APPLYING EVIDENCE TO THE CARE OF AN ADULT WITH A FIRST-TIME SEIZURE: HOW TO ESTIMATE PROGNOSIS

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One of the most important ways we can help our patients is to give them a sense of what to expect when they are faced with a clinical problem. For example, we know that viral pharyngitis improves quickly, infectious mononucleosis usually means a protracted recovery period of restricted activity, and metastatic cancer leads to the question, "how long do I have to live?"

Information on the prognosis of disease drives our attention and energies in our clinical work, and in so doing acts as the structural backbone of our clinical activities. Although intuitive methods for estimating prognosis are routinely used in clinical practice, more precise estimates of the risk for possible outcomes of disease require prognostic information from appropriate research studies.

This article uses a case of a healthy young woman with a first-time unprovoked seizure as the basis for examining how to obtain and incorporate available medical evidence when faced with estimating prognosis. The article begins with the clinical assessment of the patient and is followed by a discussion of how to formulate an answerable prognosis question and where to search for the answer. It concludes with the critical appraisal and application of a published study of the prognosis for seizure recurrence in adult patients with an idiopathic first-time seizure.

Assessing the Clinical Problem

You are an internal medicine–pediatrics resident seeing patients at a primary care continuity clinic affiliated with a large teaching hospital. Ms. Kindel, a 19-year-old woman, is here for follow-up on a first-time seizure she experienced 9 days ago. You have seen her once before for a sinus infection. The patient is accompanied by her sister, who witnessed the seizure, and her mother.

The seizure occurred on a Saturday evening. The patient was taken to the hospital's emergency department (ED) immediately after the event, where she was evaluated, scheduled for an electroencephalogram (EEG), and discharged to follow-up at the clinic. Notes from the ED physician's evaluation as well as EEG results are in Ms. Kindel's chart and available for your assessment. Notes from the ED evaluation conclude that Ms. Kindel had an unprovoked generalized tonic-clonic seizure with no apparent underlying cause. Electrolytes, urine toxicology screen, and computed tomography of the head were all normal. Standard and sleep deprivation EEGs revealed normal findings.

Recounting the events leading to the seizure, the patient describes a feeling of uneasiness that lasted approximately 20 to 30 minutes while she was getting ready to go out for the evening with her sister. The next thing she remembered was waking up on the bathroom floor with emergency medical personnel standing over her. The patient's sister describes seeing the patient brushing her hair in the bathroom and then slumping over onto the floor. She then noted her sister to "go stiff all over" for less than a minute and then to "twitch and jerk" for 1 or 2 minutes, perhaps longer. The patient was sleepy for approximately 30 to 60 minutes after the event but then returned to her normal self. She never lost control of her bowel or bladder function, nor did she bite her tongue.

The patient is otherwise healthy. Her past medical history is unremarkable, and her only medication is an oral contraceptive pill. She has never had neurologic problems and complains only of an occasional tension headache on review of systems. There is no history of head trauma. She denies use of

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alcohol or illicit drugs. The patient's mother confirms that her daughter was a healthy child and adolescent. To her knowledge, there is no history of epilepsy in her or her husband's family. The patient lives at home in order to save money while attending evening classes at a local community college. She works during the day as a bank teller. She does not drive and uses public transportation to and from work and school.

On examination today, the patient is afebrile, with a blood pressure of 108/62 mm Hg and a pulse of 73 bpm. The general medical examination is completely normal. The neurologic examination also is normal, including examination of the cranial nerves, cerebellar function, motor and sensory function, language, and deep tendon reflexes.

Although she does not drive, Ms. Kindel notes that she spends many hours away from her home. She is frightened by the thought that such a significant event may occur again while she is at work, school, or on the bus. She asks, "What are the chances of an attack like this happening again?"

You pause before responding and realize you have no idea how likely it is that your patient will experience another seizure. While your examination findings and the negative ED workup and normal EEG results reassure you that important underlying causes of seizure have been ruled out, you also know that epilepsy often is idiopathic. Given your patient's fear of having another seizure and the fact that these events can be dramatic in presentation and have significant psychosocial implications, you wonder whether it might be in the patient's best interest to start on antiepileptic medication.

