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Comorbidity: The Ultimate Geriatric Syndrome

Framework for Evaluating Disease Severity Measures in Older Adults With Comorbidity

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Background. Accounting for the influence of concurrent conditions on health and functional status for both research and clinical decision-making purposes is especially important in older adults. Although approaches to classifying severity of individual diseases and conditions have been developed, the utility of these classification systems has not been evaluated in the presence of multiple conditions.

Methods. We present a framework for evaluating severity classification systems for common chronic diseases. The framework evaluates the: (a) goal or purpose of the classification system; (b) physiological and/or functional criteria for severity graduation; and (c) potential reliability and validity of the system balanced against burden and costs associated with classification.

Results. Approaches to severity classification of individual diseases were not originally conceived for the study of comorbidity. Therefore, they vary greatly in terms of objectives, physiological systems covered, level of severity characterization, reliability and validity, and costs and burdens. Using different severity classification systems to account for differing levels of disease severity in a patient with multiple diseases, or, assessing global disease burden may be challenging.

Conclusions. Most approaches to severity classification are not adequate to address comorbidity. Nevertheless, thoughtful use of some existing approaches and refinement of others may advance the study of comorbidity and diagnostic and therapeutic approaches to patients with multimorbidity.

COMORBIDITY affects the progression of concurrent disease (1,2), decreases quality of life (3,4), and increases the risk and severity of disability (5,6) and mortality (3). Comorbidity may alter treatment efficacy and the risk of adverse effects and has been observed to be associated with utilization of standard treatments (7). The efficacy of complex, interacting regimens often administered to older persons has not been tested in most cases (8–11). Thus, understanding comorbidity severity can be the key to understanding the difference between inappropriate treatment, realistic prioritization, and justifiably avoiding standard treatment on the basis of concerns about decreased benefit or increased harm.

Inadequate attention to comorbidity stems in part from the lack of established tools and procedures for classifying the severity of coexisting conditions. Improved attention to comorbidity-related research and clinical issues requires the development and validation of new ways for establishing the presence and severity of coexisting and potentially interacting disease states and their treatments. Although understanding the true impact and consequences of one disease requires accounting for the severity of specific comorbid diseases, this is rarely done (12).

Research on and clinical decision making for patients with comorbidity require accurate and comparable characterization of severity of individual, concurrent diseases (Table 1). Consider the question of how to identify the nursing home residents with osteoporosis who are most likely to benefit from bisphosphonate treatment (13). Eighty percent of nursing home residents have osteoporosis (14), but many will die without a new fracture and thus would never experience a benefit from therapy. The severity of comorbid diseases affects life expectancy and risk of falls and adverse drug events, all of which affect treatment decisions. Also, osteoarthritis interacts with heart disease to synergistically increase the risk of disability (6). From preventive or therapeutic perspectives, would decreasing the severity of either disease prevent the interaction (15)? Evaluation of how severity of common diseases can be currently characterized, and when such characterizations are compatible in an overall assessment, is needed.

The goal of this narrative review is to develop and apply a framework to the classification of severity for common

Table 1. Why Does Disease Severity Matter?

Issue	Examples of Questions
Causal Pathways	
1. One disease affects the progression of another disease, in relation to its severity.	1. Does severity of diabetes mellitus accelerate the progression of HIV?
2. The outcome of interest is caused by a comorbidity, where severity of the other disease is proportional to the outcome of interest.	2. Does rheumatoid arthritis affect the development and progression of coronary artery disease? By what mechanism? Does severity of rheumatoid arthritis matter in this process?
3. When multiple diseases are concurrently present, severity of one or both may increase the risk of disability, or mortality or worsening quality of life.	3. Is the disability that results from the interaction of osteoarthritis and heart disease a function of the severity of either or both disease(s)?
Treatment Effects	
4. Treatment benefit for one disease is modified by the presence of another disease. Is the severity of the other disease important?	4a. A patient with dyspnea on exertion has chronic obstructive pulmonary disease and congestive heart failure. What treatments will most improve symptoms? 4b. How does the severity of comorbid peripheral vascular disease affect the likelihood of good outcomes from coronary artery bypass?
5. The chance of an adverse effect when prescribing a medication is related to the severity of other diseases because of altered pharmacokinetics, interaction of physiologic processes, or elevation of risk.	5a. Are cyclooxygenase-2 inhibitors riskiest in people with more severe diabetes or hypertension or atherosclerosis? 5b. Does severity of chronic renal insufficiency modify tolerance of treatment for congestive heart failure?
6. Clinical standards for quality of care may need adjustment in the face of comorbid diseases with varying severity.	6. How should quality of care in disease management programs be measured for people with diabetes who have several other conditions?
Prognosis	
7. The likelihood of recovery from treatment is impeded by a second disease.	7. Will this patient with knee arthritis and dementia benefit from total knee arthroplasty?
8. Some individuals have such limited prognoses from the severity of a comorbid disease that their likelihood of benefiting from a given therapy for the target disease is very low.	8. What is the global (aggregate) risk of death in a patient, taking severity of comorbidities into account?
Generalizability	
9. Findings from a study sample do not apply to older adults with comorbid conditions.	9. Do the people in the trial reflect the patients I see in terms of the presence and severity of comorbidities?

chronic diseases and utilize it to consider the suitability of existing severity classification systems for use, jointly, in persons with comorbidity. We hypothesize that severity classification systems are meaningfully distinguished in several ways: (a) goal or purpose of the system; (b) physiological and/or functional level at which severity is characterized; and, (c) potential reliability and validity of the data, and burden and costs associated with obtaining required classification information. Implications of the findings for research and care for persons with multiple comorbidities are considered.

