

Application of Statistical Methods to the Survival Analysis for the Evaluation of the Efficiency of Resuscitation Measures in Cases of Complicated Multiple Trauma

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Abstract: In this article we consider the opportunities for the application of special survival analysis methods for the evaluation of the efficiency of different resuscitation measures for victims of injury with complicated multiple trauma (polytrauma). We introduce a number of different survival functions with various possible risk factors, as well as analyzing the dynamics of possible mortality rates with regard to the injuries suffered and the individual characteristics of the injury victim. As a result of this research the authors conclude that mathematical and statistical methods for survival analysis should find more complete implementations in the medical research of domestic scientists, especially for the studies of traumas and urgent conditions.

Keywords: Survival Analysis, Injured, Complicated Multiple Trauma, Models of Survival Analysis

1. Introduction

During the last few decades, a variety of mathematical and statistical methods have been widely used in medicine, including emergency medicine and the resuscitation of severely injured patients [2, 3, 5]. It should be mentioned that in foreign studies, survival analysis methods such as life tables, the Cox model, Kaplan-Meier estimation, exponential, normal and lognormal regression are used frequently [1, 4, 6].

In Ukraine, these methods are not used sufficiently often in medical research work, which is why there is a need for more

complete awareness about the application of mathematical and statistical tools.

Survival analysis is traditionally frequently used in medical and biological research, insurance and reliability theory. The problem under investigation is that of studying the survival time, which depends on several factors and may follow any of a number of different distributions. In these tasks baseline data on survival time are divided into two types: full, which correspond to death or failure of the device,

and incomplete, censored, which suggest that the object under study remained alive until a particular point in time, and further contact with him was lost. For example, in clinical research, data listing accident victims who have been discharged or transferred to other departments provides an example of censorship.

2. Materials and Methods

By way of an example of the use of survival analysis models we present data from about 373 victims admitted with severe injuries to the V. T. Zaicev Institute of General and Emergency surgery. There were 263 (70, 51%) favorable outcome and 110 (29, 49%) deaths. The database provides information on victims with the following injuries: open injury – 285 cases (76, 41%); closed injuries – 80 cases (21, 45%), and compound injuries – 8 cases (2, 14%). The ages of the victims range from 7 years to 84 years, the distribution of the affected age group was close to normal, and the average age was 34 ± 1.17 years.

In this study, we selected a subgroup of victims in critical condition, most of them undergoing artificial pulmonary ventilation (APV), and determined the duration of the procedure. For this subsample we identify two types of outcomes, or two types of data: complete (the patient died) or censored (the patient survived). For the calculations associated with the survival analysis model we used the program Statistica 7 [1].

3. Results and Discussion

In developed countries, from 20 to 80 people per 100 thousand of population die as a result of injury; the number of victims with severe injuries is five times greater [7]. Here we refer to the average numbers for the past few years in terms of deaths and injuries in the developed European countries. Road traffic accidents are the cause of death and serious injuries in about 32% of cases. Injuries resulting from violent actions and attacks account for about 20% of all injuries. Falls from heights account for about 10% of cases, and injuries due to fires and explosions do not exceed 5% of the cases.

The typical types of traumatic injury arising as a result of road traffic accidents and other accidents are bleeding, broken bones and spinal fractures, impaired consciousness, cardiac arrest and soft tissue injuries [10, 11, 12, 13]. A significant proportion of all injuries consists of multiple trauma (polytrauma) and injuries of the chest and abdominal cavities. Heart injuries frequently occur as a result of road traffic accidents, falls from a height, stab wounds and blows in the region around the heart, gunshot and mine-explosive injuries, or as a result of sports injuries.

Often severe accidents, assault with a weapon, falls or explosions can cause not only blunt trauma but also penetrating injuries of chest and abdomen.

According to medical reports data, 50% of victims die during the first couple of minutes in cases of severe injury to

skull, brain or major blood vessels. In cases of intracerebral bleeding, severe injuries of the thoracic cavity or the abdomen, 30% of victims die during the so-called “golden hour”. Over the next couple of days or weeks, the mortality rate is still high (up to 20%) due to multiple organ failure and systemic inflammatory syndrome. Multiple organ failure is considered to be the most common cause of death in patients with severe trauma, after the first 24 hours [7, 8, 9].