You turn to Ms. Kindel and say, "Truthfully, I'm not sure how likely it is that you will have another seizure, but I'll look into this question and let you know what I find. Meanwhile, you can be assured that the tests we've done revealed no problems that could cause seizures." You then excuse yourself and say you will return after consulting with Dr. Blake, the senior physician at the clinic.

The evidence-based medicine (EBM) process begins with a careful assessment of the patient and clinical problem, our personal knowledge and the current state of the evidence relative to the clinical problem, and—importantly—the patient's perspective on the problem. The goal of assessment is to identify critical information we need to proceed with care decisions on behalf of our patient. Before we can make these decisions, however, we need to be able to estimate prognosis. This process requires reliable information about the possible outcomes of the particular clinical problem (eg, recurrence after a first-time unprovoked seizure), the frequency with which those outcomes can be expected to occur, and the expected time frame of occurrence. Important tools for predicting the likelihood of eventual outcomes of disease are called *prognostic factors.*

Prognostic Factors

Prognostic factors are individual traits of the patient or condition that make specific outcomes—desirable or undesirable—more or less likely. Prognostic factors may be demographic characteristics (eg, race, gender), disease-specific features (eg, presence of ascites in cirrhosis, stage in cervical cancer), or coexisting health-related conditions.

Consider for example the condition of fatty liver, which is associated with a 10% risk for development of cirrhosis and a 50% risk for death over 10 years [1]. The etiology of fatty liver is known to significantly influence the risk of these outcomes. Among patients whose fatty liver is secondary to alcohol consumption, the risk for developing cirrhosis is 21% compared with 1% for those whose condition is not secondary to alcohol intake, and the risk for death is 74% versus 25%, respectively. Reliable prognostic information such as this enables us to assess the seriousness of a particular condition and focuses our attention more intently on it. Knowing the prognosis of a condition also helps us to be more specific when we counsel our patients about the risk for specific outcomes of the condition. For example, an exact percentage, such as "74%," is much more easily understood than a vague and potentially confusing term such as "high" or "common" [2].

Sources of Prognostic Information

Information on the prognosis of specific disorders comes from two types of research studies.

Cohort study. The best study design for identifying prognostic factors and for assessing the association between these factors and specific outcomes is a cohort study. In this type of study, one or more groups of patients are identified based on the presence or absence of exposure to a suspected risk factor for a disease. Cohort studies can be done prospectively or retrospectively, depending on the temporal relationship between the initiation of the study and the occurrence of the disease. In a prospective study, patients enter the study at a similar point in their disease process (before the outcome of interest has

occurred) and are followed forward in time to determine the percentage of those who develop the outcome of interest. In a retrospective study, the exposures and outcome of interest have already occurred when the study is undertaken. Although more expensive, prospective cohort studies allow the investigators to more fully assess exposure and to obtain information on potential confounders. In retrospective cohort studies, the investigators must rely on patient records or memories to gather their information.

With both types of cohort studies, certain prognostic factors can be studied along the way to determine whether they confer a greater or lesser risk for the outcome of interest. In the case of Ms. Kindel, a useful cohort study would be one that followed a group of patients forward in time from their first seizure, ascertaining the overall recurrence rate. Even more valuable would be a study in which the investigators collected a variety of possible prognostic factors at the beginning of the study and calculated whether they made seizure recurrence more or less likely.

Randomized trial. Prognostic information also can be provided by a randomized trial of a treatment intervention. In this case, the treatment and control groups each act as their own cohort study. The treatment group in a randomized trial provides information about the prognosis for patients who receive the treatment being examined; the control group provides information about the prognosis for patients who are untreated. For example, in a randomized trial of the use of polymyxin-bacitracin ointment for treatment of conjunctivitis in children, the children in the control group, who received placebo, had a prognosis for clinical resolution at 9 days of 72% [3]. In this same study, the children in the treatment group, who received the antibiotic treatment, had a prognosis for clinical resolution at 9 days of 91%.

Asking a Focused Clinical Question

You present Ms. Kindel's case to Dr. Blake, your attending preceptor. You summarize, saying that your examination combined with the negative ED workup and normal EEG findings suggest no obvious cause of seizure in this otherwise healthy young woman. However, you state your concern that many cases of epilepsy have no identifiable cause and ask whether it may be best to err on the side of caution and prescribe anticonvulsants in cases such as this. You add that while Ms. Kindel does not drive, she is afraid of having another seizure while she is alone or away from her house. You then remember the question that you could not answer.

