in predicting stroke outcomes, there is a growing interest in developing tools that globally measure the pre-stroke status of an individual, which could contain a clustering of diseases, impairments and risk factors.[47-50]

MCC and Functional Decline Among Elderly

MCC is commonly known as the "concurrent presence of two or more medically diagnosed diseases in the same individual".[51] Comorbidities of stroke are a subset of MCC that existed or may co-occur during the clinical course of stroke.[52] In the US, more than 1 in 3 people have MCC.[53] Prevalence of MCC increases with age.[49,53] Fifty percent of those aged 45–64 report MCC in the US, with this number reaching 81% at age 65 years and older.[53] MCC prevalence has increased over time.[54,55] Among the elderly, MCC contributes to frailty, mortality, and functional disability,[49] primarily through pathophysiological changes and organ-level impairments.[56-60] Consistent associations between MCC and function in a variety of populations were demonstrated in a recent systematic review.[61] Importantly, MCC heightens the risk of disability, over and above the risk from each individual condition,[60,62-66] and is associated with greater use of inpatient and ambulatory care.[67,68] It is also known that the presence of certain combinations of conditions, such as heart disease and osteoarthritis, arthritis and visual impairments, arthritis and high blood pressure, heart disease and cancer, lung disease and cancer, and stroke and high blood pressure, can have a synergistic effect on the risk of disability.[51,64-66] With the aging of the population, more people will be living with MCC, which makes an understanding of the impact on the outcome of common diseases, such as stroke, critical.

Existing Research on MCC and FO

Among stroke patients, pre-stroke MCC appears to explain variation in post-stroke functional outcome at 3 months, over and beyond the damage caused by the stroke.[38,69] However, the proportion of variation explained by comorbidity is highly

measurement-dependent and varies from one MCC index to another,[38,69,70] and is also affected by the adjustment used in prediction models.[32,69] Further, the variance of functional outcome explained depends on both the range of outcome and the range of MCC, as most MCC indices have considered only a small number of conditions.[32,38,71]

The Charlson Comorbidity Index (CCI) and the Modified CCI (mCCI) have been the predominant MCC measures used in stroke research.[32,38,44,70,71] CCI includes 19 conditions weighted by their strength of associations with mortality.[72] CCI was originally developed as a prognostic indicator in patients with a variety of conditions and validated in breast cancer patients [72]. The mCCI is similar but excludes cerebrovascular disease and hemiplegia.[71] An additional three indices have been developed to predict FO and have been used in stroke patients. The Functional Comorbidity Index (FCI) was originally developed by Groll et al. [73] This index includes 18 conditions and was shown to have a much stronger association with FO compared to CCI among orthopedic populations.[38] The LiuCI was designed to be a stroke-specific comorbidity index to predict FO in 106 Japanese rehabilitation patients from a single center study.[70] This rather complex MCC-measuring tool grades included 38 medical conditions in 18 diagnostic categories and 5 severity levels, taking into account both pre-stroke comorbidities and post-stroke complications.[70] The final index, the COM-SI, accounts for pre-stroke comorbid conditions and was developed in a smaller number (85) of patients from a single-centered rehabilitation institution in Italy.

The small number of studies that considered the association between MCC and FO are summarized in Table 1.1. Briefly, Chang et al. found that the CCI was associated with 6 month FO, measured by Functional Independence Measure (FIM),[74] a

standardized measure including 18 items and covering 6 functional domains, in a Korean stroke cohort.[32] However, the association was no longer significant after controlling for confounding factors, including stroke severity and pre-stroke function.[32] Using the modified Rankin Scale (mRS) as the FO measure, Fischer et al.[44] reported similar findings in hospitalized ischemic stroke patients from two hospitals in Switzerland and found that the CCI-FO association was no longer significant after adjusting for stroke severity and atrial fibrillation.[75-77] Goldstein et al. assessed the MCCI in predicting mortality and discharge mRS using administrative data among veterans and found that mCCI was independently associated with poor outcome at hospital discharge, controlling for age and stroke severity.[71] Tessier and colleagues compared five comorbidity indices, which included three newly-developed stroke-specific comorbidity indices using different weights for comorbid conditions, the mCCI, and the FCI in noninstitutionalized Canadian stroke patients who were hospitalized in 10 selected hospitals.[38] They found that MCC, measured by the new indices, mCCI and FCI, were all associated with FO at 3 or 6 months without any adjustment and that FCI was slightly better in predictivity compared to CCI and the new indices.[38] Liu and colleagues compared their stroke-specific comorbidity index (LiuCI) with CCI. They found that although LiuCI was predictive of FO at rehabilitation discharge, CCI was not.[70] Ferriero et al. compared LiuCI with the other stroke-specific comorbidity index, COM-SI, and found that, compared to LiuCI, COM-SI had a stronger correlation with FO at rehabilitation admission and discharge.[78] In addition, they also found that MCC impacted the course and outcome of stroke rehabilitation controlling for FO at admission. [78] Research from the BASIC Project showed that the sum of 15

comorbidities was independently associated with functional outcome at 90 days measured by an ADL/IADL[79] score in an ischemic stroke population controlling for many confounding factors including stroke severity and pre-stroke function[29]. In summary, although negative associations between MCC and FO have been demonstrated in different populations using different MCC measures, there has been some inconsistent findings across the studies, and the predictive performance of MCC in predicting FO has varied by index, outcome and model adjustment.[32,38,69-71]

Limitations to Existing Work on MCC and Stroke Outcome

There are a number of limitations to the existing research of MCC and FO. **First**, although MCC has long been known as an independent predictor of stroke mortality,[71,80-82] studies of MCC and FO are still limited in number, and the findings have been inconsistent, especially when controlling for other FO predictors. **Second**, existing studies have predominantly measured MCC using mCCI or CCI indices developed in non-stroke populations to predict mortality.[38,44,71] Some conditions that predict function in the elderly, including osteoarthritis, arthritis, hypertension, visual and hearing impairments, and atrial fibrillation, have been missing from the CCI and mCCI.[44] **Third**, most studies have failed to include or adequately control for important confounders of the MCC-FO association, such as stroke severity, age, sex, socio-economic status, and stroke therapy, which has limited the interpretation of the observed associations. **Fourth**, existing MCC indices have failed to capture possible synergistic interactions among MCC clusters that may lead to worse FO.[51] **Finally**, none of the MCC indices have been developed from or validated in population-based prospective stroke cohorts. Studies have been conducted in rehabilitation settings, foreign countries, or in selected

hospitals, where the characteristics of the source population and comorbidity spectrum vary.[38,70,73] **Further**, work in diverse populations, where the greatest stroke burden is seen, has been virtually non-existent.

MCC in Prognostic Models for Post-stroke FO

Limited research has focused on the development of risk scores to predict post-stroke FO that comprise comorbid conditions.[83-85] Both the iScore and the PLAN score are prediction tools validated in ischemic stroke patients for FO at hospital discharge.[83,85] The PLAN score considers four comorbidities (cancer, atrial fibrillation, congestive heart failure, and preadmission dependence) in addition to age, consciousness level, and neurologic deficit. The iScore, adds four other comorbidities (myocardial infarction, kidney disease on dialysis, hyperglycemia, and smoking) in addition to age, sex, and stroke-related factors (stroke severity measured by the Canadian Neurological Scale and stroke subtype by TOAST criteria[86]). The ASTRAL score is designed to predict FO at 3 month in ischemic stroke patients but considers only hyper/hypoglycemia for comorbidity. Currently, available risk scores for post-stroke FO prediction are therefore limited in the number of comorbid conditions included. Pre-stroke cognitive and psychosocial status have not been considered, although they are important factors for neuroendocrine responses, neuronal viability, and neuropsychological adaption after stroke, which impact patient adherence with rehabilitation and treatment.[39,87-96] Comorbid conditions in these prognostic models are considered as individual predictors, while the possible synergistic interactions between conditions and the clustering effect have not been examined in the current literature on post-stroke FO prediction, although many have identified the topic to be important and challenging.[97-103]

Re-defining MCC to Predict Post-Stroke FO

Recent research defining MCC is now moving beyond the traditional approach of defining MCC based on the presence of clinically diagnosed chronic conditions alone.[104,105] MCC in the general population has recently been conceptualized as the co-occurrence of *functional limitations* (difficulty in performing mobility, strength, and ADL/IADL tasks), *geriatric syndromes* (e.g., vision/hearing impairment, depression, urinary incontinence, low cognitive function, etc.), and *chronic conditions*.[104] Building on this Koroukian model of MCC,[104] I plan to conceptualize MCC in stroke patients as the co-occurrence of *chronic conditions and pre-stroke functional, cognitive, and psychosocial impairments* (Figure 1.2), with the idea that together these factors capture the "reserve" which an individual has to aid in stroke recovery. The rationale is briefly described.

Post-stroke functional limitations can be caused directly by a stroke but often occur in individuals who are physically and cognitively frail before the stroke.[29,40,87-90] Pre-stroke cognitive and physical functioning play inseparable parts in the neuropsychological process of post-stroke adaption and recovery.[106,107] Specifically, frail individuals who are *functionally impaired* often have poorer cardiovascular and functional neuromuscular reserve due to decreased pre-stroke physical activity [108], which may lead to worse post-stroke hemodynamics and collateralization of flow after arterial occlusions, impeding functional recovery [29,40,108]. On the other hand, *cognitively impaired* individuals often have more severe strokes and an increased risk of post-stroke cognitive decline, which hinders the post-stroke neuropsychological adaption process.[87-95] Pre-stroke *psychosocial impairments*, such as poor social support and

social isolation, can act as chronic stressors that modulate the hypothalamic-pituitary-adrenal axis and affect functional recovery through increasing the cortisol level.[109-112] Individuals who have larger pre-stroke social networks might also have greater motivation to remain physically active, and an enhanced ability to cope with stroke and the aftereffects.[39,113] Social isolation and lower social activity are also linked to pre-stroke depression,[114-116] which is associated with post-stroke depression and FO.[114,116-118] Together, these psychosocial factors may impact recovery directly through neuroendocrine responses and neuronal viability in the hippocampus,[96] as well as indirectly through their associations with depression,[114,116-118] and adherence with rehabilitation and treatment.[39] I believe this new conceptualization of MCC will capture more comprehensively the pre-stroke reserve that individuals have to aid in functional recovery than existing indices that focus on diagnosed comorbid diseases alone.[98,119] **Further**, I will also consider the interactions between individual conditions and pre-stroke impairments to identify synergistic effects that have been shown to have a greater impact on FO previously. [49, 64-66, 98]

Novel Techniques to Develop an MCC Index for FO

Comorbid conditions included in existing MCC indices were often chosen based on clinical judgment and literature review, and then pruned based on their frequency, severity, and relationship with the outcome, or grouped based on body systems. Given the number of candidate conditions and interactions to be considered in developing an MCC index, conventionally used methods such as ordinary least squares regression with subset selection is not stable and can reduce prediction accuracy when the number of predictors (p) exceeds the number of individuals (n).[120,121]

Variable selection methods from machine learning, such as the least absolute shrinkage and selection operator (*Lasso*) regression method and its derivatives, have been developed to perform simultaneous model selection and estimation to overcome the drawbacks of the conventional methods.[122-126] Specifically, by putting a constraint, the *lasso* minimizes the residual sum of squares and accomplishes subset predictor selection through shrinking some of the regression coefficients to exactly zero to solve the problem of sparse modeling. For example, given a design matrix $\boldsymbol{X} \in \mathbb{R}^{n \times d}$ and response vector $y \in \mathbb{R}^{n}$, the *lasso* solves the convex optimization problem by

$$\textbf{Minimize } \frac{1}{2} \left\| \boldsymbol{\beta}_0 \mathbf{1} + \boldsymbol{X}\boldsymbol{\phi} - \boldsymbol{y} \right\|_2^2 + \boldsymbol{\lambda} \left\| \boldsymbol{\phi} \right\|_1$$

where $\mathbf{1} \in \mathbb{R}^{n}$ is the vector of ones. The tuning parameter, $\boldsymbol{\lambda} \geq \mathbf{0}$. The *lasso* will simultaneously regularize the least squares fit and shrink some components of $\boldsymbol{\phi}$ to zero ($\boldsymbol{\ell}_1$-norm penalty) to achieve “sparsity”.

One challenge in using the penalized shrinkage method to explore the impact of interactions between MCC is to fit a hierarchy model - only allowing an interaction into the model if at least one of the corresponding main effects are also in the model.[126] Hierarchy models have demonstrated strong predictive power among patients with neurological problems.[127] A natural extension of the lasso to include the interactions would be to apply lasso to a data matrix including all pairs of interactions in addition to all main effects. However, since lasso’s $\boldsymbol{\ell}_1$-norm penalty is neutral to the pattern of sparsity (not distinguishing main effects and interactions), the fitted model could include an interaction without the corresponding main effects (allowing sparsity that violating strong hierarchy to emerge). However, models violating hierarchy are criticized.[126,128]

Including interactions with their corresponding main effects is favored because “large component main effects are more likely to lead to appreciable interactions than small components” and interactions corresponding to larger main effects may be of “more practical importance”.[129] Thus, hierarchy models that include corresponding main effects are more commonly accepted when examining the impact of interactions.

The *Lasso regression method for hierarchical interactions* (hierNet) method, or “hierNet” developed by Bien, Taylor and Tibshirani allows us to explore the impact of interactions between MCC by fitting a hierarchy model.[126,130] Specifically, hierNet solves the optimization problem

$$\textbf{Minimize}\ \left(\boldsymbol{\beta}, \mathbf{0}, \in \mathbb{R}, \ \boldsymbol{\beta} \in \ \mathbb{R}, p, \Theta \in \ \mathbb{R}, p \times p, \Theta = \ \Theta, T, \ \frac{1}{2}, \boldsymbol{y} - \boldsymbol{\beta}, \mathbf{0}, \mathbf{1} - \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{Z}\textbf{vec}\,\Theta, \mathbf{2}, 2, + \boldsymbol{\lambda}\boldsymbol{j}\,\textbf{max}\,\left|\boldsymbol{\beta}, \boldsymbol{j}, \right|, \ \Theta, \mathbf{1}, + \boldsymbol{\lambda}, \mathbf{2}, \ \Theta, \mathbf{1},\right.$$

where $\boldsymbol{Z} \in \ \mathbb{R}, n \times p(p-1),$ correspond to elementwise products of the columns of $\boldsymbol{X}$. The main effects are represented by $\boldsymbol{\beta}$, and interactions are given by the matrix Θ. Through choosing the tuning parameter ($\boldsymbol{\lambda}$), the constrain implies that if some components of the jth row of Θ are estimated to be nonzero, then the main effect $\boldsymbol{\beta}, \boldsymbol{j},$ will also be estimated to be nonzero, yielding a hierarchy model. Applying this method to develop an MCC index will allow the consideration of a larger number of potential predictors with improved predictivity and accuracy, as well as the consideration of hierarchical interactions among the predictors that is critical to the MCC concept.[122-124]

Ethnicity, MCC, and FO

Stroke disproportionately impacts minorities in the US. MAs, the largest subgroup of Hispanic Americans, the largest minority group in the US [131], have an increased stroke risk compared with NHWs,[132] a disparity that has not lessened over time.[4,133] Compared with NHWs, MAs have worse FO-90,[29,43,46,134] greater neurological deficits,[29,134] higher odds of exceeding the median length of hospital stay,[135] and are less likely to return to work[134] following a stroke. The underlying reasons for these ethnic disparities in stroke outcome are unknown, but differences do not appear to be driven by demographics, stroke risk factors or stroke severity.[29]

Regarding individual comorbidities, MAs stroke patients are more likely to have pre-existing hypertension, diabetes, and previous stroke/TIA, but are less likely to have atrial fibrillation and coronary artery disease compared with NHWs.[136-138] In two studies, no difference was found in the simple sum of 14 comorbidities between MA and NHW stroke patients.[29,139] However, since the prevalence of specific comorbid conditions could be different by ethnicity, the comorbidity spectrum likely differs in MAs and NHWs. A simple sum of comorbidities does not capture these differences or the fact that certain comorbidities might carry more weight than others with respect to predicting FO. Moreover, the role of MCC in stroke outcome may vary by ethnicity. MAs may have more barriers to the treatment of pre-stroke conditions and therefore may have more uncontrolled conditions or conditions with greater severity compared with NHWs.[43,140-142] For example, Hispanics have worse blood pressure control, even among those treated for hypertension, compared with NHWs,[143] and they are more likely to suffer from diabetic complications such as retinopathy and nephropathy.[144,145] Given known

ethnic differences in the prevalence of comorbid conditions as well differences in the treatment of comorbid conditions, MCC may play a role in the ethnic disparity in FO, but has not been investigated.

1.4 Significance

With the projected increase in the number of disabled stroke survivors,[24,25] it's crucial that new research is undertaken to identify factors that are associated with worse post-stroke FO. MCC is an important risk factor for poor physical function in the elderly [146,147] and will increase in prevalence with our aging population.[68,148,149] MCC adds complexities to patient management, the safety of regimens, adherence to clinical practice guidelines, as well as an assessment of clinical outcomes.[50,150,151] Identifying limitations in previously used MCC indices and improving the measurement of MCC could potentially improve the prediction of post-stroke FO, which has both clinical and research implications. Clinically, accurate prediction of post-stroke FO could aid in decision-making regarding the balance of side effects and benefits of aggressive treatments.[152,153] It would help patients, families, and physicians to have realistic expectations, set attainable rehabilitation goals, and plan for home adjustment, community support, or institutional care.[152,153] From a research perspective, prognostic factors are important in observational studies for case-mix adjustment and in clinical trials for consideration of imbalance in treatment arms.[152,153] Stratifying patients into prognostically comparable groups can increase power to detect clinically relevant differences.[154,155] From a public health standpoint, accurate prognosis helps to align the allocation of health care services and resources more closely with the overall disability burden in the population. Additionally, evidence of differential MCC burden by ethnicity

and the contribution of MCC to ethnic disparities in post-stroke FO would highlight the importance of preventing and treating MCC, which could lessen the ethnic disparity in post-stroke FO by improving the use of and benefit from treatment, rehabilitation, and post-stroke care, as well as reduce the risk of complications and new cardiovascular morbidity among stroke patients in all ethnic groups.

Figure 1.1 Known predictors and their associations with post-stroke functional outcome measured at different time point

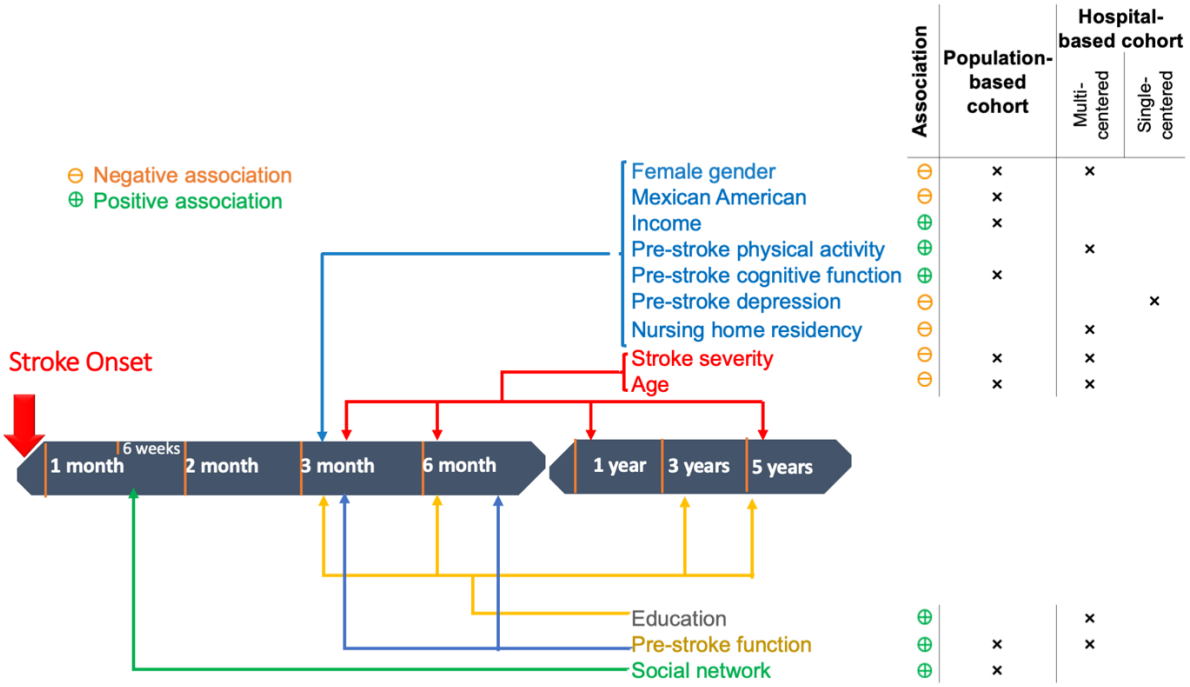


Figure 1.2 Conceptual model of MCC

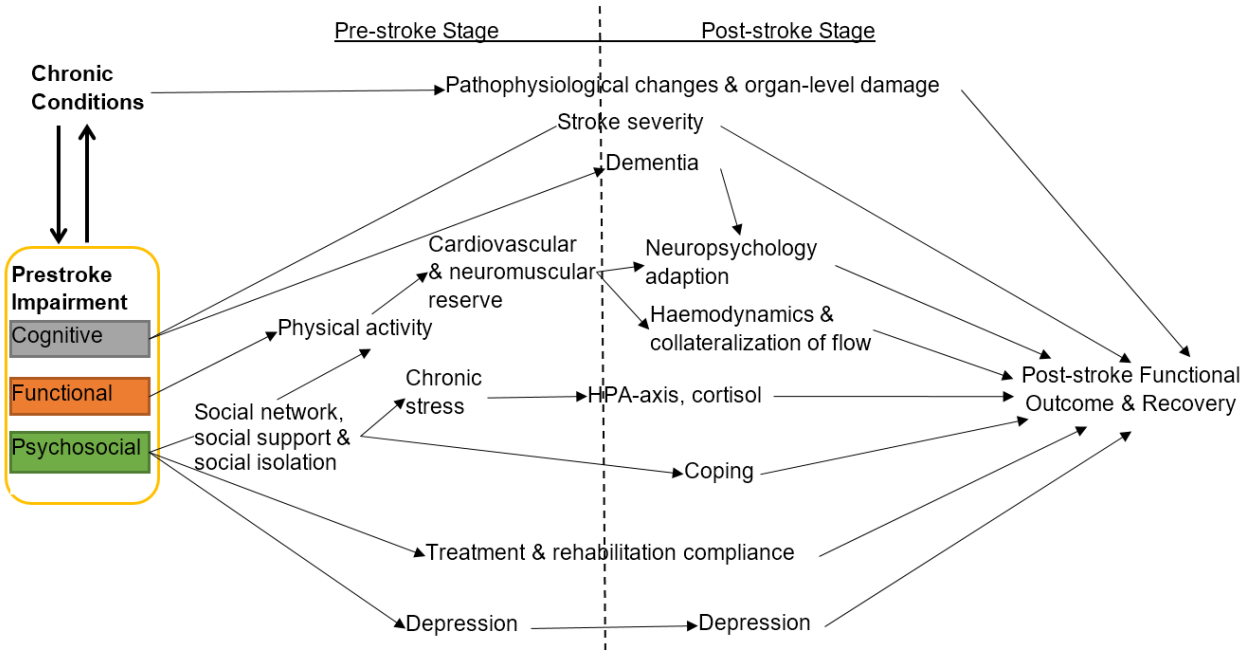


Table 1.1 Selected Work of MCC and Post-stroke FO

Author-year	Stroke type	Country	N	FO measure, time point	MCC Index	Association		Adjustment Factors
						Univariate	Multivariate	
Multi-centered, Hospital-based cohort								
Chang [32] 2016	IS	South Korea	2289	FIM, 6 mo	CCI	*	NS	Age, sex, stroke severity, health behaviors, education, pre-stroke functions, duration of hospitalization, and discharge functions
Goldstein 2004 [71]	IS	US	960	mRS, Hospital discharge	MCI	*	*	Age, stroke severity
Tessier [38] 2008	IS+HS	Canada	437	Combined FO indices 6 mo	CCI, FCI	*	NA	None
			235	Combined FO indices 3 mo	CCI, FCI	*	NA	None
Fischer [44] 2006	IS	Switzerland	266	mRS, 4 mo	CCI	*	NS	Stroke severity
Population-based, bi-ethnic cohort								
Lisabeth [156] 2014	IS	US	510	ADL/IADL, 90 days	Count	NA	*	Age, sex, stroke severity, SES, pre-stroke functional and cognitive status, treatment and previous stroke.
Rehabilitation (RH)-based cohort								
Liu [70] 1997	IS+HS	Japan	106	FIM, RH discharge	CCI	NS	NA	None
					LiuCI	NA	*	Age+ FIM at RH admission
Ferriero [78] 2006	IS+HS	Italy	85	FIM, RH discharge	LiuCI, COM-SI	*	*	FIM at RH admission, complications

*: significant negative association; NS: non-significant; NA: not applicable.
IS: Ischemic stroke; HS: Hemorrhagic stroke;
All are prospective studies except the Liu study;

Chapter 2: Multiple Chronic Conditions and Functional Outcome after Ischemic Stroke: A Systematic Review and Meta-Analysis

2.1 Introduction

Stroke is the 2th leading cause of death and the 3rd leading cause of disability worldwide.[157,158] About 37 to 45% stroke survivors are functionally dependent at 1 year after stroke.[159,160 7] More than 30% of stroke survivors are dependent in one or more activities of daily living (ADLs), such as feeding, dressing, bathing, grooming, toileting, transfers and mobility.[161] Limitations in ADLs are associated with decreased quality of life and increased use of hospital and nursing home care.[162,163] With the aging of the population and declining stroke mortality across the globe, there will be more stroke survivors having to cope with functional disability.[158,164] Ischemic stroke is the most prevalent stroke type, representing about 82% and 67% of all stroke events in high and low to middle income countries, respectively.[158,165] In the last two decades, thrombolytic treatments, such as intravenous tissue plasminogen activator and endovascular therapy, have improved functional outcome (FO) after ischemic stroke, but are received by only a small minority of stroke patients.[166] FO in non-thrombolysed stroke survivors has been largely unchanged.[19] Similarly, acute inpatient rehabilitation, which reduces long-term disability and enhances FO, is received by only a minority of stroke patients after the acute hospitalization.[20]

The aging of the world's population will also lead to an increase in the prevalence of multiple chronic conditions (MCC) at stroke onset.[49,167,168] MCC can be defined as the "concurrent presence of two or more medically diagnosed diseases in the same individual".[51] The presence of MCC contribute considerably to frailty and functional impairment,[49] primarily through pathophysiological changes and organ-level impairments.[60] Older patients with MCC who are physically and/or cognitively frail before stroke often have: 1) poorer cardiovascular and neuromuscular reserve due to decreased prestroke physical activity;[108] 2) worse hemodynamics and collateralization after arterial occlusions which impedes post-stroke functional recovery;[108] and 3) higher stroke severity with increased risk of post-stroke cognitive decline that hinders neuropsychological adaption after stroke.[90-92,95] In sum, MCC is considered to play an important role in diminishing the pre-stroke "reserve" that aids the neuropsychological process of post-stroke adaption and recovery.

A modest association between MCC and post-stroke FO in patients from inpatient rehabilitation was reported in a recent literature review;[169] however, this patient population is not a representative sample of the stroke patient population. The role of MCC in predicting FO in the broader stroke population is less well understood. In fact, although negative associations have been found, some studies showed that MCC was not independently associated with post-stroke FO when other important predictors (e.g. age and stroke severity) were adjusted for.[32,44,170] Therefore, this systematic review aims to summarize the findings in studies that have investigated the relationship between MCC and FO after ischemic stroke.

2.2 Methods

This study was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[171] The authors declare that all supporting data are available within the article.

Study Identification

A systematic search of publications from January 1, 1990, to December 3, 2017 was carried out in the PubMed and Embase databases for relevant studies by the first author. The following keywords were used with their synonyms or similar terms in the search: (“stroke,” or “cerebrovascular accident,”) and (“multiple chronic conditions,” or “multimorbidity,” or “comorbidity,” or “”comorbid conditions,” or “predict,” or “adjust,”) and (“functional outcome,” or “functional independence,” or “activities of daily living,” or “functional limitation,” or “functional disability,” or “functional recovery,” or “Rankin,” or “FIM,” or “mRS,” or “Barthel”). The search strategies (Table 2.1) were developed in conjunction with an experienced medical research librarian. MCC are often included in prognostic modeling as an adjustment factor and therefore, restriction on studies mentioning terms related to MCC or comorbidity may exclude studies that did not focus on but included MCC in their analysis. For this reason, the search strategies aimed to find studies that used multivariable modeling to predict FO which potentially included a MCC index as one of the covariates.

