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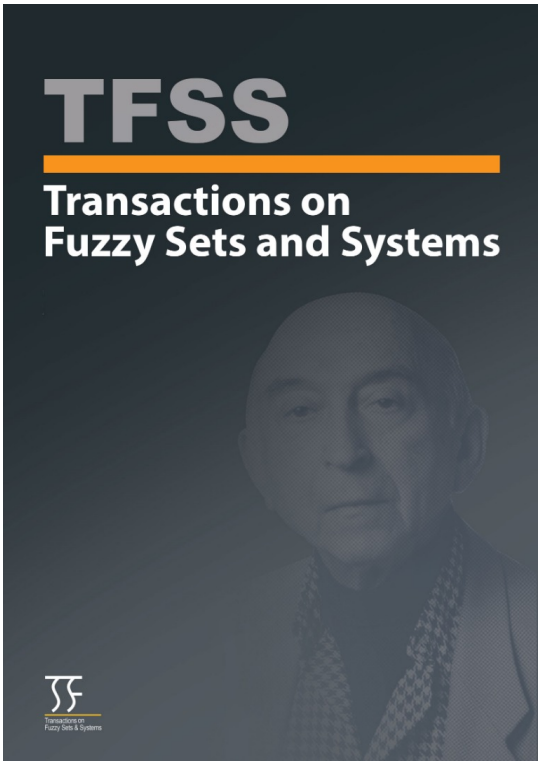

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Shannon Entropy Analysis of Serum C-Terminal Agrin Fragment as a Biomarker for Kidney Function: Reference Ranges, Healing Sequences and Insights

Mehmet Şengönül*

Abstract. This article focuses on evaluating the success or failure of kidney transplantation using Shannon entropy, fuzzy sets, and Scaf. The data for Scaf references used in this study for both healthy individuals and kidney transplant recipients have been collected from the relevant literature. For both groups, Scaf's Shannon entropy values have been calculated using an appropriate probability density function and formulation, and sequences have been generated for CAF and Scr biomarkers from entropy values, with findings interpreted. These sequences are called healing sequences. A case study demonstrating whether the transplant procedure was successful or unsuccessful was presented using sequences that we refer to as healing sequences. In this context, the utilization of mathematical tools such as fuzzy sets, Shannon entropy, and reference intervals becomes evident. These tools provide a systematic and quantitative approach to assessing the outcomes of kidney transplantation. By leveraging the principles of Shannon entropy, we gain insights into the degree of unpredictability and fuzziness associated with biomarker values, which can be indicative of the transplant's success. Furthermore, the concept of healing sequences provides a valuable framework for tracking the progression of patients post-transplantation. By monitoring changes in CAF and Scr biomarkers over time, healthcare professionals can make informed decisions and interventions to ensure the well-being of kidney transplant recipients.

AMS Subject Classification 2020: 03E72
Keywords and Phrases: Healing sequence, Shannon entropy, Fuzzy set, Renal transplant, Biomarker.

1 Introduction

In recent years, a rapid increase in the applications of fuzzy sets and fuzzy logic across various disciplines has been observed. One of these disciplines is medicine. For instance, in medical diagnostics [1], ECG interpretation [2] and [3], image processing [4], pacemaker control [5], anesthesia control [6], lung disease control [7] fuzzy sets or fuzzy logic have been widely used. Similarly, when we look at the literature, it will be seen that Ahmad et al., in [8], have used fuzzy logic-based systems to monitor chronic kidney diseases. Furthermore, Hamedan [9] and Norouzi [10] have used fuzzy expert systems to predict kidney diseases and predicting renal failure progression in chronic kidney disease, respectively. From another point of view, the ECG signal process was investigated by Czogala [11]. In [12] Rakkus, in [13] Tunç and Bloch[14] followed a different approach to medicine using fuzzy sets. Generally, when examining the previous studies related to this field, the severity of disease symptoms is transformed into fuzzy clusters, and with the assistance of

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expert systems, tasks such as sequencing during organ transplantation and determining the nature of the disease is addressed [15].

A literature review has revealed that there are either very few or no scientific studies specifically focusing on the compatibility or incompatibility of transplanted organs within the context of organ transplantation. This area has remained an open problem. As a starting point, Kılınç [16] has conducted research on patients with systemic lupus erythematosus, providing information about the condition of the tissue using entropy. However, the health status of an organ has not been investigated by Kılınç.

The scientific innovation, in this study, is that after kidney transplantation it is the application of Shannon entropy for the purpose of analyzing Serum C-Terminal Agrin Fragment (Scaf) as a biomarker to evaluate kidney function. While the use of biomarkers in clinical research and medical applications is increasing, the specific application of Shannon entropy to Scaf interval is a new approach in this study. Researchers can assess the degree of impairment in kidney function by calculating the Shannon entropy values of Scaf intervals for both healthy individuals and kidney transplant recipients. The findings indicate that the Shannon entropy of Scaf values is an indicator of the success or failure of kidney transplantation. This innovative use of Shannon entropy adds new insights to the assessment of kidney function using Scaf as a biomarker, potentially contributing to advanced diagnostic and treatment approaches in the field of nephrology. Thus, we believe that employing Shannon entropy in conjunction with a biomarker like Scaf can yield more insights into the health status of kidney transplant patients and enable more effective monitoring of kidney functions. It is important to note that the choice of using Shannon entropy is specific to this study, and while other types of entropy could also be used; the results should be evaluated accordingly.

2 Preliminaries

At the core of our research are reference intervals, fuzzy sets, and Shannon entropy. Therefore, in the following subsections, we will provide explanations of kidney reference intervals and subsequently, achieve the main goal of the study, we will define fuzzy sets and Shannon entropy.

