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# APPLICATIONS OF SURVIVAL ANALYSIS IN PUBLIC HEALTH STATUS

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## ABSTRACT

In public health research, it is typical to examine survival data using basic statistical approaches, which are discussed in this work. It is impossible to analyse the data using the standard way because of the censoring. Since the rise of personal computers and statistical computing, nonparametric techniques have become more popular than parametric ones. The first had less restrictions. Because of these assumptions, it is possible to get estimates with fewer standard errors and a better understanding of the data. For example, the Kaplan-Meier method for calculating the survival function and the Cox proportional hazards model to identify risk variables and provide adjusted risk ratios are nonparametric approaches. Data may be stratified and a model fitted with distinct baseline functions in each stratum if the assumption of proportional risks is not tenable. Modeling techniques such as parametric regression may also be used. Hazard functions for the exponential, Weibull, gamma, Gompertz, lognormal, and log-logistic distributions are given. Various techniques are shown using examples taken from the available literature. Those who are interested in survival data analysis should read this publication.

## KEYWORDS: Competing Risks, Public Health Study, Risk Prediction, Survival Analysis

## **1.1 INTRODUCTION**

Consider a case where the result of interest is the time to occurrence of a certain event, such as the time to death for lung cancer patients or the time to recovery for pneumonia patients. 'Analysis of 'time to event' or 'survival time' data presents two distinct challenges. Event timings may not follow a normal distribution in a set of research participants because they are skewed, for example, as may be the case with the time to discharge from the hospital for patients with a severe asthma attack. It is possible, secondly, that participants in the study will not have had a chance to witness the event before its conclusion or will have been lost to further investigation before it has taken place. Some of the participants in this study had a 'censored' event date. The existence of censoring in a time-to-event result necessitates the use of specialized statistical techniques due to the unusual distribution of event timings. In this article, relevant regression techniques for relating patient survival time to explanatory factors will be introduced.

The Kalbfleisch and Prentice Veterans Administration lung cancer study is used to demonstrate survival analysis methodologies. One of two therapies was administered randomly to male patients with inoperable lung cancer (standard or experimental chemotherapy). In addition to the patient's age (in years), Karnofsky score, whether or not they had previously received therapy, and the histological tumour type, the survival time (or time to censoring) was recorded for each patient (classified as adenocarcinoma, squamous, small cell or large cell carcinoma). Therapy, past treatment, and the kind of tumour are all discrete variables (adenocarcinoma is taken as the reference level). As a continuous variable, we regard the Karnofsky score3 as a measure of the patient's quality of life, with values ranging from 0 to 100. Those patients who were still living at the time of this article's publication were not included in the study. the study's remaining patients had censored survival

periods since a significant number of trial participants passed away over this time period. The percentage of patients that were censored may be higher in other trials. In the next analysis, we'll focus on the connection between therapy and overall survival time.

### **1.2 LITERATURE REVIEW**

Hyunsoon Cho et. al, (2022): Survivability statistics are of special importance in medical and public health research because they may provide insight into patient prognoses and the progress of health care systems. However, the usage and interpretation of survival metrics might vary depending on how they deal with competing causes of mortality, and this can have a significant impact. The "net" effect of cancer on survival is represented by cause-specific survival, which uses the event of interest as the basis for estimating survival function while considering all other occurrences as censored. On the other hand, in their formulations, the cumulative incidence function and the sub-distribution hazard take into account the number of individuals who are exposed to competing hazards. Here, we discuss different hazards survival models utilised in public health research. Comparing classic net techniques to competing risks, we present the idea of competing risk methodologies (e.g., relative and cause-specific). We utilize the Surveillance, Epidemiology and End Result (SEER) cancer registry data to illustrate how competing risks analysis may be employed in population-based cancer survival analysis. A competing risks approach is also being used in public health research that go beyond prognosis and risk prediction. We also talk about how customized and precision medicine is adopting the competing risks approach. It is hoped that this overview of risk prediction prognostic models would give useful analytical tools for researchers who want to employ competing risk models in public health studies to predict outcomes.

