The Use of Survival Analysis for the Evaluation of Musculoskeletal Therapy

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Survival analysis is seldom used in studies of the effectiveness of musculoskeletal therapy. Most clinical studies of musculoskeletal therapy use parametric statistical methods such as analysis of variance (ANOVA) to illustrate the effects of treatment on outcomes.[1-11] Nonparametric techniques of analysis such as survival analysis are less frequently used.[12-15]

Survival analysis has a number of advantages that make a research design a better choice than ANOVA for clinical evaluation studies. Among these advantages are that survival analysis uses a patient-specific response as an output measure whereas ANOVA requires the valid generation of a group mean response. Comparison of the results of studies is clear and unambiguous with survival analysis, which produces a survival function that represents the effect of treatment over the entire course of the study. Comparison of the results of studies is difficult with ANOVA, which produces estimates of effectiveness at a few discrete points during the study. Survival analysis is "distribution free" and enables the direct analysis of highly skewed distributions that are commonly encountered in studies where patients respond as individuals to treatment and do not require data transformations to meet the underlying assumptions of parametric statistical methods such as ANOVA. Lastly, survival analysis incorporates a method of explicitly dealing with the problem of incomplete observations, which is not available in ANOVA.

Analysis of variance is used to study the mean values of 2 populations, often the distribution of some measure of response to treatment. Analysis of variance is termed a parametric method of analysis because it depends on the calculation of parameters of the distribution of measures of interest such as the mean and standard deviation. Analysis of variance is based on the mathematical concept of least squares. The least squares formulation requires that each incidence of the measure of response be subtracted from the mean value of all scores obtained from the population. The theorems underpinning the use of the least squares formulation assume that the distributions from which the measure of response is drawn are symmetric (in fact, normal). The valid application of ANOVA requires that the measures used may validly be summed, that the distribution of those measures is normal, and that the measures selected validly reflect the state or condition under study.

Because patients respond as individuals to clinical intervention, not all patients will achieve the same level of response at a given time after the initiation of treatment. Therefore, when using ANOVA, some estimate of group response must be constructed to enable changes in average patient response to be analyzed. The most commonly used measure of therapeutic effectiveness is the visual analogue scale (VAS). The VAS, combined with research designs using statistical methodology on the basis of the least squares formulation such as ANOVA and regression analysis where each VAS score is subtracted from the mean value of all scores as part of the analysis, presents immediate problems. An initial pain intensity score on the VAS of 100 for one individual and a VAS of 20 for a second individual may be elicited by the same experimental pain stimulus.[16] Because the VAS is a measure of pain intensity specific to an individual, with possibly different meaning for each individual, the addition of 2 VAS scores, a requirement for the construction of a mean score, may not be valid.[17] Survival analysis does not depend on the construction of a valid mean value of the subjects' responses. This frees the analysis of the need for normality in the distribution of responses because the analysis is not dependent on knowing the mean response.

A second problem with musculoskeletal studies using the VAS and ANOVA is that comparison of the results of studies is problematic. It is not clear that a change in a mean VAS score of any specific magnitude in one study has any valid relationship to another study or clinical significance in itself. This is especially true when the length of the studies is different. Because the results of survival analysis are presented in the form of a survival function that represents the probability of achieving the event of interest at any point during the study, the results of one study are more easily compared to another. One simply compares the survival functions generated by both studies. Parameters of the resulting survival function, such as the time for 50% of the patients to reach a pain-free state, may be of assistance in comparison of the results as well.

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Survival analysis is a powerful means of illustrating and analyzing the course of patient progress while undergoing therapy that is "distribution free." That is, the distribution from which the measure of response is drawn is not assumed to be normal. In fact, no assumption regarding the distribution need be made. This enables highly skewed distributions such as those associated with time-to-event data to be directly analyzed without the use of data transformations to normalize the data before analysis, as would be required with ANOVA. Time-to-event data are normally highly skewed, with most responses occurring in the initial stages of the study, and with a long tail to the right of the interval containing most responses. The results of survival analysis comprise an estimate of the probability of occurrence of an event of interest (eg, the relief of pain in musculoskeletal studies) in the study population as the course of treatment proceeds. Simultaneous analysis of 2 or more treatment protocols is used to analyze and illustrate differences in treatment effect.

