

Review article

Co-morbidity does not reflect complexity in internal medicine patients

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Abstract

Internal medicine patients are mostly elderly; they have multiple co-morbidities, which are usually chronic, rather than self-limiting or acute diseases. Neither administrative indicators nor co-morbidity indexes, though validated in elderly patients, are able to completely define these "complex" patients or to allow physicians to correctly "cope" with them. For the complex patients found in internal medicine wards, internists need not only to find the best diagnosis and treatment, but also to apply a complex intervention (i.e., a comprehensive assessment and both continuous and multi-disciplinary care) in order to maintain their health and ability to function and to prevent or delay disability, frailty, and displacement from home and community. The aim of this review is to underscore the differences between the concepts of co-morbidity and complexity, to discuss instruments for their measurement, and to highlight related implications, areas of uncertainty, and the responsibilities of internists in the assessment and management of inpatients of their wards. The conclusion we come to is that it is mandatory to shift from a finance/administrative-based management system to a clinical process model (clinical governance) driven by the quality of the medical outcome and the cost of achieving that outcome. From a "complexity theory" standpoint, patient-centered care and collaboration can be seen as simple rules that guide desirable behaviors in a complex system. By exploring the real complexity of our patients, we exercise the holistic, anthropologic medicine of the person that is internal medicine.

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1. Introduction

Internal medicine patients are mostly elderly [1] and have multiple co-morbidities, owing to the progressive and chronic nature of their diseases. Internal medicine has been defined as “the speciality of complexity” [2–4]. The aim of this review is to underscore the differences between the concepts of co-morbidity and complexity, to discuss instruments for their measurement, and to highlight related implications, areas of uncertainty, and the responsibilities of internists in the assessment and management of inpatients of their wards.

2. The concept of co-morbidity

2.1. Definition of co-morbidity

A simple definition of co-morbidity is “the concurrent existence and occurrence of two or more medically diagnosed diseases in the same individual, with the diagnosis of each contributing disease based on established, widely recognized criteria” [5,6]. A co-morbidity, as a pre-existing secondary diagnosis of the admitted patient, differs from a complication, a condition acquired during a hospital stay [7]. Co-morbidities are serious medical conditions that are not directly related to the primary diagnosis itself but that involve any other major organ system. These are usually chronic, rather than self-limiting or acute and easily treated conditions. Co-morbidity should not be regarded as the sum of a number of diseases or as the coexistence of more than one disease (multi-morbidity) in the same patient. Multi-morbidity is the “co-occurrence of two or more diseases within one person, without defining an index disease” [8]; it refers to the total burden of all concurrently occurring pathological processes (clinical and sub-clinical) that are intrinsic to the individual and excludes socioeconomic factors, lifestyle factors, and

access to health care; impairment is included, while disability, which is dependent on the environment, is excluded. Because of the decision-making that must follow, co-morbidity is defined by establishing a hierarchy and relationships (e.g., in drug–drug interactions or in selecting priorities) existing in those situations.

2.2. Epidemiological data

Increasing numbers of people are found to have two or more diseases at the same time, and the prevalence of multi-morbidity increases as one ages [9]. Patients with three or more chronic diseases make up half of the population above 65 years of age [10]. Some 35%, 47%, and 53% of men aged 60–69, 70–79, and 80 years and older, respectively, have two or more chronic conditions, with higher levels among women [11,12]. Only 16.4% of the non-institutionalized population are free from a chronic health problem; 20.5% have a single chronic condition and the remainder (63.1%) report two or more chronic illnesses [13].

2.3. Measurement of co-morbidity

2.3.1. Four ways to approach co-morbidity

Studies of co-morbidity reveal that there is no consensus about how the co-occurrence of diseases should be measured [14,15].

