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Stochastic Model to Find the Prognostic Ability of NT Pro-BNP in Advanced Heart Failure Patients Using Gamma Distribution

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Abstract: *The selection of The selection of patients for cardiac transplantation (CT) is notoriously difficult and traditionally involves clinical assessment and an assimilation of markers of the severity of CHF such as the left ventricular ejection fraction (LVEF), maximum oxygen uptake (peak VO_2) and more recently, composite scoring systems e.g. the heart failure survival score (HFSS). Brain natriuretic peptide (BNP) is well established as an independent predictor of prognosis in mild to moderate chronic heart failure (CHF). However, the prognostic ability of NT-proBNP in advanced heart failure is unknown and no studies have compared NT-proBNP to standard clinical markers used in the selection of patients for transplantation. The purpose of this study was to examine the prognostic ability of NT-proBNP in advanced heart failure with the help of sojourn time distribution in a Markovian G-Queue by using Gamma distribution.*

Keywords: *Brain Natriuretic Peptide, Moderate Chronic Heart Failure, Markovian G-Queue, Heart Failure, Sojourn Times, First Passage Times, Gamma Distribution.*

2010 Mathematics Subject Classification: 60H99, 60G99

1. Introduction

Despite recent advances in medical therapy, the mortality of advanced chronic heart failure (CHF) due to left ventricular systolic dysfunction (LVSD) remains high. Although donor organ availability restricts its use, cardiac transplantation (CT) remains an option for those patients with advanced CHF who do not respond to medical therapy [1].

The aims of this study were firstly to evaluate the prognostic value of NT-proBNP in patients with advanced heart failure referred for consideration of cardiac transplantation, and secondly to compare the prognostic ability of NT-proBNP to that of the HFSS, and its individual component parameters.

We consider a single server Markovian queue with two types of customers; positive and negative, where positive customers arrive in batches and arrivals of negative customers remove positive customers in batches. Only positive customers form a queue and negative customers just reduce the system congestion by removing positive ones upon their arrivals. We derive the LSTs of sojourn time distributions for a single server Markovian queue with positive customers and negative customers by using the first passage time arguments for Markov chains.

The minimal non negative solution $W^*(s) = \frac{\mu(1-\rho)}{\mu(1-\rho)+s}[1 - H^*(\mu(1-\rho)+s)]$ where $H^*(s) = \frac{1}{2\lambda^+}\left[\lambda^+ + \lambda^- + s - \sqrt{(\lambda^+ + \lambda^- + s)^2 - 4\lambda^+\lambda^-}\right]$ of the $m \times m$ matrix equation is used to evaluate the prognostic value of NT-proBNP in patients with advanced heart failures.

2. Notations

CT	-	Cardiac Transplantation
CHF	-	Chronic Heart Failure
$LVEF$	-	Left Ventricular Ejection Fraction
$LVSD$	-	Left Ventricular Systolic Dysfunction
BNP	-	Brain Natriuretic Peptide

$NT-proBNP$	-	N-Terminal Brain Natriuretic Peptide
LST	-	Laplace Stieltjes Transform
λ^+	-	Positive Customers
λ^-	-	Negative Customers
OS	-	Overall Survival
λ_1	-	Shape Parameter
λ_2	-	Scale Parameter
s	-	Assuming Time

3. G - QUEUE

We consider a queue with two types of customers; positive and negative. Positive customers are ordinary ones who, upon arrival, join the queue with the intention of being served. In contrast to the positive customers, the arrival of negative customers removes some of the positive customers from the system, if any available, and then disappears; otherwise the negative customer is lost. Only positive customers can from a queue and negative customers just reduce system congestion. Such queues have been called G-queue [5].

Since [3] introduced the notion of negative customers to represent the inhibitator signal in neural networks and commands to delete some transactions in distributed computer systems or databases, there has been a growing interest not only in networks of queues [3] [5] & [7] but also in single node queues with negative customers [6] & [8]. Interest in time delays in the G-queue has increased recently. From [4] derived the LSTs of the sojourn time distributions for the M/M/1 G-queue under the combinations of various queueing disciplines and removal strategies. From [5] investigated the end to end delay in an open tandem pair of a G-queue with FCFS discipline and RCE removal strategy. Most papers assume that upon arrival to a queue, a negative customer removes an ordinary customer from the queue. Recently, several authors have generalized this concept, allowing a negative arrival to remove a batch of customers [7], a random amount of workload or even all work in the system [8].

However, the results about sojourn time distribution even for single node G-queues with batch arrival or batch removal are few to the author's best knowledge. In this paper, we use the first passage time arguments of Markov chains to derive the LST of the sojourn time distribution in single server Markovian G-queues with a batch arrival of positive customers and/or batch removal by a negative arrival. The mathematical accessibility of our model compared with that of [4] represents a part of the motivation for the study of batch arrivals/removals. Furthermore, our model is related to the inventory systems with perishable products such as fruit, vegetables and meat, in which arrival and removal occur in batches and instantaneous removal of inventory usually depends on the length of time that the products spent it the system.