Sampurna Kundu et. al, (2021): This pandemic sickness has been represented via studies of the transmission dynamics of COVID-19. On March 25, 2020, the Indian government proclaimed a state of emergency to stop the spread of the sickness inside the country. The number of COVID-19 instances topped 450,000 even after the severe lockdown was implemented throughout the country. The number of recovered cases has begun to overtake the number of current instances, which is a good sign. As far as mortality is concerned, the survival of patients, taking age and gender into account, is significant. An investigation on COVID-19 survivability in India by age group and sex was the goal of this research, which was conducted at the national, state and district levels. The research included the time period from January 30, 2020, the date of the first case of COVID-19 in India, until June 30, 2020. A total of 26,815 patients were included in the study because of underreporting and the elimination of missing columns. Cox proportional hazard model and multi-level survival model were employed in the study of life expectancy. Survival rates for patients with COVID-19 dropped significantly throughout the course of the five-month research period, as seen by the Kaplan-Meier survival function and the log rank test (P.001) and the Wilcoxon test (P.001). As can be seen from all the survival estimates, there was significant age variation; the chance of dying with COVID-19 rose with increasing age. Male patients with COVID-19 had a 1.14 times greater chance of dying than female patients, according to the Cox proportional hazard model (hazard ratio 1.14; SE 0.11; 95 percent CI 0.93-1.38). The survival rates in Western and Central India were declining over the time frame, but the survival rates in Eastern, North Eastern, and Southern India were somewhat improving during this time period. This research paints a bleak picture of dwindling survival rates in many parts of India, and it reveals how these rates differ depending on age and gender. This study's careful evaluation of survival rates and in-depth analysis of patient data allowed us to pinpoint high-risk populations in India and conduct cross-sectional comparisons across different subgroups.

**Lisa B. Mirel et. al, (2021):** Linking national survey data with administrative data allows researchers to do studies that are not feasible with each data source on its own." Updated Linked Mortality Files from the National Center for Health Statistics (NCHS) Data Linkage Program include data from the National Health and Nutrition Examination Survey (NHNES) that was linked to the National Death Index mortality files. In addition to the public-use data, the NCHS and the Federal Statistical Research Data Centers provided restricted-use files that may only be accessed via those institutions. Before making the public-use files available, statistical disclosure

limiting procedures were used to minimize the possibility of reidentification. This includes restricting the quantity of mortality data accessible and disrupting the reason of death and the duration of follow-up for selected files. Relative hazard ratios for all-cause and cause-specific mortality were computed and compared using Cox proportional hazards models in order to test the comparability of the restricted-use and public-use data. There were no significant differences in descriptive and model findings between the two datasets compared.

**Shalini Chandra and Akanksha Sekhsaria (2017):** Health of women in poor and disadvantaged nations has long been an issue. The Indian government has made several initiatives to improve the health of women across the nation based on trends and estimations from statistical methods used in the country's National Family Health Surveys. As a statistical technique, survival analysis has become more popular in recent years. Survival analysis methods have been used in this article to examine the elements that affect women's health in India and how they might be used.

**Joel A. Dubin & Peter Hall (2013):** An exposure variable is linked to a chance of a certain outcome over time using a variety of survival analysis approaches. Survival analysis may be used to determine the time it takes for current smokers to relapse, to monitor medication nonadherence among diabetics, and to forecast death as a function of cognitive capacity, among other uses. This example illustrates a cognitive epidemiological method to survival analysis. In this section, we'll try to find out whether executive functioning has anything to do with how long we have left on this planet. Cox proportional hazards modelling, one of the most widely used models in biostatistics and public health, is what we use to get there (Cox 1972). In this model, we will be able to analyse the survival connection of interest while correcting for relevant confounding factors. We believe that this example will persuade readers that examining the time till an event happens, rather than a binary representation of the event, is important since the former method gives more information.

# **1.3 APPLICATIONS IN PUBLIC HEALTH**

Analysis of survival distributions, testing of equal distribution assumptions, and finding risk variables are all examples of how survival analysis may be used in public health. An nonparametric, parametric, or semi parsimonious strategy may be used to analyse the data.

Descriptive statistics like median survival time and the likelihood of living longer than a specific time period may be estimated regardless of whatever method is used to estimate the survival distribution. Two-sample and K-sample tests, which compare the survival distributions of two or more groups, have been devised for this purpose. Typical examples include looking at how long men and women can go without becoming sick, as well as comparing the overall survival rates of patients from three distinct ethnic groups. It is common practice to use these kinds of comparisons as a first step in the search for significant risk or prognosis indicators. In order to sort out the interrelationships between risk factors, a simultaneous examination of many variables is required in addition to investigating each possible risk/prognostic factor separately. Parametric or semi-parametric techniques to regression analysis are often used.