A common approach is to count the number of diseases, but the prevalence of co-morbidity estimated this way is influenced by the number of chronic conditions included in the adopted list. A common variant of the simple count is a conditional count, i.e., the number of chronic diseases associated with a particular index disease. For instance, using arthritis as the index disease, Verbrugge and colleagues [16] found that people over the age of 55 with arthritis experience,

Table 1
Attributes of a hospital's case mix

Attribute	Meaning and features
Severity of Illness	Refers to the extent of physiologic decompensation or organ system loss of function
Risk of mortality	Refers to the likelihood of dying
Prognosis	Refers to the probable outcome of an illness, including the likelihood of improvement or deterioration in the severity of the illness, the likelihood for recurrence, and the probable life span
Treatment difficulty	Refers to patient management problems that a particular illness presents to the health care provider. Such management problems are associated with illnesses without a clear pattern of symptoms, illnesses requiring sophisticated and technically difficult procedures, and illnesses requiring close monitoring and supervision
Need for intervention	Relates to the consequences, in terms of severity of illness, that lack of immediate or continuing care would produce
Resource intensity	Refers to the relative volume and types of diagnostic, therapeutic, and bed services used in the management of a particular illness

on average, 3.8 chronic conditions compared with 1.8 conditions among people without arthritis.

A second approach takes into account both the severity and the number of co-morbid conditions. Most often, this approach creates a cumulative index weighted by the severity of the individual conditions or a co-morbidity severity score based on the most severe condition. For example, in patients undergoing total hip replacement, hospital complication rates are strongly associated with the severity of co-morbidity; no patients with level 4 co-morbid severity (uncontrolled, life-threatening disease) are allowed to undergo hip fracture replacement [15].

A third approach to studying co-morbidity is to assess the proportion of people who have pairs of co-morbid diseases. Typically, this approach studies co-morbidity from the perspective of an index disease. In the example of arthritis, co-morbid pairs consider the proportion of those who have

arthritis and a second co-morbid condition (e.g., arthritis and high blood pressure).

A fourth approach to studying co-morbidity is to assess the relative association between diseases by using a measure of association. In addition to crude descriptive measures, odds ratios and relative risks can be used to study co-morbidity, whereas multi-morbidity can be studied using observed/expected ratios, such as the odds ratio [8,17].

2.3.2. Co-morbidity indexes

Several indexes have been proposed to evaluate co-morbidity in patient populations with complex health situations [18–20]. Each includes a series of domains that vary according to the authors' view of co-morbidity. These indexes were validated under different conditions with similar targets. Their validation fields limit their use and the ability to extrapolate results. Only the CIRS, the Charlson index, the Kaplan–Feinstein index, the Geriatric Index of Co-morbidity (GIC), and the ICED have been validated and applied to elderly patients. Among these, the CIRS appears to be sufficiently reliable because it allows for a comprehensive recording of all co-morbid diseases from the clinical examination and medical file data [18] (Appendix).

3. The concept of complexity

The concept of complexity is not unequivocal. For hospitalized patients, the term “case mix complexity” has been used by clinicians and administrators to refer to a set of multiple attributes that include, in addition to co-morbidity, severity of illness, risk of dying, prognosis, treatment difficulty, need for intervention, resource intensity, etc. Each of these attributes has a very precise meaning that describes a particular aspect of a hospital's case mix (Table 1).

Administrators and regulators usually use the concept of case mix complexity to indicate that the patients treated require more resources, which results in a higher cost of providing care.

Table 2
Features of understanding complex systems and models for decision-making

Category	Features	Example	Main referring models for clinical decision-making
Known	Analytical/reductionist evidence-based care	Most efficacious drug treatment for uncomplicated angina	Evidence-based medicine, clinical judgment
Knowable	Potentially ascertainable by application of evidence-based methods	Most cost-effective treatments for patients with angina, hypertension, arrhythmia, osteoarthritis, and depression	Evidence-based medicine, clinical judgment, defining the “hierarchy” of priorities
Complex	Non-predictable, but potentially understandable by pattern observation	Best practice complex chronic disease care for a person from a disadvantaged population group who has angina, diabetes, and depression, as well as alcohol, legal, and family problems	Clinical judgment, cost-effective analysis, ethical/legal analysis, selection of priorities, coordination
Chaotic	Out of control, with no discernable order	Managing alcoholic binge crises in complex chronic disease care for a person with angina, diabetes, chronic renal failure, and depression, with family and legal problems in a disadvantaged, remote population	Clinical judgment, cost-effective analysis, ethical/legal analysis, selection of priorities, coordination, charisma or “dictatorship”

3.1. Definition of complexity

The concept of complexity lacks a precise definition. Complexity is the quality of being intricate and compound. It refers to the degree of complication of a system or of a system component, determined by such factors as the number and intricacy of interfaces, the number and intricacy of conditional branches, the degree of nesting, and the types of data structures [21]. Complexity is the property of a “real world” system that is manifested in the inability of any one schematic model to adequately capture all of its properties. Complexity science suggests an alternative model in which illness (and health) result from complex, dynamic, and unique interactions between different components of the overall system [22]. According to these meanings, complexity in a patient involves the intricate entanglement of two or more systems (e.g., body-diseases, family-socioeconomic status, therapies).