Selection Criteria

Studies were included if they satisfied the following criteria: 1) included adult ischemic stroke patients; 2) used a statistical method to analyze factors that are associated with FO; 3) used a global measurement of post-stroke FO; 4) used a cumulative measurement of MCC; 5) reported associations between MCC and FO; and 6) were published in English.

Studies were excluded if they met any of the following criteria: 1) conducted only in patients who had hemorrhagic stroke, transient ischemic attack (TIA), or stroke types other than ischemic stroke; or 2) MCC was assessed dichotomously (with/without multiple conditions) or as a count of the number of comorbid conditions; or 3) the adjusted association between MCC and FO was not reported; or 4) was a systematic or topic review, letter, case report or guideline; or 5) secondary analysis of clinical trials or cross-sectional studies. The first author screened all studies identified from the systematic search following these inclusion and exclusion criteria. Studies with questionable inclusion/exclusion criteria were resolved by consultation with a second reviewer.

Data Abstraction

A detailed data abstraction plan was developed by two authors (X.J., L.L.) before the first author extracted the following characteristics for each study: first author, year of publication, characteristics of the study population (country, number of subjects, age, stroke types, recruitment settings), study design, FO assessment (instrument and timing), MCC assessment, MCC-FO associations (univariate, multivariable) measured

by odds ratios, relative risks, correlation coefficients, etc., covariates included in the multivariable model, and model performance.

Quality Appraisal

A 26-item checklist was developed to examine the methodological quality of the included studies based on the risk of bias (RoB) from 6 domains: study participation, study attrition, MCC measurement, outcome measurement, statistical analysis, and clinical performance. This checklist was first developed using the guidelines from the Quality In Prognosis Studies (QUIPS) tool [172] and the framework for assessing internal validity discussed by Altman,[173] both geared to assess the risk of bias in studies of prognostic factors. Items that have been previously used in the quality appraisal for stroke prognostic studies were also considered.[174] The final checklist was tailored to consider items specific to the assessment of MCC.

Table 2.2 shows the quality criteria, which were graded as low (0 points) to high risk of bias (1 point) with a few items including a level of medium risk of bias (0.5 points). Items with insufficient information were assigned the high risk of bias (1 point). A total score ranging 0 to 26 was calculated by summing points from the 26 items for each study, and a study scored ≤ 5 points (approximately < 80% of the maximum score) was considered as a high-quality study.

Analysis

A meta-analysis was performed to synthesize the information on the association between MCC and FO using the DerSimonian and Laird random-effects model to calculate a pooled effect-size estimate of the log relative risks (RRs) or odds ratio

(ORs).[175] Assuming the effect-sizes and confidence intervals (CIs) reported by each study were based on a Wald-like test of the null hypothesis that the true RR or OR is equal to 1, the bounds of CIs were converted into the standard errors for each study. For studies that did not report CIs, p-values were converted into the corresponding z-values. The calculated log ORs or RRs and the z-values were then used to calculate the standard errors. When p-values were only reported as falling below a certain threshold (e.g., p<0.01) or said to be significant (p<0.05), the cutoff value was then used as a conservative estimate of the true p-value. Subgroup analysis was performed by MCC index used and the definition of poor outcome. Heterogeneity between studies was assessed using the Q-test, and the percentage of the variability in effect estimates due to heterogeneity between studies was reported using the I^2 index. Funnel plot and Egger's regression test[176] for small meta-analysis (<25 studies) was used to assess the risk of publication bias. All statistical analysis were performed using R v 3.5.0.

2.3 Results

Study Selection

The electronic database search resulted in 10,491 records, with an additional 42 articles identified from other sources. After the duplicate records were removed, 7,247 articles were screened. Among the 48 articles that assessed the MCC-FO relationship using valid MCC indices, 30 studies were ineligible. The reasons for exclusion are shown using the PRISMA flowchart (Figure 2.1).

No population-based cohort study was identified. Among the 18 eligible cohort studies, 6 were conducted in inpatient rehabilitation settings.[70,78,170,177-179] Patients

recruited from inpatient rehabilitation cohorts only represent a subset of the overall stroke population in the severity of comorbid conditions, cognitive status, and post-stroke functioning (e.g. ADLs, motor involvement).[70,78,170,177,178] Therefore, these studies were separately summarized (Table 2.3), and the qualitative and quantitative analysis of this review focused on the 12 hospital-based cohort studies.

Study Characteristics

Characteristics of the hospital-based cohort studies are summarized in Table 2.4. Among the 12 studies, 11 studies were prospective cohorts recruited during hospitalization[32,71,180-188]. There was 1 US [71] and 1 Asian cohort,[32] while the majority of cohorts were from European countries.[180-189]

All studies were published in the last ten years except for one,[71] with the number of participants ranging from 131 to 2,289. The assessment of the MCC-FO relationship was restricted to ischemic stroke patients in 9 studies,[32,71,180,182-184,186,187,189] while the rest were mixed cohorts that included hemorrhagic stroke or TIA patients in addition to ischemic stroke patients. Two studies excluded patients with previous stroke.[32,189] One study was conducted in veterans.[71] In the majority of the studies, the mean/median age of the participants was between 70 and 75 years old.[180-188]

Risk of Bias Assessment

The median risk of bias total score was 4.75 points for the hospital-based cohorts (range 1[187] -9 points[182]). Seven of the 12 studies were of high quality with low risk of bias.[180,183-185,187-189] The scores of the included studies were detailed in Table 2.5.

Outcome Assessment

The modified Rankin scale (mRS) measured at 1,[189], 3[180,181,183,184,187] or 6[185] months after stroke onset was the most commonly used measure for FO (6 out of 12 studies). Other FO measures, including the Functional Independence Measure (FIM),[32] SF-12 physical functioning domain/component score,[186] or the Barthel Index (BI),[188] were also used. Two studies assessed FO at hospital discharge using mRS[71] or the number of impaired basic ADLs.[182]

Among studies that assessed mRS at 3 to 6 months[180,181,183-185,187], the proportion of patients with favorable outcome (mRS 0-2) was similar, ranging from 54.0%-61.7%, with the exception of one that included TIA patients and reported a higher proportion (68.7%).[181] Patients from these cohorts had similar baseline stroke severity (median NIHSS score, 5-6) with the exception of 1 study that only included thrombolyzed patients (median NIHSS score of 14).[183]

MCC Assessment

Two comorbidity indices were used in the hospital-based studies. Half of the studies used the Charlson Comorbidity Index (CCI).[32,180,182,185,186,188] A stroke-adjusted version of the CCI or the Modified Charlson Index (mCCI) was used in the remaining studies. Briefly, CCI includes 19 chronic conditions weighted by their strength of associations with mortality.[72] CCI was originally developed as a prognostic indicator in patients with a variety of conditions and validated in breast cancer patients.[72] mCCI is similar but excludes cerebrovascular disease and hemiplegia.[71]

Associations between MCC and FO

The MCC-FO associations were investigated using multiple logistic regression and linear regression models, and the strength of multivariable associations were reported as ORs [32,71,180-185,187-189] or a regression coefficient (β).[186] All studies adjusted for age and stroke severity measured by NIHSS, with the exception of two.[182,186]

Among the 7 high-quality studies, 3[180,185,187] of 5 studies that measured FO using mRS at 3-6 months found significant associations between MCC and poor FO, after adjusting for confounders including age and stroke severity. Specifically, the odds of poor FO were 5%,[180] 11%,[185] or 31%[187] higher with every 1 point increase in CCI or mCCI. The other 2 high-quality studies that measured mRS at 1 month or BI at 6 months failed to find significant associations with mCCI after adjusting for age and NIHSS.[188,189]

Among studies with lower methodological quality,[32,71,181,182,186] MCC was found to be significantly associated with poor FO measured by mRS[71] and ADL impairments[182] at hospital discharge; SF-12 at 6 months[186] but not FIM measured at 6 months.[32] Therefore, significant associations between MCC and poor FO after adjustment were reported in half of the hospital-based cohort studies.

Data Synthesis and Meta-Analysis

Significant heterogeneity existed among the studies in terms of study population, outcome and MCC measure, as well as analytical methods and covariate adjustment for the multivariable models. Consequently, quantitative analysis was limited to 7 hospital-based cohorts that used similar MCC and outcome measures, namely a continuous

MCC measure using mCCI/CCI and a dichotomized FO measure using mRS.[71,180,181,183-185,187] Five of the studies included in the meta-analysis were deemed high-quality studies.

The pooled ORs overall and by subgroups are shown in Figure 2.2. MCC was significantly associated with poor FO (pooled OR=1.11; 95%CI, 1.05-1.18). In subgroup analysis, the pooled OR for studies using mCCI was somewhat larger than that for studies using CCI (pooled OR=1.17 vs. 1.07). Associations were statistically significant in both subgroups defined by MCC measure. A significant association was found for studies that defined poor outcome as mRS 2-6 (pooled OR=1.13; 95%CI, 1.07-1.19) and for studies that defined poor outcome as mRS 3-6 (pooled OR=1.12; 95%CI, 1.00-1.25). Heterogeneity between the 7 studies was low to moderate, with 45% of the variability in ORs due to heterogeneity between studies (=45%, p=0.1). The funnel plot demonstrated some asymmetry (Figure 2.3), and the Egger's regression test showed evidence of publication bias (p= 0.0153).

2.4 Discussion

This review investigated the association between MCC and post-stroke FO in the general stroke population. In the absence of population-based studies, the review focused on single and multi-centered, hospital-based cohort studies. Two indices, CCI and mCCI, were used to assess MCC burden in the examination of the multivariable adjusted MCC-FO association. Although the outcome assessment varied in terms of scale and timing of the assessment, half of the twelve included studies reported a significant association between increased MCC and worse FO. In our meta-analysis

that included primarily high-quality studies with low to medium heterogeneity, a significant association between increased MCC and worse FO was also found. Therefore, the current review supports that MCC is negatively associated with post-stroke FO.

Through our review, we identified gaps and limitations in the current literature regarding the association of MCC and post-stroke FO, which could inform future research directions. Specifically, there is potential for improving the prediction of FO through the development of more refined MCC indices so that the impact of MCC can be assessed more accurately. Key areas for developing refined indices include: 1) consideration of a larger number of conditions with a focus on conditions relevant for function, 2) consideration of the possible synergistic effects of conditions, 3) consideration of the severity of conditions, 4) consideration of prestroke function, and 5) development of new indices in population-based stroke studies reflective of the broader stroke population. Limitations of the current research in each of these areas are briefly discussed.

The predominantly used MCC indices, CCI and mCCI, consider a limited number of conditions originally included to predict mortality,[71,72] and the weights used reflect the degree of their impact on mortality rather than function.[70] Importantly, conditions that predict function in the elderly, including osteoarthritis/arthritis, hypertension, visual and hearing impairments, and atrial fibrillation, are not captured in CCI or mCCI.[60,78] This could result in an observed smaller range of values in MCC indices, and thus a comparatively smaller proportion of variance in FO explained by MCC than that in the clinical reality.

It is known that certain combinations of conditions can have a synergistic effect on risk of disability;[51,65,66] however, these interactions among MCC are not captured by currently used MCC indices.[51] The development of novel MCC indices that include a greater number of conditions, as well as the possible synergistic interactions between conditions, would be challenging with conventional statistical methods, such as multivariable regression, due to the high-dimensionality of the data. More contemporary methods, such as machine learning techniques that have the ability of performing simultaneous model selection and estimation may be an ideal approach for developing more refined MCC indices in the future.[125]

Neither CCI nor MCCI consider the severity of conditions when measuring MCC burden. Previous research conducted with patients during acute rehabilitation found a stronger association between FO and MCC measures with severity weights compared to MCC measures without severity weights.[100] Inclusion of weights allows an index to quantify the difference between patients in MCC burden driven by differences in severity levels of the conditions rather than condition types alone. Unfortunately, such indices have only been developed in select rehabilitation populations limiting their utility.

While studies examining the association between MCC and FO were often adjusted for age and stroke severity (NIHSS), prestroke function was less often considered in the analysis. Prestroke functional status largely defines the patients' post-stroke FO. Prestroke cognitive and physical function play inseparable parts in the neuropsychological process of post-stroke adaption and recovery.[106] Future research should consider patients' prestroke status in the analysis, or consider inclusion of pre-stroke functional and cognitive status as part of MCC as has been done in research of

the general population.[104] To date, none of the currently used MCC indices were developed in population-based studies which reflect the full spectrum of chronic conditions in the stroke population. Some indices were developed only in rehabilitation patients, which represent less than one-third of the total stroke population.[20] Because patients with more severe comorbid conditions are often excluded from rehabilitation, patients from inpatient rehabilitation have a different distribution and level of severity in comorbid conditions compared to the majority of stroke patients,.[78,179] Further, MCC indices used in rehabilitation studies often mix post-stroke complications with pre-stroke comorbidities (e.g. the Liu comorbidity index),[70,78,177] which limits the applicability of their findings to early FO prediction during acute stroke hospitalization when complications of stroke may still be evolving. Thus, new MCC indices developed and validated in population-based studies with thorough adjustment for confounding factors are needed to minimize bias and better predict FO.

Another limitation of existing studies is the use of global disability measures, predominantly the mRS, which while useful for distinguishing broad categories of disability, does not measure function related to ADLs and is not sensitive to smaller differences in FO between patients.[190] For example, a patient who cannot walk independently scores 4 for mRS, whether or not he/she also needs help in eating, going to the toilet, and bathing. Dichotomizing the mRS score also adds to this insensitiveness of partial differences between patients (mRS 3 vs. 5).[191] The mRS score does not measure post-stroke impairments in cognitive function, language, vision, emotion and pain, although these deficits could have a substantial impact on performing ADLs. Post-stroke cognitive function is especially relevant to the success of stroke rehabilitation.

With a growing number of stroke patients with cognitive impairment, measuring cognitive function is becoming a necessary part of post-stroke FO assessment. In addition, using mRS to measure FO is a limitation due to its low inter-rater agreement, which can range from 0.25 to 0.74 depending on whether a structured interview is used.[191] Further, studies using mRS often include death in the definition of poor FO making it difficult to distinguish the impact of MCC on function versus mortality. More detailed measures of post-stroke FO, including FIM, were seldom used in the hospital-based studies. Future research using more refined FO measures is likely to provide a more nuanced understanding of the links between MCC and FO in stroke patients.

Our study is not without limitations. First, as the funnel plot and the Egger's regression test indicated, publication-bias may exist in the included studies, where significant MCC-FO associations are more likely to be published, presented and subsequently included in our meta-analysis. Second, we excluded studies that used present/absent or a count of the number of comorbid conditions as MCC measurement, the discussion of which is beyond the scope of this work. Third, we excluded studies conducted purely among other stroke types, such as intracerebral/subarachnoid hemorrhage and lacunar infarction. Therefore, caution should be taken generalizing our findings to patients with other types of stroke.

In conclusion, we found that greater pre-stroke MCC was associated with worse post-stroke FO in hospital-based cohorts after adjusting for stroke severity and age. New MCC measures which capture conditions that are more relevant for predicting post-stroke FO among stroke survivors are needed. A greater understanding of the association between MCC and post-stroke FO could contribute to more personalized

prognosis regarding FO, greater attention to prevention and management of MCC, and an understanding of the specific rehabilitation needs of stroke patients with MCC to aid in the successful recovery of stroke patients.

Figure 2.1 PRISMA Flow Chart of Literature Search

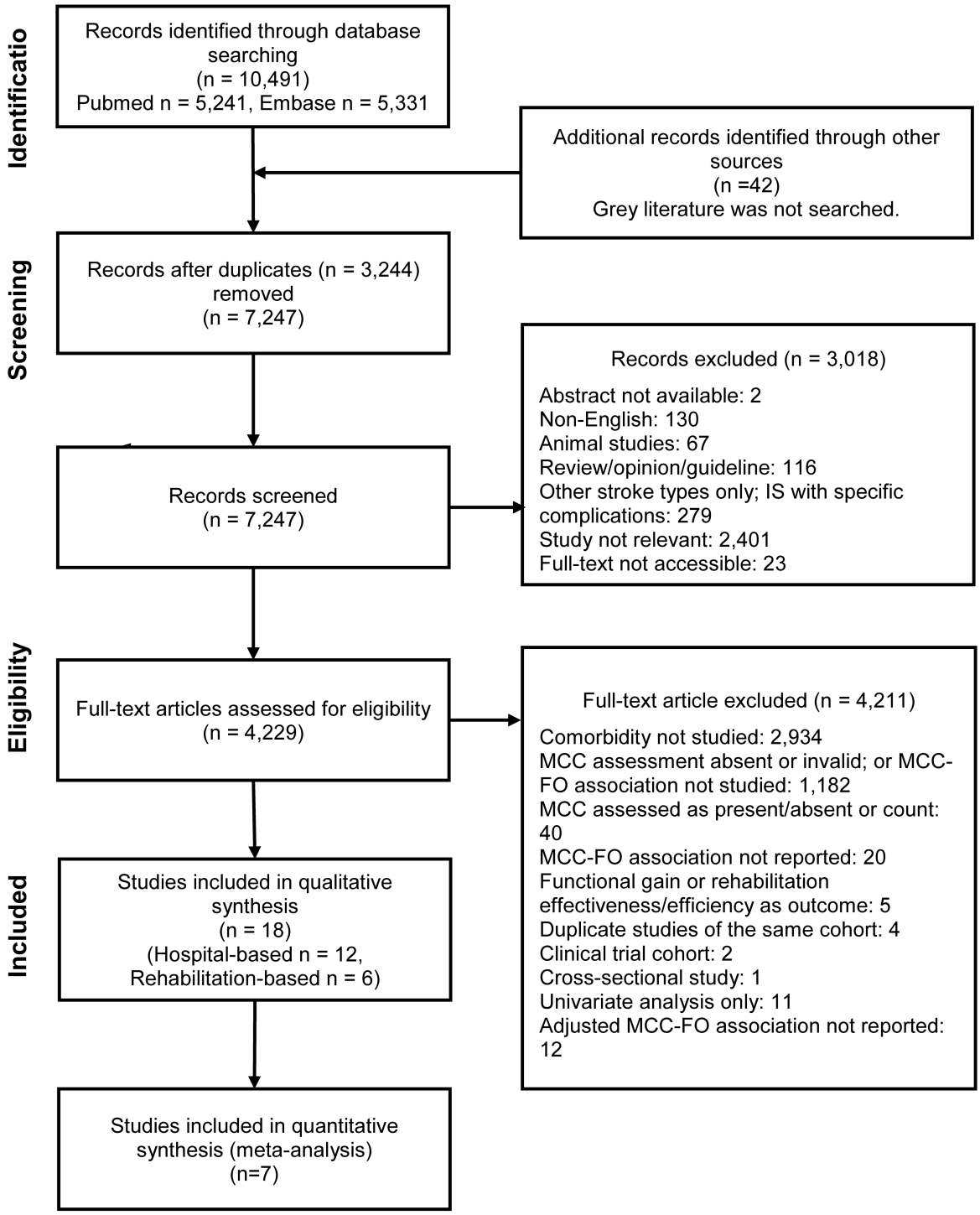


Figure 2.2 Forest Plot for Odds Ratios of Poor Functional Outcome

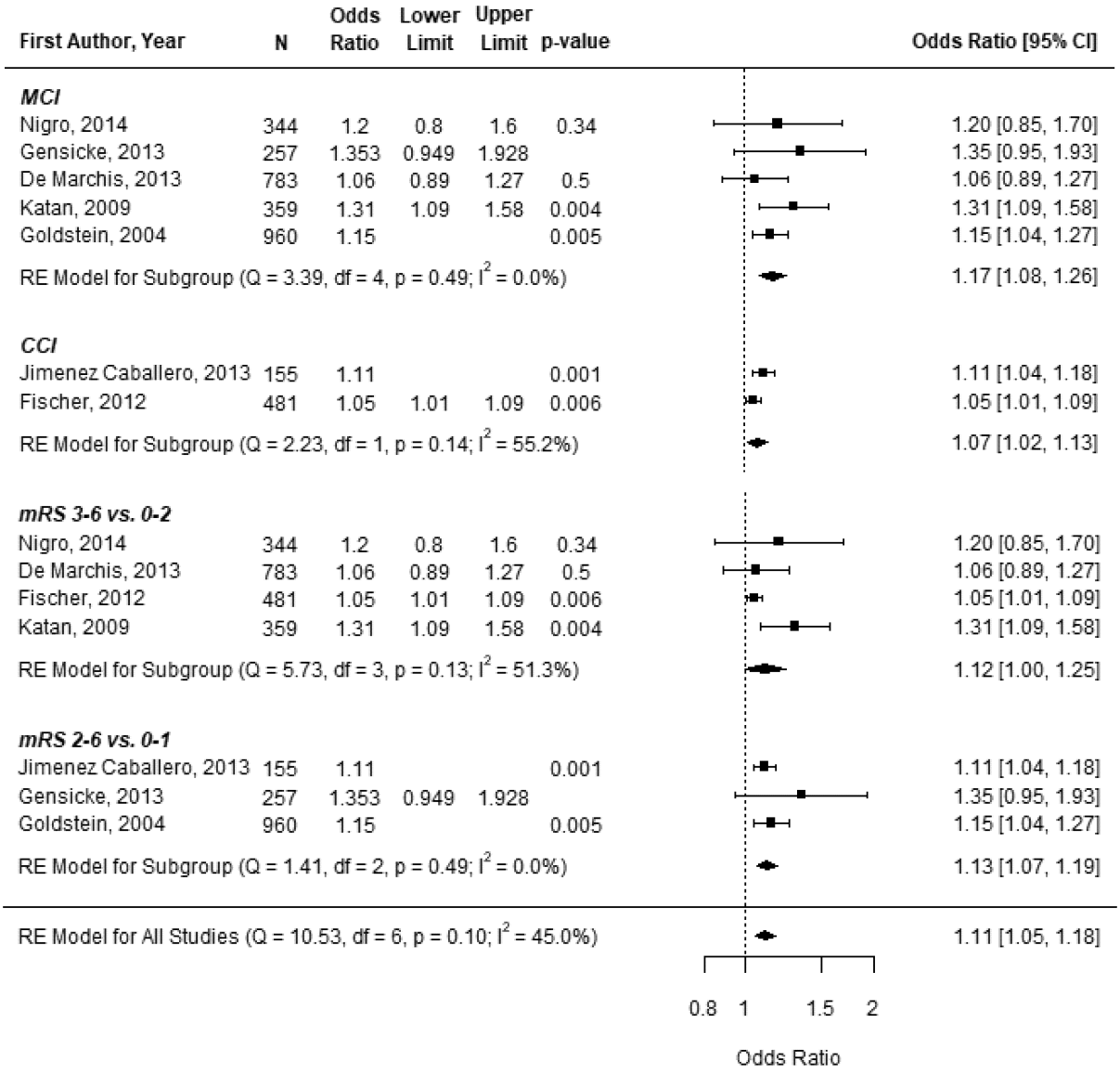


Figure 2.3 Funnel Plot for Included Studies

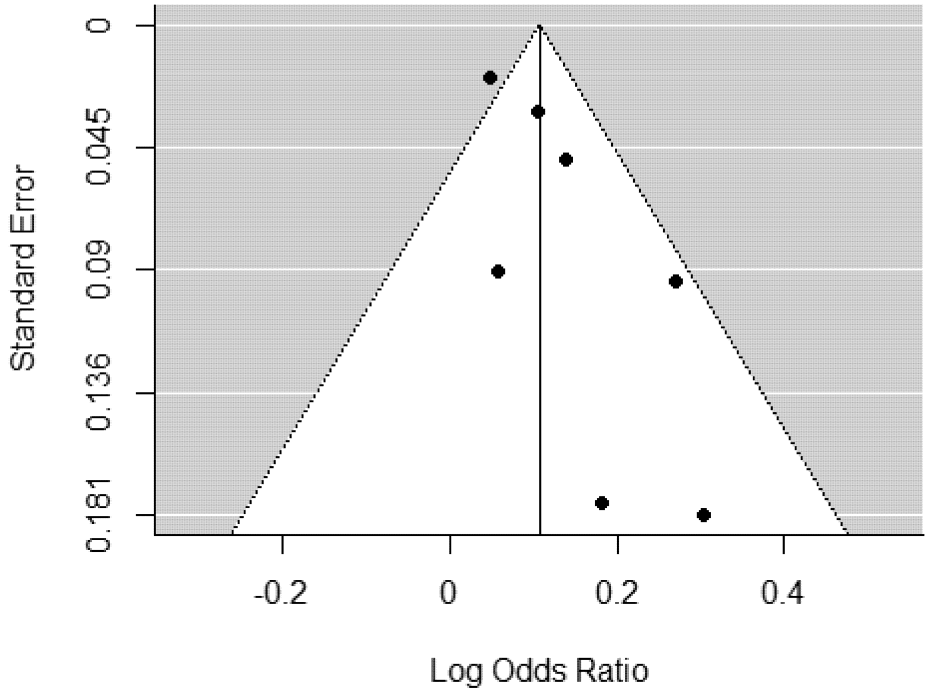


Table 2.1 Search Strategy

Pubmed (n=5241)	
Stroke	(stroke[mh] OR stroke[Title])
Comorbidity	(multiple chronic conditions[mh] OR multiple chronic conditions[tiab] OR multimorbidity[tiab] OR comorbidity[mh] OR comorbidity[tiab] OR comorbid conditions[tiab] OR comorbid diseases[tiab] OR comorbid illnesses[tiab] OR premorbid condition[tiab] OR premorbid disease[tiab] OR premorbid illness[tiab] OR pre-morbid condition[tiab] OR pre-morbid disease[tiab] OR pre-morbid illness[tiab] OR preexist condition[tiab] OR preexist disease[tiab] OR preexist illness[tiab] OR pre-exist condition[tiab] OR pre-exist disease[tiab] OR pre-exist illness[tiab] OR pre-existing condition[tiab] OR pre-existing disease[tiab] OR pre-existing illness[tiab] OR Predict[tiab] OR Predictor[tiab] OR Predicting[tiab] OR Prediction[tiab] OR Predictive[tiab] OR adjust*[tiab] OR Multivariate Analysis[MeSH Terms] OR regression analysis[MeSH Terms])
Functional outcome	(Disability Evaluation[MeSH Terms] OR Recovery of Function[MeSH Terms] OR Activities of Daily Living[mh] OR Functional outcome[tiab] OR Functional independence[tiab] OR Functional independent[tiab] OR Functional dependence[tiab] OR Functional dependent[tiab] OR Functional limited[tiab] OR Functional limitation[tiab] OR Functional impairment[tiab] OR Functional impaired[tiab] OR Functional disabled[tiab] OR Functional disability[tiab] OR Functional ability[tiab] OR Functional recovery[tiab] OR Rankin[tiab] OR mRS[tiab] OR FIM[tiab] OR Barthel[tiab])
Filter	Filters: Publication date from 1990/01/01 to 2017/12/03
Embase (n=5331)	
Stroke	('cerebrovascular accident'/exp OR 'stroke':ab,ti)
Comorbidity	('multiple chronic conditions':ti,ab,kw OR 'multimorbidity':ti,ab,kw OR 'comorbidity':ti,ab,kw OR 'comorbid conditions':ti,ab,kw OR 'comorbid diseases':ti,ab,kw OR 'comorbid illnesses':ti,ab,kw OR 'premorbid condition':ti,ab,kw OR 'premorbid disease':ti,ab,kw OR 'premorbid illness':ti,ab,kw OR 'pre-morbid condition':ti,ab,kw OR 'pre-morbid disease':ti,ab,kw OR 'pre-morbid illness':ti,ab,kw OR 'preexist condition':ti,ab,kw OR 'preexist disease':ti,ab,kw OR 'preexist illness':ti,ab,kw OR 'pre-exist condition':ti,ab,kw OR 'pre-exist disease':ti,ab,kw OR 'pre-exist illness':ti,ab,kw OR 'pre-existing condition':ti,ab,kw OR 'pre-existing disease':ti,ab,kw OR 'pre-existing illness':ti,ab,kw OR 'predict':ti,ab,kw OR 'predictor':ti,ab,kw OR 'predicting':ti,ab,kw OR 'prediction':ti,ab,kw OR 'predictive':ti,ab,kw OR 'adjust':ti,ab,kw OR 'adjustment':ti,ab,kw OR 'adjusting':ti,ab,kw OR 'adjusted':ti,ab,kw OR 'multivariate analysis':ti,ab,kw OR 'regression analysis':ti,ab,kw)
Functional outcome	('disability':ti,ab,kw OR 'recovery of function':ti,ab,kw OR 'activities of daily living':ti,ab,kw OR 'functional outcome':ti,ab,kw OR 'functional independence':ti,ab,kw OR 'functional independent':ti,ab,kw OR 'functional dependence':ti,ab,kw OR 'functional dependent':ti,ab,kw OR 'functional limited':ti,ab,kw OR 'functional limitation':ti,ab,kw OR 'functional impairment':ti,ab,kw OR 'functional impaired':ti,ab,kw OR 'functional disabled':ti,ab,kw OR 'functional disability':ti,ab,kw OR 'functional ability':ti,ab,kw OR 'functional recovery':ti,ab,kw OR 'rankin':ti,ab,kw OR 'mrs':ti,ab,kw OR 'fim':ti,ab,kw OR 'barthel':ti,ab,kw)
Filter	AND [article]/lim AND [english]/lim AND [1-1-1990]/sd NOT [3-12-2017]/sd