"What is the likelihood that Ms. Kindel will have another seizure?"

Dr. Blake says that if the workup for underlying causes of a first seizure is negative, the common local practice is to observe without prescribing antiepileptic medications, as the rate of recurrence is perceived as low. She suggests this course of action for Ms. Kindel but notes that it would be best to support this management approach with sound evidence. Dr. Blake then adds that the decision to initiate antiepileptic therapy should take into account the potential adverse effects of these drugs, which include drowsiness, liver and bone marrow toxicity, and osteoporosis.

"Because the risk of seizure recurrence is important to Ms. Kindel and seizures are a common problem seen in primary care, I suggest you research this question so you can provide your patient with the best possible answer. Perhaps certain prognostic factors can predict a higher or lower risk of seizure recurrence."

You return to the examination room and inform Ms. Kindel that with normal test results, like hers, it is believed that the risk for another seizure is low. Furthermore, with a presumed low risk for seizure recurrence, she can return to her normal routine without the need for medications, although she should avoid high places (ladders, roofs) for the next 6 to 12 months. You tell her that you would like to see her again in a month to see how she is doing. You close saying that you intend to research the question of seizure recurrence risk in her case and will try to provide her with more precise information at her next visit.

Focusing a Prognosis Question

Prognosis questions are interested in the specific outcomes that may occur relative to a clinical diagnosis or problem as well as the likelihood and expected time frame of occurrence. Thus, a prognosis question seeks to gain insight into a patient's future health, life span, and quality of life *over time*. By contrast, a therapy question seeks to gain insight into the expected outcome of a specific treatment intervention for the diagnosis or problem at hand.

As we have learned, the PICO format (patient, intervention, comparison, outcome) is a useful approach to formulating a structured clinical question. With prognosis questions, the PICO exercise is perhaps less important than defining elements that will help us search the literature, identify abstracts of potential value, and interpret the information we find. These elements include the disease or problem at

hand (P) and the outcome of interest (O). In questions of prognosis, the intervention is simply the passage of time, and there is no real comparison. However, potential prognostic factors that may predict a higher or lower rate of outcome are another important element to help with searching and interpreting the literature. The PICO components for this case may be defined as:

P = healthy adult with a single unprovoked seizure
I = the passage of time
C = N/A
O = seizure recurrence

Combining all elements relevant to our search, our question in Ms. Kindel's case would be:

> What is the likelihood that a **healthy adult with a single unprovoked seizure** will experience **another seizure over time**, and do any **prognostic factors** influence this outcome?

Acquiring the Evidence

You decide to use 20 minutes while eating lunch to begin researching Ms. Kindel's question. Using a clinic computer, you start with the online version of *ACP Journal Club*. You're familiar with this filtered evidence resource from EBM seminars and know you can search specifically for prognosis information. Using "seizure" as your search term and limiting to "prognosis" yields eight citations, two of which look promising. Clicking on each title yields a structured abstract and expert commentary [4,5]. You print each article summary in case you want to look for the full text of either study later.

The first study is a 1990 cohort study by Hart et al [6], which investigated the risk for recurrence after a first epileptic seizure in patients of all ages (newborn to older than 90 years) and assessed five prognostic factors. The second is a 1991 cohort study by van Donselaar et al [7], which sought to determine the rate of seizure recurrence in adult patients with an untreated idiopathic first seizure; nine prognostic factors were assessed in this study. After reading both abstracts, you decide that both studies are potentially applicable to your patient. The study by Hart et al [6] reported a recurrence rate of 67% within 1 year following a first seizure and 78% within 3 years. The study by van Donselaar et al [7] reported an overall recurrence rate of 40% at 2 years of follow-up. These rates strike you as being higher than you anticipated.

Although happy you've found two studies that appear to address your prognosis question, you're concerned that they are more than 12 years old. You wonder whether any new diagnostic tools for assessment of first-time seizure patients may have been factored into more recent studies. You decide to take some time at the end of clinic to attempt a MEDLINE search for any newer studies addressing your prognosis question.