Although not frequently used in musculoskeletal studies, survival analysis has seen extensive use in almost all other areas of medical research. Examples of the use of survival analysis include time to the discontinuation of the use of an intrauterine device, prognosis for women with breast cancer, survival of patients with multiple myeloma, comparison of 2 treatments for prostate cancer,[18] remission duration for acute leukemia, time to infection of patients with kidney dialysis, time to infection for patients with burn, time to first use of marijuana, and so on.[19] In all of these examples, the research question is formulated as a "time to an event." That is, the question of interest is, "How long does it take to achieve the desired result?" An intuitive way of posing the research question in musculoskeletal research is, "How long does it take for the patient to get better?" or "Do patients get better faster under treatment A or under treatment B?" Because survival analysis was invented specifically to deal with time-to-event problems, it is not clear why survival analysis has not found wider application in musculoskeletal research.

One possible reason might be that musculoskeletal therapies do not always achieve a clear end-point such as the pain-free state. Why this is so is not clear. Waddell[20] characterizes low back pain as a benign and self-limiting condition characterized by recovery in approximately 6 weeks independent of the administration or type of treatment. That is, most individuals with the condition do not seek treatment, and of those that do, most (80%-90%) recover in approximately 6 weeks. If the results obtained in clinical trials of musculoskeletal therapy do not achieve clear-cut end points, it may be that the output measure is flawed, the research design is inadequate, the method of therapeutic intervention is not effective or actually interferes with the natural course of recovery, or the trial is simply not continued for sufficient time to allow the participants to achieve pain resolution.

No single statistical methodology will be appropriate for all formulations of all research questions relating to the evaluation of musculoskeletal therapy, but when the research design is formulated as a time to a specific event such as the time to resolution of pain under a particular mode of musculoskeletal therapy, then the researcher should consider survival analysis. Selection of one method of analysis for a study does not exclude the use of other analyses where appropriate. For example, the use of survival analysis using the no-pain end of a pain relief scale does not preclude using regression analysis or ANOVA using the graded response provided by pain relief scores to examine other aspects of the study that are important to the researcher such as the variation of patient response with age, sex, body mass index, or other covariates.

Survival analysis may be used to directly examine the effect of covariates such as age, sex, and the like, by grouping. For example, separate analyses may be conducted to compare the response to treatment of males vs females or the influence of age by binning or grouping. However, these techniques can quickly become cumbersome and the field of survival analysis has developed its own approach to the analysis of both variates and factors that may affect the outcome of survival times. This approach is referred to as the proportional hazards model. Originally proposed by Cox in 1972,[21] it is also known as the Cox regression model.

One factor that may explain the relative neglect of survival analysis in musculoskeletal research may be that researchers are simply not familiar with the technique. The first step in research design is to define the research question to be examined by the study. After that initial crucial step, the measures that will best describe the independent and dependent variables are chosen. The final step is choosing the method or methods of analysis that enable the researcher to most clearly reject the research hypotheses posed by the study. The development of a final research design is complex and interactive, initial decisions being revised as the design progresses. The overall process is influenced by the researcher's knowledge of and familiarity with specific methods of analysis. If the researcher is not aware of a specific methodology of analysis, then making an informed choice of analysis technique is not possible. This paper proposes that research designs for the evaluation of musculoskeletal therapy using a time-to-event model in which the event is defined as the resolution of pain (the pain-free state) are not only possible but also productive and addresses the issue of informed choice by introducing researchers and potential researchers to the methodology of survival analysis.

Discussion

Calculation of Survival Analysis

In addressing the problem of evaluating the effectiveness of multiple impulse therapy, the basic question is, "How long

does it take for the patient to get better?" We have defined "get better" as the time at which the patient reports that she or he has reached the pain-free state. The analysis used to answer this question is referred to as a product limit estimate, survival analysis, or Kaplan-Meier survival analysis. This procedure is referred to as a survival analysis because a common early use was the determination of how long it takes for someone to die. That is, given a population of individuals, what is the frequency of occurrence of the event (in this case, death) in the population as a function of time? Now, the "frequency of occurrence" of an event sounds suspiciously like a probability. In fact, the concept of probability defined as the probability of an event (an event is defined as any set of outcomes of interest) is the relative frequency of the event over an indefinitely large (or infinite) number of trials.