Framework for Classifying Severity of Disease

Severity of disease is assessed for diverse purposes. One goal is to create a standardized basis for evaluation and communication. We hypothesized that severity of disease is measured to meet one or more of the following objectives: (a) to establish prognosis (risk of death or other common morbid sequela or events); (b) to characterize the impact of the disease on the person's well-being at a given point in time (experiential classification); (c) to establish the basis for treatment decisions; (d) to evaluate disease activity and response to treatment; or (e) other.

Measurement of severity may use information from any level or levels along the pathway from disease to disablement: from the cellular pathologic processes that initiate the disease, to limitations in basic physiologic functions, to impairments in organ system performance, to symptoms, to complex function at the level of the whole person, and finally through quality of life and dependency (Figure 1) (16).

Severity classification may also differ greatly with respect to feasibility, patient or participant burden, and costs of ascertainment. In addition, data from self-report, laboratory tests, direct examination or functional testing, diagnostic tests administered and/or interpreted by an advanced specialist, and treatment information vary in reliability and validity.

METHODS

Chronic diseases and conditions of interest were selected on the basis of: (a) high prevalence in older adults, (b) measurable impact on mortality or disability, and/or (c) causal relationship to other prevalent diseases. Diseases selected (and their prevalence among older persons) were: osteoarthritis and/or rheumatoid arthritis (47%–57%) (17,18); hypertension (42%) (17); hypercholesterolemia (41%) (19); chronic kidney disease (CKD) (moderate to severe CKD: 26%) (20); type 2 diabetes mellitus (20%–25%) (21,22); angina (21%) (18); cancer (15%–19%) (17,18); lower extremity peripheral vascular disease (PVD) (15%) (23); congestive heart failure (CHF) (10%) (24); chronic obstructive pulmonary disease (10%–40%) (25); anemia (11%) (26); stroke (9%) (18); osteoporosis (9%) (18); and asthma (7%–9%) (27).

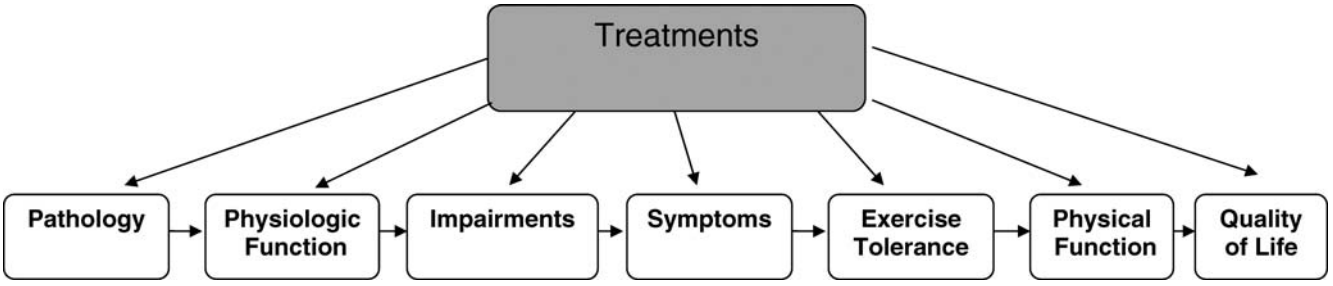

Figure 1. Causal pathway of disease to disability, permitting classification of severity at each point.

Severity classification systems were first identified through a search of the Medline database using Medical Subject Heading terms for each condition, along with the key words ''severity'' and either ''stage'' or ''classification,'' limited to all adults aged 19+ years, humans, and English language. Results were reviewed by one author (C.M.B., L.P.F., or C.O.W.), and appropriate articles were retrieved. References in the first round of articles were reviewed; additional appropriate studies were retrieved. Opinions of an expert for each disease were solicited to identify additional classification systems. This search was intended to provide important and representative examples.

No standard exists to define severity classification systems. For this review, a severity classification system was defined as ''any categorization approach that distinguishes, among those with a given disease, the presence of greater or lesser disease (i.e., a minimum of two levels).'' In some instances and for some conditions there may be no specifically identified severity system (e.g., diabetes), but there have been systematic attempts to categorize gradients of subclinical disease or risk for overt disease. As severity can fluctuate over time with acute and chronic phases for some diseases (e.g., CHF, stroke, asthma), classification systems that incorporate acute markers of severity have also been included. Indices that seek to account for ''global'' severity of all comorbidities simultaneously or the severity of all diseases within an organ system are less useful for studying the relationships between diseases, and are discussed elsewhere (28).