At the end of the day, you return to your search for evidence on seizure recurrence. Consulting notes from your EBM seminars, you recall that a good way to find prognosis studies is to explode the MESH term "cohort studies." You also enter and explode the MESH term "seizure." Combining these two searches results in 538 citations. You further limit your search to your outcome of interest (recurrence), using the truncated textword "recur$.tw" to pick up any words in the title or abstract with that trunk, such as "recur," "recurrence," or "recurring." Combining these three search terms results in 74 articles. Scanning the abstracts, you find approximately four to six cohort studies of seizure recurrence, with the abstracts reporting recurrence rates between 40% and 80%.

You confer with Dr. Blake about the two studies you found on the *ACP Journal Club* Web site and the abstracts you found on MEDLINE. For several reasons, Dr. Blake recommends focusing on the study by van Donselaar et al [7] for appraisal. First, you can assume that the study, like the one by Hart et al [6], is valid or the *ACP Journal Club* editors would not have selected it for abstracting. But unlike the Hart study, the van Donselaar study included only adults. It also assessed for more prognostic factors. Dr. Blake asks you to report back on your findings at the time of Ms. Kindel's scheduled follow-up visit.

Seeking Answers to Prognosis Questions

When taking an EBM approach to care decisions, it is important to keep in mind the type of question being asked and the type of study best designed to address such questions. Since a cohort study typically is most helpful for answering prognosis questions, we will want to search information sources we know are reliable for including evidence of this type.

Filtered evidence sources. A time-saving approach to finding answers to EBM questions is to search databases of prefiltered and preappraised research studies. The editors of these databases systematically comb the evolving literature, select articles that are most valid and relevant to generalist practice, and apply rigorous standards of literature appraisal.

Expert commentary also is provided to help clinicians apply the evidence to their patients.

The online version of *ACP Journal Club* is perhaps the best filtered evidence resource for researching prognosis questions because the database includes studies of prognosis dating back to roughly 1990. This database is searched using words found in the title or abstract of the article, known as *textwords*, rather than MESH terms. Searches can be further narrowed by specifying type of article (eg, therapy, diagnosis, prognosis). It takes approximately 6 to 9 months for an article to go through the editorial process from its time of original publication to its inclusion in the *ACP Journal Club* database, but this lag time generally is not significant for prognostic information. In fact, because the natural history of clinical disorders remains relatively stable over time, evidence from prognostic studies is likely to be reliable even 10 or more years after it is initially reported. As illustrated in the scenario, some of the more recent cohort studies found on MEDLINE reported similar seizure recurrence rates (40%) as were reported in the 1991 study by van Donselaar et al [7].

MEDLINE searches. If a search of filtered evidence sources produces no useful prognostic information to address our question, the next step is to search unfiltered databases of medical information (eg, MEDLINE, PubMed) using the terms from our PICO question as well as search terms to find prognosis studies. The single best term to use when searching for studies of prognosis is to explode "cohort studies." This strategy has a sensitivity of 60% and a specificity of 80% [8]. Combining this term with the patient/problem (in this case, seizure) and outcome (in this case, recurrence) is the most efficient way to acquire the prognostic information we need. The major drawback of MEDLINE is that it often produces a large number of articles that must be sifted through. To avoid looking at such a large number, additional search terms can be used at the risk of excluding some studies from the results. When in doubt, it is useful to consult with a local medical librarian, who is trained in efficient searching of the medical literature. Librarians often are available by e-mail.

Appraising Evidence for Validity and Importance

The following day you stop at the university's medical library. Because the article by van Donselaar et al [7] is older and unavailable online in full text form, you need to find the print version of the journal in which the article appeared and make a copy. Over the next several days, you read the article and proceed with critical appraisal. Using criteria recommended in the *Users' Guides to the Medical Literature* (**Table 1**), you begin your examination of the study by considering validity criteria for a prognosis study.

You read that the study involved 165 patients aged 15 years or older with a presumed idiopathic first seizure. The patients were obtained through referral to any of four hospitals. Patients with a history of seizures, seizures lasting longer than 30 minutes, or status epilepticus were excluded. Seizures believed induced by sleep deprivation were included unless they were under extreme circumstances, such as lack of sleep for several days. The diagnosis of seizure was based on the description of the episode and comparison to a standardized set of criteria, with good reported reliability. What strikes you most about this cohort is that all patients with a known cause of seizure (eg, drugs, trauma) or prolonged seizures were excluded, leaving only those patients with unexplained and mild seizures.