4. QUEUE LENGTH DISTRIBUTION

In this section, we describe the mathematical model in detail and derive the queue length distribution in equilibrium at the arrival instants of positive customers. We consider a single server queue in which positive customers arrive in batches according to a Poisson process with rate λ^-, which is independent of the arrival process of positive customers. We assume that each arrival of a negative customer removes a random number B of positive customers in the system. This is, upon a negative arrival, if there are k positive customers in the system, $min(B,k)$ positive customers are removed and the negative customer disappears. The service time distribution of all customers is exponential with mean $\frac{1}{\mu}$. For the notational simplicity, we let $\tilde{\mu}=\lambda^-+\mu$ and $\lambda=\lambda^++\lambda^-$. We assume that the batch size A of positive customers and the quota B of a negative customer take finite values to avoid calculations of infinite matrices. However, this assumption is not a strong restriction, since the supports of A and B may be arbitrarily large and one can apply our model to A and B taking infinite values by truncating the tail pats of the state spaces with sufficiently small tail probabilities. Let $P(A=n)=a_n$ and $P(B=n)=b_n, n=1,2,\ldots$ with $a_n=0, n\geq l+1$ and $ba_n=0, n\geq m+1$ for some $1\leq l,m<\infty$. We denote the means $\bar{a}=E(A)$ and $\bar{b}=E(B)$ and generating functions $A(z)=\sum_{n=1}^{l}a_nz^n$ and $B(z)=\sum_{n=1}^{m}b_nz^n$.

Note that the stationary distribution of the queue length in this system is invariant under the service discipline and removal strategies and concern only positive customers. This model is equivalent to the $M^A/M^B/1$ queue where customers arrive in batches with batch size A according to a Poisson process with rate λ^+ and the customers are served in batches of maximum size $\tilde{B}$ with $\tilde{b}_k = P(\tilde{B} = k), 1 \leq k \leq m$, where

$$\tilde{b}_k = \begin{cases} \frac{\lambda^- b_1 + \mu}{\tilde{\mu}} & k = 1 \\ \frac{\lambda^- b_n}{\tilde{\mu}} & 2 \leq k \leq m \end{cases}$$

and the service time distribution is exponential with parameter $\tilde{\mu}$. The necessary and sufficient condition for this system to be positive recurrent is given (e.g [9]) by

$$\rho = \frac{\lambda^+ \bar{a}}{\mu + \lambda^- \bar{b}} < 1$$

We assume that $\rho < 1$ throughout.

Now we turn our attention to the queue length distribution at the epochs of positive customers, which will be imperative in the upcoming sections. Let $\{N_n\}$ be the number of positive customers in the system at the epoch immediately before the arrival of the n[th] batch of positive customers. Let A_n be the batch size of the n[th] arrival of positive customers with the same distributions as A and D_{n+1}, where D_{n+1} is the number of positive customers departed from the system during the $(n+1)^{th}$ inter arrival period of the batch of positive customers. Then it a be seen that

$$N_{n+1} = \max\left(N_n + A_n - D_{n+1}, 0\right)$$

The probability d_n that n positive customers potentially leave the system during the inter arrival time of a batch of positive customers is given by

$$d_n = \begin{cases} p & n = 0 \\ \sum_{j=1}^{n} 1^b\,(j,n) p q^j & n \geq 1 \end{cases}$$

Where $p = \frac{\lambda^+}{\lambda^+ + \tilde{\mu}}, q = 1 - p$ and $b(j,n)$ is the j-fold convolution of the probability mass function $\{\tilde{b}_k, 0 \leq k \leq m\}$. Simple calculations yield

$$\tilde{B}(z) = \sum_{n=1}^{m} \tilde{b}_n z^n = \frac{1}{\tilde{\mu}}(\mu z + \lambda^- B(z))$$

and hence the probability generating function $d(z) = \sum_{n=0}^{\infty} d_n z^n$ is given by

$$d(z) = \frac{\lambda^+}{\lambda^+ + \mu(1-z) + \lambda^-(1 - B(z))}$$

Denoting $d_n = 0$ for $n \leq -1$ and $\bar{d}_n = \sum_{k=n}^{\infty} d_k, n \geq 0$, we deduce that the transition probability matrix $P = (p_{ij})$ of $\{N_n\}$ is given by

$$p_{ij} = \begin{cases} \sum_{k=1}^{l} a_k \bar{d}_{i+k} & j = 0 \\ \sum_{k=1}^{l} a_k \bar{d}_{k+i-j} & 1 \leq j \leq i + l \\ 0 & j \geq i \geq l + 1 \end{cases}$$

