Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs

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Abstract: The proportion of older people in the world population is expected to increase rapidly during the upcoming decades. Consequently, the number of patients with multimorbidity will increase dramatically. In epidemiologic research, the concepts of multimorbidity, comorbidity, and complications have been confusing, and some of these concepts are used interchangeably. In this commentary, the authors propose a clear terminology for clinical concepts describing different aspects of multimorbidity and elucidate the relationship between these clinical concepts and their epidemiologic analogs. Depending on whether a study uses causal or predictive models, a proper distinction between concepts of multimorbidity is important. It can be very difficult to separate complications of the index disease under study from comorbidity. In this context, use of comorbidity indices as confounding scores should be done with caution. Other methodologic issues are type, duration, severity, and number of comorbidities included in the ascertainment methods, as well as sources included in the research. Studies that recognize these challenges have the potential to yield valid estimates of the comorbidity burden and results that can be compared with other studies.

Keywords: epidemiology, epidemiologic methods, comorbidity, complications, diagnosis-related groups, risk adjustment

Multimorbidity
The major challenge facing modern health care systems is aging of the population in the context of significant pressure to contain costs. The proportion of people aged 60 years or more in the world population is expected to increase rapidly from 10% in 2000 to 21% in 2050. Concurrently, the number of patients with multimorbidity, ie, coexistence of several chronic diseases, will increase dramatically. The prevalence of multimorbidity has been estimated at more than 80% among persons aged older than 85 years. Up until now, clinical research has focused predominantly on single disease and episode, often with a focus on mortality as the main endpoint. Thus, one of the most important tasks in clinical medicine today is managing multimorbidity. This requires an evolution away from the single disease focus that has dominated medicine for centuries. The aim of this commentary is to propose clear terminology for the clinical concepts describing different aspects of multimorbidity and to elucidate the relationship between these clinical concepts and their epidemiologic analogs.

Confusion concerning terminology used in clinical epidemiology
The concept of multimorbidity varies widely in the literature. It has been used to describe the number of morbidities, the number and severity of morbidities, and the...
number and severity of morbidities together with concurrent
limitations in functional status or frailty. In addition, multimorbid
ty is often measured by the burden of comorbidity
at time of diagnosis of an index disease.\textsuperscript{4} The numerous
definitions of multimorbidity include predefined medical
conditions or unlimited numbers and types of medical
conditions, chronic conditions, or both acute and chronic
conditions, physical diseases alone, or physical and psychiatric
conditions. Further, the various definitions include comorbid
ities diagnosed before or both before and concurrent with
the index disease.\textsuperscript{6–14}

Because of the existing confusion concerning terminology,
we propose more stringent definition of five commonly used
concepts. We suggest that the “index disease” describes the
main condition under study, while “comorbidity” describes
medical conditions that exist at the time of diagnosis of the
index disease or later, but that are not a consequence of the
index disease. In contrast, “multimorbidity” can be described
as existence of two or more chronic diseases. “Complications”
of an index disease are adverse events occurring after diag
nosis of that disease. “Case-mix” refers most often to the
mix of patient types treated at hospitals or departments, and
the case-mix index is a measure of the complexity of illness
used in health service research or in clinical medicine as, for
example, a clinical prediction score.

In clinical epidemiology, these concepts are used in two
main types of models with the purposes of control for con
founding (causal models) or clinical prediction.

Causal models
These concepts can be translated into epidemiologic analogs
in causal models with a well-defined exposure and outcome.\textsuperscript{15}
In this context, the index disease defines the study popu
lation or the exposure under study. The term “comorbidity”
can have three roles in epidemiologic studies, depending
on the exposure and endpoint. First, in some circumstances,
comorbidity can be a part of the exposure complex under
study. An example is the impact of comorbidities on mortality
in patients with diabetes. Second, comorbidity can interact
with the exposure and modify the association between that
exposure and an endpoint. Third, in many studies of a defined
index disease, comorbidity qualifies as a potential confound
ing factor in the association between an exposure and an
endpoint, given that the burden of comorbidity varies for
different patient populations based on characteristics such as
age and lifestyle.\textsuperscript{16} It is important to emphasize that there are
three criteria for a confounding factor: a confounder must be
associated with the disease (either as a cause or as a proxy
for a cause but not as an effect of the disease); a confounder
must be associated with the exposure; and a confounder must
not be an effect of the exposure.\textsuperscript{15}

In contrast, “complications” of the index disease can arise
after diagnosis of that disease and therefore qualify as an
endpoint or an intermediate step in the pathway from expo
sure to a more distal endpoint in the clinical pathway. For
example, multiple sclerosis and sarcoidosis can be comorbid
conditions in diabetics, while retinopathy, cardiomyopathy,
and nephropathy are well defined complications of diabetes.\textsuperscript{17}
Other comorbidities may modify the effect between the index
disease and survival. Thus, cancer may modify the effect
between diabetes and survival (Figure 1).