Because there would never be enough time and/or money to conduct indefinitely large trials, probability analyses are termed *probability estimates*. It is assumed that the larger the trial, the closer the results of the analysis will be to the true frequency of occurrence of the event in the population under study. Survival analysis is indeed a form of probability analysis, and the key to understanding these types of analyses lies in the concept of *conditional probability*.

Because the progress of each of the patients in the study is followed, after some number of visits, which are associated with the number of days since treatment was initiated, some patients have reached the state of no pain, which is the event of interest of our study. At the start of the study, all patients were in pain. Therefore, the probability that the patients were in pain at the start of the study was equal to 1 and was calculated as the number of patients in pain divided by the number of patients in the study. This proportion is the *unconditional probability* of the patients having pain at the start of the study. As the study progressed, some patients reached the pain-free state. When the first patient reached the pain-free state, the number of patients in pain has changed compared to the number of patients in pain at the beginning of the study. The effect of this change can be represented as the difference between the initial proportion of patients in pain and the proportion of patients that have reached the pain-free state. This difference can be represented as

$$(n_0 - 1)/n_0 \tag{1}$$

where n_0 equals the number of patients in pain at the beginning of the study and 1 is the number of patients that reached the pain-free state. The proportion $1/n_0$ represents the change in the initial proportion of patients in pain at the beginning of the study caused by the fact that one patient has reached the pain-free state.

This modified proportion is referred to as the *conditional probability* of the patients remaining in the study having pain, that is, the probability that a patient will be in pain given the fact that one patient has recovered from pain.

The formula for calculating the probability of patients having pain as the study progresses over time may be generalized from Eq. (1). The ratio n_0/n_0, which represents the proportion of patients in pain at the beginning of the study (all patients are in pain at the beginning of the study), may be set to 1 and does not change as the study progresses. The proportion $1/n_0$ may be modified to represent the effect of additional patients reaching the pain-free state by setting 1 in the proportion to the variable e_i, where e_i is the number of patients who have attained the pain-free state (ie, the number of events of interest when the patients' progress is observed) between the time t_{i-1} and t_i when the conditional probability is calculated. Using statistical notation to represent the conditional probability at time t_i yields the relationship in the following equation:

$$Pr[\text{ pain at } t_i|\text{ pain at } t_{i-1}] = 1 - e_i/(n_{i-1}) \tag{2}$$

where Pr[pain at t_i | pain at t_{i-1}] equals the conditional probability of a patient having pain at time t_i given the probability of a patient having pain at the prior sample time t_{i-1}; e_i is the number of patients that reached a pain-free state between the t_{i-1} and t_i; n_{i-1} equals the number of patients still in pain at time t_{i-1}.

Being able to compute the conditional probability of getting to the pain-free state at each point in time is relatively straightforward but is only the first step. Of greater interest is the unconditional probability of attaining the pain-free state after some treatment time. That is, what is the probability of a patient being in pain after 7 days of treatment using multiple impulse therapy? To compute this probability, we first need to review the relationship between conditional and unconditional probability.

One of the major assumptions of simple survival analysis procedures such as the one described here is that the events of interest are independent. That is, the occurrence of one event does not influence the occurrence of a second event of the same type. This means that if one patient reaches the pain-free state, that patient has no effect on other patients' achievement of the pain-free state. One could postulate that patients might be influenced by the progress of other patients if, for instance, a chart of each patient's progress was posted in view of all patients and patient progress became a competition. Although this may indeed be a good idea, it would complicate the analysis (and confound researchers). However, no such coupling of patient progress is normally allowed, and the assumption of independence is assumed to be valid. Under the assumption of independence, the relationship between unconditional and conditional probability[22] is represented in the following equation:

$$Pr(\mathrm{B}) = Pr(\mathrm{B}|\mathrm{A}) \times Pr(\mathrm{A}) + Pr(\mathrm{B}|\mathbf{A}) \times Pr(\mathbf{A}) \tag{3}$$

where Pr(B) is the unconditional probability of the event B, Pr(B|A) is the conditional probability of event B given that event A has occurred, Pr(A) is the unconditional probability

of the event A, Pr(B|**A**) is the conditional probability of event B given that event A has not occurred, and Pr(**A**) is the unconditional probability of A not occurring.