Looking at a table of possible predictive factors for risk of seizure recurrence, you see that patients were divided into subgroups based upon age, gender, family history of seizure, tongue biting during the seizure, occurrence of the seizure during sleep, provocative circumstances of the seizure, and presence of abnormalities on EEG. You see that the presence of

Table 1. Criteria for Appraising and Applying the Results of an Article About Prognosis

Are the results valid?
Was the sample of patients representative?
Were the patients sufficiently homogeneous with respect to prognostic risk?
Was follow-up sufficiently complete?
Were objective and unbiased outcome criteria used?
What are the results?
How likely are the outcomes over time?
How precise are the estimates of likelihood?
How can I apply the results to patient care?
Were the study patients and their management similar to patients in my practice?
Was the follow-up sufficiently long?
Can I use the results in the management of patients in my practice?

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epileptic discharges on EEG was the strongest predictor of recurrence. In fact, the authors concluded that the decision to initiate or delay treatment for idiopathic first seizure should be based on EEG findings.

Patients were followed for 1 to 2 years, with 100% follow-up. You surmise that this is a sufficient time period for seizure recurrence, particularly since most of the recurrent seizures happened in the first 6 months of the study.

After reading the study and considering the points on validity, you conclude that this cohort study is indeed valid. It included a representative sample of patients with first-time idiopathic seizures. The fact that the authors excluded patients with known precipitants and status epilepticus truly defines this cohort as those with mild, first-time, idiopathic seizures. Follow-up was sufficiently long to capture the recurrent seizures, and the authors achieved 100% follow-up. They also gathered a number of logical prognostic factors along the way. However, you are left to wonder how they defined a recurrent seizure, as this is not explicitly stated.

Criteria for Appraising Validity

To appraise a prognosis study, it is important to evaluate whether the investigators used sound research methodology to ensure validity of the results. Four criteria should be considered when appraising a prognosis study to ensure its methods will have the least bias toward any result.

Representative sample of patients. It is crucial to know what criteria the investigators used to include and exclude patients from their cohort. This information allows us to determine whether the study population is representative of our patient. The most common form of bias introduced in a cohort study is *referral bias*, where the patients are drawn not from the community but from specialty practices. Referral bias often results in a higher rate of outcomes, because the study patients generally are sicker than those in the general community. Such bias does not render a study invalid, as long as we keep it in mind and adjust our thinking accordingly.

Homogeneous prognostic risk. The study sample should include individuals who are at a similar point in the disease process, which ideally is an early phase, although this is not absolutely necessary. Each cohort of patients will have a variety of prognostic factors that divide them into subgroups. For example, smokers have a worse prognosis for recurrent myocardial infarction than nonsmokers do. When subgroups such as this are defined, the authors should follow the prognosis of both groups of patients—those with the prognostic factor and those without the prognostic factor. Common sense and clinical experience may suggest prognostic factors that the authors may have omitted. If several such factors have been omitted, validity is compromised.

Sufficiently complete follow-up. The study by van Donselaar et al [7] had perfect follow-up, which is impressive. Although it is ideal for investigators to have followed 100% of patients in the cohort, this is uncommon. Patients are lost to follow-up because they move, lose interest in the study, or perhaps even die. To qualify for inclusion in the *ACP Journal Club*, a study of prognosis must attain at least 80% follow-up for the time period of the study. How far above 80% a study must be in order for follow-up to be valid depends on the percentage of patients lost to follow-up compared with the percentage who suffered the outcome of interest. If an outcome is rare in the study (eg, occurs in 1% of patients), each additional patient accounted for in the cohort would result in a significant change in the actual outcome. Alternatively, if the outcome is relatively common (eg, occurs in 50% of patients), each additional patient would result in a much less meaningful change in the actual outcome. Completeness also depends on any differences that exist between those who could be tracked and those who could not. One could infer that the patients who could not be tracked were lost because they died or were too sick. As well, they could have been difficult to track because they simply got better and went about their lives.