Table 2.2 Quality Appraisal Checklist

Risk of Bias Assessment of the Included Studies		
Evaluation of	Scale*	Risk of Bias Criteria
1. Study Participation		
D1 Source population	H/M/L	Low if the study was population or community-based; Medium if the study was multi/single-centered and hospital-based High if the study was multi/single-centered and rehabilitation-based; or was done in veterans/ad hot analysis of clinical trials
D2 Prospective design	H/L	Low when a prospective cohort design was used High when retrospective or cross-sectional study design was used;
D3 Inclusion and exclusion criteria	H/L	Low if all ischemic stroke cases from the study time frame were eligible; Medium if patients were excluded due to factors other than their status of comorbidity, stroke severity, age, treatment or rehabilitation; High if patients were excluded due to the status of comorbidity, stroke severity, treatment or rehabilitation; or if patients were excluded due to other restriction on age (other than age ≥18);
D4 Recruitment	H/L	Low if all recruitment information (place, time-period, and methods used to identify ischemic stroke cases) were reported. High if any one aspect of the recruitment information was missing.
D5 Important baseline characteristics of the study population	H/M/L	Low if all of the following key characteristics of the study population were described, including the distributions of gender, age, stroke type, stroke severity and history of strokes*; Medium if any one of the key characteristics was missing; High if two or more of the key characteristics were missing; *history of strokes was adequate when the study reported if patients with 'history of stroke', 'recurrent stroke' or 'cerebrovascular disease' as a comorbidity were included/excluded;
2. Study attrition		
A1 Proportion of loss to follow-up	H/L	Low if the number of loss to follow-up is ≤20%.
A2 Reasons for loss to follow-up	H/L	Low if reasons for loss to follow-up were specified, or there was no loss to follow-up High if reasons for loss to follow-up were not specified even if the number of loss to follow-up is ≤20%.
A3 Methods dealing with missing data	H/M/L	Low if methods of dealing with missing values were presented (e.g. multiple imputations), or there were no missing values. Medium if the study conducted using complete-case analysis and the proportion of missing data is 5% or less;[192-194] High if the complete-case analysis was conducted and the proportion of missing data is more than 5%;[192-194]
A4 Comparison completers and non-completers	H/L	Low if there were no significant differences between participants who completed the study and who did not, concerning key characteristics gender, age, and stroke severity, MCCs and functional status, or there was the number of follow-ups is ≤20%), or if methods (e.g. inverse probability weighting) or sensitivity analysis were used to consider loss to follow-up.
3. MCC measurement		
M1 Definition of MCC	H/L	Low if the measurement of MCC was clearly defined.
M2 Temporality	H/L	Low if MCC conditions were identified before or during the index stroke; High if MCC conditions were identified at rehabilitation admission;
M3 MCC weighting	H/L	Low if conditions included in the MCC measurement indices were weighted in the calculation of an MCC score;
M4 Scoring scheme and cut-off points	H/L	Low if the scoring scheme for MCC were defined, including cut-off points and rationale for cut-off points was given;

M5 presentation	H/L	Low if frequencies, percentages, mean (SD/CI), or median (IQR) were reported for MCC, or for each condition included in the MCC index.
4. Outcome measurement		
O1 Definition of outcome	H/L	Low when the functional outcome was clearly defined.
O2 Functional outcome assessment	H/L	Low when there's no differential assessment for patient included. High when outcome assessment was different for included patients, or if the proxy were used in the outcome assessment.
O3 Scoring scheme and cut-off points described	H/L	Low if the scoring scheme of the functional outcome was described, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization or classification.
O4 Appropriate timing for functional outcome measurement	H/L	Low if the functional outcome was measured at a fixed time-point after stroke onset (e.g. 3 or 6 months); High if functional outcome measurement was obtained at hospitalization and rehabilitation discharge.
O5 Data presentation	H/L	Low if frequencies, percentages or mean (SD/CI) or median (IQR) were reported of the functional outcome measure.
5. Statistical analysis		
S1 Sufficient sample size	H/L	Low if in multivariate logistic regression analysis number of patients with a positive or negative outcome (event) per variable was adequate, i.e. was equal to or exceeds 10 events per variable in the multivariable model (EPV) [195], or in case of linear regression analysis, N ≥ 104+m, where m is the number of predictor variables.[196,197]
S2 MCC presentation in univariate analysis	H/L	Low if univariate crude estimates and confidence intervals (β/SE, OR/CI, RR, HR) were reported for MCC; High when only p-values or correlation coefficients were given, or if the univariate analysis was not performed at all.
S3 MCC presentation in multivariable analysis	H/L	Low if for the multivariable models point estimates with confidence intervals (β/SE, OR/CI, RR, HR,) were reported for MCC; High when only p-values or correlation coefficients were given, or if no multivariable analysis was performed at all.
S4 MCC analyzed continuously	H/L	Low if MCC was analyzed continuously (not dichotomously or categorically) in the multivariable model.[173]
6. Study confounding		
C1 Controlling for important confounders	H/M/L	Low if both age and stroke severity were controlled in the multivariable model; Medium if either age or stroke severity was controlled; High if neither age nor stroke severity was controlled;[174] or if no multivariable analysis was performed at all.
C2 Confounding measurement	H/L	Low if stroke severity was measured in a valid and reliable way to reflect patients' neurological status using either the National Institutes of Health Stroke Scale (NIHSS) or the Canadian Neurological Scale (CNS).[174] High if stroke severity was assessed in other measurements, or if stroke severity was not controlled, or if no multivariable analysis was performed at all.
7. Clinical performance		
P1 Clinical performance	H/L	Low if article provided information concerning ≥1 of the following performance measures: discrimination (e.g. ROC), calibration (e.g. Hosmer-Lemeshow statistic), explained variance, clinical usefulness (e.g. sensitivity, specificity, PPV, NPV)
*H=High risk of bias (1 point); M=Medium risk of bias (0.5 point); L=low risk of bias (0 point) Total score: The higher the worse for study quality (high risk of bias);		

Table 2.3 Characteristics of the eligible rehabilitation-based studies

First author	Year	Country	N	Source population	Prospective Study Design	Exclusion criteria	Year of admission	Stroke type	MCC measure
Liu	1997	Japan	106	Single-centered	N	Bilateral hemiplegia, ataxia, or no motor involvement	1994-1995	IS 52 + ICH 51 +IS-2rd to-SAH	LiuCI-w CCI
Desrosiers	2002	Canada	102	Single-centered	Y	Unable to consent; in program<10d; **severe comorbidities;** lived far away; too sever impaired to be compliant with rehab	1997-1999	mixed	LiuCI-modified version
Duncan	2002	US	123 123 122 66	Multi-centered; Veterans	Y	Including: live place before stroke; medical conditions related to survival; ADLs; post stroke inpatient care/rehab;	1998 -1999	IS 144 + HS 12 + both 1	CCI
Desrosiers	2006	Canada	66	Single-centered	Y	Cognitive status; severe comorbidities	1997-1999	mixed	CCI-customized: adding communication, oral expression and urinary and faecal incontinence
Ferriero	2006	Italy	85	Single-centered	Y	ADLs;prestroke independence; excluded: bilateral hemiplegia, brain-stem or cerebellar stroke and without motor involvement	2003	IS 70+HS 15	COM-SI LiuCI
Karatepe	2008	Turkey	94	Single-centered	Y	Bilateral hemilplegia; lack of motor involvement; history of stroke		mixed	LiuCI

First author	Outcome Measure	Outcome follow-up	Univariate analysis	Significance	Effect Estimate (CL)	P	performance
Liu	FIM	Discharge	Y	Y	r= -0.499	<0.0001	NR
	FIM	Discharge	Y	N	r= -0.197	0.1036	NR
Desrosiers	Handicap level (LIFE-H)	6 months after discharge	Y	Y	r= -0.32	0.001	NR
Duncan	FIM-motor	6 months	N				
	SF-36 physical dimension		N				
	Lawton IADL scale		N				
	SIS physical domain	6 months+2 weeks	N				
Desrosiers	LIFE-H daily activities subscore	2-4 years	N				
Ferriero	FIM	Discharge	Y	Y	r= -0.35	0.001	NR
			Y	Y	r= -0.39	0.0004	NR
Karatepe	FIM	Mean follow-up: ~32.7+28 days	Y	Y	r= -0.18	<0.01	NR

First author	Multivariate analysis	Significance	Model	Effect Estimate (CL)	P	Adjustment	Model Performance
Liu	Y	Y	Linear	β= -0.346 (CL NR)	<0.001	days from onset to admission; admission FIM; tape bisection task(TAPE); #=4	Adjusted R^2=0.798
	N						
Desrosiers	Y	Y	Linear	β= -0.03 ()	0.049	Age; Affect-depression manifestation measured by Beck Depression Inventory (BDI); Lower extremity coordination; Length of stay in rehab; Balance;#=6	adjusted R2=0.68
Duncan	Y	N	Linear	β= -1.4 (1.37)	0.3091	age; race (% white); full social support; MMSE at baseline; FIM-motor at baseline; Acute/postacute compliance; #=9	R2=0.38
	Y	N	Linear	β= -1.13 (2.14)	0.5971		R2=0.24
	Y	N	Linear	β= -0.24 (0.41)	0.5565		R2=0.41
	Y	N	Linear	β= -0.24 (2.52)	0.9232		R2=0.28
Desrosiers	Y	Y	Linear	β= -0.14 (CL NR)	<0.001	Age; motor coordination (Finger–Nose test); Upper extremity abilities (four unilateral and five bilateral tasks of the TEMPA); Affect-depression manifestation (Beck Depression Inventory); #=5	Adjusted R^2=0.53
Ferriero	Y	Y	Linear	β= -6.64 (CL NR)		admission FIM; complications during stay; #=3	Adjusted R^2=0.82
	Y	Y	Linear	β= -1.14 (CL NR)		admission FIM; #=2	Adjusted R^2=0.80
Karatepe	Y	Y	Linear	β= 6.34 (3.32-9.36)	<0.001	FIM at baseline (mean=32.7 d after stroke); Stroke severity (CNS at baseline ~32.7d); #=3	R^2=0.553

Table 2.4 Characteristics of the eligible hospital-based studies

First author	Year	Country	N	Source population	Prospective Study Design	Exclusion criteria	Year of admission	Stroke type
Goldstein	2004	US	960	Multi-centered; Veterans	Y		1995-1997	IS
Katan	2009	Switzerland	359	Single-centered	Y		2006-2007	IS
Fischer	2012	Switzerland	481 433	Multi-centered	Y		2007-2008	IS
De Marchis	2013	Switzerland & Germany	783	Multi-centered	Y		2009 -2011.	IS
Gensicke	2013	Switzerland	257	Single-centered	Y	Non-IVT patient	1988-2007	IS
Jimenez Caballero	2013	Spain	155	Single-centered	Y		2009-2011	IS+8.6%SICH
Tuttolomondo	2013	Italy	843	Multi-centered	Y		1993, 1995, 1997, and 1998;	IS
Nigro	2014	Switzerland	344 342	Single-centered	Y	Non-consent	2006-2007	IS 342 + TIA 99
Denti	2015	Italy	297	Single-centered; geriatric patients	N	Age; severe comorbidities; standardized clinical pathway (CPW)	2001-2011	IS
Lopez-Espuela	2015	Spain	131	Single-centered	Y	NIHSS=0; premorbid mRS>2; non-consent to participate	2010	IS
Chang	2016	Korea	2289	Multi-centered	Y	onset of symptoms>7 days; non-consent	2012-2014	IS
López-Espuela	2016	Spain	152	Single-centered	Y	non-consent	2010	IS 160 + HS 15

First author	MCC measure	Outcome Measure	Outcome follow-up	Univariate analysis	Significance	Effect Estimate (CL)	P	performance
Goldstein	MCI ≥ 2	mRS 2-6 vs. 0-1	Discharge	Y	Y	NR	<0.001	NR
	MCI			N				
Katan	MCI	mRS 0-2 vs. 3-6	90 days	Y	Y	OR=1.34(1.15-1.56)	<0.0001	NR
Fischer	CCI	mRS 0-2 vs. 3-6	3 months	N				
	CCI		12 months	N				
De Marchis	MCI	mRS 3-6 vs. 0-2	90 days	Y	Y	NR	<0.001	NR
Gensicke	MCI	mRS 0-1 vs. 2-6	3 months	Y	Y	OR=1.604(1.187-2.167)	<0.05	NR
			Long-term; median ~3y	Y	Y	OR=1.342(1.014-1.774)	<0.05	NR
Jimenez Caballero	CCI ≥2	mRS≥2 vs. 0-1	6 months	Y	Y	OR=1.373(CL NR)	0.025	NR
	CCI			N				
Tuttolomondo	CCI	no vs. 1-2 ADL impairment	Discharge	Y	Y	NR	<0.005	NR
	CCI<2			Y	N	NR	0.71	NR
Nigro	MCI	mRS>2	90 days	Y	Y	OR=1.3(1.1-1.6)	<0.001	NR
			1 year	Y	Y	OR=1.4(1.2-1.6)	<0.001	NR
Denti	MCI ≥ 2	mRS 3-6	1 months	Y	N	OR=1.62(0.98-2.68)	0.06	AUC= 0.56
		mRS 3-5		Y	N	OR=1.45(0.86-2.45)	0.17	
	new index for poor outcome (mRS 3-6)	mRS 3-6		Y	Y	OR=2.74(1.64-4.59)	0.0001	AUC= 0.64
	new index for disability (mRS 3-5)	mRS 3-5		Y	Y	OR=2.76(1.62-4.72)	1.0001	
Lopez-Espuela	CCI	SF-12 physical functioning domain (a component of PCS)	6 months	N				
		SF-12 physical component score (PCS)		N				
Chang	CCI	FIM	6 months	Y	Y	OR=0.902(0.860-0.946)	<0.001	NR
López-Espuela	CCI	BI (grouped for 5 levels of independency)	6 months	Y	N	OR=1.233(0.962-1.579)	0.1	NR

First author	MCC measure	Outcome Measure	Multivariate analysis	Significance	Model	Effect Estimate (CL)	P
Goldstein	MCI ≥ 2	mRS 2-6 vs. 0-1	Y	Y	Logistic	OR=~1.36 (CL NR)	0.038
	MCI		Y	Y	Logistic	OR=~1.15 (CL NR)	<0.005
Katan	MCI	mRS 0-2 vs. 3-6	Y	Y	Logistic	OR=1.31 (1.09–1.58)	0.004
Fischer	CCI	mRS 0-2 vs. 3-6	Y	Y	Logistic	RR=0.95 (0.92-0.99)	0.006
	CCI		Y	Y	Logistic	RR=0.96 (0.91-0.98)	0.011
De Marchis	MCI	mRS 3-6 vs. 0-2	Y	N	Logistic	OR=1.06 (0.89-1.27)	0.5
Gensicke	MCI	mRS 0-1 vs. 2-6	Y	N	Logistic	OR=1.353 (0.949-1.928)	≥0.05
			Y	N	Logistic	OR=0.849	≥0.05
Jimenez Caballero	CCI ≥2	mRS≥2 vs. 0-1	Y	Y	Logistic	OR=1.373 (CL NR)	0.025
	CCI		Y	Y	Logistic	OR=1.11 (CL NR)	<0.001
Tuttolomondo	CCI	no vs. 1-2 ADL impairment	N				
	CCI<2		Y	Y	Logistic	OR=2.44 (1.7-8.5)	≤0.0001
Nigro	MCI	mRS>2	Y	N	Logistic	OR=1.2 (0.8-1.6)	0.34
			Y	N	Logistic	OR=1.2 (0.9-1.5)	0.29
Denti	MCI ≥ 2	mRS 3-6	Y	N	Logistic	OR=1.7 (1.01-2.84)	0.04
						OR=1.37 (0.73-2.55)	0.32
						OR=1.31 (0.68-2.52)	0.42
		mRS 3-5	Y	N		OR=1.53 (0.9-2.66)	0.12
						OR=1.33 (0.71-2.50)	0.37
						OR=1.31 (0.68-2.53)	0.42
	new index for poor outcome (mRS 3-6)	mRS 3-6	Y	Y		OR=2.44 (1.44-4.13)	0.001
				N		OR=1.47 (0.78-2.77)	0.23
				N		OR=1.21 (.62-2.37)	0.57
	new index for disability (mRS 3-5)	mRS 3-5	Y	Y		OR=2.54 (1.48-4.37)	0.001
				N		OR=1.65 (.88-3.09)	0.12
				N		OR=1.38 (.71-2.68)	0.35
Lopez-Espuela	CCI	SF-12 physical functioning domain (a component of PCS)	Y	N	Linear	β= -0.149 (CL NR)	0.054
		SF-12 physical component score (PCS)	Y	Y	Linear	β= -0.225 (CL NR)	0.003
Chang	CCI	FIM	Y	N	ordinal logistic	OR=0.987 (0.929-1.048)	0.658
López-Espuela	CCI	BI (grouped for 5 levels of independency)	Y	N	ordinal logistic	OR=1.292 (0.973-1.716)	0.08

First author	Adjustment	Model Performance
Goldstein	Stroke severity (CNS); Age; #=3	NR
		NR
Katan	Copeptin level; age; gender; stroke severity; Total anterior circulation syndrome; #=6	AUC=0.85
Fischer	In-hospital vs. prehospital event; gender; age; stroke severity (NIHSS); Family history of stroke/MI; Diabetes; smoking; hyperlipidemia; Hypertension; Thrombolysis treatment; #=15	NR
De Marchis	age; Hypertension; Diabetes; Atrial fibrillation; Kidney impairment; stroke severity (NIHSS at admission); total anterior circulation stroke(TACS); Copeptin, glucose and CRP levels; DWI lesion size; stroke onset to blood collection time; gender; unclear cause of stroke; #=16	AUC=0.86
Gensicke	age; stroke severity (NIHSS at admission); Glucose levels; Symptomatic intracranial hemorrhage; total anterior circulation stroke(TACS); Hypertension; Coronary artery disease; #=9	NR
	age; stroke severity (NIHSS at admission); CRP levels; SBP at onset; Symptomatic intracranial hemorrhage; total anterior circulation stroke(TACS); Coronary artery disease; Atrial fibrillation; Epileptic seizures; Unfavorable 3M outcome; Long-term follow-up; #=14	NR
Jimenez Caballero	age, sex, stroke severity (NIHSS), hypertension, diabetes mellitus, dyslipidemia, smoking status, subtype of stroke, baseline mRS; #=10	NR
		NR
Tuttolomondo		
	age; Glucose level; SBP; WBC; Medications; #=13	NR
Nigro	BNP; age; gender; stroke severity (NIHSS); CRP; History of heart failure; Atrial fibrillation; lesion size; #=9	NR
	BNP; age; stroke severity (NIHSS); History of heart failure; Atrial fibrillation; lesion size; #=7	NR
Denti	age	AUC=0.879
	age; neurologic scores (SSS and GCS);	
	age; neurologic scores; premorbid disability; #=4	
	age	
	age; neurologic scores (SSS and GCS);	
	age; neurologic scores; premorbid disability; #=4	
	age	
	age; neurologic scores (SSS and GCS);	
	age; neurologic scores; premorbid disability;	
	age	
	age; neurologic scores (SSS and GCS);	
	age; neurologic scores; premorbid disability;	
Lopez-Espuela	gender; BI and IADL at hospital discharge; #=4	adjusted R^2=0.282
	gender; BI and IADL at hospital discharge; social risk (family situation, economic situation, housing, relationships, and social support); #=5	adjusted R^2=0.313
Chang	age; gender; Behavior factors (BMI, smoking and alcohol); education; Individual medical conditions; premorbid mRS; stroke severity (NIHSS at admission); Neurologic aggravation; Complications during hospital stay; LOS; Functional level at discharge; neurologic aggravation; Ambulation; swallowing; Aphasia; #=24	NR
López-Espuela	Gender; age; Stroke severity (NIHSS); Depression; Social risk; #=5	NR

Table 2.5 Risk of Bias Assessment of the Eligible Studies

Cohort type	First author	Year	D1	D2	D3	D4	D5	A1	A2	A3	A4	M1	M2	M3	M4	M5	O1	O2	O3	O4	O5	S1	S2	S3	S4	C1	C2	P1	Total Score	Mean	Median	Min	Max
Rehabilitation-based	**Liu**	1997	1	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	0	1	1	0	12				
	Desrosiers	2002	1	0	1	1	0.5	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	1	1	0	0.5	1	0	13				
	Duncan	2002	1	0	1	0	0.5	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0.5	1	0	9				
	Desrosiers	2006	1	0	1	1	1	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	1	1	0	0.5	1	0	13.5				
	Ferriero	2006	1	0	1	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	1	1	0	8.5				
	Karatepe	2008	1	0	1	1	0.5	1	0	0	1	0	1	0	0	0	0	0	0	1	0	1	1	0	0	0.5	0	0	10	11	11	8.5	13.5
Hospital-based	**Goldstein**	2004	0.5	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0	1	6				
	Katan	2009	0.5	0	0	0	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1				
	Fischer	2012	0.5	0	0.5	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	5				
	De Marchis	2013	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1.5				
	Gensicke	2013	0.5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.5				
	Jimenez Caballero	2013	0.5	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	4.5				
	Tuttolomondo	2013	0.5	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0.5	1	1	9				
	Nigro	2014	0.5	0	0.5	0	0.5	1	0	1	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	8.5				
	Denti	2015	0.5	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	4.5				
	Lopez-Espuela	2015	0.5	0	0.5	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	1	1	0	6				
	Chang	2016	0.5	0	0.5	0	0	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	6				
	Lopez-Espuela	2016	0.5	0	0.5	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	4	4.875	4.75	1	9
	Mean score																												6.916667				
	Median																												6				
	Min																												1				
	Max																												13.5				

Chapter 3: A New Index for Multiple Chronic Conditions Predicts Functional Outcome in Ischemic Stroke

3.1 Introduction

Up to 53% of stroke patients have long-term disability in activities of daily living.[13,16] Clinically, accurate prediction of post-stroke functional outcome (FO) could aid in decision-making regarding the balance of side effects and benefits of aggressive treatments.[152,153] It would help patients, families, and physicians to have realistic expectations, set attainable rehabilitation goals, and plan for home adjustment, community support, or institutional care.[152,153] From a research perspective, prognostic factors are important in observational studies for case-mix adjustment and in clinical trials for consideration of imbalance in treatment arms.[152,153] Stratifying patients into prognostically comparable groups can increase power to detect clinically relevant differences.[154,155]

Comorbidity increase risk of poor post-stroke FO.[83-85,97] Although many studies have linked individual comorbid conditions to FO, most patients have multiple chronic conditions (MCC) at stroke onset, which may impact FO synergistically.[51,198] Hospital-based studies have shown that MCC, measured by the modified Charlson Comorbidity Index (mCCI), predicts FO,[71,180,187,199] but it's not clear if the conditions in the mCCI are adequate for MCC assessment in stroke patients. Comorbidities have been included in prognostic scores for post-stroke FO, although the comorbid conditions have varied

across studies.[83-85] Further, cognitive and psychosocial impairments have not been considered although they may interact synergistically with other comorbidities to influence post-stroke FO.[39,200] The prediction of FO can potentially be improved by adding functional-relevant conditions, pre-stroke impairments, and synergistic interactions to MCC assessment.[199] Using machine learning, we aimed to develop and internally validate a new MCC index that improves the prediction of post-stroke FO at 90 days.

3.2 Methods

We conducted a prospective, cohort study nested in the Brain Attack Surveillance in Corpus Christi (BASIC) Project (November 8, 2008 - March 31, 2017). BASIC methodology has been previously described.[201,202] BASIC is an ongoing, population-based stroke surveillance study in Nueces County, Texas. In 2016, the county population was 361,350, with 63% being Mexican Americans (MA), who are mostly 2nd or 3rd-generation US-born citizens.[202,203] Stroke case ascertainment is accomplished through active and passive surveillance in the seven hospitals in the county.[29,201,202] Active surveillance identifies cases through daily screening of admission logs, medical wards, and intensive care units for validated cerebrovascular diagnostic terms. Passive surveillance identifies cases through searching hospital and emergency department discharge diagnoses using International Classification of Diseases, Ninth and Tenth Revision codes (ICD-9/10: 430–438/I60-I69).[204] Strokes are defined as a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution that lasts >24 hours. All stroke cases were validated by a fellowship-trained stroke physician blinded to race-ethnicity and age. To study additional comorbid conditions that were not included in the BASIC medical record abstraction, hospital

discharge data were requested but only available from three hospitals, which covers ~70% acute strokes in the area. In this study, only the first ischemic stroke event for each patient was included, although a patient may have had prior strokes or TIA events. Patients aged <45, living outside of Nueces County, or with traumatic strokes were excluded based on the BASIC exclusion criteria.[202] Patients of race/ethnicity other than MA or NHW (6.3%) were excluded to reduce sparsity.

Structured, in-person interviews (English/Spanish) were conducted shortly after stroke onset (baseline interview) and at ~90 days after stroke (outcome interview). If a patient was unable to complete an interview, a proxy interview was conducted. Patients who died before the outcome interview were excluded. Post-stroke FO score was measured at ~90 days using an average score of self-reported levels of difficulty with 7 activities of daily living (ADLs)/instrumental activities of daily living (IADLs) tasks. Self-reported level of difficulty for each task was recorded as 1 (no difficulty), 2 (some difficulty), 3 (a lot of difficulty), or 4 (can only do with help).[79] The total FO score was dichotomized into none/mildly impaired ($\leq$ 3) and dependent (> 3, a lot of difficulty with ADL/IADLs). Patients from recent years (since October 2014) also have the mRS-9Q scores at ~90 days, a 9-question “yes/no” survey that measures post-stroke modified Rankin Scale (mRS) scores.[205]

Chronic conditions were abstracted from medical records and complemented by extracting ICD-9 and 10 codes from hospital discharge data. A total of 22 chronic conditions were considered, including those in the mCCI and Elixhauser Comorbidity index.[206] Information on pre-stroke functional, cognitive, and psychosocial impairments was ascertained from the baseline interview. Pre-stroke function was measured by the

pre-stroke mRS using a series of structured questions referring to the pre-stroke period.[75] Pre-stroke cognitive function was measured by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a validated 16-item questionnaire completed by a proxy informant who knows the patient.[101] Patients were classified as having normal cognition (IQCODE ≤ 3), mild cognitive impairment (IQCODE: 3.01-3.43), or dementia (IQCODE ≥ 3.44 or medical recorded dementia) before stroke.[102] Patients without a proxy informant have missing information on IQCODE. Social support, marital status, self-reported depression and current/previous use of antidepressants were used to measure pre-stroke psychosocial impairments. The social support index was a sum of 7-item scale adapted from the Sacramento Area Latino Study on Aging.[103] Each item is scored 0 (never/rarely) to 2 (always) with the final score ranging from 0-14 (higher for more social support). Patients with a total score of more than 7 were considered as having high social support.[103] Information on social support and depression status was not available if a proxy interview was conducted. Race, ethnicity, education, and insurance status were also collected in the baseline interview.[202] Medical record data included age, sex, smoking status, alcohol use, body mass index (BMI), history of stroke/TIA, and initial stroke severity measured by the NIH Stroke Scale (NIHSS).[207]

Statistical Analysis

Data was divided into training (Nov 8, 2008 – Sep 30, 2016, 90%) and validation datasets (Oct 1, 2016 - Oct 31, 2017, 10%). In the training dataset, baseline characteristics were compared by FO status at 90 days using Kruskal–Wallis and χ tests. Pairwise correlations (Spearman) and linearity between each continuous predictor and FO score were examined, and suitable transformations were explored. Information

on social support and depression status were missing when proxy interviews were conducted among patients with more severe strokes. IQCODE, however, would less likely be missing when a proxy interview was conducted. Twenty-three percent of baseline and 21% of outcome interviews were proxy interviews. To limit potential selection bias in the analysis due to excluding patients with missing information for these variables, multiple imputation with the fully conditional specification (FCS) method was used to impute pre-stroke impairment variables (pre-stroke mRS, IQCODE, social support index, and depression status) for both the training and validation datasets. We performed 10 imputations with 100 burn-in iterations. The predictive mean matching (PMM) method was used for the continuous variable (pre-stroke IQCODE). The distributions of IQCODE (median: 3.06, IQR: 3-3.31) and social support index (median:11, IQR: 8-12) in the imputed and complete dataset were similar. The proportions of patients being dependent before stroke (25%) and with pre-stroke history of depression (13%) or current antidepressant use (20%) were also similar to those in the complete dataset, respectively. The percentage imputed for pre-stroke IQCODE, social support index, depression status, and mRS were 11.6%, 25.7%, 22.5%, and 2.2%, respectively.