Now, our interest is in determining the unconditional probability of a patient being in pain at time t_i, and we already know the conditional probability of the patient being in pain at time t_i. Eq. (3) may be used to express this relationship as the following equation:

$$\begin{aligned} Pr[\text{ pain at } t_i] = {} & Pr[\text{ pain at } t_i | \text{ pain at } t_{i-1}] \\ & \times Pr[\text{ pain at } t_{i-1}] \\ & + Pr[\text{ pain at } t_i | \text{ no pain at } t_{i-1}] \\ & \times Pr[\text{ no pain at } t_{i-1}] \end{aligned} \quad (4)$$

where Pr[pain at t_i] is the unconditional probability of a patient being in pain at time t_i, Pr[pain at t_i | pain at t_{i-1}] is the conditional probability of a patient being in pain at t_i given that the patient was in pain at time t_{i-1}, Pr[pain at t_{i-1}] is the unconditional probability that a patient will be in pain at time t_{i-1}, Pr[pain at t_i | no pain at t_{i-1}] is the conditional probability of a patient being in pain at time t_i given that the patient was not in pain at time t_{i-1}, and Pr[no pain at t_{i-1}] is the unconditional probability of a patient being in pain at time t_{i-1}.

Because the unconditional probability of a patient being in pain at time t_i given that the patient was not in pain at time t_{i-1} is equal to 0 (the patient is already out of pain and therefore no longer has any chance of being in pain), Eq. (4) reduces to the following equation:

$$\begin{aligned} Pr[\text{ pain at } t_i] = {} & Pr[\text{ pain at } t_i \text{ | pain at } t_{i-1}] \\ & \times Pr[\text{ pain at } t_{i-1}] \end{aligned} \quad (5)$$

Now, we still cannot calculate the unconditional probability of the patient being in pain at time t_i because the unconditional probability of pain at time t_{i-1} is not known. However, we can express the unconditional probability of pain at time t_{i-1} in terms of the conditional probability at time t_{i-1} and the unconditional probability of pain at the previous time t_{i-2}. This still does not allow us to solve the problem, because the unconditional probability at time t_{i-2} is not known. However, by continuing to express each unknown unconditional probability in terms of a conditional probability and the unconditional probability at the previous time, we eventually arrive at the start of the study. This process leaves only one unconditional probability in the calculation, that unconditional probability is the probability of the patients being in pain at the start of the study, which, unless we recruited pain-free patients, is equal to 1. The unconditional probability at time t_i may now be computed because we have expressed its calculation in terms of conditional probabilities at each previous time in the study and the unconditional probability at the start of the study.

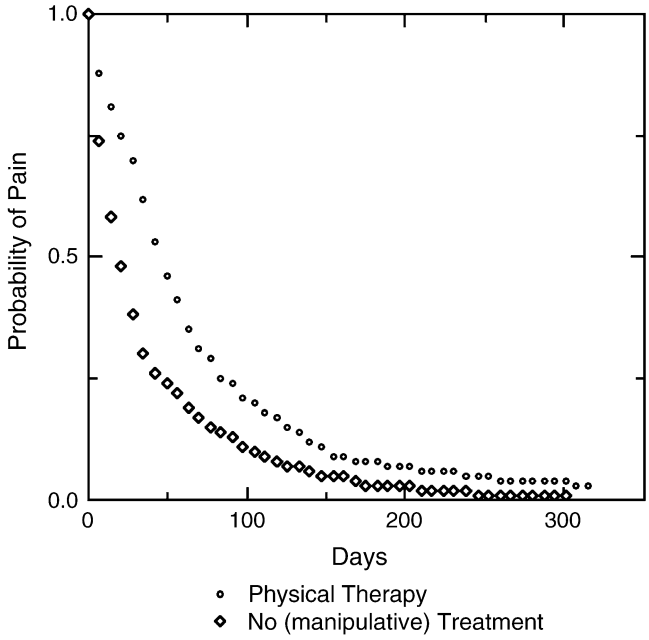

Fig 1. *Results of Kaplan-Meier survival analysis of patient response to physical therapy and "no treatment" replotted from van den Hoogen et al.*

All of these values are known. The following equation describes this calculation:

$$Pr[\text{ pain at } t_i] = \Pi_{j=1 \text{ to } i}\left\{1 - \left(e_j/n_j\right)\right\} \quad (6)$$

where the symbol II represents the multiplication of all the conditional probabilities starting at t_i and continuing until the point in time at which the first patient reached the pain-free state (because the unconditional probability of pain at the beginning of the study is 1, its multiplication may be omitted).