Using a disease-specific approach, the authors (C.M.B., L.P.F., or C.O.W.) reviewed each severity classification system based on the framework described above. Examples of such reviews are presented to illustrate how methods to classify disease severity differ and to describe the problems that would arise when trying to consider severity of multiple diseases concurrently. Due to space considerations, results are shown in tables limited to three conditions that were chosen to illustrate the diversity of classification systems.

Results

Differences in Number of Existing Severity Classification Systems

The number of methods available to classify severity varied greatly by disease. For example, for angina, CHF, and osteoarthritis we found at least five severity classification systems (29–46), whereas for other conditions fewer systems existed (47–53).

Varied Goals of Severity Classification Systems

Most systems were not designed to be used in the assessment of comorbidity. Thus, some components of the classification scheme may not be unique to a specific condition (e.g., shortness of breath) (33). Both within and among diseases, the goals of severity classification systems varied as is displayed in Table 2 (29–47,49,50,56).

Levels of Severity Classification Systems

For different diseases and within the same disease, severity has been characterized at different and sometimes multiple levels. Some classifications are based on pathologic or physiologic status (e.g., glomerular filtration rate, cholesterol); others used impairments or specific symptoms (e.g., pain); and still others characterized severity based on exercise tolerance or functional status (32–34,37,47,50,57). For stroke, different severity classification systems drew on the extent of cytotoxic edema, infarct size, symptoms, physical function, and quality of life, drawing from multiple levels simultaneously (54,55,58–74). Many severity classification systems included a functional component either as the main domain or as a contributing factor (e.g., angina, CHF, stroke, osteoarthritis, PVD) (29,30,34–38,44,46,57).

The level of focus for severity classification systems varied in objective and the nature of the condition. Symptoms and outcomes tended to be used in systems designed to reflect the patient experience, to guide treatment, or to measure treatment response. Pathologic or physiologic measures were incorporated in systems used to determine prognosis, guide treatment, or measure response to treatment. For example, disease activity measures for rheumatoid arthritis included the presence of tender and swollen joints and the laboratory demonstration of serum acute-phase reactants in addition to pain, patient and physician global assessment of disease activity, and physical function (75). For relatively asymptomatic diseases (osteoporosis, CKD, hypertension, hypercholesterolemia), severity classifications included fewer symptoms or functional components, and some relied largely on a single biological measure (e.g., bone density or cholesterol) to quantify risk (47,50,52,56,76–80).

Given diversity in purpose and levels of characterization of severity, we did not identify any compatible severity

Table 2. Purpose of Disease Classification Systems for Angina, Hip and Knee Osteoarthritis, and Hypertension

Classification/ Reference	Purpose			
	Experiential	Prognostic	Treatment To Improve Symptoms (Experience, Alter Prognosis, or Both)	Other*
Angina				
Killip and Kimball (29)		Mortality		
CCS (30)				Standardize terminology
Braunwald (31)	Quality of life	Assignment to risk groups		
SAS (32)	Symptom distress			Improve reproducibility and validity of NYHA
NYHA (33)			Describe status; information needed to plan management of patients' activities	
Osteoarthritis				
WOMAC (34)			Measure clinically important patient-relevant outcomes for therapies	
AFI (39)			Decide on and evaluate results of treatment	
WORMS (41); OMERACT and OARSI (40)			Measure change in progression of joint destruction to develop structure-modifying therapies	Evaluate structural integrity of joints
Kellgren and Lawrence (35)				Standards for grading
Ahlback (38)				Correlate cartilage destruction with bone and capsular changes
LaValley and colleagues (36)			Detect differences between groups, identify risk factors associated with disease worsening	
KSCRS (37)			Compare merits of different prostheses	
Hypertension				
JNC 7 (51)			Treatment to improve prognosis	
WHO/ISH (52), all criteria not required		Quantify prognosis	Treatment	

Notes: *Policy, cost analysis, allocation of resources, others.

CCS = Canadian Cardiovascular Society; SAS = Specific Activities Scale; NYHA = New York Heart Association; WOMAC = Western Ontario and McMasters Universities Osteoarthritis Index; AFI = Algofunctional Index; WORMS = Whole Organ Magnetic Resonance Imaging Score; OMERACT = Outcome Measures in Rheumatology Clinical Trials; OARSI = Osteoarthritis Research Society International; KSCRS = The Knee Society Clinical Rating System; JNC 7 = The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; WHO/ISH = World Health Organization/ International Society of Hypertension.

classification systems suitable for simultaneous ascertainment of disease severity across multiple conditions. Using two or more scales would result in comparison of fundamentally different aspects of severity. Angina severity classification systems were largely based on degree of patient-reported functional limitations and symptoms associated with specific activities. By contrast, some osteoarthritis severity measures relied on pathologic information obtained by radiographic imaging; some measures included symptoms and physical function (Table 3). The ability to understand the mechanisms by which these two particular diseases interact to increase the risk of disability synergistically is thus hampered.