To build the new MCC index, variable selection was conducted with adjustment for race-ethnicity, sex, and initial stroke severity. Traditional model selection approaches, such as stepwise or backward elimination, are not suitable for building the MCC index given the large pool of potential predictors (conditions and interactions) and the potential for unstable estimates and poor prediction accuracy.[120,121] Nova variable selection methods in machine learning, such as the least absolute shrinkage and

selection operator (*Lasso*) regression method and its derivatives,[123,125] can overcome these shortfalls and simultaneously select predictors, estimate their relative contribution to FO and explore interactions with improved accuracy and consistency.[123,125] We applied the *Lasso regression method for hierarchical interactions* (hierNet) method,[126] which allowed us to explore the impact of interactions between MCC by fitting a hierarchy model - only allowing an interaction into the model if at least one of the corresponding main effects are also in the model.[126] Hierarchy models have demonstrated strong predictive power among patients with neurological problems.[127] All potential predictors were standardized before model fitting, and all pairwise interactions among predictors were explored. The model was evaluated using 5-fold cross-validation and the tuning parameter was chosen based on both a smaller cross-validation error and model interpretability. The variable selection was separately done in each imputed dataset, and predictors were selected only if they appeared in all models.[208]

After variable selection, a multiple linear regression model was re-fitted using the selected predictors from hierNet. Weights for the new index were derived from the pooled β coefficients multiplied by 10 and rounded to the nearest integer. The overall score of the MCC index was a sum of the weights from each component. Collinearity was investigated using the Spearman correlation coefficients, tolerance and variance inflation factor (VIF). Tolerance, a commonly used measure of multicollinearity, grows smaller when a variable is more highly predicted by the other independent variables (collinearity). The VIF is the reciprocal of tolerance. A tolerance of less than 0.20 or a VIF greater than 5 often cast concerns for multicollinearity.[209] R^2 and adjusted R^2 were calculated for the final model.

Discrimination and calibration were assessed in the training and validation datasets. The ability to discriminate between none/mildly impaired and dependent was assessed in the training and validation datasets by the area under the receiver-operating characteristic (ROC) curve (AUC) equivalent to the c statistic. In the validation dataset, the ability of the MCC index to discriminate between favorable (mRS 0-2) and unfavorable (mRS 3-5) outcome based on post-stroke mRS-9Q at ~90 days was also assessed. The predictivity of the MCC index was compared with models using the established predictors of FO including age and stroke severity (e.g. initial NIHSS).[71,174] Calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. ROC curves for models using the new MCC index and the mCCI were compared using nonparametric DeLong tests.[210] Statistical analyses were conducted with SAS (version 9.4, SAS Institute Inc, Cary, NC) and R (version 3.5.3, RStudio).

Standard Protocol Approvals, Registrations, and Patient Consents

This project was approved by the University of Michigan institutional review board, the institutional review boards of both hospital systems. Written informed consent was obtained from all subjects.

Data Availability

The data will not be made available to the public because of its restricted nature.

3.3 Results

Between November 8, 2008, and September 30, 2016, 2,167 patients completed the baseline interviews and were followed for the outcome (Figure 3.1). Among the 1,872 survivors (86%) at 90 days, 180 (9.6%) patients refused participation and 204

(10.9%) patients or their proxies could not be located for the outcome interview. Thus 1,464 (78.2%) survivors completed outcome interviews at 90 days. Hospital discharge data containing ICD-9 or 10 codes were available for 1,064 (72.7%) patients. After excluding 29 (2.7%) patients with missing information on baseline characteristics (<2% missing in each variable), 1,035 patients were included in the training dataset.

Among the 1,035 patients, 69% were MA, and 51% were female. The mean age was 68 ± 12.1 years. The median initial NIHSS score was 4 (interquartile range [IQR], 2-8) and the median FO score at 90 days was 2.36 (IQR, 1.55-3.41) representing mild to moderate functional disability. The distribution of baseline characteristics and the FO score are included in the Table 3.1-3.4. In the unadjusted analysis, patients with higher pre-stroke mRS, antidepressant use at the time of stroke, and prior stroke/TIA had worse FO. Hypertension, diabetes, coronary artery disease, atrial fibrillation, cancer, congestive heart failure (CHF), renal failure, other neurological disorders, hypothyroidism, weight loss, and deficiency anemia were also associated with worse FO score at 90 days.

Compared to those who were analyzed, patients who were excluded due to a reason other than death (treated at the other hospital system or refusal/cannot locate for outcome interview) had a similar prevalence for all the comorbid conditions from medical record abstraction and baseline interview, although they were less likely to be dependent before stroke ($p<0.05$).

The MCC Index

Nine predictors and interactions were selected to be included in the MCC index: pre-stroke mRS, age, CHF, weight loss, diabetes, other neurological disorders,

dementia × age, CHF × renal failure and pre-stroke mRS × history of stroke/TIA. In the multiple linear regression model adjusting for race-ethnicity, sex, and initial stroke severity, the tolerance for these predictors ranged from 0.63 to 0.98 and the mean VIF ranged from 1.02 to 1.62. Given that the model included 3 interaction terms and the VIF values were still small, multicollinearity was not a concern.

The weights for each component of the MCC index are displayed in the Table 3.5 10. The actual scores that a patient got given the combination of comorbid conditions and impairment status are shown in Figure 3.2. The median of the total MCC score in the training dataset was 6 (IQR 4-11).

Discrimination and Calibration

The distribution of the FO status (FO score 1-2, 2.1-3 and 3.1-4) across the quintiles of MCC index is shown in Figure 3.3(A). The risk of worse FO increased with the quintile of the MCC index. For example, the risk of being dependent at 90 days was 10%, 23% or 78% for an MCC index score in Quintile 1 (score 0-3), Quintile 3 (score 6-7) or Quintile 5 (score 12+), respectively. The observed and predicted probabilities of being functional dependent (FO score >3) at 90 days were similar across the MCC index score subgroups ($p = 0.60$). Therefore, the MCC index was well calibrated in the training dataset (Figure 3.3[B]).

Statistics for the predictive performance for the training dataset are summarized in Table 3.6. The proportion of variability in the FO score explained by the MCC index was 34% (adjusted $R^2 = 0.34$) when FO was modeled continuously or dichotomously (FO score >3 vs. 1-3). Compared to a model including only initial NIHSS and age (adjusted $R^2 = 0.26$), including the MCC index explained an additional 16% of variability

in FO score (adjusted R^2 = 0.42). Together with age and initial NIHSS, the MCC index predicted functional dependency at 90 days with an excellent discriminating ability (AUC, 0.85).

Model Validation

The MCC index was validated in the consecutive 111 patients from BASIC (Oct 1, 2016 -Oct 31, 2017) who were alive at 90 days with FO recorded. Seven patients were excluded due to missing information for baseline characteristics. These 104 patients had similar distributions of age, sex, race-ethnicity, initial NIHSS, the FO score, and the MCC index score as patients in the training dataset (all p >0.05). Among these 104 patients, 71% were MA and 54% were female. The mean age was 66 ± 11 years. The medians for initial NIHSS and the FO score were 3 (IQR, 1 - 5.5), and 2.35 (IQR, 1.43-3), respectively. The median score of the MCC index was 7 (IQR 3-11.5). The proportion (94%) of patients with two or more conditions (of the 21 medical conditions measured) was higher than that in patients in the training dataset (88%, p <0.05).

The additional amount of variance explained by the MCC index (24%) compared to only including initial NIHSS and age was even more notable than that in the training dataset (16%, Table 3.1). The MCC index predicted functional dependency at 90 days more accurately (AUC, 0.85) than the model with initial NIHSS and age (AUC, 0.66). The observed and predicted probability of functional dependency at 90 days in the validation dataset is plotted in Figure 3.3(C). The MCC index was well calibrated in the validation dataset (p = 0.41).

The ability of the MCC index to discriminate favorable (mRS 0-2) versus unfavorable (mRS 3-5) outcome based on post-stroke mRS-9Q was also validated at 90

days (Table 3.1). Similarly, age and initial NIHSS adjusted MCC index performed well in discriminating favorable and unfavorable outcome (AUC, 0.84), much better than a model only including initial NIHSS and age (AUC, 0.71).

MCC index vs. Modified Charlson Comorbidity Index

We further compared our MCC index with the most widely used comorbidity index, the mCCI, for predicting FO in both the training and validation dataset (Table 3.1).[71,72,199] We found that mCCI alone explained little variability in FO.[38] In the training dataset when FO was modeled continuously, CCI explained 3% variability in FO in addition to age and initial NIHSS, much smaller than our MCC index (additional 16%). Findings were similar when FO was modeled dichotomously. This difference in performance was even more obvious in the validation dataset: our MCC index explained a much larger proportion of variability and predicted FO at 90 days more accurately than CCI. Adjustment by initial NIHSS and age did not change these findings. When looking at the unfavorable outcome defined by mRS (3-5), these differences in performance were largely unchanged. Comparisons of the ROC curves showed that our MCC index was significantly more accurate in predicting FO at 90 days than modified CCI with or without adjusting for initial NIHSS and age (all $p < 0.05$, Figure 3.3[D]).

3.4 Discussion

We present the development and internal validation of a new assessment tool for MCC in stroke patients that significantly improves the prediction of post-stroke FO at 90 days. This relatively simple and yet integrated measure of chronic conditions, pre-stroke functional and cognitive impairments, and their synergistic effects can be assessed by

neurologists or other healthcare providers during the acute hospitalization. Knowing the conditions that are most relevant to post-stroke FO improves the accuracy of outcome prognosis, which is crucial for treatment decisions and discharge planning. The risk of worse FO increases with the index score in a graded fashion. The index alone, and with the adjustment for initial stroke severity and age, was validated internally to perform very well in discriminating FO status measured by both ADL/IADLs and mRS at 90 days. The new index demonstrates potential as an MCC assessment tool in ischemic stroke although further external validation in other stroke populations is required.

To build the MCC index, we used machine learning to perform variable selection - a novel approach for prognostic modeling in stroke, which assured the validity and stability of the selected predictors. The penalization regression method allowed us to assess a larger number of conditions simultaneously and discover two new predictors (weight loss and other neurological disorders) that have not been considered before by other stroke risk scores that were based on clinical judgment or traditional model selection methods. The application of the hierNet method also allowed for the exploration of all possible interactions among potential predictors in a hierarchical manner, which led to the finding of three important interactions (dementia × age, CHF × renal failure and pre-stroke mRS × history of stroke/TIA). In addition, this work was nested within a population-based, longitudinal stroke cohort with ethnic diversity, where capturing a full spectrum of comorbid conditions in the broader stroke population was more possible than studies conducted in single hospitals or rehabilitation-based settings.

Our MCC index is constructed by age, pre-stroke mRS, CHF, weight loss, diabetes, other neurological disorders, dementia, renal failure and history of stroke/TIA as independent or synergistic effects. The findings of these predictors are largely in line with previous research on the associations of individual comorbid conditions and post-stroke FO. For example, CHF, diabetes, renal failure, and pre-stroke dependency have been included in existing MCC indices used in stroke patients or prognostic models for stroke, including the mCCI, iScore, and the PLAN score.[70,71,78,83,84,211] Notably, several conditions in our MCC index were not included in the commonly used comorbidity index – the mCCI.

The mCCI has been used predominantly by hospital-based studies of stroke patients.[71,199] CCI, which includes 19 chronic conditions weighted by their strength of associations with mortality, was originally developed as a prognostic indicator in patients with a variety of conditions and validated in breast cancer patients.[72] The mCCI is similar but excludes cerebrovascular disease and hemiplegia.[71] In this study, we demonstrated the superior predictive performance of our MCC index over the mCCI. Our index is also a simpler tool that requires less information on comorbid conditions. We found that the mCCI was only weakly correlated with our MCC index. Although mCCI has been widely used to predict FO after stroke, it does not appear to fully capture the impact of function-related conditions in stroke. There has been some work showing that certain comorbid conditions may impact FO through pathophysiologic mechanisms that are specific to stroke,[212-214] and therefore a stroke-specific MCC index is needed as supported by our results.

Preferably, a stroke-specific MCC index should include not only the conditions that are relevant to FO but also their synergistic effects due to certain conditions clustering within individuals. However, the impact of MCC clustering in stroke outcomes is poorly understood, and interactions between chronic conditions have never been included in stroke prognostic scores. Take the interaction between pre-stroke function and history of stroke/TIA, for example. Not only have these factors rarely examined together, many prognostic studies excluded patients with severe pre-stroke disability or were conducted in first-ever stroke patients only.[174] Given the limited data in this area, the mechanisms of the three interactions included are not clear but worth future investigation.

This research has several strengths. First, the study was nested in a population-based, longitudinal stroke cohort with ethnic diversity. With more than 7 years of data and more than 1,000 ischemic strokes, the BASIC Project provided a large study population and sufficient statistical power to capture the variance in FO explained by MCC. The surveillance and validation of ischemic stroke cases and the identification of comorbid conditions from medical records and baseline interviews in addition to hospital discharge data and FO from patient interviews limited case ascertainment and measurement bias inherent in studies using administrative data alone. Second, a new conceptual model adding pre-stroke impairments assured a comprehensive assessment of MCC. The BASIC Project collects detailed data on pre-stroke functional, cognitive, and psychosocial impairments, which allowed the implementation of such a conceptual model and the adjustment of initial stroke severity and other important confounding factors. Third, using machine learning to perform variable selection for prognostic

modeling was a novel approach in stroke outcome research, which assured the validity and stability of the selected predictors, and allowed for the consideration of synergism among identified predictors. Fourth, the developed MCC index is relatively simple and required less information compared to former MCC indices, and yet performed superiorly than the most widely used MCC indices in predicting both ADL/IADLs score and mRS.

This study has several limitations. Generalizability may be limited given the work was conducted in one community with a high proportion of MAs, and external validation is required in the future before the application of this index. Although the FO measurement by ADL/IADLs may not be available in many other study populations, external validation can be conducted to examine the performance of the MCC index in predicting post-stroke mRS. Our measurement of chronic conditions may be limited by the fact that only 25 diagnoses are available in the hospital discharge data; some individuals may have >25 conditions; information on some geriatric syndromes (urine incontinence and falls) was not available. We did not have information to measure MCC severity, although including severity measures in comorbidity indices may also add complexity that challenges clinical utility.[78] Due to the nature of the hospital discharge data and medical records, the temporality of some conditions and stroke may be ambiguous. Although some comorbid conditions may be secondary to stroke, they can still be broadly considered as comorbid conditions of stroke as they "co-occur during the clinical course of stroke."[52] Sicker patients with higher MCC at baseline may more likely be lost to follow-up at 90 days introducing some selection bias. We found that the excluded patients had a similar prevalence for all conditions abstracted from medical

records except that they were less likely to be dependent before stroke. We used multiple imputations to fill in missing values of pre-stroke impairment variables, although variables may not be missing at random. There are other potential confounders that we did not control for in examining MCC and FO, such as physical activity, income, post-stroke care, and rehabilitation that are not collected by the current study.

In conclusion, we developed a relatively simple tool for the measurement of MCC that is function-relevant and specific for ischemic stroke. Weight loss, other neurological disorders, and interactions between MCC were discovered as novel predictors. The MCC index showed superior ability in predicting post-stroke FO measured by both ADL/IADLs and mRS at 90 days. This score demonstrates potential as an assessment tool for MCC in stroke prognosis, but further external validation is needed. Efforts to improve stroke survivorship may benefit from a better understanding, prevention, and management of MCC in the population at high risk for stroke.

Figure 3.1 Flow Chart of Patient Participation

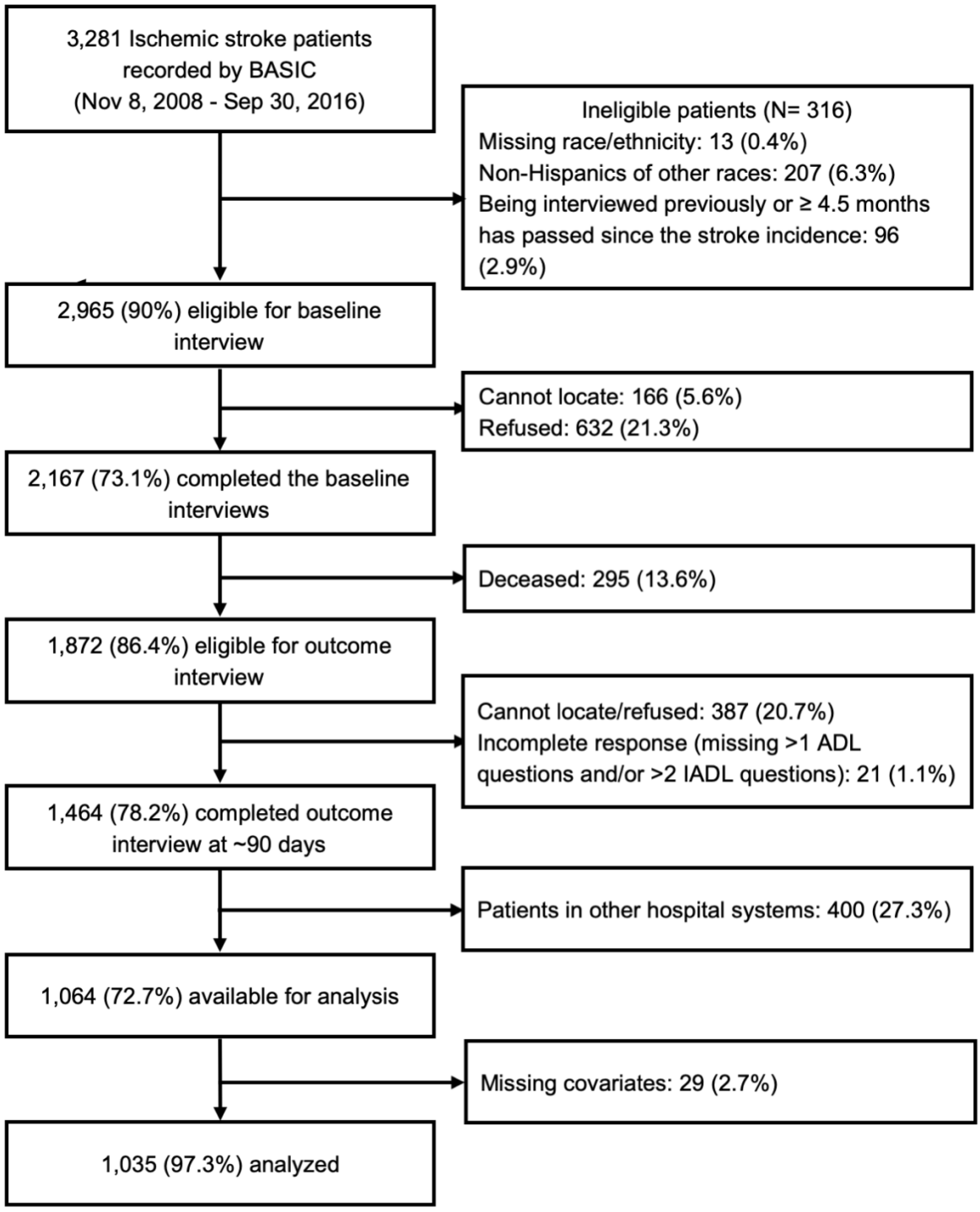
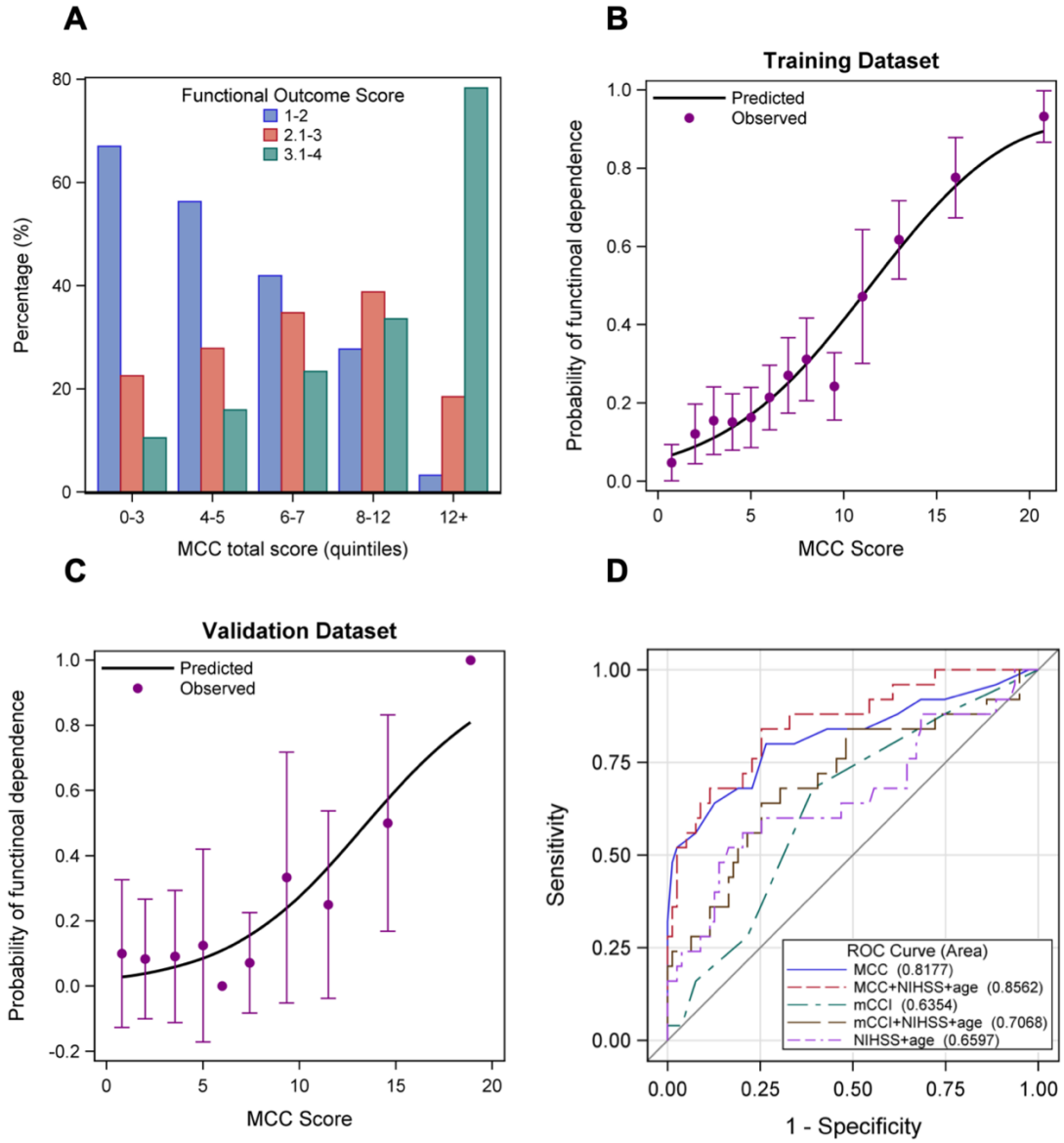


Figure 3.2 A New Index for Multiple Chronic Conditions in Ischemic Stroke

Pre-stroke mRS score	Prior stroke/TIA	No prior stroke/TIA
0	0	0
1	3	2
2	6	4
3	9	6
4	12	8
5	15	10
Age	**Dementia**	**No dementia**
45-54	0	0
55-64	2	1
65-74	4	2
75-84	6	3
85-94	8	4
95-105	10	5
CHF without renal failure		2
CHF with renal failure		4
Weight loss[a]		4
Diabetes		1
Other neurological disorders[b]		1

Abbreviations: mRS = modified Rankin Scale; CHF = congestive heart failure;
[a] Weight loss = Kwashiorkor, nutritional marasmus and protein-calorie malnutrition;
[b] Other neurological disorders = Parkinson's disease and unspecified cerebral degeneration, choreas, spinocerebellar and anterior horn cell diseases, CNS demyelinating disease, epilepsy and convulsions, encephalopathy and anoxic brain damage;
Similar definition for weight loss and other neurological disease have been used in the Elixhauser Comorbidity index;

Figure 3.3 Discrimination and Calibration



The proportions of patients in each functional outcome score levels by MCC index quintiles are showed in **A**. Observed vs. predicted proportion of functional dependency (functional outcome score >3) at 90 days in the training (**B**) and validation (**C**) dataset are showed. Dots represent the actual proportion of patients being functional dependent. Vertical lines represent 95% CIs of the actual proportion of patients being functional dependent. The continuous lines represent the predicted probability of being functional dependent in the training (**B** and validation (**C**) dataset. Receiver Operating characteristic (ROC) Curves for Models Predicting Functional Outcome at 90 days in the validation dataset are plotted in **D**. Abbreviations: MCC = the new index score for Multiple Chronic Conditions; NIHSS = NIH Stroke Scale; mRS = modified Rankin Scale; mCCI = Modified Charlson Comorbidity Index;

Table 3.1 Baseline Characteristics by Functional Outcome Status (N=1,035)

		None-mildly impaired (FO score ≤3) N=707		Dependent (FO score >3) N=328		
		N or Median	% or (Q1, Q3)	N or Median	% or (Q1, Q3)	p-value[a]
Age		64	(57,73)	77	(65,83.5)	<.0001
Female		330	46.7	195	59.5	0.0001
MA		455	64.4	255	77.7	<.0001
Smoking	Never	401	56.7	232	70.7	<.0001
	Former	122	17.3	48	14.6	
	Current	184	26.0	48	14.6	
Alcohol use	Never	162	22.9	100	30.5	<.0001
	<1 drink per week	300	42.4	163	49.7	
	1+ drink per week	245	34.7	65	19.8	
Education	< High school	105	14.9	109	33.2	<.0001
	High school	363	51.3	148	45.1	
	College +	239	33.8	71	21.6	
Insured		352	49.8	246	75.0	<.0001
Pre-stroke mRS	0-1	364	52.4	68	21.4	<.0001
	2-3	300	43.2	143	45.0	
	4+	30	4.3	107	33.6	
Marital Status	Single/Never married	49	6.9	19	5.8	<.0001
	Married/living together	350	49.5	143	43.6	
	Widowed	141	19.9	116	35.4	
	Divorced/separated	167	23.6	50	15.2	
Pre-stroke depression	None	431	65.6	93	64.1	0.0933
	History of depression	97	14.8	14	9.7	
	Current antidepressant use	129	19.6	38	26.2	
Prior stroke or TIA		162	22.9	132	40.2	<.0001
IV t-PA or endovascular thrombectomy		81	11.5	56	17.1	0.0131
Initial NIHSS		3	(1,5)	8	(3,13.5)	<.0001
IQCODE		3	(3,3.3)	3.1	(3,3.6)	<.0001
BMI		29.1	(25.6,33.5)	27.4	(23.3,32.1)	<.0001
Social support index		10	(7,12)	10	(7,12)	0.6643

Abbreviations: FO score= functional outcome score; MA = Mexican American; mRS = modified Rankin scale, tPA = tissue plasminogen activator, NIHSS = NIH Stroke Scale,

IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly
[a] Chi-square tests for categorical variables; Kruskal-wallis non-parametric tests for continuous variables.
Amount of missing: pre-stroke mRS 2.2%; IQCODE 11.6%; Pre-stroke depression 22.5%; Social support index 25.7%;

Table 3.2 Chronic Conditions of Eligible Study Participants by Functional Outcome (N=1,035)

	None-mildly impaired (FO score ≤3) N=707		Dependent (FO score >3) N=328		
	N	%	N	%	p-value[a]
Hypertension	571	80.8	284	86.6	0.0215
High Cholesterol	366	51.8	154	47.0	0.1493
Diabetes	342	48.4	163	49.7	0.6923
Coronary Artery Disease	197	27.9	109	33.2	0.0783
Atrial fibrillation	72	10.2	71	21.6	<.0001
Cancer	71	10.0	50	15.2	0.0154
COPD	75	10.6	37	11.3	0.746
Congestive heart failure	45	6.4	52	15.9	<.0001
Myocardial infarction	49	6.9	17	5.2	0.2843
Renal failure	67	9.5	72	22.0	<.0001
Other neurological disorders	122	17.3	127	38.7	<.0001
Hypothyroidism	87	12.3	67	20.4	0.0006
Peripheral vascular disorders	98	13.9	48	14.6	0.7397
Valvular disease	42	5.9	27	8.2	0.1692
Weight loss	11	1.6	23	7.0	<.0001
Rheumatoid arthritis/collagen vascular diseases	21	3.0	9	2.7	0.8399
Liver disease	18	2.5	8	2.4	0.9185
Psychoses	12	1.7	8	2.4	0.42
Pulmonary circulation disorders	7	1.0	7	2.1	0.1382
Deficiency anemia	6	0.8	7	2.1	0.084
Coagulopathy	8	1.1	4	1.2	0.9021

FO score= functional outcome score.