Up until this point, we have assumed that all of the patients in the study were "well behaved" in the sense that all patients participated in the study until, at some point, each patient achieved a pain-free state. If this were the case, then the analysis described above is appropriate for the determination of the probability of pain at each point in the study. However, not all patients are well behaved. Some may decide to leave care because they move from the area, some may become discouraged with their progress and leave, some may become pain-free and leave without reporting that fact, and some may not respond to the treatment. How do we handle these pesky patients who perversely pollute our data?

Kaplan and Meier independently developed a methodology designed to address this issue. The authors of the 1958 paper[23] titled "Nonparametric estimation from incomplete observations" that describes the Kaplan-Meier estimate and provides the answer to this question never met in person! Each author independently invented the analysis,

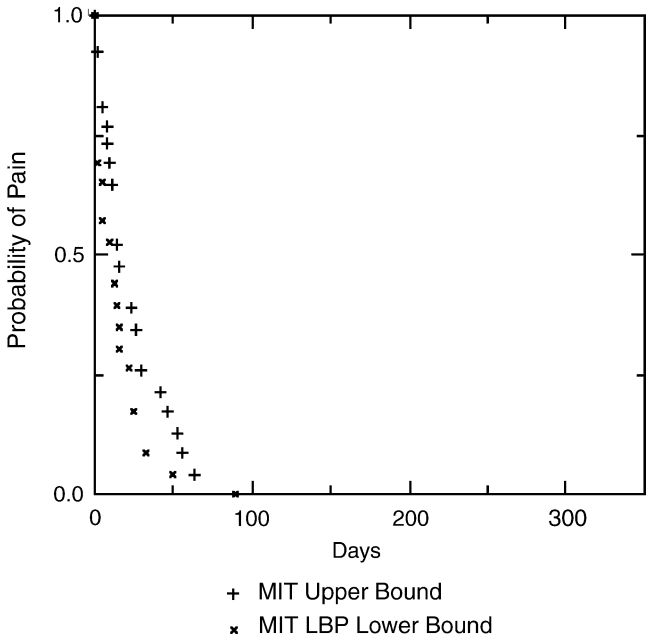

Fig 2. *Results of Kaplan-Meier survival analysis of patient response to multiple impulse therapy. MIT, Multiple impulse therapy.*

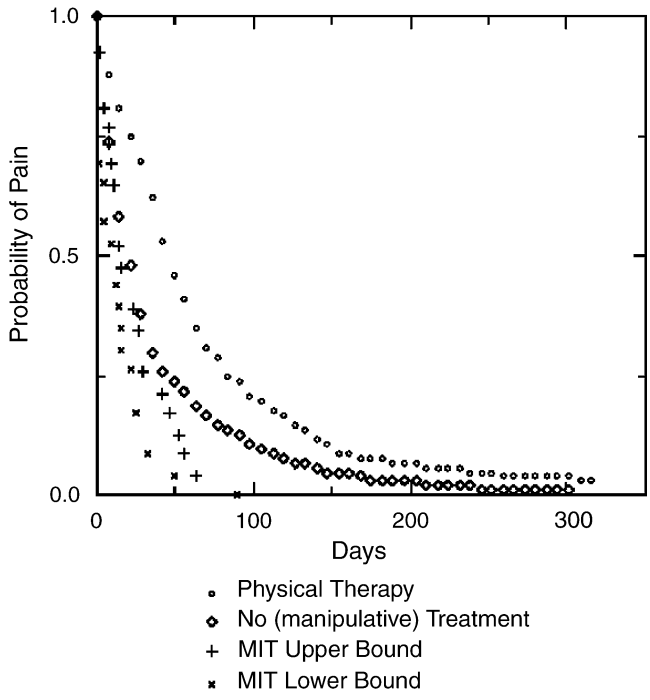

Fig 3. *A sample comparison of Kaplan-Meier survival analysis results.*

submitted a paper for publication to the same journal, and collaborated by mail to finalize the journal article! The importance of this methodology to investigators is suggested by the fact that it is number 2 on the list of most cited ever papers in mathematics, statistics, and computer science.[24]