Certain additional components do not fit into this framework. Some severity classification systems included presence of other conditions, diseases, or behaviors in their staging if they were risk factors for poorer prognosis (52). Level of treatment required for disease control was included in some systems [e.g., asthma (49,81)]. Several systems developed for prognostic purposes incorporated family history, age, race, or gender (52,76,78–80).

Cost and Burden of Components of Severity Classification Systems

Time and invasiveness, costs, and feasibility varied markedly for severity classifications within and across diseases (Table 4). Patient-reported measures are among the least expensive, but can be time-consuming to ascertain. Medical record–based information is sometimes more objective, but less complete. Standardized tests administered by a well-trained certified examiner are less costly than those requiring interpretation by an expert (e.g., echocardiogram or magnetic resonance imaging). Both may be equally burdensome on patients or participants (e.g., time, discomfort, or fatigue) (45,46,52).

Reliability and Validity of Components of Severity Classification Systems

Patient-reported measures may be most subject to criticisms over reliability and validity, but, depending on the goal of measurement, could be most relevant. Chronic diseases, in contrast with acute diseases, manifest a broader

Table 3. Domains Used for Classification of Severity of Angina, Hip and Knee Osteoarthritis, and Hypertension

	Domains–Disease Specific						Outcomes	
Classification	Pathologic*	Physiologic†	Symptoms‡	Treatment Required§	Exercise Tolerance or Exertional Symptoms‖	Other Diseases Contributing to Staging¶	Physical Function#	Quality of Life**
Angina								
Killip and Kimball (29)		Rales, SBP					Mobility	Self-rated health
CCS (30)			Angina		Exertion			
Braunwald (31)			Angina	Medical therapy	Occurrence at rest			
SAS (32)					Ability to perform activities			
NYHA (33)			Fatigue, palpitations, dyspnea or angina		Fatigue, palpitations, dyspnea or angina	Etiology of CHF	Physical activity ability	
Osteoarthritis								
WOMAC (34)			Pain, stiffness		Pain with exertion, rest, weight-bearing stiffness		Disability	
AFI (39)			Pain, stiffness		Pain with exertion, bed rest, standing, sitting, walking, maximal distance walked		Assistive device use, pain and difficulty; activities of daily living	
WORMS (41); OMERACT and OARSI (40)	MRI							
Kellgren and Lawrence (35)	X-ray							
Ahlback (38)	X-ray							
LaValley and colleagues (36)	X-ray							
KSCRS (37)	Stability, ROM, alignment		Pain		Pain with exertion		Ability to walk, climb	
Hypertension								
JNC 7 (51)		SBP, DBP				DM and CKD don't change stage, but change treatment		
WHO/ISH (52)* all criteria not required	End organ damage (LVH, microalbuminuria, radiographic evidence: plaque, hypertensive retinopathy)	SBP, DBP cholesterol				DM, CVD, PVD, CKD, Cerebro-vascular disease, family history of CVD, gender, age smoking, physical inactivity, obesity		

Notes: *e.g., tumor burden or evidence of end-organ damage (diabetic retinopathy, Glomerular Filtration Rate).

†e.g., inflammatory markers, blood glucose, blood pressure.

‡e.g., cough, sputum production, shortness of breath.

§e.g., number of blood pressure or glucose control medicines.

‖e.g., dyspnea with a certain task, exercise tolerance.

¶Presence of other diseases (or even sociodemographic factors) as part of the classification system: could lead to overadjustment.

#e.g., difficulty or dependency with a task or observed performance.

**Components of quality of life that do not fit neatly into one of these other categories.

SBP = systolic blood pressure; CHF = congestive heart failure; ROM = range of motion; DBP = diastolic blood pressure; DM = diabetes mellitus; CKD = chronic kidney disease; PVD = peripheral vascular disease; CVD = cardiovascular disease; CCS = Canadian Cardiovascular Society; SAS = Specific Activities Scale; NYHA = New York Heart Association; WOMAC = Western Ontario and McMasters Universities Osteoarthritis Index; AFI = Algofunctional Index; WORMS = Whole Organ Magnetic Resonance Imaging Score, OMERACT = Outcome Measures in Rheumatology Clinical Trials; OARSI = Osteoarthritis Research Society International; KSCRS = Knee Society Clinical Rating System; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; WHO/ISH = World Health Organization/International Society of Hypertension.