Following similar procedures as those in [9], the stationary distribution $\pi = \{\pi_i, i = 0, 1, \ldots\}$ of $\{N_n\}$ is given by

$$\pi_k = C \sum_{i=1}^{K} \sum_{j=0}^{n_i - 1} c_{ij} \left(\frac{d^j}{dx^j} x^k \mid x = \alpha_i\right), k \geq 0 \qquad (1)$$

where $\alpha_i, 1 \leq i \leq K$ is the solution of the equation

$$\alpha^l = d(\alpha)\left(\alpha_1 \alpha^{l-1} + \alpha_2 \alpha^{l-2} + \cdots + \alpha_l\right) \qquad (2)$$

with n_i being the multiplicity of α_i $(1 \leq i \leq K)$, such that $1 \leq n_i \leq l$ and $\sum_{i=1}^{K} n_i = l\, c_{ij}, 0 \leq j \leq n_{i-1} - 1, 1 \leq i \leq K$ are arbitrary constants, which are can be determined by the $l - 1$ simultaneous equations:

$$\pi_j = \sum_{i=0}^{\infty} \pi_i p_{ij}, j = 1, 2, \dots, l-1 \quad (3)$$

under the constraint

$$\sum_{i=1}^{K} \sum_{j=0}^{n_i-1} c_{ij} = 1 \quad (4)$$

and C, the normalizing constant (in $\sum_{i=0}^{\infty} \pi_i = 1$) is given by

$$C = \left[\sum_{i=1}^{K} \frac{c_{i0}}{1-\alpha_i} + \sum_{i=1}^{K} \sum_{j=1}^{n_i-1} c_{ij} \frac{j!}{(1-\alpha_i)^{j+1}}\right]^{-1}$$

After simple but tedious algebra, we have from (3) and (4) the following linear system of equations for $\{c_{ij}, 0 \le j \le n_{i-1} - 1, 1 \le i \le K\}$:

$$Hc = e_l$$

where $c = \left(c_{10}, c_{11}, \dots, c_{1,n_1-1}, c_{2,0}, c_{2,1}, \dots, c_{2,n_2-1}, \dots, c_{K,n_K-1}\right)^t$ and $e_l = (0, 0, \dots, 0, 1)^t$ is the l unit vector and H is the $l \times l$ matirsx with its k[th] $(1 \le K \le l-1)$ row

$$h_k = h_{10}(k), h_{11}(k), \dots, h_{1,n_1-1}(k), h_{2,0}(k), \dots, h_{2,n_2-1}(k), \dots, h_{K,n_K-1}(k)$$

and l^{th} row $h_l = (1, 1, \dots, 1)$ and for $1 \le k \le l-1, 1 \le i \le K, 0 = j \le n_i - 1$

$$h_{ij}(k) = \sum_{r=k+1}^{l} \alpha_r \sum_{n=0}^{r-k-1} (k-r+n)(k-r+n-1) \dots (k-r+n-j+1) \alpha_i^{k-r+n-j}$$

4.1 Special Cases

(i) Let $l = 1$ that is $A \equiv 1$. In this case, (2) becomes

$$\tilde{\mu}\alpha\tilde{B}(\alpha) - (\lambda^+ - \tilde{\mu})\alpha + \lambda^+ = 0$$

and is has a unique solution $0 < \alpha < 1$, say α_0, and the stationary distribution is given by

$$\pi_n = (1-\alpha_0)\alpha_0^n, n \ge 0 \quad (5)$$

(ii) Let $l = 1$ & $m = 1$ that is $A \equiv 1$ & $B \equiv 1$. In this case, (2) becomes

$$\alpha^2 - (1+\rho)\alpha + \rho = 0$$

and the stationary distribution is given by

$$\pi_n = (1-\rho)\rho^n, n \ge 0 \quad (6)$$

5. THE FIRST PASSAGE TIMES

The sojourn times, which will be treated in the upcoming sections, can be considered as the first passage times of the corresponding Markov chains. So we need to investigate the first passage times for some Markov chains related to compound Poisson processes.

First, we consider the compound Poisson process

$$X(t) = \sum_{i=1}^{N(t)} X_i$$

where $\{N(t), t \ge 0\}$ is a Poisson process with rate v and $\{X_i\}$ is a sequence of independent and identically distributed (IID) random variables, which are independent of $\{N(t), t \ge 0\}$ and have probability mass function $x_k = P(X_1 = k), k = 1, 2, \dots$ and probability generating function $\Xi(z) = \sum_{n=1}^{\infty} x_n z^n, |z| \le 1$. Let $U_X(n)$ be the first passage of time of $X(t)$ to the state n, that is

$$U_X(n) = \inf\{t \ge 0: X(t) \ge n$$

and let $U_X(n,t) = P(U_X(n) \le t)$ be the probability distribution function of $U_X(N)$. By conditioning the first transition of the process $\{X(t)\}$, we have the following proposition.

