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Stochastic Model to Find the Multidrug Resistance in Human Gallbladder Carcinoma Results Using Uniform Distribution

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Abstract: *Gallbladder Carcinoma (GBCA) is one of the most aggressive malignancies. It is usually diagnosed at an advanced stage, and prognosis remains poor despite advances in imaging techniques and aggressive surgical treatment. Over expression of multidrug resistance associated proteins (MRPs) in tumor cells is a major cause of the intrinsic multidrug resistance phenotype. Despite the documented importance of MRP expression in many carcinomas, the prognostic significance of MRP2 expression in primary GBCA is not known. Immunostaining for MRP2 was performed on tissue samples obtained from 143 patients with GBCA. We examined the association between MRP expression and clinic pathological characteristics and outcome of patients with GBCA. We found that the expression of MRP2 in GBCA contributed to aggressive tumor behavior and poor prognosis, suggesting that MRP2 expression can be used as a potential prognostic biomarker of GBCA. In addition, for univariate survival analysis, survival curves were estimated using Laplace Stieltjes transform (LST) of the renewal process*

$$LS_{S_{n+1}}(s) = \frac{\lambda}{s+\lambda}\left[\rho + (1-\rho)\frac{\lambda}{s+\lambda}\right]^n$$

Keywords: *Gallbladder Carcinoma, Multidrug Resistance, Laplace Stieltjes Transform, Polya Aeppli Process, Uniform Distribution.*

2010 Mathematics Subject Classification: 60K99, 60G99

1. INTRODUCTION

GBCA is a lethal malignancy that is difficult to cure by current treatment. The tumors are strongly associated with an increased incidence of pigmented stones in the gallbladder and bile ducts. Furthermore the delayed onset of symptoms and rapid growth of biliary tract carcinomas have resulted in limited therapeutic efficacy and a high mortality rate. Moreover, the role of systemic chemotherapy in palliative treatment of GBCA remains undefined. To date, conventional chemotherapy has been notably ineffective in improving long term survival of patients with GBCA as these tumors are highly resistant to drug treatment at the onset of therapy. Such chemotherapeutic resistance is a major obstacle to successful cancer treatment. ATP binding cassette (ABC) transporters are a super family of membrane proteins that are best known for their ability to transport a wide variety of exogenous and endogenous substances across membranes against a concentration gradient via ATP analysis [5].

The Polya Aeppli process is a generalization of the homogenous Poisson process. The risk model in which the counting process is the Polya Aeppli process is called the Polya Aeppli risk model. The stationary Poisson counting process $\{N(t), t \geq 0\}$ is said to be a Polya Aeppli process if it starts at zero, $N(0) = 0$; it has independent, stationary increments; and for each $t > 0, N(t)$ is Polya Aeppli distributed. For this process, the Laplace Stieltjes transform of the renewal process is used to find the expression of multidrug resistance associated protein 2 (MRP2) in human gallbladder carcinoma.

2. NOTATIONS

GBCA	-	Gallbladder Carcinoma
ABC	-	ATP Binding Cassette
LST	-	Laplace Stieltjes Transform

IGPSD	-	Inflated Parameter Generalized Power Series Distributions
GPSD	-	Generalized Power Series Distributions
N(t)	-	Stationary Poisson Counting Process
N	-	Inflated Parameter
S_n	-	Delayed Renewal Process
λ	-	Shape parameter
ρ	-	Scale parameter
s	-	Assuming Time

3. THE POLYA AEPPLI PROCESS

The standard model of an insurance company, called risk process $\{X(t), t \geq 0\}$ defined on the complete probability space $(\Omega, \mathcal{F}, P)$ is given by

$$X(t) = ct - \sum_{k=1}^{N(t)} Z_k \quad (1)$$

Here c is a positive real constant representing the gross risk premium rate. The sequence $\{Z_k\}_{k=1}^{\infty}$ of mutually independent and identically distributed random variables with common distribution function $F, F(0) = 0$ and mean value μ is independent of the counting process $N(t), t \geq 0$. The process $N(t)$ is interpreted as the number of claims on the company during the interval $[0, t]$.

In the classical risk model, the process $N(t)$ is a stationary Poisson counting process [4]. In this case, the aggregate claim amounting up to time t is given by the compound Poisson process $S(t) = \sum_{i=1}^{N(t)} Z_i$. If the number of claims $N(t)$ forms a renewal counting process, the model (1) is called a renewal risk model. There are many directions in which the classical risk model and the renewal model are generalized in order to become a reasonably realistic description. From [2] & [3] studied a generalization of the renewal model, assuming that claims occur as an Erlang process, and extended several classical results. References are given in [1] & [8]. Our interest is in the generalization of the counting process $N(t)$.