In the next two parts, we'll go through the most popular nonparametric/semiparametric and parametric survival analysis techniques for the three main applications. Illustrative examples are drawn from works of literature. Software for survival analysis is briefly discussed in the concluding section. A review or lesson for public health experts interested in the topic is the purpose of this publication.

# 1.4 NONPARAMETRIC AND SEMIPARAMETRIC APPROACHES

# The Kaplan-Meier Product Limit Method

Only one death happens in each time period in the Kaplan-Meier product limit (PL) approach, which is an extension of the lifetable methodology. The death occurs at the beginning of each interval. In other words, it

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calculates the odds of living for a period of time longer than the time interval t. (t). Conditional probabilities are used to arrive at the estimate. For instance, the likelihood of living for k years or more is calculated as follows:

$$\hat{\mathbf{P}}(\mathbf{T} > k) = \hat{\mathbf{S}}(k) = p_1 \cdot p_2 \cdot p_3 \cdots p_k,$$

There are four categories of patients: p1 means the percentage of patients who survive at least one year, p2 denotes how many patients live through the second year, p3 denotes the percentage of patients who survive the third year, and pk signifies how many patients survive through the kth year. Ith survival time (censored or uncensored) and an indicator variable I both express the same thing: the ith survival time (ti). The values of ti may now be ranked in order of increasing magnitude. Because of this, the Kaplan-Meier estimate might be expressed as

$$\hat{\mathbf{S}}(t) = \prod_{\mathbf{t}_i < \mathbf{t}} \left( \frac{\mathbf{n} - \mathbf{r}_i}{\mathbf{n} - \mathbf{r}_i + 1} \right)^{\delta_i}, \mathbf{t} \le \mathbf{t}_{(\mathbf{n})}$$

which has the highest recorded survival time (t(n)) and the biggest number of observations (n). Value of T at. (50th percentile estimate of median survival time) Kaplan-Meier assumes that the likelihood of censoring an observation is independent of the actual survival period. Censored observations are not connected to the study's research question, and those who are censored reflect a random sample from the same distribution as the rest of the population.

The survival distribution may be estimated using the Kaplan-Meier technique, S. (t). The PL estimations, on the other hand, are constrained by the observations' time interval. The PL estimate is always 0 if the greatest observation is not suppressed. No matter how great an observation is, the probability of zero can never be achieved until extra assumptions are made. In addition, the median survival time cannot be determined if fewer than half of the observations are uncensored and the greatest observation is censored. A parametric model may be necessary in order to improve the procedure.

Medical researchers and epidemiologists often use the Kaplan-Meier approach. There are many of examples in the literature. Fenn et al. recently used it in health economics. A survival analysis, namely the Kaplan-Meier approach, is recommended by the authors to assess the economic efficiency of treatment costs when censored cost data are available. In clinical trials, censored data are generated when patients discontinue therapy early or for reasons unrelated to the drug being studied.

In a retrospective cohort analysis, Saeki et al. used the Kaplan-Meier technique to examine the long-term trends in the percentage of patients who return to work following their first stroke. The "return to work after first stroke," which was defined as a month or longer of active employment after a stroke, is the event of interest here. As a result, patients who were monitored but did not return to work, or patients who were lost to followup, were censored cases. At the University of Occupational and Environmental Health Hospital in Kitakyushu, Japan, 183 patients who were released alive after a stroke were included in the research. Patients' ages ranged from 18 to 64, and they were all employed when they had a stroke. Additionally, the scientists looked at potential predictors such as normal muscular strength, a lack of apraxia, and employment in addition to the time it takes to return to work.

Figure 1 depicts the Kaplan-Meier method's percentage of workers returning to work following a stroke. F(t) = 1 S(t) = T is the plot that the authors used. The curve had two steep slopes. Early release from the hospital may have contributed to the initial decline in the six months after hospitalization. The second decline happened between the ages of 12 and 18 months after discharge. According to the authors, it seemed to correspond with the end of public fund patient illness benefits (generally limited to 18 months in Japan). Researchers came to the conclusion that stroke victims either return to work sooner after a stroke or chose to get lengthier illness

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benefits and put off returning to work. Muscle strength, apraxia, and occupation were also calculated and plotted (Figures 2, 3 and 4) as a first effort to discover predictors of return to work after stroke (more discussion is given in the following sections).