Objective and unbiased outcome criteria. How the outcome of interest in a prognostic study is measured is as important in a cohort study as it is in a randomized trial. The more subjective the outcome being measured (eg, residual pain on a standardized 5 point scale in patients with chronic low back pain), the more crucial it is to have the outcome assessor blinded to all prognostic factors being studied. When measuring objective outcomes (eg, death), blinding the outcome assessor is still important but not as crucial as with subjective outcomes. The investigators should clearly define the outcomes of interest and be consistent in their method of labeling patients throughout the study. In the study by van Donselaar et al [7], the authors went to great lengths to describe how the initial seizure (used to define patients entered into the study) was defined. Unfortunately, the authors did not explicitly describe the process for documenting whether a recurrent seizure had indeed occurred. We are left to

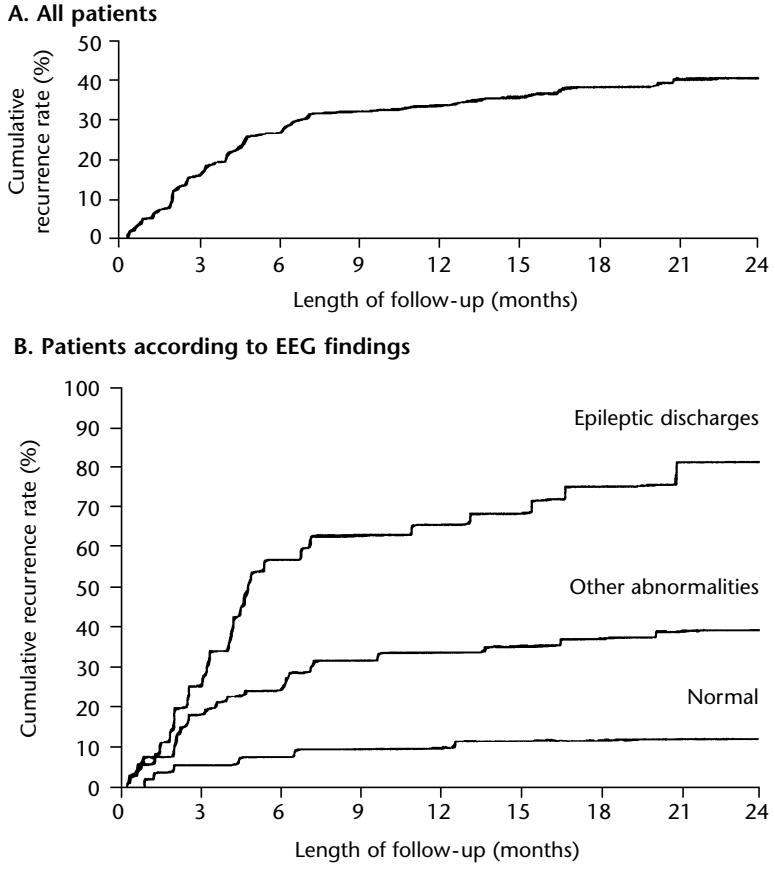

Figure. Continuously adjusted seizure recurrence rates in patients with idiopathic first-time seizures: (**A**) in all patients and (**B**) according to findings on combined standard and sleep deprivation electroencephalograms (EEGs). (Adapted from van Donselaar CA, Geerts AT, Schimsheimer RJ. Idiopathic first seizure in adult life: who should be treated? BMJ 1991;302:621; with permission from BMJ Publishing Group.)

assume the authors defined recurrent seizure in the same way they defined the first seizure (ie, based on the description of the seizure and comparison to a standardized definition).

You next move on to appraise the results of the study. Examining for the outcome of seizure recurrence, you find that the overall recurrence rate was 40% at 2 years. The recurrence rate was highest in the first few months after the initial seizure but then tapered off with time (**Figure**). Patients with epileptic discharges on combined standard and sleep deprivation EEGs had an 81% rate of recurrence at 2 years compared with a 12% rate of recurrence among those with normal EEG results. Recurrence risk also was increased by tongue biting and seizure occurrence during sleep. Finally, age affected recurrence risk. The authors divided the cohort into three age-groups; those in the youngest age-group (15 to 24 years) had the highest recurrence rate, and those in the oldest age-group (45 to 85 years) had the lowest recurrence rate. Gender and family history of epilepsy had no bearing on recurrence risk.

Criteria for Appraising Importance of Results

Likelihood of outcome over time. The main result of a prognosis study is the percent likelihood that the main outcome of interest occurs over the time course of the study. Two questions can be asked about the point estimate of outcome likelihood:

- Is the risk of the outcome constant over time, or does it change?
- Are there any subgroups with different prognoses?