[a] Chi-square tests.

Weight loss = Kwashiorkor, nutritional marasmus and protein-calorie malnutrition;
Other neurological disorders = Parkinson's disease and unspecified cerebral degeneration, choreas, spinocerebellar and anterior horn cell diseases, CNS demyelinating disease, epilepsy and convulsions, encephalopathy and anoxic brain damage;
Similar definition for weight loss and other neurological disease have been used in the Elixhauser Comorbidity index; All missing <1%;

Table 3.3 Functional Outcome Score by Baseline Characteristics (N=1,035)

		Median	(Q1, Q3)	p-value[a]
Sex	Male	2.05	(1.32, 3.09)	<.0001
	Female	2.64	(1.86, 3.59)	
Race/ethnicity	NHW	1.95	(1.32, 2.91)	<.0001
	MA	2.55	(1.73, 3.5)	
Smoking	Never	2.50	(1.6, 3.59)	<.0001
	Former	2.33	(1.55, 3.18)	
	Current	2.05	(1.39, 2.77)	
Alcohol use	Never	2.59	(1.82, 3.5)	<.0001
	<1 drink per week	2.50	(1.73, 3.55)	
	1+ drink per week	1.91	(1.27, 2.77)	
Education	< High school	3.11	(2.32, 3.91)	<.0001
	High school	2.32	(1.59, 3.18)	
	College +	1.95	(1.27, 2.95)	
Insurance	None	2.00	(1.27, 2.77)	<.0001
	Insured	2.74	(1.82, 3.68)	
Pre-stroke mRS	0-1	1.84	(1.2, 2.55)	<.0001
	2-3	2.50	(1.81, 3.38)	
	4+	3.77	(3.23, 4)	
Marital Status	Single/Never married	2.18	(1.56, 3.09)	<.0001
	Married/living together	2.14	(1.32, 3.32)	
	Widowed	2.91	(2.23, 3.81)	
	Divorced/separated	2.14	(1.48, 2.95)	
Pre-stroke depression	None	1.91	(1.27, 2.73)	<.0001
	History of depression	2.05	(1.41, 2.75)	
	Current antidepressant use	2.36	(1.91, 2.95)	
History of Stroke or TIA	None	2.18	(1.41, 3.09)	<.0001
	Prior stroke/TIA	2.91	(2, 3.68)	
IV t-PA or endovascular thrombectomy	None	2.32	(1.57, 3.32)	0.1913
	Yes	2.59	(1.41, 3.64)	

Abbreviations: MA = Mexican American; NHW = Non-Hispanic white; mRS = modified Rankin scale, tPA = tissue plasminogen activator, NIHSS = NIH Stroke Scale, IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly

[a] Kruskal-wallis non-parametric tests or analysis of variance (ANOVA)

Amount of missing: pre-stroke mRS 2.2%; Pre-stroke depression 22.5%;

Table 3.4. Functional Outcome Score by Status of Chronic Conditions (N=1,035)

		Median	(Q1, Q3)	p-value[a]
Hypertension	None	1.9	(1.23, 3)	<.0001
	Yes	2.5	(1.6, 3.45)	
High Cholesterol	None	2.4	(1.41, 3.45)	0.9066
	Yes	2.3	(1.6, 3.36)	
Diabetes	None	2.2	(1.35, 3.41)	0.0026
	Yes	2.5	(1.81, 3.36)	
Coronary Artery Disease	None	2.3	(1.48, 3.27)	0.0276
	Yes	2.5	(1.64, 3.55)	
Atrial fibrillation	None	2.3	(1.47, 3.27)	<.0001
	Yes	3.0	(1.95, 3.82)	
Cancer	None	2.3	(1.5, 3.36)	0.0014
	Yes	2.8	(1.95, 3.59)	
COPD	None	2.4	(1.5, 3.38)	0.3943
	Yes	2.5	(1.64, 3.41)	
Congestive heart failure	None	2.3	(1.45, 3.32)	<.0001
	Yes	3.1	(2.55, 3.77)	
Myocardial infarction	None	2.4	(1.55, 3.41)	0.7198
	Yes	2.3	(1.68, 3.05)	
Renal failure	None	2.3	(1.45, 3.27)	<.0001
	Yes	3.1	(2.14, 3.82)	
Other neurological disorders	None	2.2	(1.45, 3.05)	<.0001
	Yes	3.1	(1.9, 3.91)	
Hypothyroidism	None	2.3	(1.5, 3.32)	0.0001
	Yes	2.8	(1.86, 3.82)	
Peripheral vascular disorders	None	2.3	(1.5, 3.41)	0.1679
	Yes	2.5	(1.73, 3.5)	
Valvular disease	None	2.3	(1.55, 3.36)	0.3209
	Yes	2.5	(1.41, 3.55)	
Weight loss	None	2.3	(1.55, 3.32)	<.0001
	Yes	3.6	(2.77, 3.91)	
Rheumatoid arthritis/collagen vascular diseases	None	2.4	(1.55, 3.41)	0.3642
	Yes	2.5	(1.91, 3.5)	
Liver disease	None	2.4	(1.55, 3.41)	0.2828
	Yes	2.7	(2.05, 3.18)	
Psychoses	None	2.4	(1.55, 3.41)	0.3388
	Yes	2.4	(1.88, 3.84)	
Pulmonary circulation disorders	None	2.4	(1.55, 3.41)	0.5334
	Yes	3.0	(1.09, 4)	
Deficiency anemia	None	2.4	(1.55, 3.41)	0.0459
	Yes	3.1	(2.48, 4)	

Coagulopathy	None	2.4	(1.55, 3.41)	0.9791
	Yes	2.2	(1.82, 3.23)	

[a] Kruskal-wallis non-parametric tests;
Weight loss = Kwashiorkor, nutritional marasmus and protein-calorie malnutrition;
Other neurological disorders = Parkinson's disease and unspecified cerebral degeneration, choreas, spinocerebellar and anterior horn cell diseases, CNS demyelinating disease, epilepsy and convulsions, encephalopathy and anoxic brain damage;
Similar definition for weight loss and other neurological disease have been used in the Elixhauser Comorbidity index; All missing <1%;

Table 3.5 A New Index for Multiple Chronic Conditions in Ischemic Stroke

		Weights
Main effects	Age[a]	1
	Pre-stroke mRS[b]	2
	CHF[c]	2
	Weight loss	4
	Diabetes	1
	Other neurological disorders	1
Interactions	Dementia × age[a]	1
	CHF × renal failure[c]	2
	Pre-stroke mRS × prior stroke/TIA[b]	1

Abbreviations: mRS = modified Rankin Scale; CHF = congestive heart failure;
[a] 1 point per decade from the age of 45; additional 1 point per decade from the age of 45 for patients with dementia (due to dementia × age interaction);
[b] 2 point per 1 unit increase in pre-stroke mRS; additional 1 point per 1 unit increase in pre-stroke mRS if patient had prior stroke/TIA (due to interaction);
[c] 1 point if CHF is present; additional 2 points if both CHF and renal failure are present (due to interaction);
Weight loss = Kwashiorkor, nutritional marasmus and protein-calorie malnutrition;
Other neurological disorders = Parkinson's disease and unspecified cerebral degeneration, choreas, spinocerebellar and anterior horn cell diseases, CNS demyelinating disease, epilepsy and convulsions, encephalopathy and anoxic brain damage;
Similar definition for weight loss and other neurological disease have been used in the Elixhauser Comorbidity index;

Table 3.6 Discrimination and Model Fit Statistics for Functional Outcome at 90 days

		Multiple Linear Regression		Logistic Regression					
				FO score >3			mRS 3-5		
Dataset	Model	R^2	Adjusted R^2	AUC	R^2	Adjusted R^2	AUC	R^2	Adjusted R^2
Training	MCC	0.34	0.34	0.79	0.24	0.34			
	MCC + NIHSS + age	0.42	0.42	0.85	0.32	0.45			
	mCCI	0.05	0.05	0.59	0.03	0.05			
	mCCI + NIHSS + age	0.29	0.29	0.81	0.24	0.34			
	NIHSS + age	0.26	0.26	0.79	0.22	0.31			
Validation	MCC	0.32	0.31	0.81	0.26	0.39	0.75	0.16	0.24
	MCC + NIHSS + age	0.4	0.39	0.85	0.3	0.45	0.84	0.28	0.4
	mCCI	0.13	0.12	0.64	0.03	0.04	0.72	0.13	0.19
	mCCI + NIHSS + age	0.26	0.24	0.71	0.11	0.17	0.79	0.22	0.33
	NIHSS + age	0.16	0.15	0.66	0.09	0.14	0.71	0.12	0.18

Abbreviations: MCC = the new index score for Multiple Chronic Conditions; NIHSS = NIH Stroke Scale; mRS = modified Rankin Scale; mCCI = Modified Charlson Comorbidity Index;
All statistics were very close among the 10 imputed datasets in the training and validation data; only the minimum value for each statistics among the 10 datasets were reported. The differences between the maximal and minimal values of R^2, adjusted R^2 and AUC among the 10 datasets were all <0.01;

Chapter 4: Multiple Chronic Conditions Explains Ethnic Difference in Functional Outcome Among Ischemic Stroke Patients

4.1 Introduction

Stroke is a leading cause of serious long-term disability in the United States (US).[158] More than 30% of stroke survivors are dependent in one or more activities of daily living (ADLs) and up to 45% are functionally dependent at 1 year after stroke.[7,159-161] Stroke disproportionately impacts minorities in the US. Mexican Americans (MAs), the largest and fastest-growing subgroup of Hispanic Americans, the largest minority group in the US,[131] have an increased stroke risk compared with non-Hispanic whites (NHWs),[132] a disparity that has not lessened over time.[4,133] Compared with NHWs, MAs have greater neurological deficits, higher odds of exceeding the median length of hospital stay, are less likely to return to work after stroke, and have worse post-stroke functional outcome (FO) at 90 days.[43,46,134,200] The underlying reasons for these ethnic disparities in stroke outcomes are unknown, but differences are not fully explained by demographics, socioeconomic status, stroke risk factors, stroke severity and differential poststroke mortality by ethnicity.[200] The combination of increased stroke risk and post-stroke disability, prolonged survival, and rapid growth in the MA population will amplify the burden of care in MA stroke survivors, thus further investigation on the drivers of the ethnic disparity in post-stroke FO is warranted.

Among stroke patients, multiple chronic conditions (MCC) appears to explain variation in post-stroke FO at 3-6 months, over and beyond the damage caused by the stroke.[38,69,180,185,187] MCC is often referred to as the "concurrent presence of two or more medically diagnosed diseases in the same individual."[51] The prevalence of MCC will increase with the aging population in the US and is associated with pathophysiological changes and organ-level impairments that could lead to frailty and functional impairment among the elderly.[49,60] Many individual conditions, including congestive heart failure (CHF), diabetes, chronic kidney disease (CKD), malnutrition, and preexisting neurological diseases, have been found to impact FO potentially through stroke-specific pathophysiological pathways, and may collectively deplete the overall cardiovascular reserve or impair the neuroplasticity that aids in post-stroke recovery.[212,215-221] However, research on MCC and post-stroke FO in diverse populations is lacking and the role of MCC in the ethnic disparity in post-stroke FO is poorly understood.

MA stroke patients have a different MCC spectrum than NHWs, and the role of MCC in post-stroke FO may vary by ethnicity. Regarding individual conditions, MA stroke patients are more likely to have pre-existing hypertension, diabetes, and previous stroke or transient ischemic attack (TIA), but are less likely to have atrial fibrillation and coronary artery disease compared with NHWs.[138,222,223] Two studies found no difference in the count of 14 comorbidities between MA and NHW stroke patients.[29,139] However, since the prevalence of specific comorbid conditions differs by ethnicity, a simple sum of conditions does not fully capture the ethnic difference in the MCC spectrum or the fact that certain conditions might carry more weight than others with respect to predicting FO. Moreover, MAs may have more barriers to the treatment of MCC and therefore

more uncontrolled conditions or conditions with greater severity compared with NHWs.[43,140,141,224] For example, Hispanics have worse blood pressure control, even among those treated for hypertension, compared with NHWs,[143] and they are more likely to suffer from diabetic complications such as retinopathy and nephropathy.[144,145] These known ethnic differences in the severity and control of comorbid conditions raise the possibility of differential impact of MCC on post-stroke FO by ethnicity, which has not been investigated.

To comprehensively measure MCC by capturing the stroke-specific and function-relevant conditions, as well as important synergistic effects of MCC clustering within individuals, we previously developed and internally validated a new assessment tool for MCC in stroke, which improves the prediction of post-stroke FO at 90 days (Chapter 3). This relatively simple and yet integrated measure considers chronic conditions, pre-stroke functional and cognitive impairments, and their synergistic effects. The index is constructed by nine predictors, including age, pre-stroke function assessed by modified Rankin Scale (mRS), CHF, weight loss, diabetes, other neurological disorders, dementia, renal failure and history of previous strokes or TIA as independent or synergistic effects (Figure 3.2). The index score alone and together with initial stroke severity and age outperformed the predominantly used index, the modified Charlson Comorbidity Index,[71,72,199] in predicting post-stroke FO at 90 days, even though the index requires less information on comorbid conditions.

The goal of this study was to understand the contribution of MCC to ethnic disparities in post-stroke FO at 90 days between MA and NHW ischemic stroke patients using the new MCC index. Additionally, we sought to understand whether the

association of MCC with post-stroke FO at 90 days differs between MA and NHW ischemic stroke patients.

4.2 Methods

A prospective cohort of ischemic stroke patients was identified from the Brain Attack Surveillance in Corpus Christi (BASIC) project between November 8, 2008, and October 1, 2016. BASIC is an ongoing population-based stroke surveillance study in Nueces County, Texas.[46] Based on the 2016 Census, Nueces County has a population of 361,350, with 63% of the residents being MAs who are mostly second or third generation US residents and representative of the broader MA population in the state of Texas.[203] The majority of this non-immigrant, bi-ethnic community (95%) resides in the urban city of Corpus Christi.[202,203] Detailed methods of BASIC have been described previously.[202,225]

Study Population

Patients with stroke aged ≥ 45 years presenting to one of the seven hospitals serving the county were identified through active and passive surveillance. Active surveillance involves daily screening of hospital admission logs, medical wards, and intensive care units for validated cerebrovascular diagnostic terms. Passive surveillance involves searching hospital and emergency department discharge diagnoses using International Classification of Diseases, Ninth and Tenth Revision codes (ICD-9/10: 430–438/I60-I69).[204] Strokes are defined as a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution that lasts >24 hours. Stroke diagnosis was validated by fellowship-trained physicians using source documentation

blinded to ethnicity and age. Only the first ischemic stroke event for each patient during the time period was included in this study, although some patients may have had prior strokes or TIA. Patients who lived outside of Nueces County or with traumatic stroke were excluded per BASIC protocol.[202] Hospital Discharge Data that contained important comorbid condition information were only available from the three major hospitals, which contains ~70% acute stroke patients in the county. Patients from the other hospitals are missing information on comorbid condition information from Hospital Discharge Data and were excluded.

Eligible patients were invited to participate in a structured, in-person baseline interview (English/Spanish) shortly after stroke occurrence and an outcome interview at ~90 days after stroke. A proxy was interviewed if a patient was unable to complete the in-person interview. Patients who died before the outcome interview were excluded. Self-reported race-ethnicity was ascertained from the baseline interview. Information on medical records was used when self-reported race or ethnicity was not available. Patients of race-ethnicity other than MA or NHW (6.7%) were excluded to reduce sparsity in the analysis. The sample for primary analysis contained 661 MA and 280 NHW patients who 1) were alive at 90 days after stroke; 2) completed baseline and outcome interview; and 3) had pre-stroke cognitive function assessment. The flow chart of the study sample is shown in Figure 1. The potential difference in attrition due to not completing the baseline or outcome interview or not having the pre-stroke cognitive function assessment was later accounted for in the analysis using the inverse probability weighting method as described in the statistical analysis.

Functional Outcome Score at 90 Days

At the outcome interview ~90 days after the onset of ischemic stroke, patients were asked to self-rate levels of difficulty with ethnic disparity ADLs and IADLs tasks, with each task being recorded as 1 (no difficulty), 2 (some difficulty), 3 (a lot of difficulties), and 4 (can only do with help).[79] Post-stroke FO score was calculated as an average score of the 22 tasks (7 ADLs and 15 IADLs), ranging from 1 to 4. Patients with the FO score >3 (indicating a lot of difficulty with ADL/IADLs) were considered as being dependent.

Multiple Chronic Conditions

Information on the presence of CHF, diabetes, and history of stroke/TIA was abstracted from medical records. Renal failure, weight loss, and other neurological diseases were identified from hospital discharge data using ICD-9 and 10 codes based on algorithms used for the Elixhauser comorbidities.[206,226] Weight loss includes Kwashiorkor, nutritional marasmus, and protein-calorie malnutrition. Other neurological disorders include Parkinson's disease and unspecified cerebral degeneration, choreas, spinocerebellar and anterior horn cell diseases, central nervous system demyelinating disease, epilepsy and convulsions, encephalopathy and anoxic brain damage. Pre-stroke function was measured by the pre-stroke modified Rankin Scale (mRS, range 0 to 5, higher score for more disability) at the baseline interview using a series of structured questions referring to the pre-stroke period.[75] Pre-stroke cognitive function was measured by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a validated 16-item questionnaire completed by a proxy informant who knows the patient.[101] Patients with IQCODE ≥ 3.44 or documentation of dementia in the

medical record were classified as having pre-stroke dementia.[102] Patients without a proxy informant have missing information on IQCODE. To appropriately assess the impact of MCC, we used our previously developed MCC index that predicts post-stroke FO at 90 days.[227] Figure 2 shows the assigned scores depending on the level of impairments and the presence of chronic conditions in the MCC index. The weights for each component in the index were assigned based on the strength of association with the post-stroke FO score in the multiple linear regression model. The total score for MCC was a sum ranging from 0 to 35 (higher for greater comorbidity burden).

Covariates

Educational attainment (less than high school, high school, college and above), insurance status (insured or uninsured), marital status, and pre-stroke depression status (none, depression history, current antidepressant use) were collected in the baseline interview. Medical record data contained age, sex, behavior risk factors (smoking status, alcohol use, body mass index or BMI), thrombolytic therapy (intravenous tissue plasminogen activator use and/or endovascular thrombectomy), and initial stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) ranging from 0 to 42 (higher scores indicating more stroke impairment).[29,207]

Statistical Analysis

Descriptive statistics for baseline characteristics and comorbid conditions were calculated and compared by ethnicity using χ^2 and Kruskal–Wallis tests. Pairwise correlations (Spearman) between continuous predictors and the FO score were investigated. Linearity between each continuous predictor and the FO score was examined, and suitable transformations were explored. The ethnic difference in the

MCC total score was calculated using an age-adjusted Tobit regression model due to the MCC score having a truncated distribution with lower and upper bounds (range, 0-35). To eliminate potential bias due to differential study attrition and conduct the analysis in a sample representative of all patients who were alive at 90 days, we used inverse probability weighting to upweight those patients in the analysis dataset who were similar to the excluded patients (Figure 1). The non-stabilized weights for each patient were the inverse product of the predicted probabilities from three logistic regression models: 1) the probability of completing the baseline interview; 2) the probability of completing pre-stroke cognitive function assessment; 3) the probability of completing the outcome interview. The predictors in these three models were selected using backward elimination with a significance level of 0.20 for removal from the model (Table 4.5). The stabilized weights were constructed by multiplying the non-stabilized weights by the conditional probability from a nested model given a subset of covariates (age, sex or ethnicity, depending on the full model).[228] The stabilized weights were trimmed at the 1st and 99th percentiles to limit the impact of extreme values. The final weights ranged from 0.61 to 1.36.

To understand the role of MCC in ethnic disparities in post-stroke FO, we investigated its potential both as a confounder and an effect modifier of the association between ethnicity and post-stroke FO. Specifically, to examine whether MCC confounded the ethnicity-FO association, the ethnic difference in the FO score was estimated and compared in models with and without MCC adjusting for other confounders. We used directed acyclic graphs (DAGs) to identify a minimally sufficient set of measured confounders to be adjusted for in estimating ethnic differences in post-

stroke FO.[229] The construction of the DAGs was based on empirical knowledge, previous studies in the BASIC Project, and other cohort studies (Figure 4.3). We hypothesized that the association between ethnicity and MCC was largely related to environmental and lifestyle risk factors and other unmeasured confounding (association) versus genetic susceptibility (causation), and therefore considered the potential contribution of MCC to ethnic differences in post-stroke FO as confounding rather than mediation. Similarly, we also considered the effect of age, sociodemographic factors, including sex, education, marital status, and insurance status, behavioral risk factors (alcohol use, smoking status, and BMI) given the differences in distribution among MAs and NHWs. Specifically, behavioral risk factors, which are associated with sociodemographic factors, are causally associated with MCC and stroke severity and hence may impact post-stroke FO indirectly. Age and sociodemographic factors may impact post-stroke FO directly or indirectly through their effect on MCC, stroke severity, and the probability of getting thrombolytic therapy, post-acute stroke care, and inpatient rehabilitation. Based on our hypothesis and the constructed DAG, we determined that adjustment for age, stroke severity, MCC, and sociodemographic factors is minimally sufficient to control for confounding in estimating the ethnic differences in post-stroke FO.[229] These confounders were sequentially controlled for in the weighted Tobit regression models to assess the adjusted ethnic difference in the FO score.

To examine the potential differences in MCC-FO association by ethnicity, we first conducted a stratified analysis to examine the impact of MCC on the FO score in MAs and NHWs, respectively, adjusting for other confounders. We then included an interaction between ethnicity and MCC in addition to ethnicity, MCC and other

confounders in an extended model, which allowed for a formal statistical test of the potential ethnic difference in the strength of association between MCC and FO score. We used similar methods as above with DAGs (Figure 4.4) and determined that the adjustment for age, sociodemographic factors, and stroke severity was minimally sufficient to control for confounding in examining the impact of MCC on post-stroke FO among MAs and NHWs, respectively. Patients with missing information on confounder variables were excluded from the primary analysis. The 95% bootstrap confidence intervals (CIs) were constructed using the adjusted bootstrap percentile (BCa) method for regression coefficients. Statistical analyses were conducted with SAS (version 9.4, SAS Institute Inc, Cary, NC) and R (version 3.6.2, RStudio).

This project was approved by the University of Michigan institutional review board and the institutional review boards of the two local hospital systems. Written informed consent was obtained from all subjects.

4.3 Results

From 2008 to 2016, 1,769 patients survived 90 days after stroke and were eligible for the study (Figure 1). Baseline interviews were completed by 1,361 (77%) patients, of which 1,182 (87%) had their pre-stroke cognitive function (IQCODE) measured. Among these patients, 941 (80%) completed an outcome interview at 90 days. After excluding 45 (4.8%) patients with missing information on covariates, 896 patients were included in the primary analysis.

Baseline characteristics of the study participants are presented in Table 4.1. Among the 896 patients, 70% were MA and 51% were female. The mean age was 68 ±

12.2 years, and the median initial NIHSS score was 4 (interquartile range [IQR], 2-8). The median FO score at 90 days was 2.47 (IQR, 1.55-3.45), with 33% patients being dependent in ADL/IADLs (FO score >3, representing a lot of difficulty with ADL/IADLs) at 90 days. Compared to NHWs, MAs were younger, less likely to smoke or use alcohol, and had higher average BMI and lower educational attainment. MAs had worse post-stroke FO (higher FO score) than NHWs. About 37% of MAs were dependent at 90 days after stroke, while 25% of NHWs were dependent. MAs were more likely to have hypertension, diabetes, and renal failure, but less likely to have atrial fibrillation, cancer, and chronic obstructive pulmonary disease (COPD) (Table 4.2). The median MCC score was 6 (IQR 4-10) for NHWs and 7 (IQR 4-11) for MAs. The distribution of MCC score for MAs was right-skewed with a slightly heavier right tail compared to NHWs (Figure 3). After adjusting for age, MAs on average had 1 point higher MCC score than NHWs (95%CI, 0.29-1.62).

MCC, Ethnicity, and Post-stroke FO at 90 days

MCC score was significantly associated with worse post-stroke FO at 90 days with and without adjustment for confounders. Patients with high MCC score (at the 75th percentile) on average scored 0.70 point higher in the FO score (indicating worse FO) compared to those with low MCC score (at the 25th percentile) after adjusting for age, initial NIHSS, and sociodemographic factors. MAs, on average, scored 0.52 points (95% CI 0.37-0.64) worse in the FO score than NHWs after adjusting for age and initial NIHSS (Table 4.3). Including MCC in the model attenuated the ethnic difference in the FO score by 19% (from 0.52 to 0.42 points). Adjusting for sociodemographic factors attenuated the ethnic difference by 19% when MCC was not included (from 0.52 to

0.42). However, the attenuation in the ethnic difference was less obvious when MCC was included in the model (10%, from 0.42 to 0.38). This indicates that the contribution of sociodemographic factors to the ethnic difference in post-stroke FO may operate, to a great extent, through the pathway of MCC. Adjusting for sociodemographic factors and MCC together explained 27% of the ethnic differences in post-stroke FO (27% attenuation from 0.52 to 0.38).

The association between MCC and poor post-stroke FO was somewhat stronger in MAs than NHWs in the stratified analysis. Comparing to patients with low MCC score (MCC at the 25th percentile), those with high MCC score (at the 75th percentile) scored 0.72 and 0.64 point higher in the FO score among MAs and NHWs, respectively (Table 4.4). However, the interaction between MCC score and ethnicity was not statistically significant in the weighted Tobit regression model adjusting for age and initial NIHSS (p for interaction =0.56). This result did not change with further adjustment for sociodemographic factors (p for interaction =0.74).

4.4 Discussion

In this prospective cohort of ischemic stroke patients nested in a population-based study, we found that MAs have greater age-adjusted MCC burden at stroke onset and worse post-stroke FO at 90 days compared to NHWs. MCC, measured by a stroke-specific index, was found to be an important contributor to worse FO in MAs compared with NHWs, explaining approximately one-fifth of the ethnic difference in FO at 90 days. These results suggest that the prevention of MCC may not only improve post-stroke FO but lessen the gap between MA and NHW stroke patients in FO at 90 days.