Polytrauma causes asystemic reaction in the body, which is determined by three components:

- a Microcirculation failure because of hemorrhagic shock, hypovolemia, hypoperfusion and hypoxia with consequent development of metabolic impairment
- b Immune response, taking the form of systemic inflammatory syndrome
- c Coagulopathy caused by the injury

Today the management of patients with multiple trauma, almost regardless of its severity, is reduced to the standardized approach, which includes adequate external and internal breathing, and efficient hemodynamics (ABC-protocol). This should be followed by the correction of secondary pathogenic mechanisms which occurred at the injury and are associated with a decrease in adequate circulation volume, in the cessation of bleeding and in the sequestration of fluids in the “third space” – the correction and stabilization of cardiac performance, the correction of electrolyte abnormalities and the acid-salt balance.

According to various sources and treatment protocols for patients with severe polytrauma, one of the priorities is to ensure hemodynamic and respiratory functions, which are often carried out in these patients using artificial pulmonary ventilation [5, 7, 8, 9].

Table 1 shows the sample distribution of the victims admitted to the V. T. Zaicev Institute of General and Emergency surgery who required the use of artificial pulmonary ventilation. Twelve time intervals were selected using the Statistica program, with a difference of 11 minutes. As seen from Table 1, artificial pulmonary ventilation (APV) was performed during the first time interval, on 181 patients, 27 of whom died within the first 11 minutes. Thus 181 people were put on the APV, 27 of them died within the first 11 minutes of starting the artificial pulmonary ventilation, 129 were taken off the APV in the first 11 minutes because they didn't need it any more. The proportion of deaths in the first interval was 0, 232. This proportion is computed as the ratio of the number of cases failing in the respective interval, divided by the number of cases at risk in the interval. In other words it is number dying/number exposed or $27/116,5$.

Number exposed or number of cases at risk is the number of cases that entered the respective interval alive, minus half of the number of cases lost or censored in the respective interval. Thus, number of exposed is calculated as: number entering – (number withdrawn/2). Then 25 patients were still on the APV after 11 minutes and started on the second interval, 3 people died in the 2nd interval, 11 were taken off because they didn't need it and 11 were still on the ventilator after 22 minutes. In this interval the proportion of deaths was

0,154 (3/19,5).

A detailed analysis shows that these were the most severe cases, with injuries incompatible with life. In the third time

interval, when the duration of the application of the ventilator exceeded 22 min. but was less than 33 min., the number of deaths was 3 and proportion of deaths was 0,3 (3/10).

Table 1. Characteristics of survival time distribution among victims after APV.

Time interval number	Start of time interval, min.	Number entering	Number with-drawn	Number exposed	Number dying
1	0	181	129	116,5	27
2	11	25	11	19,5	3
3	22	11	2	10	3
4	33	6	0	6	0
5	44	6	0	6	0
6	55	6	0	6	2
7	66	4	1	3,5	1
8	77	2	0	2	0
9	88	2	0	2	0
10	99	2	0	2	1
11	110	1	0	1	0
12	120	1	0	1	1

Table 1. Continue.

Time interval number	The proportion of dead	The proportion of survived	The cumulative proportion of survived	Probability density	Hazard Rate
1	0,232	0,768	1	0,0212	0,024
2	0,154	0,846	0,768	0,0108	0,0153
3	0,3	0,7	0,65	0,0179	0,0324
4	0,083	0,917	0,455	0,0035	0,008
5	0,083	0,917	0,417	0,0032	0,008
6	0,333	0,667	0,382	0,0117	0,0367
7	0,286	0,714	0,255	0,0067	0,0306
8	0,25	0,75	0,182	0,0042	0,0262
9	0,25	0,75	0,137	0,0031	0,0262
10	0,5	0,5	0,102	0,0047	0,0611
11	0,5	0,5	0,051	0,0023	0,0611
12	0,5	0,5	0,026	-	-

Source: data processed by the authors in Statistica

In the Table 1 the cumulative proportion of survived is given. This is the cumulative proportion of cases surviving up to the respective interval. Since the probabilities of survival are assumed to be independent across the intervals, this probability is computed by multiplying out the probabilities of survival across all previous intervals. The resulting function is also called the survivorship or survival function [1].