3.2. Approaches to complex systems: the complexity theory

Approaches to understanding complex systems, developed by Kurtz and Snowden [23], have been successfully applied with frontline health care providers [24]. They categorize activities on four levels of knowledge and organization, which are described as “the known”, “the knowable”, “the complex”, and “the chaotic”. Each is governed by a particular evidence and decision-making mode (Table 2) [23,25].

Complexity theory is the study of systems characterized by non-linear dynamics. It suggests that practices are complex adaptive systems consisting of local agents whose interactions lead to continually emerging novel behavior [26]. Recent developments in medicine provide the physician with newer approaches to understanding the scope of the complex adaptive processes of medical decision-making [27]. Change emerges as a result of interactions between agents at a local level in the complex system and between the system and its environment. The belief is that efforts to change practice should be preceded by efforts to understand

it. The focus is on informally reviewing processes and structures in a way that helps a team to have a sense as to what works well and what could be improved.

3.3. Further variables for the “complex patient” concept: disability and frailty

3.3.1. Disability

Although physical function is believed to be an important predictor of outcomes in older people, it has seldom been used to adjust for prognosis or case mix in evaluating mortality rates or resource use. Activities of daily living (ADL) function measurement contains important information about prognosis and case mix beyond that provided by routine physiologic data and co-morbidities in hospitalized patients. Prognostic and case mix adjustment methods may be improved if they include measures of function as well as routine physiologic measures and co-morbidity [28]. Limited ADL (Barthel index on admission), pre-morbid disability, and polypharmacy are the strongest predictive factors of outcome, independent of diagnosis, in acute geriatric wards [29]. The prognosis of older patients hospitalized in medical intensive care units depends not only on their acute physiological impairments, but also on a series of pre-existing conditions, such as loss of functional independence, severe and moderate cognitive impairment, and low BMI [30].

3.3.2. Frailty

Frailty is not easy to define. It is a condition with a high risk of a negative outcome and a worsening quality of life that is frequently associated with disability and socioeconomic problems. Recalling the complexity concept, Rockwood et al. defined frailty as “a vulnerable state of health, arising from the complex interaction of medical and social problems, resulting in a decreased ability to respond to stress, and associated with a decline in functional performance” [31]. From a clinical perspective, it is characterized by a high susceptibility to developing acute diseases, reduced motor

Table 3
Co-morbidity and complexity and their major health care implications [6]

The complex patient	Implications
Co-morbidity	— Assessment of frailty–disability prone patients — High susceptibility to develop acute diseases, mostly expressed by atypical clinical pictures
The concurrent presence of two or more chronic diseases or conditions	— Rapid fluctuations in health status — Remarkable tendency to develop complications (decompensation cascade)
Complexity	— Slow recovery capacity
The intricate entanglement of two or more systems (e.g., body-diseases, family-socioeconomic status, therapies)	— High risk of mortality — Minimizing disease severity — Need for a “tailored” treatment — Complexity of treatment and high risk of iatrogenic problems and adverse events (polypharmacy, drug interactions, adverse drugs reactions, adverse outcomes, incompatibility, contraindications) — Risk management — Need for a prioritization of treatment (“hierarchy” of priorities) — Fragmented, multi-provider, multi-setting care — Constant request for medical interventions — Frequent and repeated hospitalizations and the need for continuous care

skills and immobility that are not entirely justified by the diseases present, rapid fluctuations in health, a remarkable tendency to develop complications (cascade events), and a high risk of adverse events; slow recovery capacity, failure to thrive, a constant request for medical interventions, frequent and repeated hospitalizations and the need for continuous care; and a high risk of mortality. The elusiveness of a definition of frailty reflects not only the challenges in defining a clinical syndrome where the exact etiology and pathophysiology are unknown, but also the challenges of defining the boundaries of a syndrome that has medical, functional, and social components [32].

