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STATISTICAL ANALYSIS OF WEIBULL DISTRIBUTION ON PATIENTS PAIN RELIEF IN CLINICAL TRIAL

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Abstract: Clinical pain is an unpleasant situation. Clinicians have come out with decisive measure to reduce body pain. 20 patients who went through pain and receiving an analgesic to relieve headache pain at Konfo Anokye Teaching Hospital, Kumasi were studied. Two parameter Weibull distribution was applied to the data. The study revealed that the patients mean relief time from pain is 1.92 hours. The shape Weibull parameter that defined the behavior of patient's failure rate is 3.15. the scale parameter that determines the propensity of the patient's pain in Weibull distribution is 0.09.

Keywords: *Weibull Distribution, Patients, Pain, Clinical Trial.*

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Introduction

Socio economic factors influence how Ghanaians and other African countries attribute source of pain to family members and the society at large. Africans see pain as irreversible curse on people do not follow societal norms and laws. In Ghana, when someone, primitive method of farming in rural areas, coupled with hash weather conditions with severe sunshine during farming seasons bring untold body pain to the rural folks. Healthcare facilities which are to serve the people are woefully inadequate. Access to quality healthcare in rural areas where farming activities are predominant is not available. Some of these facilities are sparsely located and the people are to use the facilities are distance from it. During rainy season, the situation worsens and the people in rural communities' resort to traditional way of eradicating body pain. Due to poor road network, linking these health facilities, the rural communities resort to over the canter drugs. Those who sell these drugs are mainly not qualified health personnel and the implications of drug administration leaves mush to desire

Pain

Pain is an unpleasant sensory and emotional feeling accompanying existing or impending tissue damage or referenced to such damage. Pain is the most common experience reported by patients, and patient anxiety is a form of warning signal. It is a sensual and perceptual phenomenon, which causes suffering and emotional state of risks connected with anxiety. Pain has many forms. It warns against damage to the body, which is important for avoiding injuries and consequently for survival. Pain not caused by acute injuries can be unpleasant for the patient, or it can alter a person's life, reduce the quality of life, and also have an impact on the patient's family. The word "pain" for the patient means disease and suffering, for the doctor it is a symptom, and for the physiologist it is a kind of feeling that has its own anatomical and physiological system which begins with the receptors and ends up in the brain cortex. Feeling is a physical sensation that can be confirmed by electrophysiological methods, but in practice it is only a subjective sensation. It's intensity and quality come under various internal and external factors; therefore, the same stimulus can be experienced differently in different circumstances, somatic and psychiatric conditions. The way of receiving pain is very individual and varies from time-to-time in the same individual. The intensity of pain is difficult to measure and an individual's perception of pain depends on the individual's emotional state, circumstances under which the pain was acquired, and whether it is perceived as a threatening signal. The perception of pain depends on such factors as arousal, attention, distraction and expectation. Before we realize that something hurts, there are a number of physiological processes in our body. Painful stimuli have to be passed quickly – in (milli) seconds. Acute pain warns about impending or ensuing danger while chronic pain causes the afflicted part of the body, such as an immobilized and unused limb, increasing the chance for recovery. A single, sharp stimulus to pain can disappear, and probably not leave a trail. Stimuli that are repeated, cause adaptive changes in the central nervous system and the activation of a number of systems, both supporting and inhibiting pain. In the spinal cord and the brain there occurs synthesis and the activation of various receptor systems, as well as synthesis of various compounds modifying the sense of pain. It is known that an important role in this process is played the glial cells. It is a very complicated process that can lead to the preservation the pain, even after the disappearance of the pain stimulus. Pain can also be generated without receptors, from the peripheral and central nervous systems. This is always a pathological pain which arises due to damage to the nervous system, and has a different nature from physiological pain and clinical presentation. It is important to distinguish receptor pain –

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nociceptive, physiological pain from non -receptor pain – pathologic