5.1 Proposition

The LST $U_X^*(n,s)$of $U_X(n,t)$ is given recursively by

$$U_X^*(1,s) = \frac{v}{v+s},$$

$$U_X^*(n,s) = \frac{v}{v+s}\left(\bar{x}_n + \sum_{i=1}^{n-1} x_i U_X^*(n-i,s)\right), n \ge 2$$

where $x_i = \sum_{k=i}^{\infty} x_k, i \geq 1$. The double transform $\widetilde{U}_X^*(z,s) = \sum_{n=1}^{\infty} z^n\, U_X^*(n,s)$ is given by

$$\widetilde{U}_X^*(z,s) = \left(\frac{z}{1-z}\right)\left(\frac{v(1-\Xi(z))}{s+v(1-\Xi(z))}\right)$$

Now we consider the difference of two independent compound Poisson processes

$$X_1(t) = \sum_{i=1}^{N_1(t)} X_{1,i} \text{ and } X_2(t) = \sum_{i=1}^{N_2(t)} X_{2,i}$$

where $\{N_1(t)\}$ and $\{N_1(t)\}$ are independent Poisson processes with rates λ_1 and λ_2 respectively, and $\{X_{1,i}\}$ and $\{X_{2,i}\}$ are independent sequences of IID random variables with $P(X_{1,i} = k) = x_{1,k}, k \geq 1$ and $P(X_{2,i} = k) = x_{2,k}, 1 \leq k \leq m$. We assume that the random variable $X_{2,i}$ is bound by m. Define a Markov chain

$$Z(t) = X_1(t) - X_2(t), t \geq 0$$

with $Z(0) = 0$. Let Z_n be the state at the instant immediately after the nth transition of the process $\{Z(t), t \geq 0\}$ and τ_n the time interval between the nth and n+1th transitions. Then $\{(Z_n, \tau_n), n \geq 0\}$ is a Markov renewal process with the transition probability matrix $Q_Z(t)$ of the form

$$Q_Z(t) = \begin{matrix} \\ \vdots \\ -2 \\ -1 \\ 0 \\ 1 \\ 2 \\ \vdots \\ \vdots \end{matrix} \begin{pmatrix} \cdots & -2 & -1 & 0 & 1 & 2 & \cdots & \cdots & \cdots \\ & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \cdots & C_1 & C_2 & C_3 & C_4 & C_5 & \cdots & \cdots & \cdots \\ \cdots & C_0 & C_1 & C_2 & C_3 & C_4 & \cdots & \cdots & \cdots \\ & & C_0 & C_1 & C_2 & C_3 & \cdots & \cdots & \cdots \\ & & & C_0 & C_1 & C_2 & \cdots & \cdots & \cdots \\ & & & & C_0 & C_1 & \cdots & \cdots & \cdots \\ & & & & \vdots & \vdots & \vdots & \vdots & \vdots \\ & 0 & & & \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix} \left(1 - e^{-(\lambda_1+\lambda_2)t}\right)$$

where each level $i = ((i,1),(i,2),\ldots,(i,m)), i = 0, \pm 1, \pm 2, \ldots$ is the set of m states, the state (i,k) in level i means the state $(i,k) = mi + k - 1, C_0$ is the upper triangular matrix

$$C_0 = \begin{pmatrix} c_{-m} & c_{-m+1} & c_{-m+2} & \cdots & c_{-1} \\ & c_{-m} & c_{-m+1} & \cdots & c_{-2} \\ & & c_{-m} & \cdots & c_{-3} \\ & & & \ddots & \vdots \\ 0 & & & & c_{-m} \end{pmatrix}$$

and

$$C_{n+1} = \begin{pmatrix} c_{mn} & c_{mn+1} & \cdots & c_{mn-m+1} \\ c_{mn-1} & c_{mn} & \cdots & c_{mn-m+2} \\ \vdots & \vdots & & \vdots \\ c_{mn-m+1} & c_{mn-m+2} & \cdots & c_{mn} \end{pmatrix}$$

where

$$c_i = \begin{cases} \frac{\lambda_1}{\lambda_1+\lambda_2} x_{1,i} & i \geq 1 \\ \frac{\lambda_2}{\lambda_1+\lambda_2} x_{2,-i} & -m \leq i \leq -1 \\ 0 & i = 0 \end{cases} \tag{7}$$

Define the first passage time as

$$G_Z(n) = \inf\{t \geq 0 : Z(t) \leq n\}$$

and denote its distribution function $G_Z(n,t) = P(G_Z(n) \leq t)$. Now we derive the LST $G_Z^*(-n,s)$ of $G_Z(-n,t), n \geq 1$.

5.2 Proposition

The LSTs $G_Z^*(-n,s)$ for $1 \leq k \leq m$ are recursively given by

$$G_Z^*(-1,s) = \sum_{j=1}^{m} [H^*(s)]_{ij} \tag{8}$$

$$G_Z^*(-k,s) = \sum_{j=1}^{m-k+1}[H^*(s)]_{ij} + \sum_{j=m-k+2}^{m}[H^*(s)]_{ij} G_Z^*(m-k+1-j,s)$$

and for $n \geq 2$ and $k = m, m-1, \ldots, 1$ by

$$G_Z^*(-mn+k-1,s) = \sum_{j=1}^{m}\left[\left(H^*(s)\right)^n\right]_{ij} + \sum_{j=k+1}^{m}\left[\left(H^*(s)\right)^n\right]_{ij} G_Z^*(k-j,s) \quad (9)$$

where $H^*(s)$ is an $m \times m$ matrix, which is the minimal non negative solution of the matrix equation.

$$H^*(s) = \left(\frac{\lambda_1+\lambda_2}{\lambda_1+\lambda_2+s}\right)\sum_{n=0}^{\infty} C_n [H^*(s)]^n \quad (10)$$

While $[H^*(s)]_{ij}$ denotes the (i,j) entry of the matrix $H^*(s)$.