At the moment, we do not have a decisive and unequivocal tool to evaluate frailty. Flugelman's index is based upon the evaluation of seven parameters in hospitalized patients, namely, mobility, sphincter control, mental competence, feeding ability, presence of pressure sores, medical condition, and family state. The sum of the scores of all parameters gives the final prognostic index. This is a simple and relatively accurate tool for assessing the prognosis of elderly patients. A score of 17 or more indicates a poor prognosis [33]. Another reliable and sensitive clinical measure of frailty was introduced by Jones et al. in 2004 [34]. Their frailty index is based upon a multi-dimensional comprehensive assessment in ten standard domains: cognitive status, mood and motivation, communication (vision, hearing, speech), mobility and balance, bowel function, bladder function, ADLs and IADLs, nutrition, and social resources [35]. Mitnitski et al. examined the relationship between a frailty index and age and mortality. In their studies, they took into account a range of co-morbid illnesses, measures of disability, and social and psychological issues in their frailty index, a measure converting the percentage of deficits present or absent in a particular patient into an index score that varies between 0 and 1, with 0 reflecting no deficits and 1 the presence of all deficits [36,37].

3.4. Consequences of co-morbidity and complexity

Co-morbidity and complexity underlie demographic, genetic, biological, lifestyle, and related risk factors, as well as physical, psychological, economic, and social causes. Their consequences are reflected in mortality, functional status and disability, quality of life, treatment, complications, use of health services, length of hospital stay (LOS), hospital charges, and quality and costs of care [14,38–41]. The increase in costs with increasing co-morbidity affects both primary and specialty care [42]. Co-morbidity is a strong confounding factor, especially for elderly patients with multiple diseases, in evaluating the outcomes and the effectiveness of treatment, as well as in choosing the best “tailored care” for a patient (Table 3).

4. The need for a comprehensive, multi-dimensional assessment

Many studies describe benefits of a comprehensive assessment of elderly patients by an interdisciplinary team

followed by multi-disciplinary intervention after discharge [43]. A comprehensive geriatric assessment (CGA) allows one to gain insight into the frail, elderly patient's condition. It is a multi-dimensional, often interdisciplinary, diagnostic process focused on determining a frail, elderly person's medical, psychological, and functional capabilities in order to develop a coordinated and integrated plan for treatment and long-term follow-up [44–48]. The principal domains assessed in all forms of geriatric assessment are functional ability, physical health, cognitive and mental health, and the socio-environmental situation. Standardized instruments include the Katz ADL Scale and the Lawton IADL Scale for the evaluation of functional ability: activities of daily living (ADLs) and instrumental activities of daily living (IADLs); the Tinetti Balance and Gait Evaluation, the Mini-Mental State Examination, the Geriatric Depression Scale, and the Hamilton Depression Scale for cognitive and mental health. A socio-environmental situation is difficult to quantify but includes the social interaction network, available social support resources, special needs, and environmental safety [49].

5. Administrative data do not reflect the complexity of internal medicine patients

The usual hospital indicators are not able to reflect the complexity of internal medicine patients' needs. Administrative data based on hospital discharge codes consistently underestimate, or at least under-report, the presence of co-morbid conditions [50–52]. The concept of a principal diagnosis is not transferable to internal medicine and general practice. The range of problems encountered often crosses multiple body systems and may include undiagnosed symptoms, psychosocial and economic problems, or chronic disease [53]. The original objective of diagnosis-related groups (DRGs) was to develop a patient classification system focused exclusively on resource intensity. Yet, the DRGs system has many limitations. For example, it does not take into account illness severity and complexity of the patient or his/her social and living setting. The APR-DRGs (all patients refined DRGs), a modification of the traditional DRGs, expand the basic DRG structure by adding four subclasses to each DRG. The four severity of illness subclasses and the four risk of mortality subclasses are numbered sequentially from 1 to 4, indicating respectively, minor, moderate, major, or extreme severity of illness or risk of mortality. The underlying clinical principle of APR-DRGs is that the severity of illness or risk of mortality subclass of a patient is highly dependent on the patient's underlying problems and that patients with a high severity of illness or risk of mortality are usually characterized by multiple serious diseases or illnesses. In the APR-DRGs, the determination of the severity of illness and risk of mortality is disease-specific. Thus, the significance attributed to complicating or co-morbid conditions is dependent on the underlying problem. Moreover, the APR-DRG system has been found to be able to evaluate the clinical and functional impairment of elderly inpatients, as properly assessed by the CGA [54].

