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TOPIC HIGHLIGHT

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Methodology for high-quality studies on course and prognosis of inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBDs) are characterized by a chronic course with an alternation of relapses and remissions. Questions about prognosis are important for the patient who wants to know how the disease will affect his/her life and also for clinicians to make management decisions. Correct selection of the patients is the basis for good methodological studies on the course of IBD. A great proportion of data on the course of IBD is derived from a limited number of cohort studies. Studies help to define the endpoints for clinical trials and to identify subsets of patients in whom the prognosis of the disease can be stratified according to clinical features. Specific scientific requirements for high-quality studies on prognosis are the following: use of inception cohort, description of referral patterns, completeness of follow-up, objective outcome criteria, blind outcome assessment, adjustment for extraneous prognostic factors and statistical issues. We analyzed each of these requirements in studies on IBDs. To date, prospective and population-based cohort studies are the standard for an unbiased assessment of prognosis. A better knowledge of the course of disease of chronic disorders ideally requires: (1) data from population-based studies, to avoid selection bias from referral centers in which patients with a more severe disease are usually treated; (2) inclusion of patients seen at the onset of the disease excluding misdiagnosed cases; and (3) follow-up from the onset of the disease to the end without dropouts.

Key words: Methodology; Inflammatory bowel disease course; Prognosis; Population-based studies; Prospective cohort studies

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are characterized by an alternate course of relapses and remissions. A better knowledge of the course of a chronic disease permits us to answer correctly the questions about the response to therapy, disability, the rate of surgery and mortality, and to identify subsets of patients in whom disease prognosis can be stratified according to clinical features. Finally, studies of the course may increase our knowledge of disease pathology and etiological factors, possibly result-

ing in the prevention of disease.

Until 1970, the course and prognosis of the IBDs were derived initially from tertiary referral centers showing high morbidity and mortality, because they concerned more severe and complicated diseases. Subsequently, several cohort studies have been carried out showing better prognosis than previously described. In fact, for prognosis studies, it is preferable to analyze an unselected group of patients, ensuring the reliability of study results.

Since 1950, drug therapies for IBDs have been introduced, so it is impossible to have any long-term natural history data even if the placebo arms of the clinical trials can be utilized as a source of data on short-term natural history.

According to Sackett *et al*[1], natural history is the course of a disease from its biological onset to its recovery or permanent disability or death. In the spectrum of the course of the disease, we can identify different phases: (1) biological onset, "the initial interaction between man, environment and casual factors"; actually it is not certain what the initial event is; and (2) preclinical phase, interval between biological onset and clinical manifestations. To date, we do not know of any specific markers of disease that allow early diagnosis in this phase. The importance of an early diagnosis is also questionable because of the lack of specific treatment, which can alter the natural history of the disease if initiated in a preclinical phase.

In these first two phases, we deal with natural history because patients have not been treated. However, in all the population studies it is better to use the terminology "course of disease" more than "natural history". The following phases deal with the course of disease: (1) clinical diagnosis that does not correspond to the onset of symptoms (often there is a long gap between the onset of the disease and the time of diagnosis, which represents an important source of bias); and (2) outcome: recovery, permanent disability, mortality. In chronic disease, the interim outcomes (i.e., complications, cancer, impairment of the quality of life, the need of immunosuppression) also represent relevant endpoints in prognostic studies.

In this review, we emphasize the methodological requirements for high-quality studies on the course and prognosis of IBDs. According to Sackett *et al*[1], specific scientific requirements for high-quality studies on prognosis are the following: (1) use of inception cohort; (2) description of referral patterns; (3) completeness of follow-up; (4) objective outcome criteria; (5) blind outcome assessment; (6) adjustment for extraneous prognostic factors; and (7) statistical issues. We analyzed each of these requirements within the studies on IBDs.

INCEPTION COHORT

To evaluate the prognosis of a disease in a cohort of patients, it is important to start the follow-up at a common point; preferably as early as possible in the course of the disease (i.e., onset of symptoms or clinical diagnosis). For this reason, inception cohorts, preferably prospective, now represent the standard design to minimize bias. Bias in cohort studies can create apparent differences when they do not actually exist in nature.