The probability density is the estimated probability of failure in the respective interval, computed per unit of time, that is:

$$F_i = \frac{P_i - P_{i+1}}{h_i} \quad (1)$$

In this formula, F (i) is the respective probability density in the i'th interval, P (i) is the estimated cumulative proportion surviving at the beginning of the i'th interval (at the end of interval (i-1)), P (i+1) is the cumulative proportion surviving at the end of the i'th interval, and h_i is the width of the respective interval [1].

Then the hazard rate was calculated (see Table 1.). The hazard rate is defined as the probability per time unit that a

case that has survived to the beginning of the respective interval will fail in that interval. Specifically, it is computed as the number of failures per time units in the respective interval, divided by the average number of surviving cases at the mid-point of the interval [1].

Analyzing the dynamics of the proportion of victims who died, as a function of APV duration (Table 1), we can see its non-linear character. So, in the first interval (up to 11 min APV), the proportion of deaths was 0,232; in the second interval (from 11 to 22 minutes of pulmonary ventilation), the proportion of deaths was 0,154; in the third interval (from 23 to 32 minutes), the proportion of deaths almost doubled, to 0,3; in the 4th and 5th intervals (33- 54 minutes APV), the proportion of deaths decreased and remained stable at the level of 0,083; then in the 6th interval (55 - 65 min APV), the proportion of deaths increased again to 0,333 and remained fairly high for the next interval. Isolation of these critical time periods of APV, where there is a sharp jump in the proportion of deaths, is important for analyzing the prevention of various complications and the application of additional resuscitation.

The Table 1 gives a good indication of the distribution of failures over time. However, for predictive purposes it is

often desirable to understand the shape of the underlying survival function in the population. The major distributions that have been proposed for modeling survival or failure times are the exponential distribution, linear exponential distribution, the Weibull distribution of extreme events, and the Gompertz distribution [1].

The regression procedure for fitting the four theoretical distributions to the life table is based on algorithms proposed by Kennedy and Gehan (1971), and discussed in detail in Lee (1980). Basically, the hazard functions (specifically, the logarithmic transforms of the hazard functions) of all four theoretical distributions are linear functions of the survival times (or log-survival times). If we set $y = h(t)$, then all four models can be stated in the general form: $y = a + b \cdot x$. Gehan and Siddiqui (1973) suggest weighted least squares methods to fit the parameters of the respective models to the data [1]. Specifically, the program Statistica will minimize the quantity:

$$WSS = \sum_i \left(w(i) \cdot [y(i) - a - b \cdot x(i)]^2 \right) \quad (2)$$

Three different weights are used in the estimation:

- (1). $w(i) = 1$ (unweighted least squares)
- (2). $w(i) = 1 / v(i)$
- (3). $w(i) = n(i) \cdot h(i)$,

where $v(i)$ is the variance of the hazard estimate, and $h(i)$ and $n(i)$ are the interval width and number of observations exposed to risk in the i 'th interval, respectively [1].

In our analysis we tested the results of fitting the Weibull model to the data with different weightings (weight 1, weight 2, weight 3).

Table 2 shows the estimates of Survival Function for our data.

Table 2. Estimates of Survival Function (Model: Weibull).

Time interval number	Interval Start	Weight 1	Weight 2	Weight 3
1	0	1	1	1
2	10.909	0.868	0.783	0.775
3	21.818	0.709	0.589	0.61
4	32.727	0.561	0.436	0.484
5	43.636	0.434	0.319	0.385
6	54.545	0.329	0.231	0.307
7	65.455	0.246	0.167	0.245
8	76.364	0.181	0.119	0.196
9	87.273	0.132	0.085	0.157
10	98.182	0.095	0.06	0.126
11	109.091	0.067	0.042	0.102
12	120	0.047	0.03	0.082

Source: data processed by the authors in Statistica

Figure 1 represents the estimates of the Survival Function.

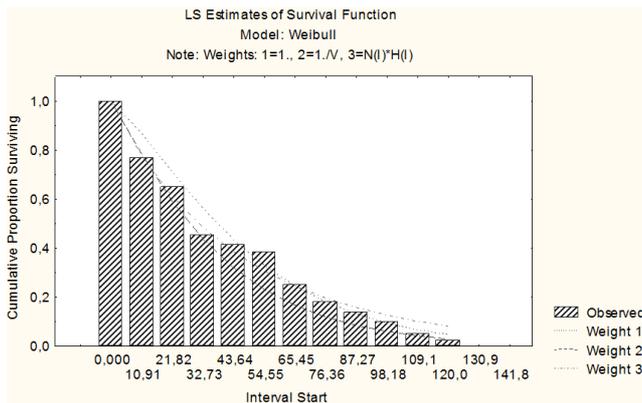


Figure 1. The Estimates of Survival Function.