6. Clinical decision-making in complex conditions of uncertainty

Complexity theory is based on understanding patterns that are not predictable by traditional evidence and social knowledge within a complex adaptive system [55]. Effective clinical decision-making requires a holistic approach that accepts unpredictability and builds on subtle, emergent forces within the overall system [22]. Evidence-based care is based upon known, knowable, and ideal experimental conditions. Most clinical trials base their protocol exclusion criteria on comorbid conditions, often considered as “confounders”, thus disqualifying and excluding “real” older patients. Complex patients, who are excluded from randomized, controlled trials and who rarely fit into the standard care guidelines, become the “grey zone”, requiring special, tailored treatments. Most clinical practice guidelines (CPGs) do not take into account or discuss their applicability for older patients with multiple co-morbidities. This may compromise the ability to generalize the results since the frail, older patients with significant co-morbidities may have a different benefit-to-risk ratio for any given intervention [56]. Physicians’ poor adherence to protocols and guidelines is well documented. Moreover, CPGs and recommendations typically do not take into account the incremental effects on regimen complexity. Adhering to current CPGs in caring for an older person with several co-morbidities may have undesirable effects, such as multi-prescription, higher costs, and adverse drug–drug interactions [57]. Complex patients often require special, expensive treatments and procedures ordered by multiple physicians. Care decisions are seldom well coordinated and communicated among the patient’s multiple caregivers, which may result in duplicate, unnecessary, or even inappropriate treatments and tests. The typical result is higher costs and decreased patient satisfaction. Moreover, the complex patient’s illness is often compounded by significant social or economic problems. In this situation, clinical practice implies a certain degree of uncertainty. Making a medical decision often involves considering different factors that go beyond the field of technical and scientific knowledge (family, social, economic problems, etc.) and may demand an ethical analysis of the decision, including cost-effective and legal considerations of the outcomes. Any enthusiasm for evidence-based medicine and related guidelines must be tempered with the knowledge that they are fallible, particularly if applied to complex elderly patients. They should not replace clinical judgment or previous gold standard experience [58].

7. The importance of being a competent internist

Internists, often referred to as “doctors for adults”, provide most of the medical care given to older patients, especially those with serious chronic disease. They have to cope with complicated clinical problems by being an efficient diagnostician of complex diseases and they must also be skilled in understanding and managing disorders of various organs and

systems. Their patients’ high complexity, extreme instability, and vulnerability call for management that comes from extensive clinical expertise combined with “common sense” and longstanding experience [59–62]. An internist should be concerned with his patient’s “whole health” status, and he should include in his management all factors related to social, behavioral, environmental, functional, and medical problems.

Internal medicine is a specialty derived from the 19th century idea of clinical medicine; however, during the 20th century it was broken down into several pieces of knowledge. Reduced preconceptions of patient approach, a broad-based clinical view for generating diagnostic hypotheses as opposed to a biased-domain approach, the capability to manage diagnostic and therapeutic complexity, and flexibility to different epidemiological and organizational contexts are the main characteristics required of internal medicine hospitalists today in order to make suitable decisions in complex and uncertain situations [63]. Other characteristics that are needed to increase competence are: 1) optimization of critical pathways based on a broad clinical view; 2) effective patient global risk management; 3) better coordination of sub-specialist support; and 4) better communication with primary care providers to improve overall patient-case management [64].

8. Managing complexity in the care of internal medicine patients: conclusions

While the elderly make up the largest part of hospital populations [1], “we are still practicing acute care medicine in a world of chronic disease” [65,66]. Future hospital planning for the elderly should target the 75+ age group because they represent most of the frail elderly with complex problems and multiple illnesses. The high burden of illness and frailty, common among our growing population of older adults, often results in fragmentation of care among providers and health care systems, increasing the complexity and costs of caring for these patients. To provide health care for older adults, physicians must typically deliver long-term care for several chronic and acute conditions and follow-up a wide variety of clinical measures and interventions [67]. The single organ system approach has its limitations in hospital care of frail elderly patients. Pitfalls in diagnosis, investigation, and management, including iatrogenesis and adverse drug reactions, are prone to occur. It is not sufficient to identify acute illnesses and medically deal with them in a narrowly defined sense. The essence of management in our patients is to embrace their complexity and needs for care. These patients require a complex intervention (comprehensive assessment, continuous and multidisciplinary care) in order for them to maintain their health, function, and ability to play a vital role in the life of their community, as well as to prevent or delay disability, frailty, and displacement from home and community [68]. No measure of case mix complexity can be equally effective for all of the different aspects of case mix complexity. Several health researchers have measured co-

morbidity and this has advanced our understanding, but there is still a need for better ways of measuring the health status of individuals with complex disorders.