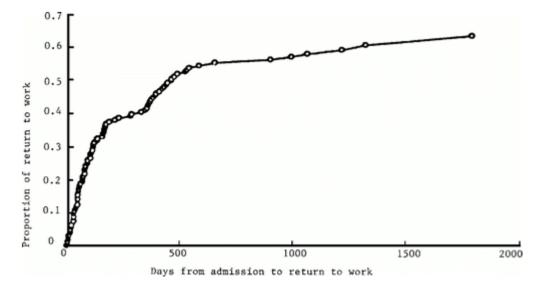


Figure 1: Graph shows proportion of return to work after stroke in Kaplan-Meier method (n = 183). Source: Saeki et al, 1995. Reproduced with permission from Stroke.

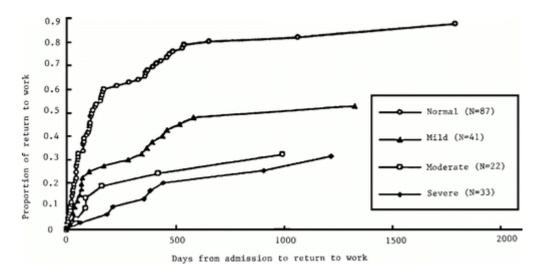


Figure 2: Graph shows proportion of return to work after stroke by muscle strength in Kaplan-Meier method (n = 183). Curves differ by log-rank test (P = .0001). Source: Saeki et al, 1995. Reproduced with permission from Stroke.

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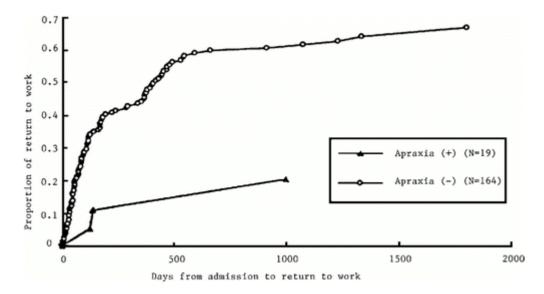


Figure 3: Graph shows proportion of return to work after stroke by apraxia in Kaplan-Meier method (n = 183). Curves differ by log-rank test (P = .0010). Source: Saeki et al, 1995. Reproduced with permission from Stroke.

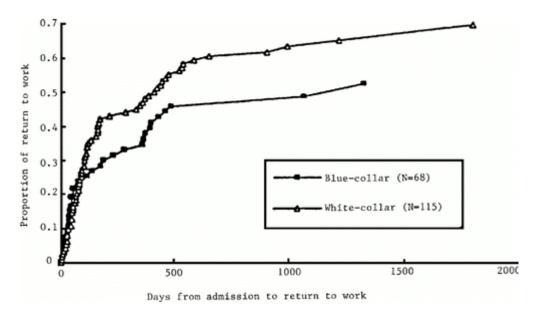


Figure 4: Graph shows proportion of return to work after stroke by occupation in Kaplan-Meier method (n = 183). Curves are not significantly different by log-rank test (P = 0981), but significantly different by Wilcoxon's test (P = .0492). Source: Saeki et al, 1995. Reproduced with permission from Stroke.

## **1.6 PARAMETRIC APPROACH**

Survival analysis has benefited from the quick development of sophisticated nonparametric and semiparametric algorithms due to the widespread availability of personal computers and the rapid advancements in statistical computation. The computer can now do tasks that would have taken hours of computation in the past in only a few seconds. When it comes to reliability studies, researchers are increasingly turning to nonparametric techniques rather of using the standard parametric approach. Assumptions for nonparametric techniques are lower than those required for parametric approaches. The survival periods are not subject to any distributional

assumptions. A person's failure or death may have been caused by a variety of physical circumstances, and it is almost hard to include all of these variables into a single mathematical model.

Nonparametric and semiparametric methods have benefits and are popular, but parametric modelling provides helpful alternatives. When the proportional risks assumption is in dispute, parametric models might be used instead of the Cox model. If the survival time distributional assumption is correct, then parameter estimates, such as the median, will have fewer standard errors than nonparametric models because of this. The findings are easy to interpret. Statistical conclusions are more exact as a consequence of using the complete probability.

#### Parametric Models

Theoretical distributions have been used to estimate survival data in several studies. We'll take a look at a few of them right now. When it comes to calculating survival time, the exponential distribution is a good starting point since it's a subset of more complex distributions like the Weibull and gamma distributions.