Few existing studies have reported the overall MCC burden among stroke patients by ethnicity. The proportion of patients with more than one comorbid condition was similar among Hispanics (64.9%) and whites (69.7%) in a stroke rehabilitation cohort.[139] Our previous study in the BASIC Project measured the simple sum of 17 conditions and showed that the median number of conditions was 3 (IQR, 2-5) for both MAs and NHWs with no crude ethnic difference.[29] However, NHWs are older than MAs at stroke onset and the prevalence of MCC is known to be higher among older adults. Thus, the crude estimate of the ethnic difference in MCC comparing MAs with NHWs is likely negatively biased without age adjustment. Another explanation for the ethnic difference in MCC burden found in our study could be the inclusion of several factors not previously considered in MCC measurement. Our stroke-specific MCC index includes function-relevant factors including pre-stroke function, weight loss, and synergistic interactions (dementia × age, CHF × renal failure). Our results showed that MAs were more likely to be severely disabled (mRS 4+) before stroke and have weight loss. Although these differences in prevalence may not be statistically significant in the crude comparisons, the clustering of these differences may collectively impose a higher MCC burden in MAs compared to NHWs. Additionally, MA stroke patients were significantly more likely to have dementia among the oldest-old (85+ years old) and CHF with renal failure rather than CHF alone (Table 4.6). Ethnic differences in these joint distributions of MCC also seem to play a part in the excess MCC burden observed among MA stroke patients in our population.

Although the association between MCC and worse post-stroke FO was slightly stronger in MAs than NHWs, effect modification does not appear to be the major

pathway by which MCC contributes to ethnic disparities. Rather, our results suggest that the ethnic difference in MCC burden contributes to worse post-stroke FO in MAs compared with NHWs primarily through the confounding pathway or, on other words, the greater burden of MCC in MAs compared with NHWs. Our estimates suggest that 19% of the ethnic difference in the post-stroke FO at 90 days is explained by MCC. There are multiple possible clinical implications of the higher MCC burden in MAs. With higher MCC burden due to a higher prevalence of diabetes and CHF with renal failure, MAs may have a lower chance of getting tPA treatment due to concerns for hemorrhage, recurrent stroke, thromboembolic events.[230-236] Higher MCC burden in MAs given the higher prevalence of weight loss and dementia among the oldest-old is associated with more difficulty in retaining the acquired physical and cognitive skills necessary for ADLs, which may lower their chance of being referred to, participating in, and benefiting from post-stroke rehabilitation.[91-94,237-244] Therefore, MAs with greater MCC burden have additional obstacles compared to NHWs along the path of post-stroke recovery including increased risks of complications and lower chances of getting and benefit from stroke treatment and rehabilitation. Efforts to reduce MCC burden by preventing individual and clustered conditions could potentially promote the use of and benefit from stroke treatment and rehabilitation, as well as reduce the risk of complications and new cardiovascular morbidity among MA stroke patients, which could ultimately lessen the ethnic disparity in post-stroke FO.

Our study has a number of strengths. This study fills the gaps in knowledge with regards to understanding the MCC burden in a stroke patient population with ethnic diversity and the contribution of MCC to ethnic disparities in post-stroke FO. The

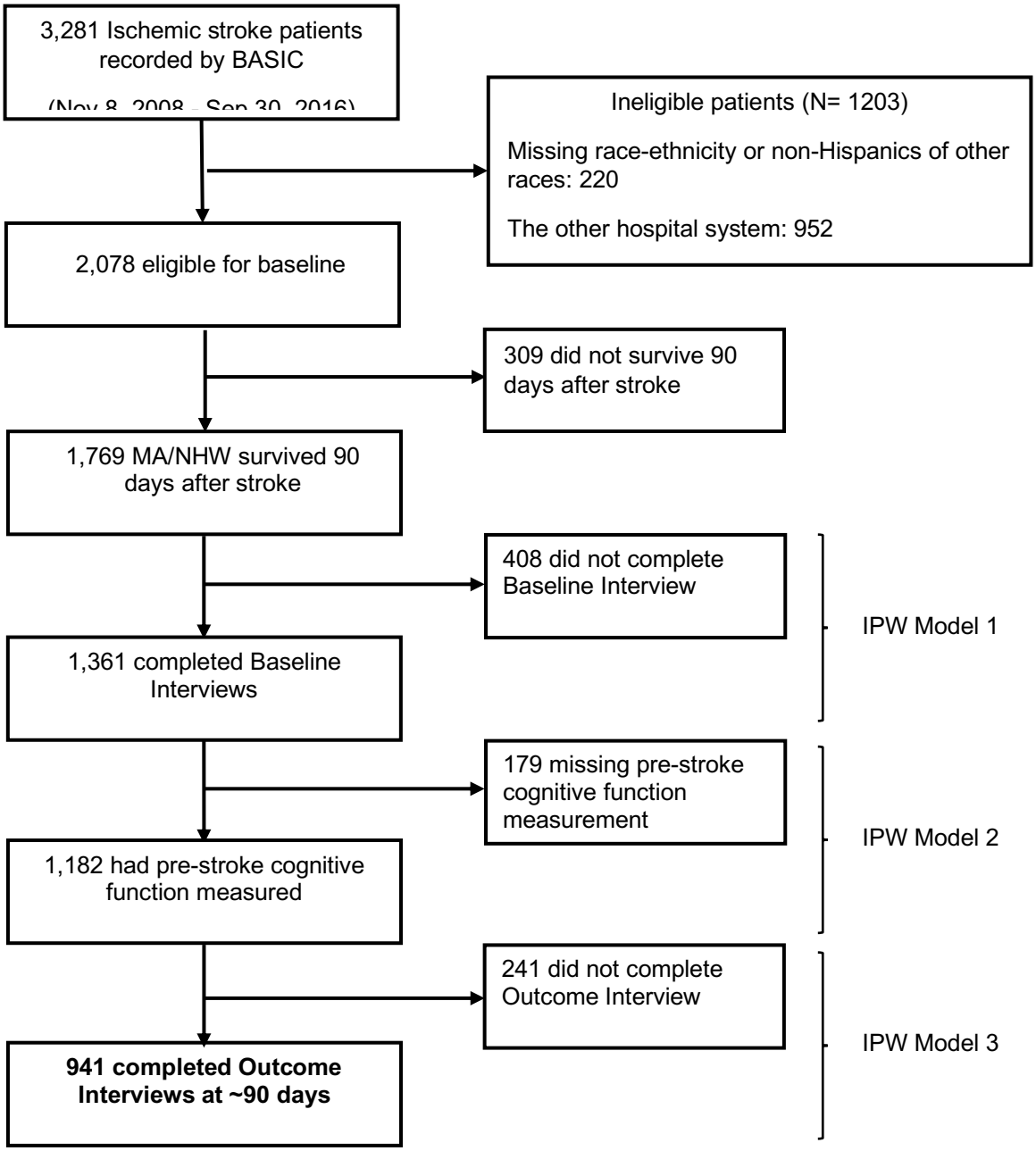
measurement tool used for MCC was designed to be stroke-specific and functionally relevant. Information on the included conditions and pre-stroke impairments was collected from baseline interviews, medical records in addition to the hospital discharge data, which minimizes measurement bias in MCC compared to only using administrative data. The use of inverse probability weighting approach limits the potential for selection bias due to missing information and non-participation which may differ by ethnicity. We measured FO using the ADL/IADL average score collected in the patient interview, which is sensitive to small changes in functioning that would not be detectable by broad disability measurement such as mRS.

There are some limitations to our study. The prevalence of MCC may be underestimated due to the fact that only 25 diagnoses are available in the hospital discharge data; however, only a small proportion of patients likely have more than 25 conditions. Underlying chronic conditions not treated during the acute hospitalization may not be reported in the hospital discharge data. Other comorbid condition, such as sleep-disordered breathing, has been found to be associated with post-stroke FO and has a higher prevalence in MAs but is not measured in all of our subjects.[245] Including sleep-disordered breathing in the adjustment could further attenuate the ethnic difference found in our study. We did not measure the severity, management, and duration of the conditions included in MCC, which may be different by ethnicity and potentially play a role in ethnic differences of FO. The ethnic difference in post-stroke FO may be further explained by other unmeasured confounders, including rehabilitation and post-stroke care. MA stroke patients are more likely to be discharged home, get less intensive rehabilitation and have less post-rehabilitation functional improvement

than NHWs.[20,139] Although differences in socioeconomic factors, MCC, and stroke severity may partially explain the ethnic difference in post-stroke care and rehabilitation, residual confounding by rehabilitation and post-stroke care may still exist after adjusting for these factors.[246,247] Thus, our estimated difference in post-stroke FO may be positively biased without adjustment for rehabilitation and post-stroke care. Our findings on ethnic differences in MCC and post-stroke FO may not be generalizable to patient populations with other types of stroke. Although we have a large study sample, we may still be underpowered to detect an effect modification in the association between ethnicity, MCC and post-stroke FO, and the results require further investigation in future studies.

In conclusion, MA patients with stroke have a higher age-adjusted MCC burden than NHWs and this difference in MCC burden explains a portion of the ethnic difference in post-stroke FO even after adjusting for to age, stroke severity, and sociodemographics. These results suggest that the prevention and treatment of MCC could mitigate post-stroke functional impairment, promote functional gain and lessen ethnic disparities in stroke outcomes.

Figure 4.1 Study Participation and Attrition



MA, Mexican Americans; NHW, non-Hispanic whites; IPW, inverse probability weighting.

Figure 4.2 MCC Burden by Ethnicity

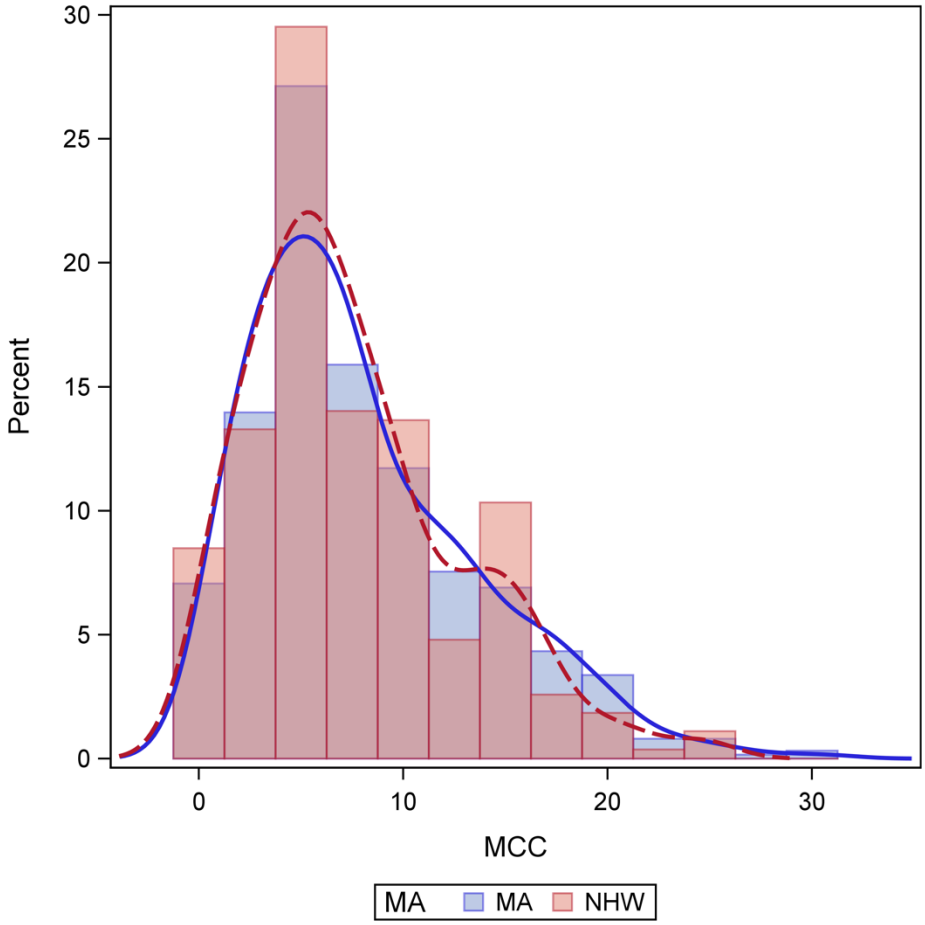


Figure 4.3 Using directed acyclic graphs to identify a minimally sufficient set of measured confounders to be adjusted for in estimating ethnic differences in post-stroke

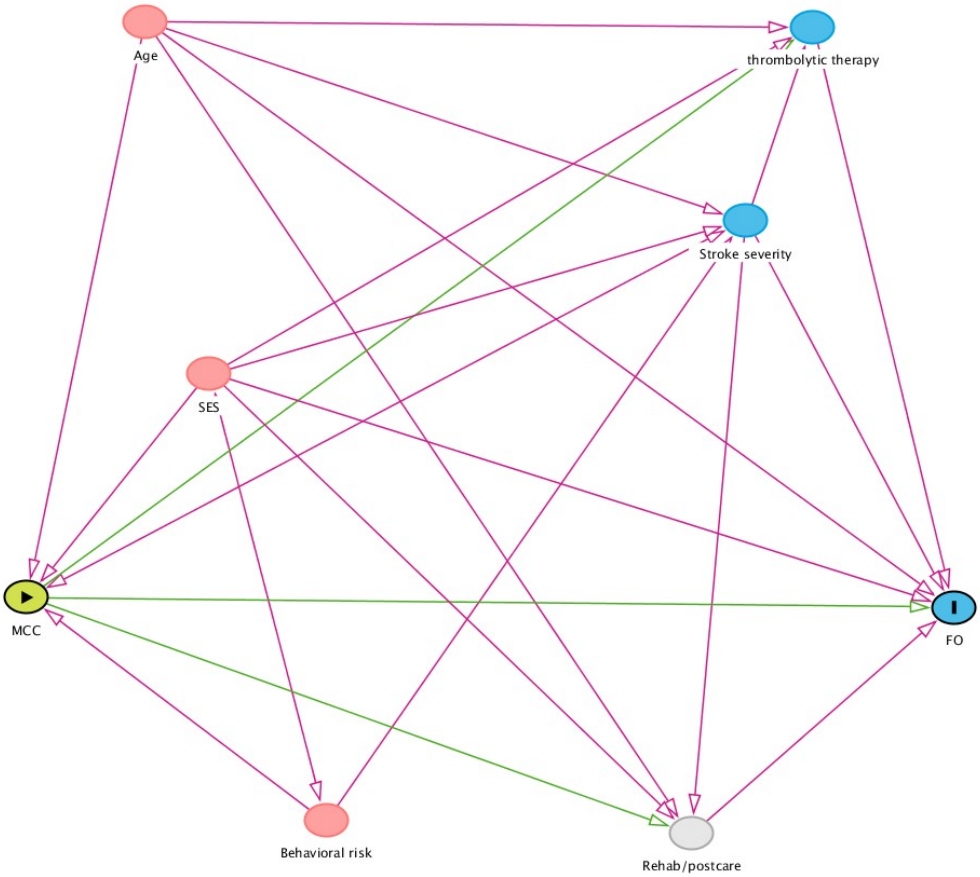


Figure 4.4 Using directed acyclic graphs to identify a minimally sufficient set of measured confounders to be adjusted for in examining the impact of MCC on post-stroke FO among MAs or NHWs

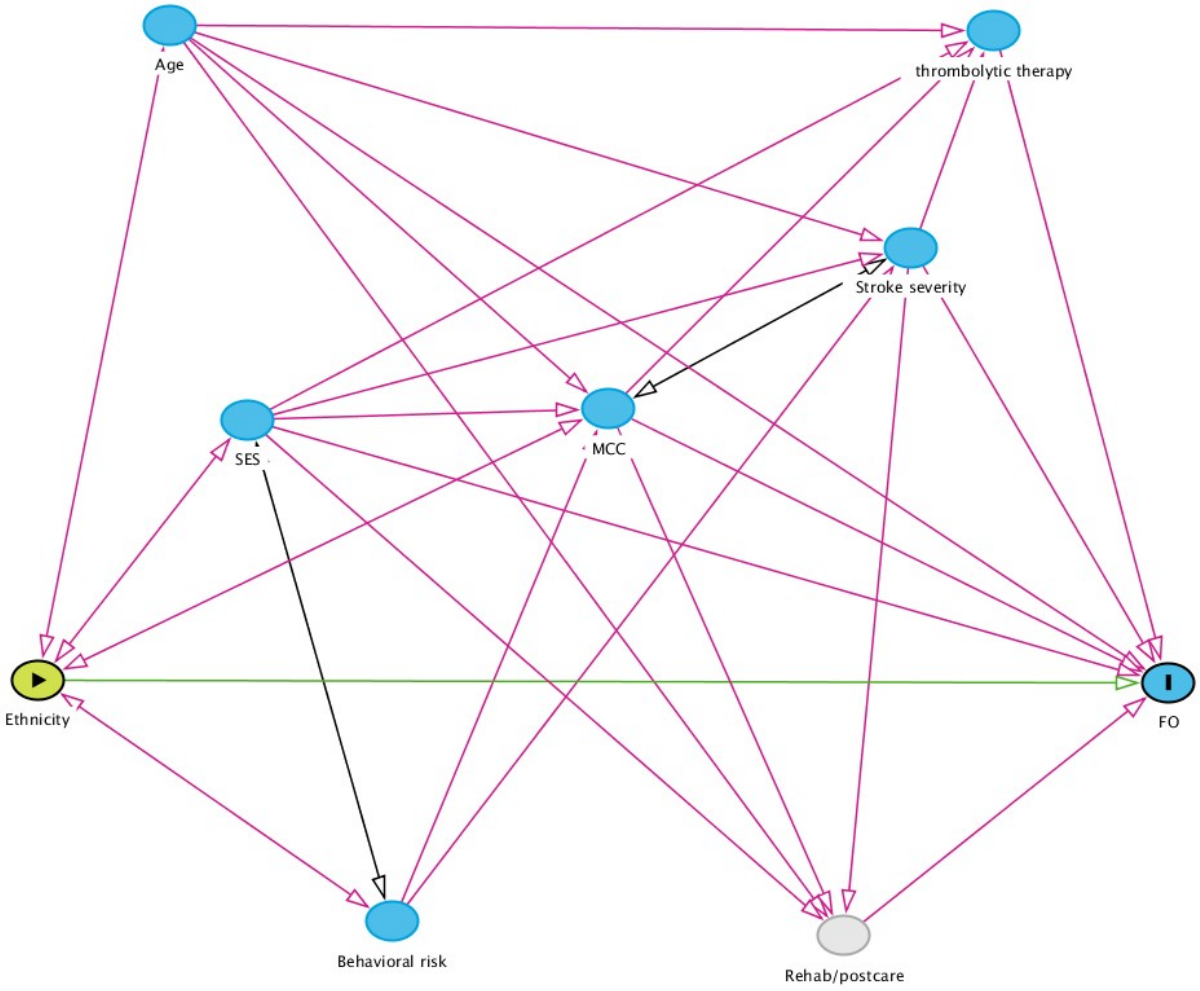


Table 4.1 Baseline Characteristics of the Study Participants by Ethnicity, 2008-2016 (N=896)

		NHW (N=272)		MA (N=624)		p-value*
		N or Median	% or (Q1, Q3)	N or Median	% or (Q1, Q3)	
Age		70	(60,80)	67	(58,78)	**0.013**
Female		140	51.5	319	51.1	0.924
Smoking	Never	146	53.7	420	67.3	**0.000**
	Former	56	20.6	81	13.0	
	Current	70	25.7	123	19.7	
Alcohol use	Never	37	13.6	201	32.2	**<.0001**
	<1 drink per week	122	44.9	278	44.6	
	1+ drink per week	113	41.5	145	23.2	
Education	< High school	9	3.3	186	29.8	**<.0001**
	High school	124	45.6	318	51.0	
	College +	139	51.1	120	19.2	
Insured		165	60.7	358	57.4	0.358
Pre-stroke mRS	0-1	120	44.1	254	40.7	0.235
	2-3	120	44.1	270	43.3	
	4+	32	11.8	100	16.0	
Marital status	Single/Never married	16	5.9	33	5.3	0.531
	Married/living together	142	52.2	310	49.7	
	Widowed	61	22.4	169	27.1	
	Divorced/separated	53	19.5	112	17.9	
Pre-stroke depression	None	145	66.8	306	67.5	0.919
	History of depression	29	13.4	63	13.9	
	Current antidepressant use	43	19.8	84	18.5	
Prior stroke or TIA		75	27.6	186	29.8	0.499
Thrombolytic therapy		44	16.2	77	12.3	0.122
Initial NIHSS		4	(2,8)	4	(2,8)	0.193
IQCODE		3.1	(3,3.3)	3.1	(3,3.4)	0.956
BMI		27.4	(24,32.2)	28.7	(25.2,33.4)	**0.004**

Social support index	10.0	(7,12)	10	(8,12)	0.899
Functional outcome score	2.0	(1.3,2.98)	2.59	(1.7,3.55)	**<.0001**

MA = Mexican American, mRS = modified Rankin scale, TIA = transient ischemic attack, NIHSS = National Institute for Health Stroke Scale, IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly

* Chi-square test for categorical variable, and Kruskal-wallis non-parametric test for continuous variables.

** Amount of missing: Pre-stroke depression 25.2%; Social support index 27.9%;

Table 4.2 Chronic Conditions in the Study Participants by Ethnicity, 2008-2016 (N=896)

	NHW (N=272)		MA (N=624)		p-value*
	N	%	N	%	
Hypertension	203	74.6	536	85.9	**<.0001**
High Cholesterol	140	51.5	306	49.0	0.503
Diabetes	84	30.9	350	56.1	**<.0001**
Coronary Artery Disease	79	29.0	194	31.1	0.541
Atrial fibrillation	53	19.5	74	11.9	**0.003**
Cancer	42	15.4	64	10.3	**0.027**
COPD	50	18.4	43	6.9	**<.0001**
Congestive heart failure	28	10.3	56	9.0	0.533
Myocardial infarction	21	7.7	38	6.1	0.366
Renal failure	26	9.6	96	15.4	**0.020**
Other neurological disorders	78	28.8	148	23.8	0.112
Hypothyroidism	41	15.1	93	14.9	0.938
Peripheral vascular disorders	35	12.9	101	16.2	0.207
Valvular disease	23	8.5	35	5.6	0.109
Weight loss	5	1.8	24	3.9	0.120
Rheumatoid arthritis/collagen vascular diseases	8	3.0	18	2.9	0.959
Liver disease	4	1.5	17	2.7	0.256
Psychoses	4	1.5	15	2.4	0.375
Pulmonary circulation disorders	5	1.8	7	1.1	0.389
Deficiency anemia	1	0.4	9	1.4	0.160
Coagulopathy	5	1.8	4	0.6	0.098
Dementia	60	22.1	147	23.6	0.625

COPD = chronic obstructive pulmonary disease; * Chi-square test. All missing <1%;

Table 4.3 Ethnicity Differences (MA vs. NHW) in Post-stroke Functional Outcome at Ninety-day Before and After Adjustment for Multiple Chronic Conditions (MCC)

Model	Mean ethnic difference in FO score (95% CI)		Attenuation in the ethnic difference due to adjusting for MCC
	Not adjusted for MCC	Adjusted for MCC	
1 Ethnicity, age, initial NIHSS	0.52 (0.37-0.64)	0.42 (0.30-0.54)	19%
2 Model 1 + SDS	0.42 (0.22-0.53)	0.38 (0.22-0.48)	10%
Attenuation in the ethnic difference due to adjusting for SDS	19%	10%	

Abbreviations: MA= Mexican American; NHW=non-Hispanic white; SDS = sex, education, marital status, and insurance status; All p <0.0001

Table 4.4 Ethnic-Specific Associations between Multiple Chronic Conditions (MCC) and Post-stroke Functional Outcome (FO) at 90 Days

	Mean difference in FO score (95% CI)	
	MA	**NHW**
MCC, every 7 points increment (1 IQR)	0.72 (0.58, 0.80)	0.64 (0.46, 0.77)

MA= Mexican American; NHW=non-Hispanic white;
Models were adjusted for age, initial NIHSS, and socio-demographic status (SDS) including sex, education, marital status, and insurance status.

Table 4.5 Odds Ratio from Inverse Probability Weighting Models with Backward Selection

	Model 1	Model 2	Model 3
Age	0.99 (0.98,1)	1.03 (1.01,1.04)	
Female			1.4 (1.03,1.92)
Mexican Americans	1.45 (1.15,1.84)	1.9 (1.32,2.73)	
Marital Status			
Widowed/divorced/separated		ref	ref
Single/Never married		0.65 (0.38,1.09)	
Married/living together		3.41 (2.29,5.08)	1.39 (1.02,1.9)
Education			
No high school			
High school education			
College or more			
Insured			
Current/former smoker		0.73 (0.52,1.04)	
Excessive alcohol use		0.68 (0.38,1.21)	
BMI	1.02 (1,1.04)		
NIHSS	0.98 (0.94,1.02)	1.07 (0.99,1.17)	0.9 (0.86,0.95)
Log NIHSS	1.29 (0.99,1.68)	0.8 (0.5,1.29)	1.69 (1.19,2.4)
Pre-stroke mRS		1.17 (1.01,1.35)	1.11 (0.99,1.24)
Medical conditions			
Dementia/Alzheimer’s		3.35 (1.01,11.17)	

ALS			
Atrial fibrillation			1.71 (1.03,2.85)
Cancer			
COPD	1.3 (0.89,1.91)		
Congestive heart failure	0.65 (0.45,0.93)		0.63 (0.38,1.07)
Coronary Artery Disease			1.4 (0.97,2.03)
Diabetes		0.74 (0.52,1.07)	
End-stage renal disease			
Epilepsy			
High Cholesterol	1.22 (0.97,1.54)		
Hypertension			
History of Stroke/TIA			
Myocardial Infarction		2.06 (0.91,4.66)	0.65 (0.36,1.17)
Parkinson’s	0.48 (0.22,1.09)		

Table 4.6 Joint distribution of selected comorbid conditions

	NHW (N=272)		MA (N=624)		p-value*
	N	%	N	%	
Dementia prevalence within age groups					
45-54	5	13.9	14	14.9	0.8846
55-64	12	19.7	30	16.2	0.5339
65-74	6	9.7	23	16.0	0.2334
75-84	24	30.8	46	31.9	0.8572
85+	13	37.1	34	59.6	**0.0360**
Prior stroke/TIA prevalence within pre-stroke mRS stratums					
mRS 0-1	19	15.8	50	19.7	0.3700
mRS 2-3	39	32.5	87	32.2	0.9568
mRS 4-5	17	53.1	49	49.0	0.6846
Renal failure prevalence among patients with CHF					
	6	21.4	20	35.7	0.1818

MA = Mexican American, mRS = modified Rankin scale, TIA = transient ischemic attack, CHF=Congestive heart failure.
* Chi-square test.

Chapter 5: Discussion

5.1 Overall Summary of Research and Finding

This dissertation investigated the association between MCC and post-stroke FO among ischemic stroke patients through a systematic literature review, meta-analysis, and data analyses using a bi-ethnic population-based stroke cohort. Chapter 2 systematically reviewed previous studies. Studies predominantly used the CCI or mCCI to measure MCC burden, and the negative association between MCC and FO was statistically significant in the meta-analysis. In Chapter 3, novel predictors of post-stroke FO were identified and a new MCC index was developed among stroke patients, which improved the prediction of post-stroke FO at 90 days and outperformed the mCCI. Chapter 4 showed that MAs have significantly greater age-adjusted MCC burden at stroke onset compared to NHWs. MCC, measured by the new index, was an important contributor to ethnic disparities in post-stroke FO at 90 days, while effect modification of the MCC-FO association by ethnicity was not a significant contributor. This body of work confirmed that the accurate measurement of MCC is important for FO prognosis in stroke, which could inform stroke treatment and post-acute care.

5.2 Aim 1

Summary

In the absence of population-based studies, the systematic literature review in Chapter 2 focused on hospital-based cohort studies. The review found that the CCI and mCCI were predominantly used to measure overall MCC burden in predicting post-stroke FO, which was mostly assessed by mRS at different time points after stroke. Six out of twelve of the hospital-based studies reported a significant negative association between MCC and FO, and the pooled analysis supported that greater MCC was associated with worse FO after stroke. Gaps and limitations were identified from the previous literature and the predominantly used indices, namely the CCI and mCCI. The review suggested that the measurement of MCC could potentially be improved by considering additional function-relevant conditions, synergistic interactions, and pre-stroke impairments, as well as by research conducted in a population-based study with race/ethnic diversity.