Table 4. Classification Systems by Source of Information for Angina, Hip and Knee Osteoarthritis, and Hypertension

	Source				
Classification	Patient Reported*	Automated Laboratory Test†	Examination or Functional Test by Trained Health Care Worker‡	Test Administered or Interpreted by Advanced Specialist§	Treatment or Utilization Related‖
Angina					
Killip and Kimball (29)			Rales, systolic blood pressure		
CCS (30)	Angina, exertion				
Braunwald (31)	Angina, occurrence at rest		Clinical circumstances (anemia or fever, e.g.)		Medical therapy
SAS (32)	Angina, stopping activity				
NYHA (33)	Fatigue, palpitations, dyspnea or angina; inability to carry out activity				
Osteoarthritis					
WOMAC (34)	Pain, stiffness, disability				
AFI (39)	Pain, stiffness, disability, assistive device use				
WORMS (41); OMERACT and OARSI (40)				MRI	
Kellgren and Lawrence (35)			X-ray	X-ray	
Ahlback (38)			X-ray	X-ray	
LaValley and colleagues (36)			X-ray	X-ray	
KSCRS (37)	Pain with exertion, walking and stair climbing ability			ROM, stability, alignment	
Hypertension					
JNC 7 (51)	DM, chronic kidney disease don't change stage, do change treatment		Systolic, diastolic blood pressure		
WHO/ISH (52)* all criteria not required	Gender, age, other diseases, family history, smoking, physical activity, obesity	Creatinine, microalbuminuria	Systolic, diastolic blood pressure	Echocardiogram, hypertensive retinopathy, plaque	

Notes: *e.g., symptoms, quality of life, disability, behaviors, other medical history.

†e.g., blood or body fluid assay.

‡e.g., auscultation for rales, inspection for ulcer, get up and go.

§e.g., histological specimen, echocardiogram, pulmonary function tests, slit lamp exam, magnetic resonance imaging.

‖e.g., number of medicines, number of emergency department visits or hospitalizations.

CCS = Canadian Cardiovascular Society; SAS = Specific Activities Scale; NYHA = New York Heart Association; WOMAC = Western Ontario and McMasters Universities Osteoarthritis Index; AFI = Algofunctional Index; WORMS = Whole Organ Magnetic Resonance Imaging Score, OMERACT = Outcome Measures in Rheumatology Clinical Trials; OARSI = Osteoarthritis Research Society International; KSCRS = Knee Society Clinical Rating System; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; WHO/ISH = World Health Organization/International Society of Hypertension; MRI = magnetic resonance imaging; ROM = range of motion; DM = diabetes mellitus.

spectrum of clinical findings, and symptoms and function sometimes correlate weakly with underlying pathology (82). Some objective measures (e.g., peak expiratory flow) can be quite variable as well (83). Symptoms from CHF correlate poorly with ejection fraction (84), and radiologic features of hip osteoarthritis do not correlate well with clinical symptoms (85). Patient-reported measures do not exist for asymptomatic problems (such as diabetes and hypertension) for which severity classification is dependent on testing by health providers (48,49,51,52).

Discussion

Improved attention to and management of comorbidity-related issues requires systematic and standardized characterization of the presence and severity of coexisting diseases and understanding of potentially interacting disease states and their treatments. The classification of disease severity is particularly critical in clinical care and research in older adults due to increased heterogeneity (86,87). A framework for considering methods to classify severity was developed and applied for illustration purposes here. For some diseases, there were many severity classification systems; for initially asymptomatic diseases, there were few. The goals, level of categorization, cost, burden, reliability, and validity of severity classification measures varied widely within and across diseases. The different methods identified were largely incompatible due to diversity in purpose and level of ascertainment within and across diseases. Many situations would require classification of severity along

parallel domains for all diseases, but existing severity classification systems draw from divergent domains for differing purposes. Thus much work remains in developing a unified system of severity classification.

The lack of integration among severity classification systems with a single-disease focus presents a chaotic array that does not work when multiple diseases are present. Some examples of why simultaneous use of different severity assessments may be problematic follow. Many severity classifications incorporate other diseases or sociodemographic risk factors, leading to overadjustment of risk in stratified or multivariate analyses. In addition, many severity classification systems incorporate functional decline and symptoms (e.g., dyspnea). This raises several issues. Studies of disability are limited if function is included in both the independent (i.e., disease severity) and dependent (i.e., outcome) variables. Also, severity classification systems incorporating physical function, symptoms, or performance reflect the impact of multiple conditions or one physiologic system (e.g., cardiopulmonary), making it difficult to distinguish the true impact of a single disease. Finally, severity classification systems relying on experiential components may be most affected by the patient's response to the disease. In PVD, for instance, improvement in symptoms could signify improvement in underlying disease or cutting activity back to a level below the claudication threshold.

Severity classification systems have varied etiologic specificity. The underlying pathophysiology of comorbid diseases may overlap (e.g., metabolic syndrome) (88). A challenge in considering the optimal physiologic or clinical level for measuring severity is that etiologic specificity may be highest at the level of pathology or physiology, but the components most relevant and important to patients may be much less disease specific (Figure 2). For example, although ejection fraction is highly specific to severity of CHF, dyspnea on exertion, which is more salient to patients, can result from several common diseases. Choosing the right severity classification system is dependent on issues such as the compatibility measures for both independent and dependent variables, the specificity required, and the costs and burden of ascertainment. Identification of disease-specific markers of severity is important, and choice and development