For an exponential distribution, danger function is constant regardless of the age of the subject. No ageing or wear and tear; death or failure is a random occurrence regardless of time. Since t is a linear function of t, graphing versus t is a simple way to see whether data are exponentially distributed. The slope of a straight line may be used to determine the hazard rate when the data are shown in a linear fashion  $\lambda$ .

#### Parametric Two-Sample Tests

Parametric testing of parameters is more powerful than nonparametric tests if the survival distributions follow a known model. Cox's F-test and the likelihood ratio test may be employed in the exponential situation to determine whether or not the two parameters are equal. Thoman & Bain's two-sample test, which examines the equality of the two-shape parameters, may be used if the survival times in the two groups follow the Weibull distribution. Theoretically speaking,  $\gamma 1 = \gamma 1$  if the hypothesis is rejected, we don't need to test it  $\lambda 1 = \lambda 2$ , in any other case, we'll have to run some tests  $\lambda 1 = \lambda 2$ . An F-test proposed by Rao may be used to compare two gamma distributions.

Even in public health research, the parametric two-sample tests are seldom utilised. Finding a suitable modelling framework is sometimes difficult, and most software packages provide nonparametric tests, which may be just as useful in practice. As a result, we won't be discussing these exams in any detail.

#### **Parametric Regression Models**

In survival data modelling, the Cox model is the most preferred option. Because the underlying risk function is arbitrary, and because partial probability has only a little impact on the efficiency of parameter estimation, these facts are particularly appealing. A number of parametric models are also included in the model for the other function. The exponential regression model may be used to Equation if h is a constant. What if Equation provides the Gompertz regression model and Equation yields the Weibull regression model, respectively? The proportional hazards assumption is shared by the Weibull and exponential regression models and the Cox regression model. However, parametric models may be helpful. There may be a family of parametric models that may be inferred from a plot of the empirical risk function. In this instance, estimates of the parameters will be accurate and efficient. In certain cases, a parametric model may be justified, such as when the proportionate hazard assumption is violated.

In parametric regression models, the variables or risk factors that influence survival time are clearly defined via the parameters, hazard function, or survival function. To simulate the length of remission in children with leukaemia and uncover relevant prognostic markers, Breslow employs the exponential distribution. The

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exponential distribution's parameter is supposed to be dependent on prospective prognostic variables, such as, for instance,

$$\lambda = \exp\left(\sum_{j=0}^p b_j x_j\right)$$

The bj's coefficients are estimated using the maximum likelihood approach, and their significance is checked using a normal test.

Weibull, gamma and log-logistic distributions are examples of special instances in the accelerated failure model (AFT). Two people, I and j, are linked by the following survival function connection in this model.

With respect to time, Si(t) is equal to Sj (ct). With variables, a frequent assumption in the AFT model is to assume that

$$\log T = \sum_{j=0}^{p} b_j x_j + w\varepsilon,$$

where denotes the chance error, w denotes the scale parameter, and bj's denote the calculated coefficients. It is possible for a random mistake to follow any distribution such as the Weibull or lognormal distributions. The survival time cannot be 0 in the AFT model.

Between January 1977 and December 1986, researchers at the Henrietta Banting Breast Center at Women's College Hospital, University of Toronto, collected data on 323 women who had primary invasive node-positive breast cancer. Prospective monitoring of these patients continued until 1990. Patients filled out standard forms detailing their medical and treatment histories, as well as any history of cancer in their families.

## **1.7 COMPUTER SOFTWARE FOR SURVIVAL DATA ANALYSIS**

Due to the fast growth of statistical computers, the studies outlined above may be readily done using commercially available software. All calculations can be done on microcomputers, except for those that need a large quantity of data. SAS, BMDP, SPLUS, SPSS, EGRET, and GLIM are some of the most widely used software programmes. In this part, we'll take a quick look at the first two. You should reference the manuals for more information on how to use each strategy covered in this article.

PROC LIFETEST, PROC LIFEREG, and PROC PHREG are the three primary SAS methods for doing a survival analysis. The lifetable approach is used in PROC LIFETEST to derive nonparametric survival function estimations. The Kaplan-Meier product limit estimates are derived for data having individual survival times, censored and uncensored. The actuarial approach is used for grouped data. Both linear and logarithmic hazard functions may be displayed to see if any parametric models are adequate for predicting the survival time.... For comparing the equality of two or more survival distributions, it offers the logrank test and Gehan's Wilcoxon test, as well as two others.