For the first question we need a *survival curve*, which most often is depicted as a Kaplan-Meier curve showing the rate of the outcome over time. The Kaplan-Meier curve included in the study by van Donselaar et al [7] shows that recurrences were far more likely to occur in the 6 months following the first seizure than during the remainder of the study period.

To deal with subgroups with or without various prognostic factors, we need to compare the outcome likelihood in those patients with the prognostic factor to that in those without the prognostic factor. This calculation results in a *relative risk*. A relative risk of

1 means there is no increase or decrease in the likelihood of the outcome if you possess or do not possess this prognostic factor. The farther the relative risk is from 1, the more impressive the change in risk associated with that prognostic factor. A relative risk greater than 1 implies increased risk; a relative risk less than 1 implies less risk.

In the study by van Donselaar et al [7], patients with epileptic discharges on combined EEG studies had an 81% rate of seizure recurrence at 2 years, whereas those with normal results on combined EEG studies had a 12% rate of recurrence. This calculates to a relative risk of 6.75. This means that if you have epileptic discharges on standard and sleep deprivation EEGs, you are 6.75 times more likely to have a recurrent seizure within 2 years than if your EEG findings were normal. Other factors that increased recurrence risk were tongue biting (relative risk = 2), seizure occurrence while asleep (relative risk = 2.2), and age between 15 and 24 years (relative risk = 1.7).

Precision of likelihood estimates. The precision of the estimates of outcome likelihood is expressed as a 95% confidence interval around that point estimate, which in this study was 32% to 48%. This means we are 95% sure that the true value of recurrent seizure after 2 years in this study lies somewhere between 32% and 48%; 40% is simply the point estimate from the study run this time. Said another way, if this study were repeated 100 times the same way, 95 of those 100 times the point estimate would fall between 32% and 48%.

Applying Evidence to Patient Care

Based on the results of the study by van Donselaar et al [7], you now feel much better about the decision not to prescribe antiepileptic medication for Ms. Kindel. However, you are still unsure of exactly what you will tell her regarding her precise risk for another seizure. While the study suggests that the overall chance of having another seizure in the next 2 years is 40%, this risk is lowered to 12% at 2 years by Ms. Kindel's normal results on combined EEG studies. How the other prognostic factors relevant to Ms. Kindel (young age, no tongue biting, seizure while awake) modify this 12% risk for seizure recurrence is unclear to you.

You realize that you would benefit from discussing the van Donselaar study with your preceptor. The week before Ms. Kindel's visit, you meet with Dr. Blake to summarize your appraisal of the article thus far and to ask for her input on the application step. Dr. Blake informs you that the study does not report data to allow you to combine risk factors to arrive at a precise estimate of prognosis for seizure recurrence in Ms. Kindel. However, given the study authors' emphasis on EEG findings as the strongest predictor of seizure recurrence and Ms. Kindel's normal EEG findings, you can be reassured that her risk for another seizure truly is low.

In discussing the application of the study results to Ms. Kindel, you and Dr. Blake decide that the study was sufficiently community-based to capture a wide range of people presenting with first-time seizures. Follow-up was sufficiently long to capture a recurrent seizure in the study group. Thus, you can apply this evidence to Ms. Kindel.

Criteria for Appraising Applicability

Even if a prognosis study is valid and has impressive results, we need to be sure the evidence can be applied to the specific patient we are caring for at the time. This final step in the appraisal process involves consideration of three questions regarding the applicability of the study to the patient at hand.

Were the study patients similar to my patient? It is tempting when applying evidence from studies to answer this question by comparing the patient at hand to the inclusion and exclusion criteria. In general, the inclusion and exclusion criteria define the general parameters of the cohort and are quite important. However, rejecting potentially helpful evidence by rigidly applying these criteria is not appropriate. Thus, a better question may be, "Are the patients in this study so different from my patient that I cannot apply this evidence to his/her case?" Generally speaking, we want assurance that the patients studied are similar enough to our patient that the evidence can be applied to his or her specific case. Because patients in the study by van Donselaar et al [7] were referred from four centers to the study personnel, it is reasonable to assume that the study population included a wide range of people presenting with first-time seizures.