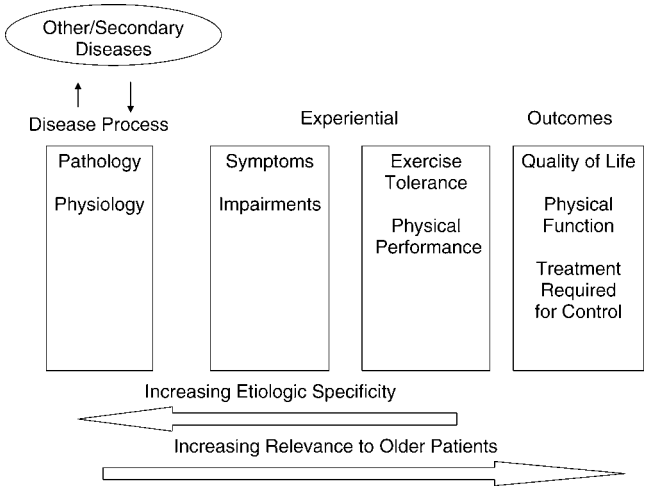

Figure 2. Components for assessing disease severity.

of measures to classify disease severity should be based on the markers that are most relevant for the question of interest.

Is the solution to measure health status globally? For many important and unanswered research questions, the answer is no. Specific relationships between diseases and their treatments are critical. Because of the demonstrated mix of purposes and components, it does not appear reasonable to create an overall index of disease severity by aggregating across the different available existing severity classification systems. Among patients with Parkinson's disease, stroke, or coronary heart disease in isolation, specific measures of disease severity are associated in different ways with health-related quality of life (89). These relationships may be more complex and even less uniform in older adults with comorbidity. A noteworthy limitation of this review is that it did not include syndromes, such as dementia, that share functional outcomes with the diseases considered here.

The study of common diseases is hampered by an inability to simultaneously account for their severity. There is a need for methods to classify severity across diseases, in

Table 5. Subclassification of Disorders

Disorder	Diseases Defined by Quantitative Measurement*	Diseases/Conditions Defined by Clinically Identified Symptoms/Findings†	Geriatric Syndromes‡	Sensory Problems§	Other Conditions That Are Not Actual Diseases, But Put People at Risk
Examples	Diabetes, osteoporosis, hypercholesterolemia, hypertension, chronic kidney disease	Arthritis, angina, gastrointestinal disorders, Alzheimer's, Parkinson's, chronic obstructive pulmonary disease, various types of cancer	Falls, incontinence, delirium	Vision, hearing problems, neuropathies	Metabolic syndrome, menopause, andropause, others

Notes: *In general, these conditions put people at risk for serious complications, but themselves are asymptomatic except in the most severe cases. In asymptomatic persons, the severity may be established by quantitative, continuous measures. A qualitative measure for the symptomatic could also be defined for most of these.

†These usually have clinical severity stages, and are not diagnosed in preclinical stages.

‡These are clinical usually qualitative: either present or absent and generally no severity index.

§There is usually a long list of causes, and dysfunction is quantifiable.

patients with multimorbidity, with categorization of severity based on comparable domains or physiologic levels. It is unlikely that researchers will be able to use a single severity classification system for every situation. The thoughtful use of current systems, with attention to purpose, domains, and source of information, is necessary for sound research in older adults with multiple chronic diseases. Furthermore, this work supports the observation that additional models of illness, beyond the disease model, may be needed (82). In some situations, severity of disease may be less relevant than a continuum of impairments, conditions, and subclinical and clinical diseases representing derangement of homeostatic equilibrium (90,91) (Table 5). The theoretical framework for classifying the severity of disease proposed here can serve as a useful guide for articulating goals and creating compatible severity classifications across diseases.