The most frequent selection biases in conducting studies on prognosis are as follows. (1) Prevalence-incidence bias: when mild or asymptomatic cases, for example, proctitis, as well as fatal short disease episodes, such as severe colitis, are missed when studies are performed late in the disease process. It could result in an overestimation of the severity of the disease if the patients with a mild disease are missed, and in a more favorable prognosis if the mortality is not included in the prevalent group; (2) Lead time bias: occurs when the outcomes such as survival, as measured from the time of diagnosis, may be increased not only, because the patients live longer, but because screening permits an early diagnosis (i.e., for the availability of a new diagnostic test). This results in an apparent prolongation of the time to a predefined event (i.e., death, time to surgery or time to relapse), when instead it only results in an earlier diagnosis when compared to traditional methods [i.e., detection of asymptomatic colon cancer during screening endoscopy in patients with ulcerative colitis (UC) could result in an apparent prolongation of survival]; and (3) Length time bias: screening tends to detect a disease that is destined to progress slowly and, therefore, has a good prognosis. Also, advances in diagnostic techniques allow an earlier diagnosis, in an asymptomatic phase of the diseases with less aggressive course. Length time bias occurs when the patients, whose disease is discovered by screening, may also appear to do better, or live longer, than people whose disease is clinically diagnosed with symptoms. For example in patients with IBDs, before the introduction of endoscopy, mild colonic or distal disease, which are often mildly symptomatic, were often missed. This distortion is called technical bias and is related to the length time bias; together with the therapeutic bias (concerning the advance in therapy) it concurs to determine the temporal bias.

DESCRIPTION OF REFERRAL PATTERNS

In a study of prognosis, it is of great importance to use unselected patients to obtain more realistic results and for a wider applicability of study results. However, it is important to describe the referral pattern, which occurs when the characteristics of patients differ between one setting (e.g., primary care) and another setting that includes only referred patients (e.g., secondary or tertiary care). Studies from referral centers include more severe and complicated cases and usually result in poor prognosis.

Another relevant bias is the diagnostic/therapeutic access bias that occurs when studies made between populations with a different access to diagnostic facilities or therapy are compared. For example, in a tertiary center, patients have more opportunities to access biological ther-

apy, allowing a better course of disease in severe patients.

The outcome could also be influenced by the different health insurance or government programs across countries, as is the limit which exists in some countries (i.e., the United Kingdom) on the maximum duration of anti-tumor necrosis factor (TNF) therapy. Few data are available on the relationship between the length of maintenance therapy with anti-TNFα and the natural history of the disease, or with the achievement of mucosal healing, which actually seems to be the main outcome correlated with the maintenance of remission. The best study is the population study in which all the incident cases in a well-defined area are identified and followed up regularly with a clear protocol.

COMPLETENESS OF FOLLOW-UP

According to Sackett *et al*[1], in an accurate study of prognosis, at least 90% of the population should complete follow-up. This statement results from the evidence that a study with many patients lost during follow-up (usually > 20%) leads to distorted results. For example, if patients are lost during follow-up, for poor compliance, it could result in a better prognosis of the cohort. If they are affected by mild disease (like proctitis in UC) and therefore omit control visits, this can result in an overestimation of poor outcomes. However, for any degree of loss during follow-up, the validity of the study could be diminished. In addition to this, the length of follow-up is also important if one is evaluating some specific outcomes like survival. In that case, the follow-up time should be long enough so that about two-thirds of the patients will have suffered the events under study at the end of the observation period. In other cases, when the outcome evaluated is more frequent and rapid in occurrence (i.e., postsurgical recurrence or response to therapy), the follow-up could be shorter.

OBJECTIVE OUTCOME CRITERIA AND BLIND ASSESSMENT

The most important outcomes to assess in a prognosis study are disease activity, intestinal complications, surgery, cancer risk and mortality. One of the most relevant problems in the study of prognosis of IBDs is the difficulty of identifying an objective outcome because of the lack of an agreement in the definition of some important outcome measures that are open to possible differences in the results.

Disease activity

For example, analyzing some of the most important studies of prognosis, the definition of disease activity is variable. Below, we report some examples of this variability in cohort studies of IBDs.

Remission or no activity: (1) In the Copenhagen study[2-7] for Crohn's disease (CD) no activity was defined as no more than two stools per day and no blood or pus in the stools, no abdominal pain and no systemic symptoms such as fever or weight loss; and (2) in the Olmsted County study[8-11], remission or no medication state was defined as a patient who required no medication for CD, excluding antidiarrheals.

Mild disease: (1) In the Copenhagen study[2-7], mild disease activity was defined as ⩾ 2 and ⩽ 4 bowel movements and/or blood or pus in the stools and/or mild abdominal pain less than daily and no systemic symptoms; and (2) in the Olmsted county study[8-11], mild disease was defined according to therapy; a patient with mild disease was a patient on sulfasalazine, 5-acetylsalicylic acid, antibiotics, or topical therapy.