In [7] & [9], a new family of discrete probability distributions is introduced. The classical Poisson, negative binomial, binomial, and logarithmic distributions are generalized by adding a new parameter $\rho \in [0,1)$. The generalized distributions are called inflated parameter distributions according to the interpretation of the parameter ρ. The new family of distributions is called inflated parameter generalized power series distributions (IGPSD). In the case of $\rho = 0$, the IGPSD becomes the family of generalized power series distributions (GPSD) or the classical discrete distributions.

We give useful interpretation of the model. Suppose that any insurance policy produces two types of claims named "success" with probability $1 - \rho$ and "failure" with probability ρ. Define the random variable N to equal the number of trials until the i^{th} successive claim appears. The random variable N is negative binomial distributed with parameters $1 - \rho$ and i. The probability mass function of N is given by

$$P(N = k) = \binom{k-1}{k-i} \rho^{k-i} (1-\rho)^i, \quad k = i, i+1, \ldots \quad (2)$$

The random variable N given by (2) can be represented as a sum $N = X_1 + \cdots + X_i$ where $\{X_j,\ j = 1,2,\ldots\}$ are independent identically $Ge_1(1-\rho)$ distributed random variables. The parameter i in (2) represents the number of geometrically distributed random variables. If we suppose that i is an outcome of the random variable Y, independent of $\{X_j,\ j = 1,2,\ldots\}$ and Y has the GPSD, then N has the IGPSD [9]. In particular, if Y has the Poisson distribution with parameter $\lambda (Po(\lambda))$, N has the inflated parameter Poisson distribution $(IPo(\lambda, \rho))$. The $IPo(\lambda, \rho)$ distribution coincides with the Polya Aeppli distribution [6] and has the following probability mass function:

$$P(N = n) = \begin{cases} e^{-\lambda}, & n = 0 \\ e^{-\lambda} \sum_{i=1}^{n} \binom{n-1}{i-1} \frac{[\lambda(1-\rho)]^i}{i!} \rho^{n-i}, & n = 1, 2, \ldots \end{cases}$$

Now we will define the Polya Aeppli process in order to describe the aggregate claim amount process as a compound Polya Aeppli process.

The $IPo(\lambda, \rho)$ distribution is a generalization of the classical $Po(\lambda)$ distribution. In this section, we will define the corresponding generalization of the Poisson process.

We consider the sequence $T_1, T_2, \ldots$ of nonnegative, mutually independent random variables and the corresponding renewal process

$$S_n = \sum_{k=1}^{n} T_k, \quad n = 1, 2, \ldots \& S_0 = 0 \tag{3}$$

The process S_n can be interpreted as a sequence of renewal epochs. T_1 is the time until the first renewal epoch and $\{T_k\}_{k\geq 2}$ are the interarrival times.

Let $N(t) = sup\{n \geq 0, S_n \leq t\}, t \geq 0$ be the number of renewals occurring up to time t. The distribution of $N(t)$ is related to that of S_n, and for any $t \geq 0$ and $n \geq 0$, the following probability relation holds:

$$P(N(t) = n) = P(S_n \leq t) - P(S_{n+1} \leq t), \quad n = 0, 1, 2, \ldots \tag{4}$$

We will suppose that $N(t)$ is described by the $IPo(\lambda t, \rho)$ distribution (or Polya Aeppli distribution) with mean function $(\lambda/(1 - \rho))t$

$$\text{(i.e).,}\ P(N = n) = \begin{cases} e^{-\lambda t}, & n = 0 \\ e^{-\lambda t} \sum_{i=1}^{n} \binom{n-1}{i-1} \frac{[\lambda(1-\rho)t]^i}{i!} \rho^{n-i}, & n = 1, 2, \ldots \end{cases} \tag{5}$$

We denote by $LS_X(s) = \int_0^\infty e^{-sx} dF_X(x)$ the Laplace Stieltjes transform (LST) of any random variable X with distribution function $F_X(x)$. Let $p_n(t) = P(N(t) = n)$

For the next considerations, we need the following result.