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REFERENCES

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
2. Yokota C, Minematsu K, Hasegawa Y, Yamaguchi T. Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-based study over a 20-year period. *Cerebrovasc Dis*. 2004;18:111–116.
3. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol*. 2001;54:661–674.
4. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2:51.
5. Verbrugge LM, Lepkowski JM, Imanaka Y. Comorbidity and its impact on disability. *Milbank Q*. 1989;67:450–484.
6. Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. *J Clin Epidemiol*. 1999;52:27–37.
7. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med*. 1998;338:1516–1520.
8. Gurwitz JH. Polypharmacy: a new paradigm for quality drug therapy in the elderly? *Arch Intern Med*. 2004;164:1957–1959.
9. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294:716–724.
10. Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Q*. 2004;82:661–687.
11. Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med*. 2004;351:2870–2874.
12. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
13. Wallace RB. Bone health in nursing home residents. *JAMA*. 2000;284:1018–1019.
14. Zimmerman SI, Girman CJ, Buie VC, et al. The prevalence of osteoporosis in nursing home residents. *Osteoporos Int*. 1999;9:151–157.
15. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59A:255–263.
16. Pope AM, Taylor AR. *Disability in America*. Washington, D.C.: National Academy Press; 1991.
17. Dawson DA, Adams PF. *Current Esimates from the National Health Interview Survey, United States, 1986*. National Center for Health Statistics. Vital Health Stat Series No. 10(164). 1987.
18. Freedman VA, Martin LG. Contribution of chronic conditions to aggregate changes in old-age functioning. *Am J Public Health*. 2000;90:1755–1760.
19. Disparities in screening for and awareness of high blood cholesterol–United States, 1999–2002. *MMWR Morb Mortal Wkly Rep*. 2005;54:117–119.
20. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41:1–12.
21. Wahl PW, Savage PJ, Psaty BM, Orchard TJ, Robbins JA, Tracy RP. Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification. *Lancet*. 1998;352:1012–1015.
22. Rodriguez BL, Curb JD, Burchfiel CM, et al. Impaired glucose tolerance, diabetes, and cardiovascular disease risk factor profiles in the elderly. The Honolulu Heart Program. *Diabetes Care*. 1996;19:587–590.
23. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation*. 2004;110:738–743.
24. Anderson G, Horvath J. Chronic Conditions: Making the Case for Ongoing Care. Partnership for Solutions; 2002. Available at: http://www.partnershipforsolutions.org/DMS/files/chronicbook2002.pdf. Last accessed December 21, 2006.
25. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance–United States, 1971–2000. *Respir Care*. 2002;47:1184–1199.
26. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104:2263–2268.
27. Braman SS. Asthma in the elderly. *Clin Geriatr Med*. 2003;19:57–75.
28. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano W, Silliman RA. Methodology, design and analytic techniques to address measurement of comorbid disease. *J Gerontol A Biol Sci Med Sci*. 2007;62A:281–285.
29. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol*. 1967;20:457–464.
30. Dagenais GR, Armstrong PW, Theroux P, Naylor CD. Revisiting the Canadian Cardiovascular Society grading of stable angina pectoris after a quarter of a century of use. *Can J Cardiol*. 2002;18:941–944.
31. Braunwald E. Unstable angina. A classification. *Circulation*. 1989;80:410–414.

32. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227–1234.
33. Consensus Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. *Ninth Ed*. Boston: Little, Brown & Co.; 1994.
34. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15:1833–1840.
35. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16:494–502.
36. LaValley MP, McAlindon TE, Chaisson CE, Levy D, Felson DT. The validity of different definitions of radiographic worsening for longitudinal studies of knee osteoarthritis. *J Clin Epidemiol*. 2001;54:30–39.
37. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society clinical rating system. *Clin Orthop*. 1989:13–14.
38. Ahlback S. Osteoarthrosis of the knee: a radiographic investigation. *Acta Radiologica Suppl*. 1968;277:7–72.
39. Lequesne MG, Maheu E. Clinical and radiological evaluation of hip, knee and hand osteoarthritis. *Aging Clin Exp Res*. 2003;15: 380–390.
40. Peterfy CG, Gold G, Eckstein F, Cicuttini F, Dardzinski B, Stevens R. MRI protocols for whole-organ assessment of the knee in osteoarthritis. *Osteoarthritis Cartilage*. 2006;14(Suppl A):A95–A111.
41. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage*. 2004;12:177–190.
42. Riegel B, Moser DK, Glaser D, et al. The Minnesota Living With Heart Failure Questionnaire: sensitivity to differences and responsiveness to intervention intensity in a clinical population. *Nurs Res*. 2002;51(4):209–218.
43. Grigioni F, Carigi S, Grandi S, et al. Distance between patients' subjective perceptions and objectively evaluated disease severity in chronic heart failure. *Psychother Psychosom*. 2003;72:166–170.
44. Tranmer JE, Heyland D, Dudgeon D, Groll D, Squires-Graham M, Coulson K. Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the memorial symptom assessment scale. *J Pain Symptom Manage*. 2003;25:420–429.
45. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95:2660–2667.
46. Zugck C, Kruger C, Kell R, et al. Risk stratification in middle-aged patients with congestive heart failure: prospective comparison of the Heart Failure Survival Score (HFSS) and a simplified two-variable model. *Eur J Heart Fail*. 2001;3:577–585.
47. National Institutes of Health, National Heart, Lung, and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report. Vol. 2004. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf. Last accessed December 21, 2006.
48. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
49. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1187.
50. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(2 Suppl 1):S1–S266.
51. National Institutes of Health, National Heart, Lung, and Blood Institute. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). Vol. 2005. Available at: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf. Last accessed December 21, 2006.
52. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003;21:1983–1992.
53. Apelqvist J, Van Houtem WH, Nabuurs-Fransen MH, Shaper NC. *International Consensus on the Diabetic Foot*. *The International Working Group on the Diabetic Foot*. Amsterdam, The Netherlands: Wiley & Sons; 1999.
54. Recommendations for clinical trial evaluation of acute stroke therapies. *Stroke*. 2001;32:1598–1606.
55. Meyer BC, Hemmen TM, Jackson CM, Lyden PD. Modified National Institutes of Health Stroke Scale for use in stroke clinical trials: prospective reliability and validity. *Stroke*. 2002;33:1261–1266.
56. Miller PD, Barlas S, Brenneman SK, et al. An approach to identifying osteopenic women at increased short-term risk of fracture. *Arch Intern Med*. 2004;164:1113–1120.
57. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol*. 1992;45:1101–1109.
58. Mao HF, Hsueh IP, Tang PF, Sheu CF, Hsieh CL. Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke*. 2002;33:1022–1027.
59. Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Phys Med Rehabil*. 2003;84:950–963.
60. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke*. 1999;30:2131–2140.
61. Duncan PW, Jorgensen HS, Wade DT. Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. *Stroke*. 2000;31:1429–1438.
62. Lyden P, Lu M, Jackson C, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. *Stroke*. 1999;30:2347–2354.
63. Johnston KC, Wagner DP, Haley EC Jr, Connors AF Jr. Combined clinical and imaging information as an early stroke outcome measure. *Stroke*. 2002;33:466–472.
64. Roberts L, Counsell C. Assessment of clinical outcomes in acute stroke trials. *Stroke*. 1998;29:986–991.
65. Muir KW, Grosset DG, Lees KR. Interconversion of stroke scales. Implications for therapeutic trials. *Stroke*. 1994;25:1366–1370.
66. van Straten A, de Haan RJ, Limburg M, van den Bos GA. Clinical meaning of the Stroke-Adapted Sickness Impact Profile-30 and the Sickness Impact Profile-136. *Stroke*. 2000;31:2610–2615.
67. Bushnell CD, Johnston DC, Goldstein LB. Retrospective assessment of initial stroke severity: comparison of the NIH Stroke Scale and the Canadian Neurological Scale. *Stroke*. 2001;32:656–660.
68. Nakajima M, Kimura K, Ogata T, Takada T, Uchino M, Minematsu K. Relationships between angiographic findings and National Institutes of Health stroke scale score in cases of hyperacute carotid ischemic stroke. *AJNR Am J Neuroradiol*. 2004;25:238–241.
69. Brott T, Adams HPJ, Olinger CP, et al. Measurements of acute cerebral infarction–a clinical examination scale. *Stroke*. 1989;20:864–870.
70. Cote R, Battista RN, Wolfson C, Boucher J, Adam J, Hachinski V. The Canadian Neurological Scale: validation and reliability assessment. *Neurology*. 1989;39:638–643.
71. Kidd D, Stewart G, Baldry J, et al. The Functional Independence Measure: a comparative validity and reliability study. *Disabil Rehabil*. 1995;17:10–14.
72. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19:1497–1500.
73. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care*. 1981;19:787–805.
74. Duncan PW, Wallace D, Studenski S, Lai SM, Johnson D. Conceptualization of a new stroke-specific outcome measure: the stroke impact scale. *Top Stroke Rehabil*. 2001;8:19–33.
75. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum*. 1993;36:729–740.
76. Lydick E, Cook K, Turpin J, Melton M, Stine R, Byrnes C. Development and validation of a simple questionnaire to facilitate