Severe disease: (1) In the Copenhagen study[2-7], moderate/high activity was defined as more than four stools daily and/or blood or pus daily and or abdominal pain either severe or daily, with or without systemic symptoms; and (2) in the Olmsted study[8-11] the authors distinguished severe disease drug responsive and severe disease drug refractory; in the former, they referred to a patient on oral corticosteroids or immunosuppressive therapy lasting > 6 mo, with documented improvements; in the latter definition they included patients on oral corticosteroids or immunosuppressive therapy with no documented improvements within 2 mo for corticosteroids or within 3 mo for immunosuppressive medications.

In another important study, as in the European collaborative study on inflammatory bowel disease[12-17], there was not a clear definition of disease activity; the course of the disease was assessed comparing the activity in a given point during the follow-up with the initial status. Any of these definitions involves subjective judgment and blind outcome assessment, one of the requirements, is not usually feasible and the study results are difficult to compare. Probably the CD activity index[18] and Mayo Clinic score[19] for UC are a more objective outcome to evaluate disease activity or response to therapy in clinical trials, but owing to their complexity, they are not often used in clinical practice.

Complications

Another bias that occurs when collecting data retrospectively, in evaluating intestinal and extraintestinal complications or need of surgery, is referral bias, which occurs when the appearance of complications has triggered the visit. Thus, it is essential that data on the occurrence of complications in IBDs are collected prospectively and in unselected samples, and the diagnostic measures are well defined. It is important to define the diagnostic and therapeutic protocol for complications because a different approach among centers influences the course of the disease. For example, endoscopic dilation is an approach adopted in stricturing postsurgical recurrence in CD in some centers, whereas in others, surgery is the preferred option and this different choice may influence prognosis.

Cancer risk and mortality

In the evaluation of cancer risk, an important concern is represented by the influence of surveillance bias. Surveillance bias, what some texts call detection bias, occurs when one group is followed more closely than another. This could lead to an outcome being diagnosed more often in the more closely followed group, but not because it really occurred more often in that group. Of course, cancer risk is linked to the surgical policy of the single center. A center that proposes early intervention may have a lower risk of cancer in long-term follow-up. It is mandatory that the cancer risk is evaluated in an incident cohort and in a population study. Another relevant requirement is the presence of a cancer registry in the area where the cohort is followed-up.

Another important outcome in prognosis studies is mortality. A recognized method to assess mortality is the calculation of standardized mortality ratio (SMR). SMR is the ratio between the observed number of deaths in a study population and the number of would-be-expected deaths, based on the age- and sex-specific rates in a standard population and the age and sex distribution of the study population. If the ratio of observed/expected deaths is > 1.0, there is said to be "excess deaths" in the study population. It is, however, a very efficient stratification method and also permits one to use retrospective data. The results of studies with good methodological requirements have been summarized in a meta-analysis[20], and give a reliable measure of this outcome correcting for differences among centers. Of course, meta-analysis should include studies with the same methodological standards. Small differences will only be detected if the studied group is very large. At the same time, if the baseline risk of an outcome (i.e., cancer or mortality) is very low, few events in the study population can identify an apparent relevant risk difference (i.e., the risk of Hodgkin lymphoma identified in the Florence cohort[21,22]).

ADJUSTMENT FOR EXTRANEOUS PROGNOSTIC FACTORS

Examining the effects of specific factors on prognosis, it is important to adjust for extraneous variables, for the potential effect of associated factors on the results, thus unmasking a possible erroneous association. These confounding factors can also influence data from different population-based inception cohort studies. Even population-based inception cohorts could be difficult to compare because of the presence of different sources of bias, such as temporal, diagnostic access and therapeutic. Thus, it is important always to give information about the distribution of potential confounding prognostic factors.

In UC, it is important to know the extent of the distribution of the disease (pancolitis, left-side colitis, or proctitis) at diagnosis and the duration of disease because of the known major risk of cancer in pancolitis and in long disease duration.

In CD, many relevant prognostic factors have been identified that should always be included in a multivariate analysis, such as smoking habits, age, site of disease, and extent of disease. Prognostic factors should be evaluated in incident cohorts prospectively.

An example of a possible bias in the evaluation of the prognostic factor is the study by Beaugerie *et al*[23]. Among 1526 patients diagnosed with CD between 1985 and 1998, those operated upon within the first month of the disease, patients with inadequate data, and patients with severe chronic nondigestive disease were excluded. The authors identified age < 40 years, perianal disease, and initial use of steroids as predictive factors for subsequent 5-year disabling. The authors suggested that referral bias could have distorted the results and a further study in a population setting was advocated. Of course, the prognostic model identified in an incident cohort should be applied in another independent cohort (the test sample).