Complexity requires an understanding of patterns that are not predictable by traditional evidence and social knowledge within a complex adaptive system [69]. Complexity is the science of the 21st century; we should not have to wait decades to see it applied [70]. We have to shift from a finance/administrative-based management system to a clinical process model (clinical governance) driven by the quality of the medical outcome and by the cost of achieving that outcome. From a complexity theory standpoint, patient-centered care and collaboration can be seen as simple rules that guide desirable behaviors in a complex system [71]. By exploring the real complexity of our patients, we exercise the holistic, anthropologic medicine of the person that is internal medicine.

9. Learning points

- Co-morbidity is the concurrent existence and occurrence of two or more medically diagnosed diseases in the same individual, with the diagnosis of each contributing disease based on established, widely recognized criteria.
- Complexity science suggests that illness (and health) result from complex, dynamic, and unique interactions between different components of the overall system. In a patient, complexity involves the intricate entanglement of two or more systems (e.g. body-diseases, family-socioeconomic status, therapies).
- Complexity requires an understanding of patterns that are not predictable by traditional evidence and social knowledge; we have to shift from a finance/administrative-based management system to a clinical process model (clinical governance) driven by the quality of the medical outcome and by the cost of achieving that outcome.
- By exploring the real complexity of our patients, we exercise holistic, anthropologic medicine of the person, i.e., internal medicine.

Appendix A. The Charlson co-morbidity index

The best known and most frequently used index is the Charlson co-morbidity index. It was developed in 1987, based on 1-year mortality data from internal medicine patients admitted to a single New York hospital and was initially validated within a cohort of breast cancer patients. This index was created to enhance prediction of 1-year mortality, but it has since been used to predict other health outcomes, such as functional status. The Charlson scale is a list of 19 conditions whose presence is associated with at least a 20% increased risk of death. On the basis of these relative risks, each condition is weighted from 1 to 6. The co-morbidity score reflects the cumulative increased likelihood of 1-year mortality; the higher the score, the more severe the burden of co-morbidity. This method of classifying co-morbidity provides a simple, readily

applicable, and valid method of estimating risk of death from co-morbid disease for use in longitudinal studies [72]. However, the Charlson index was found to be limited in recording the entirety of pathologies in old patients and in patients with cognitive deficits [18].

Appendix B. Charlson's alternative co-morbidity indexes

Roos et al. [73] quantified the effect of augmenting the Charlson Index. They developed a co-morbidity algorithm that does not use individual diagnoses directly in the co-morbidity score calculation. The individual diagnoses determine attribution to co-morbidity categories scored as binary variables. This binary attribution within a co-morbidity category limits the effect of complications in risk adjustment. Deyo et al. [74] adapted a clinical co-morbidity index that is useful in studies of disease outcome and resource use employing an administrative database. Stukenborg et al. [75] compared two co-morbidity indexes (Deyo and Elixhauser methods) and concluded that the Elixhauser index achieves better discrimination than the Deyo adapted index. Sloan et al. [76] constructed an alternative, pharmacy-based index (RxRisk-V) that provides a good description and understanding of chronic disease burden of their treated patients. Quan et al. [77] developed ICD-10 coding algorithms to define Charlson and Elixhauser co-morbidities in administrative data and to assess the performance of the resulting algorithms. These newly developed co-morbidity coding algorithms may outperform existing ICD-9-CM coding algorithms.