identification of women likely to have low bone density. *Am J Manag Care*. 1998;4:37–48.
77. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
78. Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA, Tu JV. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ*. 2000;162:1289–1294.
79. Weinstein L, Ullery B. Identification of at-risk women for osteoporosis screening. *Am J Obstet Gynecol*. 2000;183:547–549.
80. Michaelsson K, Bergstrom R, Mallmin H, Holmberg L, Wolk A, Ljunghall S. Screening for osteopenia and osteoporosis: selection by body composition. *Osteoporos Int*. 1996;6:120–126.
81. Liard R, Leynaert B, Zureik M, Beguin FX, Neukirch F. Using Global Initiative for Asthma guidelines to assess asthma severity in populations. *Eur Respir J*. 2000;16:615–620.
82. Tinetti ME, Fried T. The end of the disease era. *Am J Med*. 2004;116:179–185.
83. Bellia V, Pistelli F, Giannini D, et al. Questionnaires, spirometry and PEF monitoring in epidemiological studies on elderly respiratory patients. *Eur Respir J*. 2003;21(40 Suppl):21S–27S.
84. Smith RF, Johnson G, Ziesche S, Bhat G, Blankenship K, Cohn JN. Functional capacity in heart failure. Comparison of methods for assessment and their relation to other indexes of heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(6 Suppl):VI88–VI93.
85. Hart DJ, Spector TD. The classification and assessment of osteoarthritis. *Baillieres Clin Rheumatol*. 1995;9:407–432.
86. Dannefer D. What's in a name? An account of the neglect of variability in the study of aging. In: Birren JE, Bengston VL, eds. *Emergent Theories of Aging*. New York: Springer Publishing Company; 1988:356–384.
87. Maddox GL. Aging differently. *Gerontologist*. 1987;27:557–564.
88. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
89. Ferrucci L, Baldasseroni S, Bandinelli S, et al. Disease severity and health-related quality of life across different chronic conditions. *J Am Geriatr Soc*. 2000;48:1490–1495.
90. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*. 1995;92:720–726.
91. Karlamangla A, Tinetti M, Guralnik J, Studenski S, Wetle T, Reuben D. Comorbidity in older adults: nosology of impairments, diseases and conditions. *J Gerontol A Biol Sci Med Sci*. 2007;62A:296–300.

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