The solution provided by the Kaplan-Meier analysis involves first classifying all of the patients in the study according to whether they are well behaved or not. In Kaplan-Meier terminology, those patients who are well behaved are classified as "uncensored," and all other patients are classified as "censored." Uncensored patients are handled exactly as described above; that is, the calculation of the conditional probability is exactly as described. When a censored patient leaves the study sample for any reason, the time at which they departed is noted and the calculation of the conditional probability is changed by removing that patient from the denominator of the proportion e_j/n_j. That is, n_j is reduced by 1 whereas e_j is unchanged, unless a patient simultaneously achieved the "pain-free" state.[19]

When comparing 2 methods of treatment, 2 separate survival analyses are computed. Visual comparison of the 2 results will reveal differences in the rate of patient response of the 2 methods as well as differences in their effectiveness.[19] Statistical tests such as the log-rank or Wilcoxon are available to determine the likelihood that the observed results are due to chance. Both tests are variations of the χ^2 statistic. The log-rank test emphasizes the differences between the 2 results observed later in the experiment, whereas the Wilcoxon emphasizes the differences early in the analysis.[18]

Fortunately for the researcher, the tedious manual calculations required for completion of a Kaplan-Meier analysis are now available in commercial statistical software. In addition to MedCalc[25] used by Evans et al,[15] Peltz and Klein[26] have authored a comparison of 3 commercially available statistical software packages that all contain survival analysis capability.

Examples of Survival Analysis in Musculoskeletal Research

The work of van den Hoogen et al[27] provides an excellent example of Kaplan-Meier survival analysis applied to the study of patients who have nonspecific low back pain. All of the subjects in the study sought care from multiple clinics and multiple care providers (medical practitioners) in The Netherlands. The results of the study are shown in Fig 1. The upper curve represents the progress of those patients who were referred to physical therapy. The lower curve represents the progress of those patients who received no specific care other than analgesics and standard medical recommendations such as bed rest or limitations of activity. It is obvious that those patients who were not referred to physical therapy fared better than those who were referred to physical therapy. van den Hoogen et al speculate that those patients referred to physical therapy may have had a more serious back pain than those patients who received no special treatment. Another possible explanation might be that the natural recovery process was interfered with by physical therapy. In any case, the

difference in the response of the 2 patient groups is clear. Methods for testing the likelihood that the observed differences are due to chance, such as the log-rank test, are available.[18]

A second example of survival analysis may be found in a study of the effectiveness of multiple impulse therapy for nonspecific low back pain.[15] The results of this study are presented in Fig 2. The 2 sets of experimental points represent the estimate of the upper and lower bounds of the results. The bounds resulted from the method of measuring the output variable. Each patient was asked to score his or her pain relief at the beginning of each visit. A patient who reached the no-pain state at the beginning of the visit did so somewhere between the last visit and the current visit. The upper and lower bounds represent the spread between the visit, at which the no-pain score was achieved, and the previous visit.

Can the results of these 2 studies be compared using survival analysis? The results of both studies have been cast into what we will refer to as probability space and therefore share the same dimensions: the probability that a patient will be in pain and time. The result of such a comparison is shown in Fig 3. Qualifications of the comparison include that the patients in both studies are similar on important dimensions such as patient complaint, distribution of patient characteristics, which apply to the comparison of results obtained with any method of analysis.

Comparison of different methods and techniques of musculoskeletal therapy in the manner illustrated in Fig 3 is unlikely to result in clinicians ceasing to refer patients to physical therapists or physical therapists adopting other techniques of therapy. The comparison of these 2 studies, although provocative in that it would appear from the comparison that both multiple impulse and osteopathic therapy are more effective than physical therapy, is not definitive.

However, if these results are supported by well-designed clinical trials, such comparisons may result in a reevaluation of and/or development of more effective therapeutic techniques. The results of all published studies of musculoskeletal therapeutic techniques are formally and informally compared by clinicians, researchers, administrators, third party payers, and patients independent of the format in which they are presented. Survival analysis may enable the formal comparison of the results of studies of therapeutic effectiveness in a straightforward and unambiguous format.

Conclusion

Kaplan-Meier survival analysis techniques may provide a simple yet powerful means of visually observing the course of treatment of patients under therapy for musculoskeletal complaints such as low back pain. In addition, survival analysis may be useful as an unambiguous means of comparing study results of different musculoskeletal techniques. Further investigation into these methods should be performed.

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