Pathways of pain. The cause of pain is irritation of the receptors, called nociceptors. Nociceptors are free nerve endings that respond to painful stimuli. Nociceptors are found in skin, organ of motion (periosteum, joint capsule, ligaments, muscles), cornea of the eye and dental pulp. Inside the body they are also abundant in the meninges, pleura, peritoneum and organ walls. Stimulated by biological, electrical, thermal, mechanical, and chemical stimuli they transmit information to the brain. When stimuli are transmitted to the spinal cord, then to the central areas of the brain, pain perception occurs. Impulses run to the dorsal horn of the spine, where they synapse with dorsal horn neurons in the substantia gelatinase, and then enter the brain. The basic sensation of pain occurs at the thalamus. It continues to the limbic system (emotional center) and the cerebral cortex, where pain is perceived and interpreted. Nociceptors are simple structures because they are at the end of the nerve fibers. There are two types of fibers: Aδ and C, involved in pain transmission. The large one – Aδ fibers, produce sharp, well-defined pain, which is typically stimulated by a cut, an electrical shock, or a physical blow. They are myelinated and can allow an action potential to travel at a rate of about 20 meters/second towards the central nervous system. Transmission through Aδ fibers is so fast that the body responds faster than the pain stimulus. This results in retraction of the affected body part before the person perceives the pain. This allows a quick response: “escape” or preparation for “fight”. These fibers have practically no opioid receptors, while pain receptors located at the ends are always on standby. There are limited possibilities for pharmacological modification of these receptors. In practice, it is easy to inhibit chronic, “slow” pain, using analgesic drugs and difficult to block “sharp”, “fast” pain. After the so-called first pain, the smaller C fibers transmit dull burning or aching sensations, known as a “second pain.” C fibers are very thin and susceptible to damage. They do not

Regulators of Pain When tissue damage occurs, chemical substances that modulate the transmission of pain are released into the extracellular tissue. Pain receptors are activated by irritating the nerve endings. Chemical mediators responsible for pain activation include histamine, substance P, bradykinin, acetylcholine, leukotrienes, and prostaglandins. At the site of injury, mediators can produce other reactions, such as vasoconstriction, vasodilatation, or altered capillary permeability. Prostaglandins induce inflammation and other inflammatory mediators. Aspirin blocks cyclooxygenase 2, the enzyme needed for prostaglandin synthesis, thus reducing pain. This medication is often prescribed for painful conditions due to inflammation. Our body has a built-in chemical mechanism which can manage pain. Fibers in the dorsal horn, brain stem, and peripheral tissues release neuromodulators, endogenous opioids, that inhibit the action of neurons transmitting the pain impulses. Endorphins are natural opioid-like substances responsible for pain relief. Endorphin levels differ between individuals; therefore, different patients experience pain differently. This endogenous opioid mechanism may play an important role in the placebo effect. A placebo is an inactive substance or treatment used for comparison with “real” treatment in controlled studies, intended to deceive the recipient and determine the efficacy of the treatment under study. However, despite the lack of any actual value, placebos can also have a surprisingly positive effect on patients. Placebos can and do produce an analgesic response in many patients.

Method

Plotting position of Weibull distribution

Weibull distribution, introduced by Professor WaloddiWeibull in 1939 (Hong, 2009), is an important generalization of the exponential model with two positive parameters. The second parameter in the model allows greater flexibility of the model and allows r different shapes of the hazard function. The convenience of the Weibull model for empirical work stems from the one hand from its flexibility and on the other its simplicity when use to model the hazard and survival functions. The two parameter Weibull distribution has survival function and survival function given respectively by

$$\mathrm{S}(t) = e^{(-\lambda t^{\gamma})} \qquad (1)$$

Hazard function

$$\lambda(t) = \lambda\gamma t^{\gamma-1} \qquad (2)$$

And cumulative function as

$$\lambda t^{\gamma} \qquad (3)$$

A simple graphical method for estimating the parameters is useful for Weibull death density function. From equation (1), if we take natural logarithm twice of both sides, we obtain

$$\log_e\log_e\left[\frac{1}{S(t)}\right] = \log_e\lambda + \gamma\log_e t$$

Suppose that in a clinical trial we observe n patients doing through acute pain until they all died and we eventually record their time of death sequentially as $t_1 \leq t_2 \leq t_3 \leq \ldots t_n$. this is to say that $t_1 \leq t_2 \leq t_3 \leq \ldots t_n$ are in the n order observation s of the patients survival times that follows order statistics. In survival analysis, the usefulness of order statistics resides with the properties of t_i, which is the terminal order on functions of the same subset of the n samples, where $1 \leq i \leq n$,. For this reason, ordered values are not independent; the strength of the chain depends on either the smallest value or the largest value. If these survival times have approximately a Weibull distribution, the graph of $\log_e t_i$ plotted on the horizontal axis against $\log_e\log_e\left[\frac{1}{S(t)}\right]$ plotted on the vertical axis, should be a straight line. The slop of the plotted line is then the estimator of γ and the exponential interception is the estimator of λ.