Figure 2 represents the dynamics of the proportion of victims who die, as a function of APV duration and the results of fitting the Weibull model to the data with different weightings (weight 1, weight 2, weight 3).

As we can see from the data presented in Table 3, for all three weighting schemes (weight 1, weight 2, weight 3) there was no statistically significant difference between the fitted

Weibull distribution and the empirical distribution, using the chi-square test.

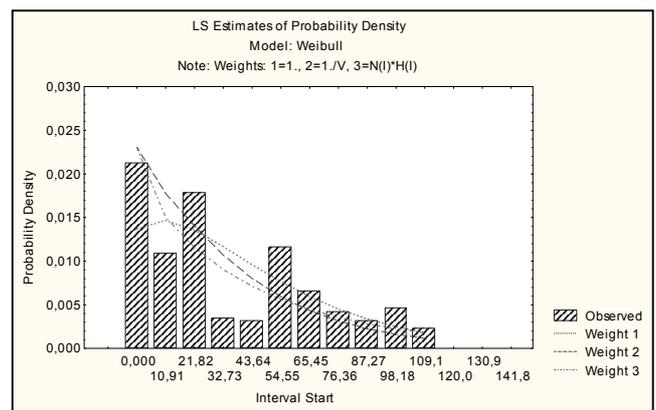


Figure 2. Dynamics of the proportion of victims who die, as a function of APV duration.

However, the closest to the empirical distribution is the distribution fitted using the third weighting scheme (weight 3), where the value of the Chi-square test statistic is lowest.

Table 3. The parameter estimates for the Weibull model.

Note: Weights: 1=1., 2=1./V, 3=N(I)*H(I)									
	Std. Err.		Std. Err.		Covariance	Log-			
	Lambda	Lambda	Gamma	Gamma	Gam-Lam	Likelhd.	Chi-Sqr.	df	p
Weight 1	0,006624	0,006664	1,280725	0,254336	-0,00164	-94,9192	14,35808	9	0,110
Weight 2	0,01717	0,00909	1,111659	0,15621	-0,00136	-91,5666	7,652955	9	0,567
Weight 3	0,026173	0,015945	0,952644	0,181525	-0,00279	-90,5439	5,607468	9	0,775

Source: data processed by the authors in Statistica

The Kaplan-Meier method of estimation was also carried out on the data in this investigation. Unlike the method of life tables, the method proposed by Kaplan and Meier does not require the subdivision of survival times into intervals. Estimation of the survival function is given by the following formula:

$$S(t) = \prod_{\forall j} \left[\frac{(n-j)}{(n-j+1)} \right]^{\delta(j)}, \quad (3)$$

where $S(t)$ is the estimate of the survival function, n is the number of events (observations), j is the position of the event when all events are arranged in increasing time order, and $\delta(j)$ is equal to 1 if the outcome of the j^{th} event was that the victim died and 0 otherwise.

Based on the Kaplan-Meier estimates we obtained a graph of victims' survival, as a function of the time of pulmonary ventilation (Figure 3).