Fits parametric models, offers maximum likelihood estimates of parameters, and assesses goodness-of-fit using graphing techniques and likelihood ratios. For this technique, we employ the AFT model that contains the gamma and log-logistic distributions as well as the exponential and Weibull models. For categorical and quantitative variables, it can manage both; however, it cannot handle time-related covariates.

This is how it's done. The Cox proportional hazards model is implemented using PROC PHREG. If the survival times are categorical or numeric with any time-dependent variables, it can handle both continuous and discrete survival times. Stratified analysis may be used if the assumption of proportionate risks does not hold. The survival function may also be estimated with variables included.

There are two survival analysis programmes in BMDP, 1L and 2L. Similar to SAS's PROC LIFESTEST, the programmed 1L performs many of the same duties. Kaplan-Meier estimations of the survival function and lifetable analysis for grouped data are provided by this software. The survival curve, hazard function, and density function are all shown graphically. Generalized Savage (Mantel-Cox) is the name given to this test. Many more two- and k-test procedures are included, but they're not discussed here. There is also the option of stratified comparisons of two different survival distributions.

Proc LIFEREG and PHREG are similar in that they offer estimates for Cox's proportional hazards model and AFT and graphs. 2L has the same characteristics. Nonproportional risks may be taken into account via a stratified analysis. Cox's model may be fitted using time-dependent variables and stepwise regression approaches. SAS does not have this feature. Exponential, Weibull, lognormal, and log-logistic distributions are all accessible in the BMDP AFT model, just as they are in SAS. The AFT paradigm allows for both stepwise and non-stepwise methods. Additionally, Program 2L offers charts for both the Cox (Cox-Snell residuals) and AFT (Cox-Snell and standardized residuals) models.

## **1.8 CONCLUSION**

From medical and epidemiological studies to social and behavioral studies, survival analysis has been extensively employed in public health research. If an incident is linked to risk variables, or if a causal model can be estimated, it is typically of interest. As a statistical technique, survival analysis is best suited to investigations in which the event of interest is observed in real time.

Since survival durations may be assessed from a known and precise beginning point in time, the techniques described in this work assume that either survival times can be accurately measured or survival times are known to be longer than the observation period (censored). This may not be the situation in reality. Studies of human immunodeficiency virus (HIV) sickness generally focus on the time period between infection and transmission of the virus to a person's sexual partners. In this instance, none of the occurrences can be precisely witnessed. The timings of both occurrences are "interval filtered" since we know that they happened at different points in time. Between the two occurrences, it's impossible to measure the precise time.

Sample independence is a presupposition for all of the approaches covered here. Public health studies may also break this premise. Correlations may be shown in a mortality study of cardiovascular disease, for example, if the sample includes siblings or father and son.

Nonfatal myocardial infarctions in people with heart disease and recurring infections in dialysis patients are also common. The intervals between recurrences are not independent, and some individuals are more susceptible or have an unidentified predisposition to repeat occurrences. Frailty, a random variable with a distribution, refers to this unidentified propensity. The variables are taken into account while calculating the distribution of the sample data. Investigate dialysis patients' fragility.

Most typically, Kaplan-Meier is employed to estimate the survival distribution. For recovering part of the data that was censored, researchers have proposed using prognostic covariate information. In cases when the covariate integrated is prognostic or there is no censoring, the estimate is more efficient than the Kaplan-Meier estimate, while the Kaplan-Meier estimate reduces to the more efficient estimate.

As a result, survival analysis is a constantly evolving field of statistics, with new approaches being developed to meet the demands of diverse applications. As a rule, nonparametric approaches are sufficient for most applications. These methods are often used in the analysis of survival data: Kaplan-Meier, log-rank and Wilcoxon, and the proportional hazards model. Additional benefits may be gained by using a parametric approach. Parametric models may be applied considerably more easily because to recent advances in computer software.

Many research has used Cox's proportional hazards model. When utilizing a commercially accessible computer software like SAS or BMDP, it does not need a specialized parametric hazard function and time-dependent variables may be easily included. If the assumption of proportionate risks is not fulfilled, stratified analysis might be beneficial. But there is still a need for alternative models, such as the family of accelerated failure time models. Increasing numbers of researchers are turning to parametric models to uncover prognostic or risk variables. The availability of software for parametric models may also be a factor. Public health researchers should be encouraged to employ a variety of models to filter through the data and identify the most relevant risk or prognostic variables.

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