STATISTICAL ISSUES

To date, to evaluate survival in prognosis studies, life-table-based methods have been used to minimize the difficulty in interpreting crude rates deriving from studies with different lengths of follow-up. During a follow-up period, a decrease in the number of patients makes it easier to detect differences in the early stages of follow-up. Some problems could derive from the lack of study power, and caution should be exercised when the effects are examined over different intervals of time. Rare events, such as lymphoma, risk being overestimated because the baseline risk in the general population is low. Finally, it would be desirable that data on the number of patients under observation at a given time are reported as confidence intervals. Cox's proportional hazard analysis is a type of multivariable analysis used when the outcome is the time to obtain the event. When data on important prognostic factors are not available, sensitivity analysis is a useful tool, assuming various degrees of maldistribution between groups, and seeing how it affects the results.

CONCLUSION

The validity of prognosis studies on IBDs is based on the presence of the above-mentioned methodological requirements. An excellent cohort study must fulfill the following criteria: (1) start of follow-up at inception; (2) population-based, or near to population-based; (3) use of standard diagnostic criteria for UC and/or CD; (4) use of survival methods; and (5) complete or near to complete follow-up (≥ 80%).

Better knowledge of the course of chronic disorders ideally requires: (1) data from population-based studies to avoid selection bias from referral centers where patients with more severe disease are usually treated; (2)

Table 1 Population-based prospective and retrospective studies

Study	Population size	Inception period	UC	CD	Surgery UC	Surgery CD	Mortality UC SMR (95% CI)	Mortality CD SMR (95% CI)
Prospective studies								
Copenhagen[2-7], Denmark	550 000	1962-1987	1160	374	24%	61%	1.1 (1-1.2)	1.3 (1.1-1.6)
		1991-1993	89	58	24%	65%	1.5 (0.9-2.5)	2.3 (1.1-4.2)
	1 211 634	2003-2004	326	209	-	-	0.9 (0.3-2.4)	0.8 (0.02-4.2)
		1962-2004	1575	641				
EC-IBD study[12-17]	NA	1991-1993	1379	706	8.70%	40%-55%	1.09 (0.86-1.37)	1.85 (1.3-2.55)
		1991-2004	-	365				
IBSEN[23-28], Norway	970 000	1990-1993	525	225	9.8% (7.4-12.4)	37.9% (31.4-44.4)	Survival 96%	Survival 96%
Retrospective studies								
Stockolm[29-31], Sweden	1 200 000	1955-1984	1547	1251	28.00%	71%	1.37 (1.2-1.54)	1.51 (1.29-1.75)
		1955-2000	-	20 120		78% (15 yr)	(15 yr)	(15 yr)
	1 470 000	1990-2001	-	1389				
Uppsala[32,33], Sweden	1 200 000	1965-1983	2509	1469	-	96% (15 yr)	1.4 (1.2-1.5)	1.6 (1.4-1.9)
Olmsted[8-11], United States	110 000	1940-1993	278	225	49.00%	49%	0.8 (0.6-1)	1.2 (0.9-1.6)
	124 000	1940-2000	372	308				
Leicester[34,35], United Kingdom	930 000	1972-1989	1014	610	-	-	0.9 (0.8-1.1)	0.72 (0.5-1)
Florence[21,22], Italy	650 000	1978-1992	689	231	-	-	0.7 (0.56-0.88)	1.51 (1.06-2.08)
Cardiff[36-41], Wales	280 000	1986-1991	-	105	-	59%	-	
		1992-1997		99		37%		
	NA	1998-2003		137		25%		
		1941-2000		394				1.29 (1.12-1.45)
Leiden[41], The Netherlands	440 000	1979-1983	-	210	-	56% (15 yr)	-	2.23 (1.75-2.85)

UC: Ulcerative colitis; CD: Crohn's disease; SMR: Standardized mortality ratio; EC-IBD study: European collaborative study on inflammatory bowel disease; IBSEN: Inflammatory bowel south-eastern Norway; NA: Not available. Number of cases may vary between various reports from same centers.

inclusion of patients seen at the onset of the disease excluding misdiagnosed cases; and (3) follow-up from the onset of the disease to the end without dropouts.

The more relevant cohort studies are summarized in Table 1 (prospective and retrospective)[2-7,12-17,23-41], which have been followed up for a long period and in which the methodological requirements listed above are satisfied. Two main outcomes are included in the table to show the variation between both types of study, despite the same methodology being adopted. Prospective cohort studies are a more relevant source of information. Although there was wide variation in the rate of surgery, which depends on the therapeutic policy adopted in different areas, mortality was homogeneous in the three main studies.

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