Let $T(i+r,j;i,j')$ be the first hitting time of $\{Z(t), t \geq 0\}$ from state $(i+r,j) = m(i+r)+j-1, r \geq 1, 1 \leq j \leq m$, to state $(i,j') = mi+j'-1, 1 \leq j' \leq m$, with the additional requirement that (i,j') is the first state at level i to be visited and $\tau_i(j,k)$ is the first passage time from state (i,j) to state $(i,k), 1 \leq j,k \leq m, j-k > 0$. When the process $\{Z_n\}$, starting at (0, 1), that is, $Z_0 = 0$, hits the level $-n$, and visits state $(-n,j) \in \{(-n,1), \ldots, (-n,k)\}$, then $G_Z(-mn+k-$ *1=T(0, 1; −n, j)*; and if the state visited is *−n, j∈−n, k+1, …, −n, m* then *GZ−mn+k−1* is the sum of $T(0,1;\ -n,j)$ and $\tau_{-n}(j,k)$. Thus we have for $n \geq 1, 1 \leq k \leq m$

$$P(G_Z(mn-k+1) \leq t) = \sum_{j=1}^{k} P(T(0,1;\ -n,j) \leq t)$$
$$+ \sum_{j=k+1}^{k} P(T(0,1;\ -n,j) + \tau_{-n}(j,k) \leq t) \quad (11)$$

Let $H_{jj'}^{[r]}(t) = P(T(i+r,j;i,j') \leq t)$ be the distribution function of $T(i+r,j;i,j')$ and $H_{jj'}^{[r]*}(s)$ be the LST of $H_{jj'}^{[r]}(t), 1 \leq j,j' \leq m$. Let $H^{[r]}(t)$ and $H^{[r]*}(s)$ denote the $m \times m$ matrices with (j,j') entry $H_{jj'}^{[r]}(t)$ and $H_{jj'}^{[r]*}(s)$ respectively. By the spatial homogeneity for levels of $Q_Z(t)$ the distribution of $T(i+r,j;i,j')$ does not depend on level i but only on r and (j,j') and hence we get

$$H^{[r]*}(s) = [H^*(s)\,]^r, r \geq 1$$

From the spatial homogeneity of the transition probability $Q_Z(t)$ for states $\tau_i(j,k), j > k$, depends only on the difference of the states $j-k$ and its distribution function is the same as that the $G_Z(k-$ *j*. Note that, by the Markovian property, *T0, 1; −n, j* and *τ−nj, k, n≥1* are independent. By taking LST in (11), we have (8). By using the same arguments as in [10] we have that $H^*(s)$ is the minimal non negative solution of

$$H^*(s) = \left(\frac{\lambda_1+\lambda_2}{\lambda_1+\lambda_2+s}\right)\sum_{n=0}^{\infty} C_n [H^*(s)]^n$$

5.3 Special Cases

1. If $m > 1$ and $l \leq m-1$, then $C_n = 0, n \geq 2$ and hence we have

   $$H^*(s) = \left(\frac{\lambda_1+\lambda_2+s}{\lambda_1+\lambda_2} I - C_1\right)^{-1} C_0$$

   where I is the $m \times m$ identity matrix.
2. If $m = 1$, that is, $X_{2,i} \equiv 1$ then $G_Z^*(n,s)$ is obtained from (8) and (10) as

   $$G_Z^*(-n,s) = [H^*(s)]^n, n \geq 1$$

   and $H^*(s)$ is the solution of the equation

   $$z = \frac{1}{\lambda_1+\lambda_2+s}(\lambda_2 + \lambda_1 z \Xi_1(z)) \quad (12)$$

   with $|z| < 1$ where $\Xi_1(z) = \sum_{i=1}^{\infty} x_{1,i} z^i$
3. If $l = m = 1$, that is $X_{1,i} \equiv 1$ and $X_{2,i} \equiv 1$, then letting $\Xi_1(z) = z$ in (12) and solving equation (12), we have

   $$H^*(s) = \frac{1}{2\lambda_1}\left((\lambda_1+\lambda_2+s) - \sqrt{(\lambda_1+\lambda_2+s)^2 - 4\lambda_1\lambda_2}\right) \quad (13)$$

6. RCE WITH FCFS DISCIPLINE

Under the FCFS queueing discipline with RCE removal strategy, upon arrival of a negative customer, if the number of positive customers is fewer than B, then all the positive customers are removed;

otherwise, B customers from the end of the queue are removed. Let W denote the time period during which the tagged customer spends in the system from the epoch of arrival to the epoch of its service completion. We assume that W is infinite if the tagged customer is removed from the system before its service completion. Let N_a and N_b be the numbers of customers ahead of and behind the tagged customer, respectively, immediately after its arrival instant, and let N be the number of customers in the system at the tagged customer's arrival. Let A^* and A^*_- be the batch size to which the tagged customer belongs and the number of customers in the preceding batch. Note that the probability mass functions of A^* and A^*_- are given by

$$P(A^* = k) = \frac{ka_k}{\bar{a}} \text{ and } P(A^*_- = j \mid A^* = k) = \frac{1}{k}, j = 0,1,2,\dots,k-1$$