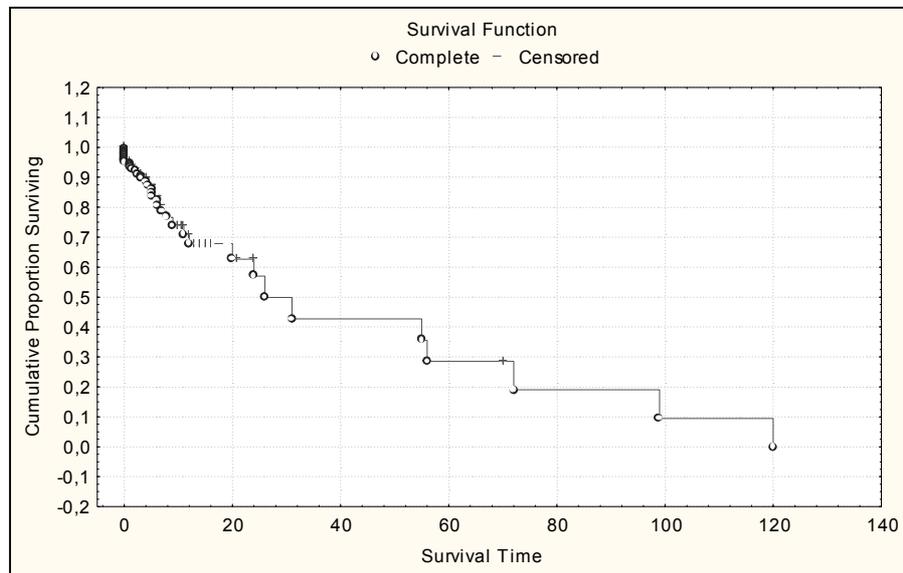


Figure 3. Victims' survival, as a function of the time of APV.

Since the survival function values are obtained by multiplying estimates of survival probabilities of previous events ordered for the relevant victims, the graph shown in Figure 2 shows that value of the function is initially equal to 1 (100%), then within 12 min the value falls to 0,67 (67%). After that, the values of survival function, although they are decreasing, take the form of a step function and decrease less rapidly than in the first interval.

In order to assess how the probability of the various outcomes for the victim is influenced by other factors in addition to the time of the APV, we constructed a Cox proportional hazards model.

In this case, the time intensity function of APV (variable X 8) depends on a number of factors included in the model: variable D 28 (the presence of lung injury), D 29 (the presence of heart injury), X 9 - the quantity of blood loss (ml), and X 6 - blood pressure value before surgery.

The results of the Cox proportional hazards model are presented in Table 4.

As can be seen from table 4, the value of the chi-square test statistic for this model is statistically significant at the level of error less than 1%. Of the factors included in the model two variables have a statistically significant effect on the duration of APV and the possible outcome for the victim: D 28 (the presence of lung injury) and X 6 (blood pressure before surgery). It should be noted that factors such as the presence of cardiac injury (D 29) and the amount of blood loss (X 9) are correlated with an arterial blood pressure index, which is measured in patients before surgery. In other words, the lack of statistical significance of the factors D 29 and X 9 is explained by the effect of multicollinearity, ie a linear correlation with the X 6 factor. Factor X 6 in victims can be determined fairly quickly, while the measurement of blood loss or determination of the presence of cardiac injury

requires much more time and the application of additional diagnostic methods.

Table 4. Cox proportional hazard model results.

Dependent Variable: X 8 (new_sh~1. sta) Censoring var.: Y Chi = 15,3084 df = 4 p =,00411						
	Beta	Standard Error	t-value	exponent beta	Wald Statist.	p
D 28 (lung injury)	0,659172	0,365658	1,802699	1,93319	3,249722	0,071445
D 29 (heart injury)	0,201824	0,442106	0,456506	1,223632	0,208398	0,648029
X 9 (quantity of blood loss)	0,000165	0,000196	0,844198	1,000165	0,71267	0,398565
X 6 (blood pressure value before surgery)	-0,01815	0,005747	-3,15759	0,982018	9,970396	0,001592

Source: data processed by the authors in Statistica

In addition to these factors, it is possible to include in the survival model other quantities which are important in monitoring patients' vital functions and in preventing the development of complications in the early and late post-traumatic periods. When changing the set of various indicators and factors affecting the condition of patients with severe polytrauma, it is possible to use the package Statistica to build a variety of survival functions for patients with different risk factors.

Another important area of research is the study of patients' survival rates during the late post-traumatic period.

Whilst the scheme for the correction of traumatic injuries is well developed and the treatment scheme works well enough, the posttraumatic period and the associated adaptational pathological processes are not. For all that, they are of fundamental importance in the development of posttraumatic syndrome. Their severity can be on weakly related to the severity of the injury, because they are also associated with the body's systemic adaptive reaction, which may be a damaging factor by not working properly.

4. Conclusions

According to this, the use of methods of mathematical statistics in survival models must find a more complete application in medical research, first of all in medical emergencies and in resuscitation.

This mathematical apparatus allows the user to conduct a more accurate analysis of processes connected with the efficiency of resuscitation measures and with serious or critical condition of the victim. Survival models also allow us to evaluate possible risks associated with the development of posttraumatic syndrome in patients discharged after severe injuries, which may pose a threat to the patient's health or life in the future.

In sum, survival models will permit the assessment of the possible risks of complications and of the dynamics of their occurrence according to the nature of the injury and the individual characteristics of the victims.

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