Was follow-up sufficiently long? Appropriate length of follow-up depends on the disease process being studied and the outcome of interest. For example, for a study assessing the prognosis of Alzheimer's disease from time of diagnosis, it would be reasonable to follow patients for only a few years if the outcome of interest is the need for nursing home placement. Follow-up would need to be longer if the outcome of interest is mortality. In the case of Ms. Kindel, the outcome of interest is seizure recurrence. Thus, it is important to consider whether the authors followed their patients long enough to actually report meaningful data on recurrence risk.

Can I use the results in management of my patient? Finally, we need to consider whether information from the study should inform the care of the patient at hand and, if so, how. Prognostic information provides the basis of care decisions. Knowing the usual clinical course of a disorder can help us determine whether therapy should be offered at all. In this case, the study results suggest that patients such as Ms. Kindel have a good prognosis without therapy. This information supports our initial recommendation to consider withholding treatment with antiepileptic medication.

The following week, Ms. Kindel comes in for her follow-up visit, accompanied by her mother. The patient reports feeling fine, with no complaints. Her examination is normal.

In discussing the information gathered since Ms. Kindel's last visit, you tell her that you have found reliable evidence that provides support for your earlier statement that her risk for another seizure is low. You explain that in a study of patients similar to her, EEG findings were found to be the strongest predictor of seizure recurrence and that normal EEG findings, like hers, were associated with a 12% risk for another seizure over 2 years. You acknowledge that this study also showed that patients who were similar in age to her, between 15 and 24 years old, had a higher risk for seizure recurrence than older patients. However, the study also showed that not biting your tongue during a seizure and having a seizure while awake were associated with lower risk for recurrence.

The patient reflects on this information with her mother, and the three of you then discuss the fact that Ms. Kindel does not drive or work in high places—two factors that might lead to a decision to start antiepileptic therapy. You also discuss the potential side effects of these medications. After taking all of these factors into consideration, Ms. Kindel and her mother decide to forego treatment with medications for now. If another seizure occurs, they would favor initiating drug therapy at that time.

Conclusion

Table 2 summarizes the five-step EBM approach as it applies to estimating the risk of seizure recurrence in the case of Ms. Kindel. Having an evidence-based estimate of the prognosis of the clinical problems we face allows us to be more specific in our counseling and clinical decision making on behalf of our patients. Precise and reliable prognostic information helps to better inform our clinical care decisions and to guide our discussions with patients regarding expected outcomes of disease, thereby allowing patients to be informed participants in these decisions. Even when the evidence is striking, however, it must be tempered and put into context. The evidence does not replace

Table 2. Summary of the Evidence-Based Medicine Approach to Estimating Prognosis for Seizure Recurrence in Ms. Kindel

Assess	
The patient	Ms. Kindel is a healthy 19-year-old woman with a single first-time unprovoked seizure. Physical and neurologic examination and results on laboratory studies, head CT, and standard and sleep deprivation EEGs are all normal.
The problem	The patient fears having another seizure and wants to know how likely it is she will have one.
Ask	What is the likelihood that a healthy adult with a single unprovoked seizure will experience another seizure over time, and do any prognostic factors influence this outcome?
Acquire	Two abstracted cohort studies from *ACP Journal Club*, one of which is chosen for appraisal (requires trip to medical library to retrieve full text of article).
Appraise	The cohort study on prognosis of first-time unprovoked seizure in low-risk patients meets validity criteria. It was a representative cohort with adequate follow-up. However, the authors do not describe how the outcome of recurrent seizure was defined or labeled. The recurrence risk was 40% overall at 2 years but was reduced in patients with certain prognostic factors, such as normal EEG results, seizure while awake, and no tongue biting.
Apply	Young adults presenting with a first-time seizure and with prognostic factors like those in Ms. Kindel are at low risk for seizure recurrence. In patients such as this, offering reassurance and follow-up while withholding antiepileptic drugs is a reasonable alternative.

CT = computed tomography; EEG = electroencephalogram.

our clinical judgment, but rather informs it. Likewise, patient values must be considered. Some patients place more stock in aggressive searching for disease and treatment options than others. Similarly, some would rather take a "watch and wait" approach to management than to opt for medications that may be unnecessary or place them at risk for side effects.

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