Thus the distribution function $W(x) = P(W \le x)$ in equilibrium is

$$\begin{aligned} W(x) &= \sum_{n=0}^{\infty} \pi_n \, P(W(x) \le x \mid N = n) \\ &= \sum_{n=0}^{\infty} \pi_n \, \sum_{k=1}^{l} P(W(x) \le x \mid N = n, A^* = k) \frac{ka_k}{\bar{a}} \qquad (14) \\ &= \sum_{n=0}^{\infty} \pi_n \, \sum_{k=1}^{l} \frac{ka_k}{\bar{a}} \sum_{j=0}^{k-1} \frac{1}{k} P(W(x) \le x \mid N = n, A^* = k, A^*_- = j) \\ &= \sum_{n=0}^{\infty} \pi_n \, \sum_{k=1}^{l} \frac{ka_k}{\bar{a}} \sum_{j=0}^{k-1} P(W(x) \le x \mid N_a = n + j, \ N_b = k - j - 1) \end{aligned}$$

To calculate the conditional distribution $P(W(x) \le x \mid N_a = n, \ N_b = k)$, we define the Markov chain

$$X(t) = X^+(t) - X^-(t), t \ge 0$$

with $X(0) = 0$, where $X^+(t)$ and $X^-(t)$ are the numbers of positive customers having arrived and potential removals by negative customers up to time t, respectively. Then the LST $G_X^*(-n, s)$ of the first passage time distribution function

$$G_X(-n) = inf\{t \ge 0 : X(t) \le -n\}, n \ge 1$$

can be obtained from (8) by replacing c_i in (7) by

$$c_i = \begin{cases} \dfrac{\lambda^+}{\lambda} a_i, & 1 \le i \le l \\ \dfrac{\lambda^-}{\lambda} b_{-i}, & -m \le i \le -1 \\ 0, & otherwise \end{cases}$$

Let S_n be the time needed to serve n consecutive customers. Since the service time distribution is exponential with parameter μ, the probability density function $s_n(t)$ of S_n is given by

$$s_n(t) = \mu e^{-\mu t} \frac{(\mu t)^{n-1}}{(n-1)!}, t \ge 0 \qquad (15)$$

Under the FCFS service discipline with RCE removal strategy, when $N_a = n, N_b = k$ for the tagged customer to complete its service without being removed, it must hold true that $G_X(-k-1) > S_{n+1}$ Hence, the conditional distribution of W given that $N_a = n$ & $N_b = k$, is represented by

$$\begin{aligned} P(W(x) \le x \mid N_a = n, N_b = k) &= P(G_X(-k-1) > S_{n+1}, S_{n+1} \le x) \qquad (16) \\ &= \int_0^x P(G_X(-k-1) > t) \, s_{n+1}(t) dt \end{aligned}$$

Letting

$$\begin{aligned} K_j(\alpha, s, t) &= \sum_{n=0}^{\infty} \alpha^n e^{-st} s_{n+j+1}(t) \\ &= \alpha^{-j} \left[\mu e^{-(s+\mu(1-\alpha))t} - \sum_{i=0}^{j-1} \frac{(\alpha\mu t)^i}{i!} \mu e^{-(s+\mu)t} \right], j \ge 0 \end{aligned}$$

and

$$W(\alpha, x) = \sum_{n=0}^{\infty} \alpha^n P(W \le x \mid N = n)$$

$$W^*(\alpha,s)=\int_0^\infty e^{-sx}W(\alpha,dx)$$

we have from (1) and (14) - (16) the following proposition.

6.1 Proposition

The LST $W^*(s)$ of $W(x)$ is given by

$$W^*(s)=C\sum_{i=1}^{K}\sum_{j=0}^{n_i-1}c_{ij}\left(\frac{\partial^j}{\partial\alpha^j}W^*(\alpha,s)\mid_{\alpha=\alpha_i}\right)$$

where

$$W^*(\alpha,s)=\sum_{k=1}^{l}\frac{a_k}{\bar{a}}\sum_{j=0}^{k-1}\int_0^\infty K_j(\alpha,s,t)\left(1-G_X(j-k,t)\right)dt$$

$$=\frac{\mu(s+\mu)\left(1-A\left(\frac{\mu}{s+\mu}\right)\right)}{\bar{a}s\left(s+\mu(1-\alpha)\right)}-\frac{\mu}{s+\mu(1-\alpha)}\sum_{k=1}^{l}\frac{a_k}{\bar{a}}\sum_{j=0}^{k-1}\alpha^{-j}G_X^*\left(j-k,s+\mu(1-\alpha)\right)$$

$$+\sum_{k=1}^{l}\frac{a_k}{\bar{a}}\sum_{j=0}^{k-1}\alpha^{-j}\sum_{i=0}^{j-1}\frac{(\alpha\mu)^i}{i!}\mu(-1)^i\frac{d^i}{ds^i}\left[\frac{G_X^*(j-k,s+\mu)}{s+\mu}\right] \tag{17}$$