Lemma (1):

The Laplace Stieltjes transform (LST) of $p_n(t)$ is given by

$$LS_{p_n(t)}(s) = \int_0^\infty e^{-st} dp_n(t)$$

$$= \begin{cases} -\frac{\lambda}{s+\lambda}, & n = 0 \\ (1-\rho)\frac{\lambda}{s+\lambda}\frac{s}{s+\lambda}\left[\rho + (1-\rho)\frac{\lambda}{s+\lambda}\right]^{n-1}, & n = 1, 2, \ldots \end{cases}$$

Now we will show that the renewal process is characterized by the fact that T_1 is exponentially distributed and $\{T_2, T_3, \ldots\}$ are identically distributed. Moreover, T_2 is zero with probability ρ, and with probability $1 - \rho$, exponentially distributed with parameter λ. This means that the probability density functions and the mean values are the following:

$$f_{T_1}(t) = \lambda e^{-\lambda t}, \quad t \geq 0, \quad ET_1 = \frac{1}{\lambda}$$

$$f_{T_2}(t) = \rho\delta_0(t) + (1-\rho)\lambda e^{-\lambda t}, \quad t \geq 0, \quad ET_2 = \frac{1-\rho}{\lambda} \tag{6}$$

Where $\delta_0(t) = \begin{cases} 1, & if\ t = 0 \\ 0, & otherwise \end{cases}$

The process S_n is called a delayed renewal process with a delay T_1.

Theorem (1):

There exists exactly one renewal process such that the number of renewals up to time t has the Polya Aeppli distribution (5). In this case, the time until the first renewal epoch T_1 is exponentially distributed with parameter λ. The interarrival times $T_2, T_3, \ldots$ are zero with probability ρ and with probability $1 - \rho$, exponentially distributed with parameter λ.

Proof:

To prove the theorem, it suffices to show that the LST of the random variable S_n is as follows:

$$LS_{s_n}(s) = \frac{\lambda}{s+\lambda}\left[\rho + (1-\rho)\frac{\lambda}{s+\lambda}\right]^{n-1} \tag{7}$$

We will prove it by induction using relations (4). For $n = 0$, (4) becomes

$$P(N(t) = 0) = 1 - P(T_1 \leq t) = 1 - F_{T_1}(t) \tag{8}$$

Where $F_{T_1}(t)$ is the distribution function of T_1. On the other hand, from (5), it follows that

$$P(N(t) = 0) = e^{-\lambda t} \tag{9}$$

Combining (8) and (9) gives that $F_{T_1}(t) = 1 - e^{-\lambda t}$, that is, the random variable T_1 is exponentially distributed with parameter λ and LST $\lambda/(s + \lambda)$.

Now from (4), for $n = 1$, we get

$$P(N(t) = 1) = P(S_1 \leq t) - P(S_2 \leq t)$$

Taking the LST leads to

$$(1 - \rho)\frac{\lambda}{s + \lambda}\frac{s}{s + \lambda} = LS_{S_1}(s) - LS_{S_2}(s)$$

After some algebra, we arrive at

$$LS_{T_1 + T_2}(s) = \frac{\lambda}{s+\lambda}\left[\rho + (1 - \rho)\frac{\lambda}{s+\lambda}\right]$$

Which means that T_2 is independent of T_1. Moreover, T_2 is an exponentially distributed random variable with parameter λ and mass at zero equal to ρ. The probability density function of T_2 is given by (6).

Suppose now that for any $n \geq 2$, the LST of S_n is given by (7). Taking the LST in (4), we get

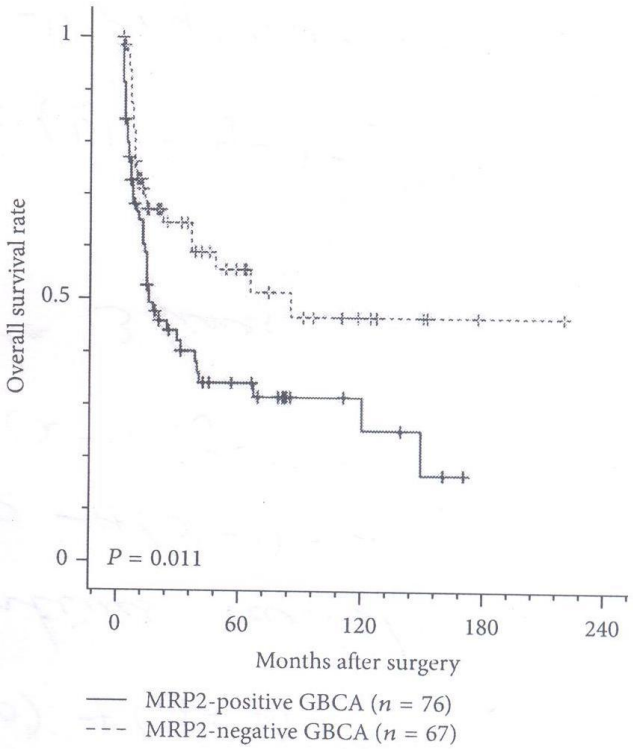
$$\begin{aligned} LS_{S_{n+1}}(s) &= \int_0^\infty e^{-st} dP(S_{n+1} \leq t) \\ &= \int_0^\infty e^{-st} dP(S_n \leq t) - \int_0^\infty e^{-st} dP_n(t) \end{aligned}$$