Advances to the Field

This work specifically adds to the literature on MCC in stroke through the detailed summary of MCC indices used previously and the pooled analysis on the MCC-FO association among stroke patients. There has been no universal agreement on the approach to measuring MCC in stroke, and findings have been mixed regarding MCC being an independent predictor for post-stroke FO. This is the first systematic review that focused on MCC in the broader population of stroke whereas previous systematic reviews on MCC in stroke patients have limited to rehabilitation settings,[169,248] which is

discussed in more detail in the following section. In previous work predicting post-stroke FO, MCC was often included as a covariate rather than the main effect. Restrictions on articles with MCC-related terms in their title/abstract would, therefore, exclude these valid studies. For this reason, the full-text screening was expanded to more than 4,000 studies that included multivariable modeling for post-stroke FO. This extensive effort successfully increased the number of eligible studies, making the subsequent meta-analysis possible. Although it was not a surprise to find the significant pooled association between MCC and post-stroke FO, this is the first study to quantify this association pooling data from multiple studies using meta-analytic techniques, which adds to the growing body of evidence that greater MCC burden is an independent predictor for worse FO after stroke. The review culminates in a discussion of the limitations of using the CCI and mCCI in measuring MCC among stroke patients, which raises the potential for developing a more refined MCC index to reflect the full spectrum of MCC in the broader stroke population by considering additional function-relevant conditions, synergistic interactions, and pre-stroke impairment.

Comparisons to Prior Work

To date, there has been no comprehensive literature review that has focused on MCC as a predictor for FO in a general or hospital-based stroke population. One review focused on the rehabilitation population of stroke and hip fracture patients, and a modest negative association between MCC and FO was reported.[169] However, rehabilitation literature focused on a different set of research questions from that studied in Chapter 2. In rehabilitation research, the goal was oftentimes to predict and select patients who would benefit from rehabilitation versus predicting FO in general. Hence,

the common outcomes of interest in the rehabilitation research were functional gain, rehabilitation efficacy, or FO at rehabilitation discharge adjusting for motor or overall function at rehabilitation admission,[70,78,170,177-179] which teased out the impact of rehabilitation potential.[249] But since MCC is associated with functional status at rehabilitation admission,[78] the estimated effect of MCC with these adjustments could only capture its impact on the rehabilitation process while ignoring the part influencing recovery up to the rehabilitation admission – an underestimation of the role MCC played in the overall stroke course even for rehabilitation participants. Moreover, only less than one-third of stroke patients eventually participate in inpatient rehabilitation.[20] Since patients with severe comorbidities and functional or cognitive impairment are often excluded from rehabilitation, patients from inpatient rehabilitation have a different spectrum and severity of comorbid conditions and cognitive or functional impairment compared to the majority of stroke patients.[70,78,170,177-179] In addition, the rehabilitation literature has used indices that do not distinguish post-stroke complications and pre-stroke comorbidities (e.g. the Liu comorbidity index),[70,78,177] and FO measurements less used in the hospital-based cohorts (e.g. FIM at discharge),[70,78,170,177] which limits the applicability of their findings to early FO prediction during acute stroke hospitalization. Therefore, findings from Chapter 2 fill these gaps and advance the understanding of MCC in post-stroke FO in the broader stroke population.

Implications

Predicting FO is becoming more challenging as the population at-risk for stroke ages and becomes more heterogeneous in pre-stroke functional and cognitive reserve, as well as comorbid conditions. Although it has been shown that a simpler model

including only stroke severity (NIHSS or Canadian Neurological Scale) and age can predict FO well,[174,250,251] recent research revealed that comorbid conditions greatly increase the risk of poor FO and using this simple model could underestimate the risk of poor FO among patients with MCC.[83-85,97] As an independent predictor for post-stroke FO, MCC should be measured routinely as an integrated part of prognosis rather than considered as a special case scenario.

The gaps and limitations identified in the current literature and MCC indices informs future research in developing better indices to measure MCC among stroke patients. More function-related conditions, pre-stroke functional and cognitive impairments, and possible synergistic interactions should be considered in a refined MCC index. Neurologic diseases including Parkinson's disease, nutritional status, hearing/vision impairments, falls, arthritis and psychiatric disorders including mood disorders are important drivers of functional decline in the elderly and should be considered in the measurement of MCC in predicting FO after stroke. There has been strong evidence showing that cognitive, functional, and psychosocial impairments are important predictors for functional decline in the elderly,[62] which should also be included in the MCC measurement to predict post-stroke FO as discussed in Chapter 1. Although the pathophysiology underlying the association of MCC with FO is unclear, it is possible that these chronic conditions and impairments could impact post-stroke FO through synergistic interactions and stroke-specific pathologies as well. To better understand the impact of MCC on post-stroke FO, a new integrated conceptual model for MCC considering the co-occurrence of chronic conditions and pre-stroke functional, cognitive,

and psychosocial impairments would assure a more comprehensive assessment of the MCC burden and clustering effects.

Using this new conceptual model, a refined MCC index can be developed to improve the accuracy of prognosis in post-stroke FO. With a growing number of patients with MCC in the US, projections for the burden of stroke-related disability could be different in the future with more accurate prognosis in these patients. More research is needed to understand the pathophysiology underlying the association of MCC with FO, including possible synergistic interactions among comorbid conditions. MCC may impact post-stroke FO through its association with other important determinants for stroke treatment and recovery, such as chances of having complications, being eligible for thrombolysis, and having the ability to participate in rehabilitation. Additional work is warranted to investigate different pathways for the impact of MCC on post-stroke FO.

5.3 Aim 2

Summary

To address the limitations in previous literature on MCC in stroke, Chapter 3 aimed to improve the measurement of MCC and focused on the development of a new function-relevant MCC index specific for ischemic stroke patients in a population-based cohort with ethnic diversity from the BASIC Project. MCC in stroke was re-conceptualized as the co-occurrence of *chronic conditions and pre-stroke functional, cognitive, and psychosocial impairments.* A new MCC index was developed using variable selection methods from machine learning by including functional-relevant conditions, pre-stroke impairments, and synergistic interactions in the MCC assessment.

The MCC index contained the pre-stroke mRS, age, congestive heart failure (CHF), weight loss, diabetes, other neurological disorders, and interactions including dementia × age, CHF × renal failure, and pre-stroke mRS × history of stroke/TIA. In the validation dataset, the index alone explained 24% of the variability in the FO score in addition to stroke severity and age, was well-calibrated ($p = 0.41$), predicted functional dependency at 90 days more accurately (AUC, 0.85) than the model with initial NIHSS and age (AUC, 0.66), and outperformed the mCCI in predicting both the FO measured by ADL/IADL and post-stroke mRS. The new index demonstrated potential as an MCC assessment tool in ischemic stroke although further external validation in other stroke populations is required.

Comparisons to Prior Work

There have been two previous efforts attempting to develop stroke-specific MCC indices for FO in the general stroke population, but both failed to develop a more valid index than the mCCI. Tessier et al. developed a stroke-specific MCC index from a list of 16 conditions commonly encountered in a multi-centered, prospective cohort of ischemic and hemorrhagic stroke patients in Canada.[38] They failed to consider several important conditions, such as CHF, renal disease, and neurologic diseases other than Parkinson's as candidates, which may contribute to the underperformance of their new indices compared to the mCCI in predicting post-stroke FO. Denti et al. re-assessed the stroke-specific weights for the conditions included in the mCCI in a single-center population of geriatric patients with ischemic stroke.[189] They showed that the new index failed to improve the AUC compared to the mCCI in predicting disability at 1 month after stroke, and the mCCI itself was not an independent predictor for disability after

controlling for age and stroke severity. Nevertheless, in re-assessing the stroke-specific weights for post-stroke disability, they found that the majority of the conditions in the mCCI in fact carried zero weight, in other words, had very little impact on post-stroke disability. This finding challenged the construct validity of the mCCI being used to measure function relevant MCC burden in stroke patients. Four out of five of the conditions that they found to be important in the mCCI for post-stroke FO, including CHF, dementia, diabetes, and moderate-severe kidney diseases, were consistent with factors included in our new MCC index. The development of both of the two indices is limited in the number of candidate conditions and lack of systematic methods for variable selection, which prevents the discovery of novel conditions and synergistic interactions between conditions that may play important roles in impacting post-stroke FO.

Several MCC indices have been developed or used in specific stroke populations. These indices, although not meeting the inclusion criteria in Chapter 2, were previously introduced in Chapter 1, including the FCI, the LiuCI, and the COM-SI.[70,78,177,178,252] None of these three indices was developed in the general stroke population. The LiuCI and the COM-SI are both stroke-specific indices but were developed in rehabilitation populations to predict functional gain (efficacy) during rehabilitation versus FO. Although both considered more than 20 conditions, they still may not capture the full spectrum of comorbid conditions in the broader stroke population given the differences in these two source populations, which were discussed in the former section. For example, the LiuCI does not consider other neurological disorders, such as CNS demyelinating diseases and Parkinson's disease, or previous

stroke/TIA, while the COM-SI does not consider epilepsy or malnutrition. The FCI was developed in orthopedic patients, who could potentially be healthier and more independent than the stroke population.[73] FCI was found to perform better in predicting FO at 3 months compared to the mCCI in a mixed cohort of ischemic and hemorrhagic stroke patients,[38] however, this association was not adjusted for other predictors, such as age and stroke severity, making the results hard to interpret. Epilepsy and malnutrition were also not included in the 18 conditions considered by the FCI. Additionally, the Cumulative Illness Rating Scale (CIRS)[253] or its adaptive version in geriatric patients (CIRS-G),[254] is a summed score that measures the level of impairment in 13 (or 14) organ systems. CIRS-G was found to be significantly correlated with post-stroke FO at hospital discharge in a cross-sectional study after adjusting for age and other predictors not including stroke severity.[255] However, using CIRS in measuring pre-stroke comorbidity is challenging since the scores for each organ system are given subjectively based on the influence on ADLs, which requires accurate recall of the level and impact of the impairments for all body systems. All of these previously used MCC indices are considerably more complex than the new MCC index. Many of the previously reported associations with post-stroke FO were either not covariate-adjusted or covariate-adjusted but not statistically significant, making the comparisons across studies challenging.

Previous hospital-based studies in this field predominantly used a global disability measure, the mRS, to measure post-stroke FO. The mRS does not measure cognitive function and is not sensitive to smaller differences in FO between patients.[190] Other recommended instruments for ADLs, such as BI and FIM,[256] were seldom used or

not modeled continuously.[32,188] Some defined poor FO as including death (mRS 6), making it hard to distinguish the impact of MCC on mortality and FO.[71,180,184,187] MRS can have a low inter-rater agreement, and dichotomizing the mRS score also adds to the insensitiveness of detecting differences between patients (mRS 3 vs. 5).[191] We measured FO using ADL and IADLs and assessed the outcome as a continuous scale, which more comprehensively measured post-stroke FO and captured more variability in FO.

Previous studies have found that the CCI and mCCI explain a comparatively smaller proportion (<10%) of variance in FO relative to stroke severity,[38,169] similar to what we found in the training and validation dataset for the mCCI (5-13%). However, the new MCC index alone explained 31% of the variance in FO as detailed in Chapter 3. And compared to the 15% explained by stroke severity and age, the new MCC index additionally explained 24% of the variance in post-stroke FO. This large improvement may be attributable to the addition of novel predictors, pre-stroke mRS, and the synergistic interactions between included conditions. The amount of variance explained by MCC depends on the range of both the FO and the MCC index used.[38] In the study population, the observed range of the new MCC index (0-31) is much larger than the range for the mCCI (0-10), although the theoretical range for the mCCI is 0 to 34. The results also found that the mCCI was only weakly correlated with the new MCC index (correlation coefficient, 0.32). As mentioned before, many conditions in the CCI (or the mCCI) were not associated with post-stroke FO.[83-85] Additionally, previous studies have found that the mCCI has a poor discriminatory ability for predicting unfavorable FO. Katan et al. reported that the mCCI performed poorly (AUC of 0.63) in discriminating

favorable (mRS 0-2) versus unfavorable (mRS 3-5) FO at 90 days after stroke in a prospective cohort of ischemic stroke patients,[187] even worse than what we showed in the validation dataset with the mRS as the outcome (AUC of 0.72). Our results further showed that the ability of the mCCI in predicting functional dependency measured by ADL/IADL was poor (AUC of 0.64). These comparisons all suggest that the new MCC index may be favored over the mCCI to accurately measure the MCC burden and predict FO in stroke patients.

Advances to the Field

With the declining stroke mortality and a projected increase in the number of stroke survivors, there's a growing interest in understanding the drivers of FO among stroke survivors. This work is an important step forward in understanding the role of MCC, an understudied predictor for disability, on FO after stroke. The new MCC index is the first stroke-specific, function-relevant MCC index developed in the general stroke population. The prospective, population-based study design allowed for the capture of the MCC spectrum in the broader stroke population for the first time. Moving beyond the traditional definition for MCC as the diagnosed diseases, the addition of pre-stroke impairments and synergistic interactions resulted in a comprehensive assessment for the pre-stroke reserve of an individual. Using variable selection methods from machine learning, a large number of more than 600 candidate predictors, including comorbid conditions, impairments, and synergistic interactions, were explored and systematically selected. This has given rise to the discovery of the novel predictors and interactions in the new index, which was not possible in the previous work in this field since their conditions were chosen based on clinical judgment and literature review, and pruned

based on prevalence, severity, or body systems. The interactions were selected along with the corresponding main effects using the hierNet method which contributed to the interpretability of the index. All of these improvements contributed to the larger proportion of variance explained by the new index compared to the previously used indices. In contrast to previous stroke-specific indices developed in hospital-based studies, the new index not only successfully improved the prediction of post-stroke FO but also outperformed the mCCI in discriminating functional dependency, even though it required less information. This work advances the field by providing a simple and integrated tool for measuring MCC burden in all ischemic stroke patients, which could have many important implications in care planning and research.

Implications

With the aging population and a majority of patients with MCC at stroke onset, the assessment of MCC could become an integrated part of the overall assessment during acute hospitalization and post-acute care. To improve the accuracy of measuring MCC burden as well as the accuracy of prognosis, our findings on novel predictors for post-stroke FO highlight the necessity of investigating a broader range of chronic conditions beyond the common risk factors for stroke (e.g. hypertension, diabetes, obesity, and hyperlipidemia) and those included in the CCI, because the knowledge on the precise nature and prevalence of MCC in stroke is still limited. Other pre-stroke limitations that do not fit into discrete disease categories, including frailty and geriatric syndromes, may be important aspects to be considered in MCC. For example, one of our predictors, weight loss, may likely be a proxy for chronic malnutrition and sarcopenia, which are indicators for frailty or geriatric syndromes.[119,257] Frailty is likely to

impact ADLs and IADLs that require energetics and performance speed, such as mobility, and consequently, contribute to disability given its central features of weakness, decreased endurance, and slowed performance.[119] Geriatric conditions are time-consuming and complex to manage, so healthcare providers are less likely to perform all appropriate tests and interventions that may impact functional recovery among patients with geriatric conditions. There may also be separate pathways by which frailty, geriatric syndromes, and chronic conditions contribute to disability among stroke patients. Therefore, a broader investigation of how MCC is related to frailty and geriatric syndromes, including malnutrition, sarcopenia, gaits, falls, incontinence, and chronic pain, would be needed in understanding post-stroke FO.

The new MCC index, a relatively simple and yet integrated tool, demonstrates potential as a useful assessment tool in research and clinical assessment for prognosis, although further validation is required. This work has implications in research, at the policy level, and in clinical practice.

From a research perspective, the MCC burden measured by the new index could be an important case-mix adjustment for observational studies. The current case-mix adjustment in the prognostic studies for post-stroke FO has widely varied from one study to another without considering interactions between the adjusted factors.[83-85,152,174,258] A relatively simple index that includes synergistic interactions like our new MCC index would make the case-mix adjustment easier in observational studies so that the results across studies are more comparable. Randomized clinical trials (RCT) for new treatments and interventions also need to consider MCC, given its strong association with post-stroke FO. Using a MCC index when balancing treatment arms or

stratifying patients into prognostically comparable groups may not only increase the power to detect meaningful treatment effects but also help conduct subsequent meta-analyses because the results across trials would be more comparable.[152-155]

At the policy level, most high-quality evidence in clinical guidelines are based on RCTs, where patients with comorbid conditions were often excluded.[259-261] Clinicians are challenged when caring for patients with MCC because of the mismatch between the study group for generating practice recommendations and the patients in the real-world. Evidence for treatment is oftentimes non-existent for patients with MCC.[259-261] MCC burden identified in this study can inform future RCTs to enroll more patients with MCC in representative numbers of the real-world stroke population. Subgroup analysis would then be feasible to provide evidence for intervention in patients with MCC, which also sensitizes the identification of complications among patients with certain disease combinations. Given the limitation in RCTs, the US Food and Drug Administration (FDA) should also consider results from large observational studies as an important supplement in discussing the harms and benefits of intervention among patients with different prognosis due to MCC. Phase 4 trials conducted in patients with MCC should include risk and prognostic stratification based on the MCC status. The enhanced clinical guidelines based on this evidence could also impact policy development in payment and reimbursement systems to ensure appropriate care delivery required by patients with MCC.

Clinically, a refined MCC measurement and more precise prognosis may facilitate decision making and communication among patients, family or caregivers, and clinicians by putting everyone on the same page. FO is oftentimes a priority over

competing health goals for older adults and should be emphasized when considering tradeoffs for multiple treatments.[262] More refined FO prognosis could minimize uncertainties in this prioritized goal so that patients with MCC and worse prognosis in FO could be treated more aggressively with potentially beneficial interventions and post-acute care. Patients without conditions that predict worse FO may be spared complications from aggressive treatments, such as mechanical thrombectomy or aggressive blood pressure management. Enhanced guidelines and prioritizing on patient-centered care may reduce treatment burden, conflicts, harms, and cost, while improving patient satisfaction and adherence.[259,263,264] The index also suggests that some practical issues related to the management of MCC may also play a role in impacting post-stroke FO. For example, patients with renal failure who need dialysis may only be able to participate in acute rehabilitation in facilities that either have dialysis on-site or can provide transportation to off-site dialysis units. Solutions to logistical issues like this through coordination and collaboration among an interdisciplinary team may lessen the impact of MCC on post-stroke FO through maximizing their access to care. Additionally, by working with patients with disability-associated conditions to educate them on stroke symptoms and enhance responsiveness to the onset of stroke, the administration of thrombolysis treatment can be expedited, which may in turn reduce complications and disabilities. Patients who are at high risk for stroke and poor post-stroke FO should be aggressively managed, with emphasis on engagement in physical activity and improving endurance and strength, which could increase their chance to engage in aggressive rehabilitation if stroke occurs.

Although the new MCC index may potentially be useful in prognosis, clinicians should be mindful when discussing the probability of being functional dependent by MCC scores based on our data. Patients nowadays and from different clinical settings may have better FO prognosis and MCC management compared to patients in our cohort recruited starting from more than 10 years ago, potentially due to advances in patient transfer, thrombectomy, and neurocritical care.[265] Caution must be taken when clinicians, patients, and family make treatment decisions relying on the prognosis based on MCC status, stroke severity, age, and/or other factors because studies have shown that early limitations in treatment intensity in patients with severe stroke are associated with poor outcomes.[266,267] Therefore, poor prognosis should not prevent patients from receiving treatment concordant to guidelines. On the contrary, one should make sure that patients with poor prognosis for FO are treated vigorously to prevent further function loss. Aggressive rehabilitation may even be more applicable to these patients given that they have greater potential for function gain.

5.4 Aim 3

Summary

Chapter 4 assessed the contribution of MCC to the ethnic difference in post-stroke FO at 90 days between MA and NHW ischemic stroke patients in the same study population using the new MCC index. The median MCC score was 6 (IQR 4-10) for NHWs and 7 (IQR 4-11) for MAs. MAs had significantly greater age-adjusted MCC burden compared to NHWs. Patients with high MCC score (at the 75th percentile) on average scored 0.7 point higher in the FO score (indicating worse FO) compared to

those with low MCC score (at the 25th percentile) after adjusting for age, stroke severity, and sociodemographic factors. MCC explained 19% of the ethnic difference in post-stroke FO, while effect modification by ethnicity was not statistically significant. The results also showed that the contribution of sociodemographic factors to the ethnic difference in post-stroke FO may operate through the pathway of MCC. Greater MCC burden in MAs explained a part but not all of the ethnic difference in post-stroke FO, suggesting that additional research on the causes of poorer FO in MAs compared with that of NHWs is warranted.

Comparisons to Prior Work

Chapter 4 was the first study to investigate the contribution of MCC to ethnic disparities in post-stroke FO using a MCC index. Few studies have investigated the difference in the overall MCC burden among stroke patients in different ethnic groups. Previously in the BASIC Project, MCC burden was measured by the simple sum of 17 conditions and no difference was found in the median number of comorbid conditions for MAs and NHWs in the crude analysis.[29] Berges et al. also used a count of 4 conditions to measure MCC, which was not significantly different between Hispanics and whites in a multi-centered, tri-ethnic rehabilitation cohort of stroke patients.[139] These findings align with our finding in crude analysis on the no-significant ethnic difference in MCC burden, although we measured MCC using the new index. However, MAs have stroke on average at younger ages than NHWs. Since MCC is more prevalent in older adults, the crude estimate of the ethnic difference in the MCC burden would be negatively biased without adjusting for age. This explained our finding of the

significant age-adjusted ethnic difference in MCC, suggesting that MAs have a greater MCC burden than NHWs of similar age at stroke onset.

Using the number of conditions to compare MCC burden by ethnicity is also challenging for interpretation because a simple count does not take into consideration the differential impact of the conditions on stroke outcomes. MA stroke patients have a different MCC spectrum than NHWs. Previous studies have found that MA stroke patients are more likely to have pre-existing hypertension, diabetes, and previous stroke or TIA, but are less likely to have atrial fibrillation and coronary artery disease compared with NHWs.[138,222,223] Findings from descriptive analysis in Chapter 4 were consistent with these findings and additionally showed that MAs were more likely to have renal failure, weight loss, and severe disability (mRS 4+) before stroke. Additionally, there were some suggestive differences in the joint distribution of MCC by ethnicity, although not statistically significant in the crude comparisons, which collectively could impose a higher MCC burden in MAs compared to NHWs. Therefore, to compare the overall MCC burden relative to the post-stroke FO in MAs and NHWs and to take synergistic interactions into consideration, the new MCC index is better suited than a simple count.

Advances to the Field

This work specifically contributes to the literature by being the first study to investigate the contribution of MCC to ethnic disparities in post-stroke FO using a MCC index. Compared to NHWs, MAs have worse FO after stroke, which was not fully explained by demographics, socioeconomic status, stroke risk factors, stroke severity, and differential poststroke mortality by ethnicity.[200] We found that MCC burden, an important predictor for FO, contributed to the ethnic disparities in post-stroke FO in

addition to age, stroke severity, and sociodemographic factors. Using a stroke-specific MCC index, we found a significant ethnic difference in age-adjusted MCC burden, which has not been reported previously. By including synergistic interactions, we were able to consider the clustering effect in quantifying the MCC burden by ethnicity for the first time. We also found that MCC explained the contribution of sociodemographic factors to the ethnic difference in FO. Although we did not find effect modification to be the major pathway by which MCC contributes to ethnic disparities and ethnic disparities still exist after controlling for MCC and other factors, this work is one step further in understanding the drivers of ethnic disparities in stroke outcomes. Our results suggest that MCC is an important contributor with multiple implications, and future work is warranted to explain the higher MCC burden observed in MA stroke patients.

Implications

The combination of increased stroke risk and worse post-stroke disability, prolonged survival, and rapid growth in the MA population will amplify the burden of care in MA stroke survivors. Although the differences in prevalence for individual chronic conditions and stroke risk factors are known contributors to ethnic disparities in stroke outcomes, the contribution by MCC clustering and synergistic interactions found in this work has additional clinical and policy implications. More caution needs to be taken when considering the prognosis of MA stroke patients. Despite MAs being younger on average, they may have greater MCC burden compared to NHW stroke patients of similar ages. Greater MCC burden in MAs could increase the concerns for hemorrhage, recurrent stroke, and thromboembolic events that require closer monitoring and more frequent follow-up. MCC may become an obstacle in almost every

step of stroke recovery, including getting treatment, preventing complications, participating in rehabilitation, and acquiring post-acute care. As discussed in the sections above, recommendations and clinical guidelines for treatment and rehabilitation based on the MCC status and FO prognosis among stroke patients would potentially lessen the ethnic disparities in post-stroke FO by providing more opportunity for maximal recovery in MAs with greater MCC.

Our results also suggest that MCC contributes to the impact of sociodemographic factors on post-stroke FO. By targeting health care professionals from communities with socioeconomic disadvantage to manage, monitor, educate, and counsel patients with MCC, ethnic disparities in MCC burden and post-stroke FO could potentially be reduced. Educating patients, family, and school children from disadvantaged socioeconomic backgrounds on the signs and symptoms of stroke may also contribute to lessening ethnic disparities through an improved likelihood of receiving thrombolysis treatment and reducing the risk of complications in MA patients by preventing transportation delay. Further research is needed to explain the mechanisms of ethnic disparities in MCC other than the association with sociodemographic factors, which could share some insight on the disease-specific pathways that lead to less disability in all patients.

5.5 Pathophysiology Linking Conditions in MCC to Post-stroke FO

The impact of MCC clustering in post-stroke FO is poorly understood and the mechanisms of the synergistic interactions between conditions and impairments are not clear in the current research but worth future investigation. There has been some work

showing that comorbid conditions may impact FO through pathophysiologic mechanisms that are specific to stroke. In this section, the potential pathophysiology linking conditions included in the new MCC index to FO after stroke is summarized.

Diabetes mellitus

Patients with diabetes are predisposed to a poorer and slower poststroke recovery in functions after adjusting for age and stroke severity.[268-275] Diabetes directly impairs synaptic plasticity, synaptogenesis, and neurogenesis, as well as neurons.[272,276] There's evidence showing that a "double-hit" phenomenon in patients with diabetes may contribute to a differential cortical function response to stroke.[212] Specifically, patients with diabetes may have preexisting alterations in cortical function that lead to an absence of ipsilateral cortical excitability change after stroke. This impaired capacity for neuroplasticity over the ipsilateral hemisphere can interfere with the overall neural adaptation in stroke recovery in diabetes.[212] Diabetes may also indicate subclinical or undiagnosed complications, such as undiagnosed neuropathy or subclinical heart diseases, that are barriers to aggressive rehabilitation.