Risk prediction models
While causal models are used in the research setting to evalu
ate the causal role of one or more exposures while simultane
ously controlling for possible confounding factors,\textsuperscript{15} risk or
prognosis prediction models may be useful tools in several
clinical settings taking multiple clinical variables into con
sideration. The American Society for Anesthesiology score,
for example, is used in acute medicine to evaluate the physi
cal status of a patient and the impact of the index disease,
comorbidity, and complications on mortality.\textsuperscript{18} The Acute
Physiology and Chronic Health Evaluation scale is used in
intensive care to evaluate the burden of morbidity from the
index disease, comorbidity, and acute clinical status.\textsuperscript{19,20}

In health service management, the Diagnosis-Related
Group system is used as a way to classify hospital cases into
one of 467 original groups (now 745). This system of classifi
cation was developed by Fetter and Thompson.\textsuperscript{21} Their inten
tion was to identify the “products” that a hospital provides.
Diagnosis-Related Groups are assigned by a “grouper”
program based on International Classification of Diseases
(ICD) diagnoses, procedures, age, gender, discharge status,
and the presence of complications or comorbidities.\textsuperscript{22}

In practical clinical epidemiology, it might be difficult to
distinguish complications from comorbidities. Such evalua
tion might most often require data information outside the
actual study.\textsuperscript{21} Evidence from particular experimental studies
and theory, for example, must be considered.

Complications versus comorbidity
in epidemiologic research
Failure to separate complications from comorbidities can
have a serious impact on clinical epidemiology research.
A very broad definition of comorbidity must be used
with caution to avoid misclassifying complications as
comorbidities. As shown in Figure 1, complications are end-points or intermediate steps in the pathway from an exposure to an endpoint. Therefore, they must be considered separately from comorbidities. Otherwise, the total comorbidity burden would be overestimated and misclassification of information about comorbidity would be introduced. If complications are regarded as comorbidities and handled as confounders, some of the effect between the exposure and outcome is masked, resulting in distorted estimates of association. At the same time, a more restrictive definition of comorbidities could misclassify comorbidities as complications, and therefore result in underestimation of the comorbidity burden, potentially leading to residual confounding if comorbidity is a confounder in the study.

Correct classification of medical conditions as comorbidities or complications is necessary to avoid inaccurate estimation of the comorbidity burden. As described above, in examining the association between diabetes and survival, diseases such as multiple sclerosis or sarcoidosis are not known to be related to diabetes. Therefore, these diseases should be clearly defined as comorbidities in patients with diabetes as an index disease. Other diseases and conditions may not clearly meet the criteria of either comorbidities or complications of diabetes. Hypertension may be a common complication of diabetes as a result of vascular changes, but may also arise independently. This illustrates the complexity of separating medical conditions into comorbidities and complications, but also stresses its importance. Directed acyclic graphs may help clarify the role of different variables in a study.

**Comorbidity scores and indices**

Comorbidity scores or indices combine information about several comorbidities into one score. The idea behind a confounder summarization, for example, is to define a single continuous variable that pulls together relevant information on the confounding properties of all variables. Several indices have been developed to account for comorbidity as a confounding factor in research studies. Frequently used indices include the Charlson Comorbidity Index, the Cumulative Illness Rating Scale, the Index of Co-existing Disease, and the Kaplan–Feinstein Index. These indices are based on information about severity or number and severity of comorbid conditions, defined by organ systems and severity of diverse aspects of each comorbid disease, or on the degree of pathologic changes of the comorbid condition defined by organ systems. These indices incorporate available information about comorbid conditions into an aggregate index, which precludes estimation of effects of individual comorbid diseases. In addition, the definition of a comorbid condition and its role in the index varies for different indices.
The Charlson Comorbidity Index is frequently used in clinical epidemiology studies to quantify the level of comorbidity. This index is based on 19 comorbid diseases weighted according to adjusted one-year cumulative mortality risk, and has been validated as a prognostic marker of comorbidity for several index diseases. However, the Charlson Comorbidity Index has several limitations. It does not include psychiatric diseases, which can confer substantial morbidity, even in patients with physical index diseases. The Charlson Comorbidity Index also evaluates disease severity only for a few diseases and to a very limited extent. Diabetes and cancer, for example, are categorized into only two severity groups, although the prognostic impact of disease severity can be more finely parsed. The prognostic impact of disease duration varies for different diseases. For instance, it increases with duration for diabetes, but may decrease for successfully treated ulcer disease and cancer.

Limitations of confounding indices
The burden of comorbidity is measured by extracting data from medical records or medical databases, physical examination, personal interview, or questionnaires. These methods have many weaknesses and there is no gold standard. First, the sensitivity and specificity of comorbid diagnoses, whether they come from medical files, databases, or patient report, are never complete. Therefore, there will be residual confounding in a study where comorbidity is a confounding factor. Due to variation in sensitivity and specificity for different comorbid diagnoses and potential failure to account for disease severity and duration, which may be highly correlated with an exposure and endpoint, comorbidity indices cannot accurately measure the comorbidity burden for each patient, thus leading to residual confounding. Any underestimation of the comorbidity burden, for example, by using restrictive definitions of comorbidity, may also introduce residual confounding into a research study. In view of these limitations, all confounding score indices must be used with caution.

Conclusion
Research on multimorbidity is urgently needed to understand the clinical course of disease in detail in order to improve clinical outcomes. Depending on whether a study uses causal or prediction models, a proper distinction between concepts of multimorbidity is important. It can be very difficult to separate complications of the index disease under study from comorbidity. In this context, use of comorbidity indices as confounding scores should be undertaken with caution. Other methodologic issues are type, duration, severity, and number of comorbidities included in the ascertainment methods, as well as sources included in the research. Studies that recognize these challenges have the potential to yield valid estimates of the comorbidity burden and results that can be compared with those from other studies.

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