Applying lemma (1), one can show that the LST of the renewal process S_{n+1} is equal to

$$LS_{S_{n+1}}(s) = \frac{\lambda}{s+\lambda}\left[\rho + (1 - \rho)\frac{\lambda}{s+\lambda}\right]^n \tag{10}$$

This proves the theorem.

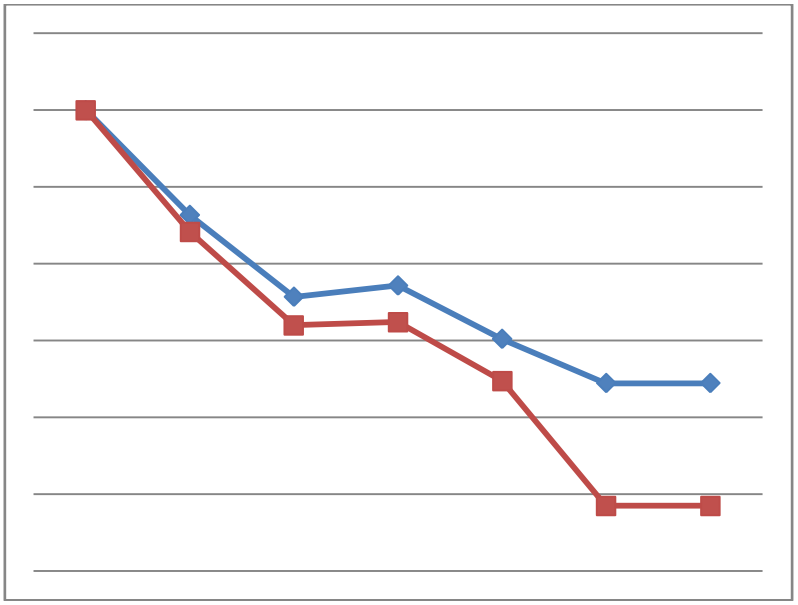
4. EXAMPLE



We investigated the prognostic value of immunohistochemical expression of MRP2 in GBCA. Adequate clinical follow up information was available for 143 patients. Of the 143 patients, 78 (54.5%) died during the follow up period and the remaining 65 (45.5%) were alive at the end of the study. The survival curves according to MRP2 expression status are shown in figure (1). The median survival of patients with MRP2 positive GBCA (15 months) was markedly shorter than that of patients with MRP2 negative GBCA (85 months; P = 0.011). the one year, three year, five year and overall survival rates were 60.3%, 38.2%, 31.6% and 16.8% respectively, for patients with MRP2 positive GBCA and 71.0%, 58.9%, 51.3% and 46.7% respectively, for patients with MRP2 negative GBCA. To estimates the clinical significance of various prognostic factors that influence survival, univariate survival analyses were performed [5] & [10].

Figure (1): Kaplan Meier survival curve for all overall survival according to the status of MRP2 expression in 143 patients with GBCA. The median survival of patients with MRP2 positive GBCA (15 months) was markedly shorter than that of patients with MRP2 negative GBCA (85 months; P = 0.011)

Figure (2):



Blue Line: MRP2 Negative GBCA
Red Line: MRP2 Positive GBCA

5. CONCLUSION

Identification of prognostic biomarkers to predict the outcome of patients with GBCA as a therapeutic target is urgently needed; MRP2 expression was associated with aggressive tumor behavior and predicted shortened overall survival. Changes in MRP2 regulation may potentially promote lymphovascular and perineural invasions in GBCA and the level of MRP2 expression may serve as a useful biomarker for local recurrence and patient outcome. This model is beautifully fitted with Laplace Stieltjes Transform of renewal process of the Polya Aeppli process. The medical report {Figure (1)} is beautifully fitted with the mathematical model {Figure (2)}; $(i.e)$ the results coincide with the mathematical and medical report.

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