6.2 Special Cases

1. If $l=1$ that is $A\equiv 1$, then we have from (5), (8) and (17) that

$$W^*(s)=(1-\alpha_0)W^*(\alpha_0,s)$$

$$=\frac{\mu(1-\alpha_0)}{s+\mu(1-\alpha_0)}\left[1-G_X^*\left(-1,s+\mu(-\alpha_0)\right)\right] \tag{18}$$

$$=\frac{\mu(1-\alpha_0)}{s+\mu(1-\alpha_0)}\left[1-\sum_{j=1}^{m}\left[H^*\left(s+\mu(1-\alpha_0)\right)\right]_{1,j}\right]$$

2. If $m=1$ that is $B\equiv 1$ then $G_X^*(-n,s)=[H^*(s)]^n$ and (17) becomes

$$W^*(\alpha,s)=\frac{\mu(s+\mu)\left(1-A\left(\frac{\mu}{s+\mu}\right)\right)}{\bar{a}s\left(s+\mu(1-\alpha)\right)}-\frac{\mu}{s+\mu(1-\alpha)}\frac{\alpha\beta(\alpha,s)\left[A\left(\beta(\alpha,s)\right)-A(1/\alpha)\right]}{\bar{a}(\alpha\beta(\alpha,s)-1)}$$

$$+\sum_{k=1}^{l}\frac{a_k}{\bar{a}}\alpha^{-k}\sum_{i=0}^{k-2}\frac{(\alpha\mu)^i}{i!}\mu(-1)^i\frac{d^i}{ds^i}\left[\frac{\left(\alpha\gamma(s)\right)^{k-i}-\alpha\gamma(s)}{(s+\mu)(\alpha\gamma(s)-1)}\right]$$

Where $\beta(\alpha,s)=H^*\left(s+\mu(1-\alpha)\right)$ and $\gamma(s)=H^*(s+\mu)$

3. If $l=m=1$ then we have from (6) and (18) that

$$W^*(s)=\frac{\mu(1-\rho)}{\mu(1-\rho)+s}\left[1-H^*(\mu(1-\rho)+s)\right]$$

Where $H^*(s)=\frac{1}{2\lambda^+}\left[\lambda^++\lambda^-+s-\sqrt{(\lambda^++\lambda^-+s)^2-4\lambda^+\lambda^-}\right]$ (19)

7. EXAMPLE

We prospectively studied 142 consecutive patients with advanced CHF referred for consideration of CT. Plasma for NT-proBNP analysis was sampled and patients followed up for a median of 374 days. The primary endpoint of all cause mortality was reached in 20 (14.1%) patients and the combined secondary endpoint of all cause mortality or urgent CTx was reached in 24 (16.9%) patients. An NT-proBNP concentration above the median was the only independent predictor of all cause mortality $(\chi^2=6.03, P=0.01)$ and the combined endpoint of all cause mortality or urgent CT $(\chi^2=12.68, P=0.0004)$. LVEF, VO2 and HFSS were not independently predictive of mortality or need for urgent cardiac transplantation in this study [2].

Kaplan Meier survival curves for all cause mortality for the variables most commonly associated with a poor outcome in advanced heart failure (LVEF, Peak VO_2 and HFSS), as well as NT-proBNP. The only predictor of all cause mortality was an NT-proBNP above the median value (log rank statistic = 10.99, P = 0.0009). The predictors of mortality or urgent CT were LVEF (log rank statistic = 5.92, P = 0.015) and NT-proBNP (log rank statistic = 15.36, P = 0.0001). Figure (1) & (2) shows poorer outcome associated with increasing NT-proBNP concentrations represented as quartiles (log rank statistic = 12.7, P = 0.005) for all cause mortality and 21.22 (P = 0.0001) for all cause mortality and urgent transplantation [2] & [11-14].

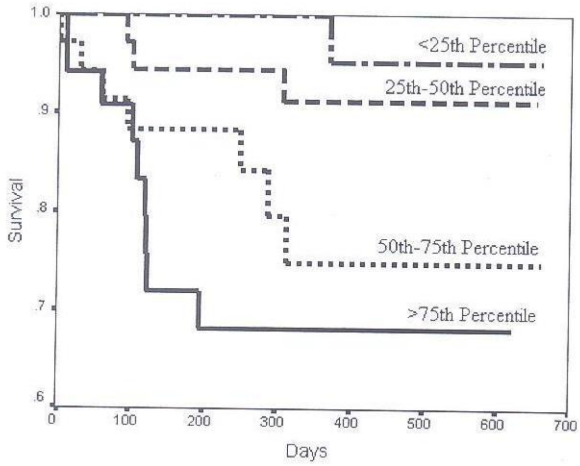


Figure (1). *Kaplan Meier Survival Curve: NT-proBNP concentrations split into quartiles in 142 patients with advanced heart failure against all cause mortality transplantation.*