Congestive heart failure (CHF) and renal disease

The association between heart failure and poor FO after stroke has been reported by several studies, although the mechanism responsible for this link remains unclear.[160,277-280] A possible explanation for the association between CHF and poor FO after stroke includes the high prevalence of atherosclerotic coronary disease, hypertension and valvular disease among patients with CHF, which exert higher atherosclerotic burden, endothelial dysfunction, more complex treatments and systemic-embolic complications that could lead to a worse FO.[215,281-283] CHF patients also have

reduced cerebrovascular reactivity, exercise capacity and neuroendocrine activation which can possibly interfere with post-stroke rehabilitation and negatively impact FO.[216,284]

Chronic kidney disease (CKD), CHF and ischemic stroke share many traditional (aging, hypertension, diabetes, etc.) and non-traditional risk factors (oxidative stress, sympathetic nerve overactivity, thrombogenic factors, etc.), although CKD tends to indicate a longer duration and more severe exposure to these risk factors which exerts additional risks of vascular damage and endothelial dysfunction and further deterioration in patients' cardiovascular reserve.[217] In renal failure, uremic toxins, sodium and water retention, anemia and malnutrition, abnormal calcium and phosphate metabolism and hyperparathyroidism can amplify the impact of these risk factors on cardiovascular function, and proteinuria and albuminuria further lead to high levels of inflammatory cytokines and oxidative stress causing excessive vascular damage systematically.[217,285,286] Given these mechanisms, patients with renal dysfunction (RD) also have a higher chance of recurrent stroke.[233] Patients with renal failure have greater risks both in thromboembolic events and bleeding which increase the risk and limit the benefit of thrombolysis treatments.[234-236] Besides, dialysis in patients who need it may also reduce rehabilitation participation due to time dedicated to dialysis. Fluid volumes removed during dialysis can often be associated with low blood pressures, fatigue, and symptoms that can interfere with aggressive rehabilitation. Recent research also emphasized the need to address the syndrome of CHF and RD as a whole instead of focusing on the failure of each organ separately given the high prevalence of RD in CHF.[287,288] Research on the impact of combined CHF and renal failure on stroke

outcomes is scarce. One large prospective cohort study that investigated the long-term impact of combined CHF and RD on cardiovascular morbidity found that when compared to stroke patients with neither HF nor RD, the hazard ratios for patients with either RD or CHF, and both CHF and RD were 1.48, 2.21 and 3.59, respectively. These findings indicate a positive additive interaction between CHF and RD on the long-term risk of new cardiovascular morbidity among these stroke patients.[232]

Weight loss and malnutrition

Many previous studies have shown that malnutrition both before and after stroke is an independent predictor for poor FO.[241,289-291] Protein-energy malnutrition can impair the recovery of hippocampal fiber by altering stress response and protein expressions in ischemic brain injury.[213] Malnutrition markers such as serum albumin have neuroprotective roles in ischemic stroke in reducing the hematocrit level, influencing erythrocyte aggregation, and defending oxidative stress.[219,292,293] Malnourished stroke patients also have a higher risk of complications, longer hospitalization and rehabilitation, and difficulties in regaining physical function in the long term.[241-244] The inflammatory responses after stroke are known to be mediated by neutrophils and lymphocytes, which have been found to be associated with poor FO after stroke.[294,295] About 20% of stroke patients are malnourished, while the prevalence of malnutrition after acute stroke varies widely between 6.1 and 62% due to the difference in timing and methods for assessment, as well as patients' characteristics.[296-299]

Pre-stroke cognitive decline, dementia, and aging

The few studies that investigated the association between pre-stroke cognitive decline or impairment and post-stroke FO had contradicting results.[200,237,300] One

explanation is that the observed difference in post-stroke FO in patients with and without pre-stroke cognitive impairment is driven by patients' baseline characteristics, initial stroke severity and comorbidities since patients with pre-stroke cognitive impairment tend to be older, have more severe strokes, higher prevalence of comorbid conditions and more stroke recurrence.[160,237] Patients with dementia are also less likely to receive intravenous thrombolysis.[237,238] There is some consensus that pre-stroke cognitive decline or impairment independently predicts post-stroke dementia,[87-90] which is inseparable from and correlated with physical function in the neuropsychological recovery of stroke.[106,107,239] Although the processes for pre-stroke cognitive impairment and stroke to produce dementia seem to be separate, infarcts in strategic regions (including basal ganglia, thalamus, and deep white matter) were found to be able to accelerate the clinical expression of dementia in patients with Alzheimer's disease.[90,214] Patients with post-stroke cognitive impairment are less likely to be referred to, participate in, and benefit from rehabilitation.[239,240] Stroke patients with severe cognitive deficits are more likely to have poor functional recovery after rehabilitation due to difficulty in appreciating their condition or acquiring and retaining the physical and cognitive skills necessary for ADLs.[91-94,240]

Moreover, aging is associated with cortical atrophy, a robust marker of the accumulation of pathological lesions and the failure of compensatory mechanisms, which mediate the relationships between multiple factors and dementia.[301-303] Some studies also showed that the pathological features and changes related to dementia are different in very advanced ages compared to the younger old.[301,302] Although it is not known how age modulates of the impact of pre-stroke cognitive impairment on post-

stroke FO, it may be worthwhile for future research to investigate if an age-related reduction in neuronal and synaptic reserve, tolerance to neuropathological lesions, and variations in compensatory processes could amplify the impact of dementia on the mental capacity to perform ADLs and IADLs.

Preexisting neurological disorders

Few studies investigated the relationship between preexisting neurological disorders and post-stroke FO.[174,304] Some neurological diseases, such as Parkinson's disease (PD), are believed to share pathological mechanisms and processes with ischemic stroke.[305,306] In both PD and ischemic stroke, increased oxidative stress leads to abnormal aggregation and forms conversion of α-synuclein which induces microglia-mediated neuroinflammation and further enhances α-synuclein-mediated neurotoxicity directly.[221,307-310] It is reasonable to hypothesize that the neuronal necrosis and synaptic loss due to acute ischemic injury of stroke could precipitate the cumulative neurodegeneration from PD and eventually impact post-stroke FO. Moreover, PD patients often experience deterioration in motor function during hospitalization due to various reasons,[311] which further reduces patient's mobility and levels of physical activity hindering post-stroke recovery.[220,311,312] Similarly, many other degenerative neurological diseases such as chorea, and demyelinating disease such as multiple sclerosis involve motor functions that potentially impact the participation and success of post-stroke rehabilitation. Besides, movement disorder, dysphagia and poor control of the respiratory muscles, chest wall rigidity, and bladder dysfunction resulting from preexisting neurological diseases could all contribute to post-stroke complications

including pneumonia, urinary tract infection, falls and subsequent traumatic brain injury which further complicate stroke recovery.[313 220,313-318]

Pre-stroke functional impairment and prior stroke/TIA

Pre-stroke functioning is perhaps the most well-established predictor of post-stroke FO next to initial stroke severity and age. Numerous studies showed that pre-stroke functional impairment or dependency is associated with poor long-term FO after stroke.[29,40,275,319-325] Pre-stroke function correlates with levels of physical activity before stroke.[326,327] Patients with low pre-stroke physical activity often had poorer cardiovascular and functional neuromuscular reserve before stroke,[108,328] and thus worse post-stroke hemodynamics and collateralization of flow after arterial occlusions, which deteriorate stroke recovery.[40,108] At the molecular level, regular physical activity improves brain tolerance to ischemia by involving the release of angiogenic factors, reducing inflammatory responses, improving endothelial function, inhibiting overexpression of glutamate, protecting the blood-brain barrier and mitigating neuronal apoptosis.[329,330] Patients with regular physical activity are more likely to have lower stroke severity, more distal versus proximal occlusions and earlier complete recanalization when treated with intravenous thrombolysis.[331]

Pre-stroke functional impairment and disability can certainly be a result of a previous stroke, which is an important predictor for post-stroke FO.[174,273,332-335] Patients with a history of stroke generally have more severe strokes.[336] It has also been observed that patients with recurrent stroke contralateral to their previous stroke have markedly worse FO than patients with ipsilateral recurrence, indicating a loss of ability to compensate functionally due to bilateral damage.[336] In this study, we found that the

impact of prior stroke/TIA on post-stroke FO depends on the level of pre-stroke function, although the explanation for which is not entirely clear. Previous prognostic studies for post-stroke FO looking at multiple factors rarely explore pre-stroke function and prior stroke together.[174] Many prognostic studies excluded patients with severe pre-stroke disability or were conducted in first-ever stroke patients only. Two studies that have considered both pre-stroke function and prior stroke excluded prior stroke in their final model because it was not independently associated with FO when pre-stroke function was included.[275,321] One recent study showed that the correlation between pre-stroke mRS and discharge mRS was stronger in patients with prior stroke compared to no prior stroke.[337] initial stroke severity Although there's not enough data in this area, we may postulate that the additional impact of pre-stroke function among patients with prior stroke reflects the impact of differential severity of their prior stroke.

5.6 Strengths and Limitations

This dissertation advances the understanding of MCC, a previously understudied aspect, in post-stroke FO with three interrelated projects. This is achieved through a systematic review of the existing knowledge, a tool developed to improve MCC measurement, and the utilization of the tool to understand ethnic disparities in post-stroke FO.

Overall, the focus of this dissertation was the broader population of ischemic stroke patients where capturing the full spectrum of MCC in stroke patients was more possible than previous studies focused solely on rehabilitation populations. This strength was reflected in the study population for Aims 2 and 3. More specifically, the

study population for the two data analysis projects was nested in a population-based, longitudinal stroke cohort with ethnic diversity. With more than 8 years of data and more than 1,000 ischemic strokes, the BASIC cohort provided a large study population and sufficient statistical power to capture the impact on and variance in post-stroke FO explained by MCC. The surveillance and validation of ischemic stroke cases, the identification of comorbid conditions from medical records and baseline interviews in addition to hospital discharge data, and post-stroke FO measured from patient interviews limited case ascertainment and measurement bias inherent in studies using administrative data alone. Further, post-stroke FO measured by a continuous score of ADLs and IADLs was more sensitive in detecting smaller differences in FO than the more widely used mRS and its dichotomous form for broad disability levels. Measuring MCC burden in Aim 2 and 3 with a new conceptual model by adding pre-stroke impairments assured a comprehensive assessment of MCC. The BASIC Project collects detailed data on pre-stroke functional, cognitive, and psychosocial impairments, which allowed the implementation of such a conceptual model and the adjustment for initial stroke severity and other important confounding factors available in the study. With the high proportion of MAs in the BASIC Project, the study population was clearly a good fit for examining ethnic disparities in Aim 3.

In Aim 1, we conducted an extensive search for all possible literature that analyzed adjusted MCC-FO association not restricted to studies that investigated MCC and FO as the primary interest. This extensive effort successfully increased the number of eligible studies, making the subsequent meta-analysis possible. In Aim 2, the hierarchical variable selection method from machine learning for prognostic modeling

was a novel approach in stroke outcome research, which was uniquely suited for developing the MCC index, as the method assured the validity and stability of the selected predictors and allowed for the consideration of hierarchical synergism among predictors. The use of inverse probability weighting approach in Aim 3 limited the potential for selection bias due to missing information and non-participation which may differ by ethnicity. We also used directed acyclic graphs (DAGs) to identify a minimally sufficient set of measured confounders to be adjusted for in estimating ethnic differences in post-stroke FO, which reduced the risk of potential bias due to over adjustment.

There are limitations to this dissertation. Bias may play a role in assessing the effect of MCC in post-stroke FO in a variety of ways. In the case of Aim 1, publication-bias may exist in the included studies, as indicated by the funnel plot and the Egger's regression test, where significant MCC-FO associations are more likely to be published, presented and subsequently included in our meta-analysis. Thus, the observed pooled association may be an overestimate of the effect of MCC. In Aim 2, sicker patients with higher MCC at baseline may more likely be lost to follow-up at 90 days introducing some selection bias. We compared patients who were analyzed and who were excluded from outcome interviews due to reasons other than death (from the other hospital system or refusal/cannot locate combined). The groups had a similar prevalence for all the comorbid conditions abstracted from medical records, although patients who were excluded were less likely to be dependent before stroke. We, unfortunately, do not know how this would impact the estimated MCC burden overall because other conditions measured by the ICD codes from hospital discharge data were not available (in patients

from the other hospital system). We tried to eliminate potential bias due to study attrition in Aim 3 by using inverse probability weighting to upweight those patients in the analysis dataset who were similar to the excluded patients. This allowed us to assess the ethnic differences in a study sample representative of all patients who were alive at 90 days after stroke.

Limitations in generalizability need to be considered in interpreting the findings. In the case of Aim 1, we excluded studies conducted purely among other stroke types, such as intracerebral/subarachnoid hemorrhage and lacunar infarction, and caution should be taken generalizing our findings to patients with other types of stroke. In Aim 2 and 3, generalizability may be limited given the work was conducted in one community with a high proportion of MAs, and external validation is required in the future before the application of this index. Challenges exist because FO measurement by ADL and IADLs may not be available in many other study populations. However, we also showed that the performance of the new MCC index is robust for predicting post-stroke functional disability measured by mRS, which is more available in other stroke studies. External validation can be conducted to examine the performance of the new MCC index in predicting post-stroke mRS.

Although this work tried to use one of the most comprehensive conceptual models for MCC, there were limitations in the MCC measurement. In Aim 1, by focusing on MCC measured by indices, we excluded studies that used present/absent or a count of the number of comorbid conditions as an MCC measurement, which precluded the discussion of the utility in these MCC measurements for predicting FO. In Aim 2 and 3, our measurement of MCC may be limited by the fact that only 25 diagnoses are

available in the hospital discharge data; some individuals may have >25 conditions; information on some geriatric syndromes (urine incontinence and falls) and sleep-disordered breathing before stroke are not measured in all or some of our subjects; underlying conditions not treated during the acute hospitalization may not be reported in the hospital discharge data. We did not have information to measure MCC severity, although including severity measures in comorbidity indices may also add complexity that challenges clinical utility.[78] We did not measure the severity, management, and duration of the conditions included in MCC, which may be different by ethnicity and potentially play a role in ethnic differences of FO in Aim 3. Due to the nature of the hospital discharge data and medical records, the temporality of some conditions and stroke may be ambiguous, and some comorbid conditions may be secondary to stroke. Collectively, the measured MCC burden in Aim 2 and 3 could be under or overestimated.

There are some potential limitations in the assessment of FO. First, using a single summary score did not consider the possibility that post-stroke FO may be multidimensional, which would probably be better assessed by a set of separate constructs than a unidimensional scale. Second, some items may indicate functional limitations that are more severe than others and therefore shall carry a higher weight in the summary score. This raises the possibility that a weighted score might be more appropriate than averaging the scores from each item. However, prior studies in functionally disabled elderlies have shown that ADL and IADL items could be unidimensional, and functional disability may be adequately measured by combining ADL and IADL items into a single overall scale with the same parameter for each item.[79]

We have chosen to measure the global FO after stroke parsimoniously using the average score of the items, although dimensionality and the protocol for combining the items need further validation given the differences between our study and the previous studies in ADL and IADL items and patient cohorts.

There are limitations specific to Aim 2 and 3. We used multiple imputation to fill in missing values of pre-stroke impairment variables in Aim 2, although variables may not be missing at random. In Aim 3, the ethnic difference in post-stroke FO may be further explained by other unmeasured confounders, including rehabilitation and post-acute stroke care. MA stroke patients are more likely to be discharged home, get less intensive rehabilitation, and have less post-rehabilitation functional improvement than NHWs.[20,139] Although differences in socioeconomic factors, MCC, and stroke severity may partially explain the ethnic difference in post-stroke care and rehabilitation, residual confounding may still exist after adjusting for these factors.[246,247] Thus, our estimated difference in post-stroke FO may be positively biased without adjustment for rehabilitation and post-stroke care.

5.7 Future Work and Considerations

Future work could expand upon the current understanding of MCC, post-stroke FO, and ethnic disparities from this dissertation in three ways: 1) additional methodological modifications to the MCC index, 2) external validation of the new MCC index and 3) additional investigation of MCC among stroke patients

Methodological Considerations

The new MCC index could be refined by additional methodological modifications to address the current limitations, specifically in the measurement of chronic conditions and FO.

1) Other chronic conditions

Apart from the 22 chronic conditions and their pair-wise interactions, other conditions that are relevant to an MCC index could be considered, for example, sleep-disordered breathing (SDB), geriatric conditions, and frailty.

SDB is common among stroke patients and is associated with brainstem involvement and worse FO after stroke.[338,339] Previously in the BASIC project, more than 62% of ischemic stroke patients were found to have SDB, defined as apnea-hypopnea index (AHI) ≥10.[245] Since 2010, SDB information has been collected in BASIC shortly after stroke using a home sleep apnea test with the ApneaLink Plus, a validated measurement for post-stroke SDB.[340] Although both stroke and SDB could predispose the other, there is some speculation that SDB may have a causative contribution to stroke.[341,342] SDB may contribute to worse post-stroke FO through the association with obstructive events and excessive daytime sleepiness.[343,344] Possible mechanisms include nocturnal hypoxemia, oxidative stress, elevated cytokines related to inflammation, dysregulation in coagulation and fibrinolysis.[345-350]

Some conditions in geriatric syndromes, such as urinary incontinence and falls, are not available in the BASIC but are strongly associated with functional impairment in elder adults and may contribute to post-stroke FO.[16,51,351] The Northern Manhattan

Study (NOMAS) is a population-based ischemic stroke study that collected information on urinary incontinence within 7 to 10 days of the index stroke.[352] Post-stroke FO measured by the Barthel Index (BI) was available in the NOMAS at 6 months after stroke and then annually for 5 years. Previously in the NOMAS, urinary incontinence was present in almost 30% of the ischemic stroke patients and was also found to be independently associated with worse FO at long term, after adjusting for stroke severity, risk factors, and demographics.[352]

Other indicators for frailty in addition to weight loss, including low grip strength, poor endurance and energy, and slow walk speed were not collected in the BASIC and the NOMAS. Information on these variables was collected in the Cardiovascular Health Study (CHS), a population-based, prospective cohort aged 65 years or older from communities in four U.S. states aimed to identify factors related to the onset and course of coronary heart disease and stroke. The CHS may be a possible data source to investigate whether frailty indicators should be included in the MCC since it also assessed disability annually using the ADLs and IADLs in all patients including those who had stroke. Using the annual disability assessment for post-stroke FO in the CHS is not without limitations and will be discussed in the following section.

Nevertheless, adding SDB, geriatric conditions, and frailty to the candidate predictors in the variable selection could also allow for the investigation of their synergistic interactions with other chronic conditions, which could further improve the accuracy of MCC measurement.

2) Ethnic-specific MCC index

MAs and NHWs have different spectrums in MCC and the contribution of each condition to post-stroke FO may differ by ethnicity. This raises the possibility that ethnic-specific MCC indices may be needed to better quantify the MCC burden in stroke patients in different ethnic groups. We adjusted for ethnicity and allowed interactions between ethnicity and individual conditions in the variable selection for the current index, but we did not find interaction effects large enough to be included in the final index because the ethnic differences in the effect of individual conditions were relatively modest compared to the included main and synergistic effects. To better understand this, stratified variable selection by ethnicity could be conducted using the BASIC data or possibly other datasets, although adding patients from more recent years would be necessary to increase statistical power because only 255 NHWs were available for the current analysis. Both the conditions and the weights for the MCC indices could be different by ethnicity, which would add complexity to the utilization of the MCC index. Additional assessments would be needed to test whether the ethnic-specific indices have the ability to significantly improve the accuracy in predicting post-stroke FO above the current MCC index.

3) Determine the temporality of MCC

Given that chronic conditions were determined from medical record abstraction and ICD codes from hospital discharge data of the acute hospitalization, it is difficult to distinguish pre-stroke chronic conditions from post-stroke complications, which is potentially important to understanding the possible mechanisms by which the MCC index affects FO and stroke recovery. However, large population-based cohort stroke

studies such as the NOMAS and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) would not be ideal data to identify temporality of the chronic conditions because they assess chronic conditions during the hospitalization after stroke ascertainment, which makes the temporality of stroke and chronic conditions ambiguous. To determine the temporality of the chronic conditions and stroke, information from a longitudinal measurement of chronic conditions before stroke is needed among patients at risk. The Cardiovascular Health Study (CHS) is a population-based, prospective cohort aged 65 years or older from communities in four U.S. states aimed to identify factors related to the onset and course of coronary heart disease and stroke. Self-reported physician diagnosis of chronic conditions, vascular risk factors, medication use, functional impairment in ADLs and IADLs, and cognitive impairment measured by the Mini-Mental State Examination and the Digit Symbol Substitution test were available from the patient interview, clinical examinations, medical record abstraction, and Medicare claim data at baseline and annual follow-up for cardiovascular diseases among community-dwelling elderly people recruited in the CHS.[353] Using a stroke sub-cohort analysis, detailed health information collected during follow-up before stroke would allow the distinction between pre-stroke comorbidities and post-stroke complications. The CHS also contained information on self-reported frequency of falls and physical activity in walking, leisure-time activity, and exercise intensity, which would complement the current measure of pre-stroke functional status in the MCC index in addition to pre-stroke functional impairment measured by mRS. Longitudinal measurement of chronic conditions, medication use, and laboratory examinations on fasting glucose, serum albumin, creatinine, and fibrinogen may also

help determine the duration and severity of CHF, diabetes, malnutrition, and renal failure, which are important aspects to be considered in MCC measurement. Since the severity, management, and duration of MCC may also be different by ethnicity, adding this information to the MCC index could potentially further explain the ethnic differences in post-stroke FO.

4) Refined assessment of post-stroke FO

Controversies exist in prior research assessing the dimensionality and items used to measure functional disability.[79,354] Although one previous study that used factor analysis and item response theory (IRT) analysis has found that ADL and IADL items can be represented as a one-dimensional construct and justified the combination of items into a single overall score with one parameter, the study was conducted in functionally disabled elderly, not stroke patients.[79] Whether a summary score is sufficient to measure functional disability also depends on the specific ADL and IADL items included, and the additional 7 items included in our FO assessment compared with the items verified to be unidimensional in the previous study may contribute to the emergence of multiple dimensions in post-stroke FO and/or the necessity of item-specific weights. First, to determine the dimensionality of the 22 ADL and IADL items that we used, exploratory and confirmatory factor analysis need to be conducted. Approximate uni-dimensionality of the items would be suggested if the first eigenvalue is relatively larger than the second and combining the 22 items in measuring FO would then be acceptable. However, if factor analysis shows that there are two or more eigenvalues greater than 1, a multi-dimensional model for FO with several constructs would then be more appropriate. Second, IRT analysis could be used to verify if

different weights for each item would be needed rather than a one-parameter model. Relative equal spacing between expected scores from IRT estimates of FO derived using the Bayesian approach would suggest that a summary score using the same scale for each item could provide a reasonable approximation to the post-stroke FO. A refined FO score with item-specific weights, if needed, would potentially measure post-stroke FO more accurately and lead to a modified MCC index with even higher prediction performance. It is also possible that different dimensions of post-stroke FO may be associated with different subsets of MCC, and further investigation using a multi-dimensional conceptual model for FO may lead to identifying dimension-specific MCC indices that could potentially be useful in identifying patients for personalized rehabilitation targeting different FO goals.

External Validation

Although the new MCC index has been internally validated to be an excellent predictor for post-stroke FO in the BASIC study population, external validation is needed before the MCC index can be used in the broader ischemic stroke patients. The CHS, as discussed above, contained information needed to calculate the new MCC index score and can be used to further assess its predictive validity for post-stroke FO.[353,355] Although pre-stroke functional status in the CHS was measured by ADLs and IADLs instead of mRS, additional work can be done to categorize ADLs and IADLs score into disability levels and use those translated disability levels to score MCC, similar to what has been done for BI and the FIM.[190] The CHS assessed disability annually using the ADLs and IADLs. A previous study in the CHS showed that more than 300 ischemic strokes occurred during follow-up and had more than 1 poststroke

disability assessment among 5639 stroke-free patients at baseline, which is relatively larger than our current validation dataset (N =104). The long-term follow-up for FO after stroke in the CHS also provides an opportunity to assess the long-term impact of MCC, which will be discussed in the following section.

Downsides of using the CHS to study post-stroke FO include that the duration between stroke incidence and FO assessment could vary by the patient due to functional status being evaluated annually. To make the FO measurement more comparable among patients, we might need to exclude functional assessment that occurred within 3 (or 6) months when FO is still subject to change due to recovery, similar to what has been done in the previous study.[355] The CHS did not collect detailed information on stroke location, size, and severity, although information on stroke etiologies (lacunar, cardioembolic, atherosclerotic, or indeterminate) is available to control for in the analysis. The performance of MCC in predicting post-stroke FO can still be compared to that in our current work in the crude analysis, although the estimated effect of MCC on FO would likely be positively biased without adjusting for stroke severity.

Few other large population-based stroke cohort studies have follow-ups for post-stroke FO beyond 3 months. The GCNKSS and the REasons for Geographic and Racial Differences in Stroke (REGARDS) study did not follow up for post-stroke FO beyond 3 months. The NOMAS assessed FO measured by BI at 6 months after stroke and then annually for 5 years but did not collect information on pre-stroke functional impairment for us to calculate the new MCC score.[352,356] Data from multi-centered, hospital-based cohorts may be used in further validation of the new MCC index. For example, the

Registry of the Canadian Stroke Network (RCSN) contains preadmission information including chronic conditions and functional dependence from medical records, although disability outcome was measured by mRS at hospital discharge, which may not be comparable from one patient to another given differences in the length-of-stay.[83,85]

Future Research on MCC among Stroke Patients

As shown in the pathophysiology section in this chapter, chronic conditions and pre-stroke impairments can potentially lead to changes in neuroplasticity and cerebrovascular plasticity that may continue after the initial stroke recovery period. It is possible that MCC may accelerate the aging-related functional decline years after stroke.[62] Future research is warranted to assess the long-term impact of MCC on longitudinal outcomes, for example, functional change over time. In the BASIC project, follow-ups on post-stroke FO beyond 90 days were conducted at 6 and 12 months. The study sample with FO measured at 6 and 12 months would be smaller in size given additional study attrition due to mortality and non-participation, which may limit our power to detect the impact of MCC on long-term functional change. Few stroke cohort studies collect post-stroke FO beyond the acute phase of stroke, and longitudinal stroke cohort studies are scarce. A stroke sub-cohort analysis in a population-based cohort, such as the CHS, may be possible to assess long-term functional change. The CHS assessed disability annually using the ADLs and IADLs with a mean (SD) follow-up time of 3.7 (2.4) years before stroke and 3.7 (2.3) years after stroke. The longitudinal follow-up of FO in the CHS has allowed the previous investigation of disability trajectories after stroke, although MCC has not been the major focus. With more patients surviving

stroke, understanding the impact of MCC on long-term functional trajectories is becoming more important than ever.

Given the demonstrated association between MCC and post-stroke FO, as well as its potential impact on pathophysiologic changes in neuroplasticity and cerebrovascular plasticity, MCC may also have an impact on other stroke outcomes such as cognitive outcome and quality of life. Post-stroke cognitive function is an important consideration for the success of stroke rehabilitation, which contributes to the recovery of post-stroke FO. Both cognitive and physical function after stroke impact the quality of life, a multidimensional construct incorporating individual perception of life circumstances. The BASIC Project measured global cognitive function by the Modified Mini-mental State Examination (3MSE) and quality of life by the 12-item short-form stroke-specific quality of life scale (SSQOL) both at the in-person outcome interview at 90 days.[357-360] Since different strategies and interventions are needed to improve these outcomes, understanding the role MCC plays in different outcomes could help to better align the resources with patients' needs given their MCC burden.

We also demonstrated the contribution of MCC to ethnic disparities in post-stroke FO in MAs and NHWs. Our approaches used in the investigation of FO disparities can also be used to study other stroke disparities in other ethnic or racial groups. For example, the NOMAS has a large population of predominantly Caribbean Hispanics. Previously in the NOMAS, Hispanic ethnicity was found to be a significant predictor for worse long-term FO among those with early favorable FO (BI ≥95 at 6 months).[352] Assessing the contribution of MCC measured by the new index would be helpful to explain the association between Caribbean Hispanic ethnicity and the delayed

functional decline. MAs have higher stroke incidence, more recurrence, longer hospital stays, get less intensive stroke rehabilitation, and are less likely to return to work after stroke compared to NHWs.[20,43,46,132,134,200] The new MCC index, as a convenient tool to measure overall MCC burden, would be useful in assessing its contribution to these ethnic disparities. Worse FO after stroke was also observed in other minority groups, such as African Americans. Blacks had worse FO at 3-month and 12-month follow-up compared to white stroke patients.[139] Understanding the role of MCC in stroke outcome disparities in African Americans and other minority groups could inform novel interventions to improve stroke survivorship in all racial and ethnic groups in the U.S.

Additional work can be done to investigate the mechanisms of MCC in driving post-stroke FO. Although physical activity, some chronic conditions, such as atrial fibrillation, and cognitive impairment were found to be associated with greater stroke severity,[237,331,361] the role of the overall MCC burden in determining stroke severity is unclear. Chronic conditions such as atrial fibrillation and myocardial infarction are associated with cardioembolic stroke etiology,[362] which tends to cause more severe strokes. Given the profound connections between MCC and pathophysiology of stroke, the association between MCC and stroke etiologies may also exist but needs further investigation. The impact of clusters of conditions and synergistic interactions on stroke etiology types is largely unclear but worth studying in the future. Information on stroke etiologic subtypes is available in the CHS and the NOMAS, which are both ideal data sources to study MCC clusters and the course of stroke.

5.8 Conclusion

This dissertation demonstrated the important role of MCC in post-stroke FO, and a new MCC index was developed to measure overall MCC burden and improve the prediction of post-stroke FO. MCC was found to be an important driver of the ethnic disparities in FO between MA and NHW stroke patients. Future work is needed to understand the mechanism of MCC in impacting stroke outcomes. Intervention efforts to better prevent and manage MCC may have the potential to mitigate post-stroke functional impairment, promote functional gain, and lessen outcome disparities.

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