Newton Raphson algorithm of least square estimators

In clinical trials, the death density for the i^{th} patient is given by

$$f(t,\lambda,\gamma) = \lambda\gamma t^{\gamma-1}e^{(-\lambda t^{\gamma})}$$

Then the likelihood function $L(\lambda,\gamma)$ is $L(\lambda,\gamma) = \prod_{i=1}^{n}\lambda\gamma t^{\gamma-1}e^{(-\lambda t^{\gamma})}$

The $\log_e L(\lambda,\gamma) = n\log_e\lambda + n\log_e\gamma + (\gamma-1)\sum_{i=1}^{n}\log_e t_i - \lambda\sum_{i=1}^{n}t_i^{\gamma}$

If we differentiate the $\log_e L(\lambda,\gamma)$ with respect to λ and γ, the process reduce to

$$\frac{d\log_e L(\lambda,\gamma)}{d\gamma} = \frac{n}{\gamma} + \sum_{i=1}^{n}\log_e t_i - \lambda\sum_{i=1}^{n}t_i^{\gamma}\log_e t_i$$

And

$$\frac{d\log_e L(\lambda,\gamma)}{d\lambda} = \frac{n}{\lambda} - \sum_{i=1}^{n} t_i^{\gamma}$$

For this reason, the maximum likelihood estimators $\hat{\lambda}$ and $\hat{\gamma}$ are obtained by solving simultaneously, the equations containing them.

$$\hat{\lambda} = \left(\frac{\sum_{i=1}^{n} t_i^{\hat{\gamma}}}{n}\right)^{-1} \qquad (4)$$

$$\hat{\lambda} = \frac{\frac{n}{\hat{\gamma}} + \sum_{i=1}^{n} \log_e t_i}{\sum_{i=1}^{n} t_i^{\hat{\gamma}} \log_e t_i} \qquad (5)$$

We eliminate $\hat{\lambda}$ from equation (4) and (5) to obtain a single equation for $\hat{\gamma}$ and this give rise to

$$\left[\frac{n}{\sum_{i=1}^{n} t_i^{\hat{\gamma}}}\right] \sum_{i=1}^{n} t_i^{\hat{\gamma}} \log_e t_i = \frac{n}{\hat{\gamma}} + \sum_{i=1}^{n} \log_e t_i \qquad (6)$$

The estimators $\hat{\lambda}$ and $\hat{\gamma}$ are obviously establish by examining the second partial derivative matrix

$$p = \begin{bmatrix} v_{11} & v_{12} \\ v_{12} & v_{22} \end{bmatrix}$$

From p, we define

$$v_{11} = \frac{d^2 \log_e L}{d\gamma^2},\ v_{12} = \frac{d^2 \log_e L}{d\lambda\gamma},\ v_{11} = \frac{d^2 \log_e L}{d\lambda^2}.$$

It is not difficult to see that $v_{11} < 0, v_{22} < 0$ but $v_{11}v_{22} - v_{12}^2 > 0$. For this reason, $(\hat{\lambda}, \hat{\gamma})$ of the vector parameter gives the maximum estimators. It is uncertain to obtain $\hat{\lambda}$ and $\hat{\gamma}$ in closed form like the least squares estimators. In clinical trial, since patients suffering from pain are sometimes lost to follow up, pain data are mostly paucity and contains censored values and least squares estimators are not good fit. It is therefore assuming that, the estimators have desirable large sample properties and by using Newton – Raphson two dimensional algorithm, the series converges rapidly. This is done by using the least squares estimators as initial estimates.

Let us define $\hat{\gamma}_{n-1}$ and $\hat{\lambda}_{n-1}$ as the values of $\hat{\gamma}$ and $\hat{\lambda}$ after $n-1$ iterations. It follows that $\hat{\lambda}_n$ and $\hat{\gamma}_n$ are estimated by solving the vector equation

$$\begin{pmatrix} \hat{\gamma}_{\infty,n} \\ \hat{\lambda}_n \end{pmatrix} = \begin{pmatrix} \hat{\gamma}_{\infty,n-1} \\ \hat{\lambda}_{n-1} \end{pmatrix} - \begin{bmatrix} \hat{v}_{11,n-1} & \hat{v}_{12,n-1} \\ \hat{v}_{12,n-1} & \hat{v}_{22,n-1} \end{bmatrix}^{-1} \begin{bmatrix} \hat{g}_{1,n-1} \\ \hat{g}_{2,n-1} \end{bmatrix}$$