(log rank statistic = 12.70, P = 0.005)

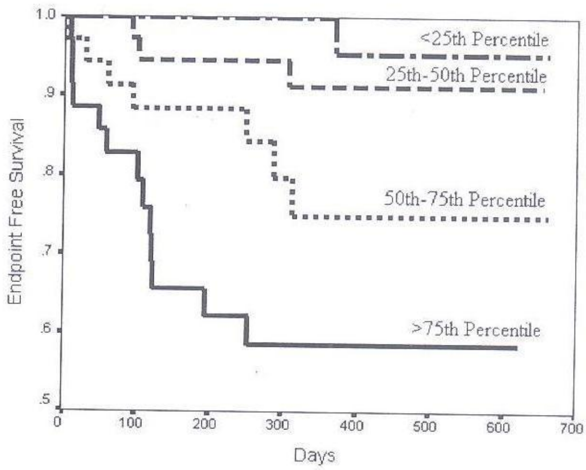
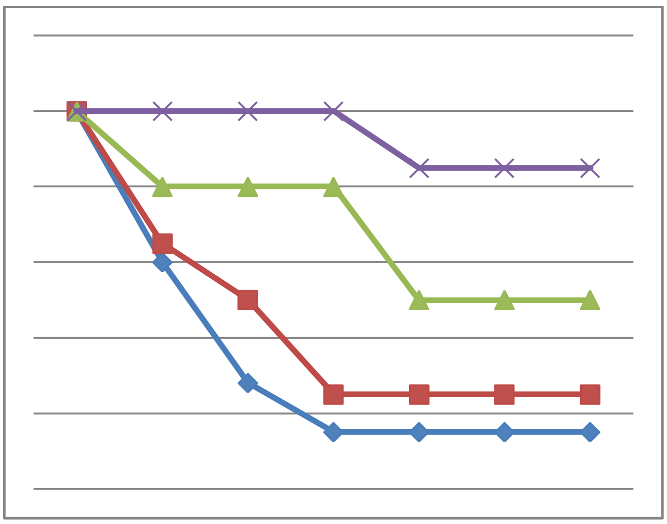


Figure (2). *Kaplan Meier Survival Curve: NT-proBNP concentrations split into quartiles in 142 patients with advanced heart failure against all cause mortality and urgent transplantation.*

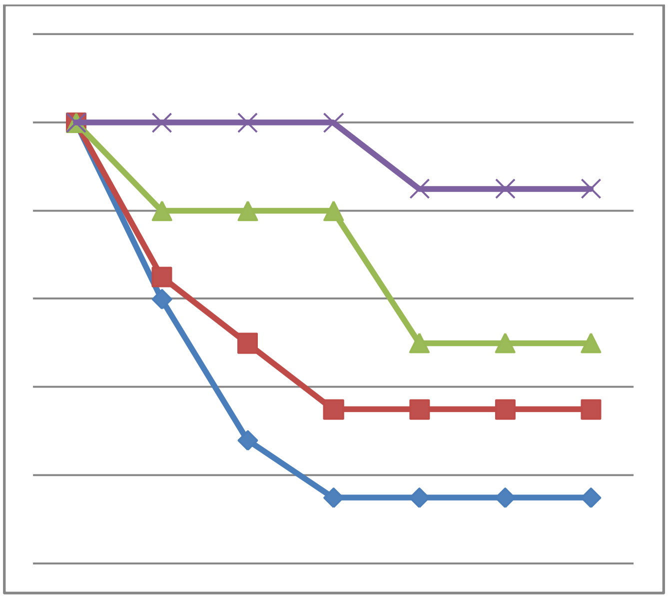
(log rank statistic = 21.22, P = 0.0001)



Violet Line: < 25th Percentile
Green Line: 25th – 50th Percentile
Red Line: 50th – 75th Percentile
Blue Line: > 75th Percentile

Figure (3). *Kaplan Meier Survival Curve: NT-proBNP concentrations split into quartiles in 142 patients with advanced heart failure against all cause mortality transplantation.*

(Using Gamma Distribution)



Violet Line: < 25th Percentile
Green Line: 25th – 50th Percentile
Red Line: 50th – 75th Percentile
Blue Line: > 75th Percentile

Figure (4). *Kaplan Meier Survival Curve: NT-proBNP concentrations split into quartiles in 142 patients with advanced heart failure against all cause mortality transplantation.*

(Using Gamma Distribution)

8. CONCLUSION

A single measurement of NT-proBNP in patients with advanced CHF, can help to identify patients at highest risk of death, and is a better prognostic marker than the LVEF, VO_2 or HFSS. The minimal non negative solution of the $m \times m$ matrix equation in the Markovian G-Queue by using gamma distribution gives the same results as the medical report mentioned above. The medical reports {Figure (1) & (2)} are beautifully fitted with the mathematical model {Figure (3) & (4)}; $(i.e)$ the results coincide with the mathematical and medical report.

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