Appendix C. The Greenfield Index of Coexisting Disease (ICED)

The Index of Coexisting Disease (ICED) has a two-dimensional structure, measuring disease severity and disability, which can be useful when mortality and disability are the outcomes of interest [78,79]. This tool has two subscales indicating the presence or absence of 15 disease categories and, for each category, five levels of physiological disease severity; moreover, it rates the severity of 11 functional impairments (e.g., respiratory, ambulation, continence) on three levels. Each scale is scored individually and is then combined to give an overall rating: none, mild, moderate, or severe co-morbidity. A major limitation of the ICED is that it requires medical records and highly trained reviewers who can follow complex decision rules in creating the index.

Appendix D. The Geriatric Index of Co-morbidity (GIC)

The Geriatric Index of Co-morbidity (GIC) is a composite score that takes into account both the number of diseases and the occurrence of very severe diseases. It has been validated in elderly disabled patients and is a good predictor of mortality [80].

Appendix E. The Cumulative Illness Rating Scale (CIRS)

The Cumulative Illness Rating Scale (CIRS), originally developed by Linn et al. [81], is a brief, comprehensive, and reliable measure of a patient's health impairment. It addresses all relevant body systems without using specific diagnoses. CIRS appears to be sufficiently reliable because it allows a comprehensive recording of all co-morbid diseases from clinical examination and medical file data [18,19]. An adaptation of CIRS is particularly interesting for geriatric patients, the CIRS-Geriatric (CIRS-G). The CIRS-G is aimed at a comprehensive recording of all the co-morbid diseases of a patient. Its principle is to class co-morbidities by organ system affected and to rate them according to their severity from 1 to 5 (1=none; 2=mild; 3=moderate; 4=severe; 5=extremely severe). CIRS-G's 14 items are based on evaluation of: the cardiovascular-respiratory system: (1) cardiac (heart only); (2) hypertension; (3) vascular (blood, blood vessels and cells, marrow, spleen, lymphatics); (4) respiratory (lungs, bronchi, trachea below the larynx); (5) EENT (eyes, ears, nose, throat, larynx); gastrointestinal system (GI): (6) upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees); (7) lower GI (intestines, hernias); (8) hepatic (liver only); genitourinary system; (9) renal (kidneys only); (10) other genito-urinary (ureters, bladder, urethra, prostate, genitals); (11) musculo-skeletal-integumentary system (muscle, bone, skin); (12) neurological (brain, spinal cord, nerves); (13) endocrine-metabolic (includes diffuse infections, poisonings); and (14) psychiatric (mental)/behavioral. For each item, the degree of impairment is described; for illnesses that cause impairment on more than one of the items, more than one item must be rated; when more than one illness occurs for a given item, it is the total impairment from these illnesses that is rated. In the CIRS, a "co-morbidity composite" (the number of items with a rating of 3–4 or 5, excluding psychiatric) and an "illness severity composite" [mean of points=(points for all items except psychiatric/13)] are measured. In this way, two parameters are obtained: the CIRS-IS (index severity), as the mean of all single item scores, and the CIRS-CI (co-morbidity index), as the number of single items with a score of 3, 4, or 5.

Appendix F. Total Illness Burden Index (TIBI)

The TIBI uses patients' self-report of symptoms, and diagnoses are made to determine not only the presence but also the severity of co-morbidities in each of 16 body system domains. This composite measure of symptoms, diagnoses, and disease manifestations helps clinicians assess the severity of illness for a particular patient. It can also be used to evaluate the severity mix of patients in a clinician's caseload, thereby enabling important comparisons of cost and outcomes [79].

Appendix G. Kaplan–Feinstein Index (KFI)— Adult Co-morbidity Evaluation (ACE 27-modified KFI)

Developed from the study of co-morbidity in patients with diabetes mellitus, the KFI has been used to study the impact of co-morbidity in several cancers. Specific diseases and conditions are classified into four groups—none, mild, moderate, or severe—according to severity of organ decompensation and prognostic impact [82]. The index has been criticized for being too complicated for routine use. Moreover, it does not include several other important conditions, e.g., AIDS and dementia. For these reasons, the KFI was modified with Ace 27, an adaptation from the Kaplan–Feinstein Index, larger in terms of number of items (27), but simple to use [83].

Appendix H. The Incalzi Index

The Incalzi Index, developed in a retrospective way, is performed after a multi-dimensional assessment and laboratory data are acquired. It includes a co-morbidity index, based upon a scoring system that quantifies the prognostic weight of individual diseases, and an age-co-morbidity index, which corrects the former for the age-related increase in death [84].

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