Application

In a study conducted, 20 patients who were receiving an analgesic to relieve headache pain at Konfo Anokye Teaching Hospital, Kumasi had the following recorded relief times (in hours):

1.1, 1.4, 1.3, 1.7, 1.9, 1.8, 1.6, 2.2, 1.7, 2.7, 4.1, 1.8, 1.5, 1.2, 1.4, 3.0, 1.7, 2.3, 1.6, 2.0

At this stage, we observe a simple graphical solution method for estimating the parameters of a Weibull death density function. Figure 1 is the plot of $\log_e t_i$ against $\log_e \log_e \left[\frac{1}{S(t)}\right]$ from table 1

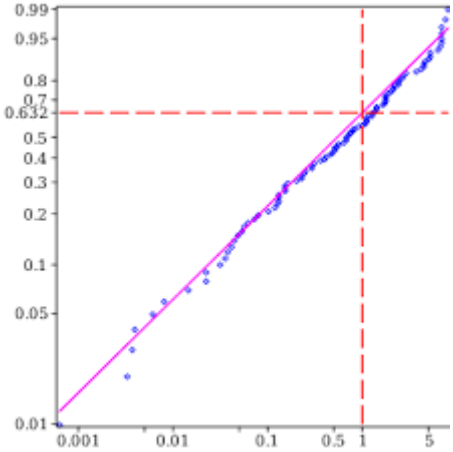


Figure 1 Weibull plot of patient's headache pain relief times

$\log_e t_i$	$\log_e \log_e \left[\frac{1}{S(t)}\right]$
0.10	-3.02
0.18	-2.30
0.26	-1.87
0.34	-1.55
0.40	-1.09
0.47	-0.90
0.47	-0.73
0.53	-0.58
0.53	-0.44
0.53	-0.30
0.59	-0.17
0.59	-0.04
0.64	0.09
0.69	0.23
0.79	0.36
0.83	0.51
0.99	0.67
1.10	0.86
1.41	1 11

Table 1

Weibull plot of the data collected from Konfo Anokye Teaching Hospital is obtained from table 1 which gives the logarithms of the ordered relief times of the patients and the logarithms of the logarithms of the inverse of the cumulative function. This plot is shown in figure 1 and the points do not perfectly lie on a straight line, the straight line fit would be perfectly fit except for the last three points. The least square estimators $\tilde{\gamma}$ and $\tilde{\lambda}$ of γ and λ respectively are obtained by the usual least square procedure. If we let $y_i = \log_e \log_e \left[\frac{1}{S(t)}\right]$ and $x_i = \log_e t_i$ then

$$\tilde{\gamma} = \frac{\sum_{j=1}^{20}(x_i - \bar{x})(y_i - \bar{y})}{\sum_{i=1}^{20}(x_i - \bar{x})^2}$$

And

$$\log_e \tilde{\lambda} = \bar{y} - \tilde{\gamma}\bar{x}$$

From this deduction, $\tilde{\gamma} = 3.15$ and $\tilde{\lambda} = 0.09$, and the estimated mean relief time is

$\tilde{\mu} = \hat{\lambda}^{-1/\hat{\gamma}}\Gamma(1+\hat{\gamma}) = 1.92$ hours. This agrees favorably with results of the Newton Raphson least square procedure below

Newton Raphson least square procedure

Starting with initial value $\hat{\gamma} = 0.5$, the Newton Raphson method applied to equation (3) gives

$$\hat{\gamma} = 2.79$$

And applying to equation (1) yields

$$\hat{\lambda} = (\frac{\sum_{i=1}^{n} t_i^{\hat{\gamma}}}{n})^{-1} = 0.2$$

The estimated mean relief time $\hat{\mu} = \hat{\lambda}^{-1/\hat{\gamma}}\Gamma(1+\hat{\gamma}) = 1.89$ hours.

Discussion

The source of pain varies from one patient to another but pain is complex entity that controls physical, mental and behavioral conditions. Many deaths are attributed to severe pains and the intensity of pain follows exponential distributions. In extreme case, Weibull Distribution depicts the pattern of severe pain the study of 20 patients the received analgesic to relief pain had estimated mean relief time from pain in 1.92 hours. The shape Weibull parameter that defined the behavior of patient's failure rate is 3.15. the scale parameter that determines the propensity of the patient's pain in Weibull distribution is 0.09

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