2.1 References Intervals

Biomarkers are used to provide information about a biological condition, in clinical research and medical practice for diagnostic, prognostic, and therapeutic purposes. Biomarkers can include molecules, genes, cells, or physiological functions that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions [17]. In addition to its wide use as a biomarker associated with neuromuscular junction (NMJ) dysfunction [18], C-terminal agrin fragment (CAF) has also been utilized by Yu et al. as a biomarker to evaluate kidney function after kidney transplantation [19]. Scaf consists of the C-terminal fragment of agrin, a protein secreted from kidney glomeruli. Agrin is an important protein for the formation and maintenance of the glomerular filtration barrier in the kidney. Scaf is a fragment of agrin that is released into circulation as a result of protein breakdown. As mentioned above, SCAF has been considered a promising biomarker for the evaluation of kidney function in recent years. Based on medical research, it has been demonstrated that when the kidney glomeruli are damaged, Scaf levels increase [20]. Therefore, biomarkers have great importance for the early diagnosis and treatment of significant health problems such as chronic kidney disease (CKD). Here are some scientific papers about Serum C-Terminal Agrin Fragment (Scaf) as a biomarker for evaluating kidney function [19, 18, 20]. These papers investigate the utility of Scaf as a biomarker for evaluating kidney function in various patient populations, highlighting its potential in clinical applications for the diagnosis, prognosis, and monitoring of kidney disease.

2.2 Fuzzy Sets

The following sentence emphasizes that medical data is a very rich source for fuzzy sets theory.

"Everything in medicine is fuzzy [21]."

Fuzzy sets are mathematical sets in which each element is defined by a certain degree of uncertainty. Considering an interval [a, b], where a and b are real numbers, it may initially seem that there is no specific uncertainty associated with the elements within this interval. However, this assumption may not reflect the reality. Therefore, a membership function can be used to provide a certain degree of uncertainty for each element in the interval [a, b]. This function, known as the membership function, expresses the degree of membership of a particular element in the interval. More formally, a fuzzy set is defined as follows:

Let $\mathscr{X}$ be a nonempty crisp set, $\mathbb{R}$ and $\mathbb{N}$ for the set of all real and natural numbers, respectively. According to Zadeh, a fuzzy subset of $\mathscr{X}$ is a nonempty subset $\{(x, u(x)) : x \in \mathscr{X}\}$ of $\mathscr{X} \times [0,1]$ for some function $u : \mathscr{X} \to [0,1]$, [22]. Consider a function $u : \mathbb{R} \to [0,1]$ as a subset of a nonempty base space $\mathbb{R}$. If there exist reference functions L and R and scalars α and β, then a continuous fuzzy number (or fuzzy set) u can be represented in the $L-R$ form, where the membership function $u(x)$ of u, is defined as

$$u(x) = \begin{cases} L\left(\frac{\lambda - x}{\alpha}\right), & x \in [\lambda - \alpha, \lambda) \\ R\left(\frac{x - \lambda}{\beta}\right), & x \in [\lambda, \lambda + \beta] \end{cases} . \tag{1}$$

The notation $\lambda \in \mathbb{R}$ is called the mean value of u, α and β are called the left and right spreads, respectively. The support of u is stated as an interval $[\lambda - \alpha, \lambda + \beta]$. If take $L(x) = R(x) = 1 - x$ then the graphic shape of the membership of fuzzy set u will be triangular shape which is mostly used in the application of fuzzy sets [12]. In this study, we will also use a triangular membership functions.

2.3 Shannon Entropy

In the fuzzy set theory, measuring the degree of fuzziness of a fuzzy set is an important aspect, and various methods have been developed to determine it. Initially, it was believed that the degree of fuzziness could be quantified as the distance between a fuzzy set and its nearest non-fuzzy set. However, this method was later replaced by the use of entropy as a measure of fuzziness [23] and [24]. Thus, what exactly is entropy and how is it used to measure the fuzziness of a fuzzy set? The answer to this question is given as "Entropy is an information theory measure that quantifies the amount of uncertainty or unpredictability in a given set of data." In the context of fuzzy set theory, entropy is used to measure the degree of fuzziness of a fuzzy set by taking into account the membership values of the set's elements. Essentially, the higher the entropy value, the greater the degree of fuzziness of the set. Therefore, entropy provides a useful tool for evaluating the degree of fuzziness in fuzzy sets, which in turn can be used in a variety of applications, such as decision-making and pattern recognition. The entropy is defined as follows:

Let $u \in \mathscr{F}$ and $u(x)$ be the membership function of the fuzzy set u and consider the function $H : \mathscr{F} \to \mathbb{R}^+$, where $\mathscr{F}$ denotes all fuzzy sets on real numbers set.

If the function H satisfies the following conditions, then H is called an entropy function [25]:
(i) $H(u) = 0$ iff u is crisp set,
(ii) $H(u)$ has a unique maximum, if $u(x) = \frac{1}{2}$, for all $x \in \mathbb{R}$
(iii) For $u, v \in \mathscr{F}$, if $u(x) \leq v(x)$ for $u(x) \leq \frac{1}{2}$ and $u(x) \leq v(x)$ for $u(x) \geq \frac{1}{2}$ then $H(u) \geq H(v)$,
(iv) $H(u^c) = H(u)$, where u^c is the complement of the fuzzy set u.
Let's suppose that the function $h : [0,1] \to [0,1]$ satisfies the following properties:

1. Monotonically increasing at $[0, \frac{1}{2}]$ and decreasing $[\frac{1}{2}, 1]$,

2. $h(x) = 0$ if $x = 0$ and $h(x) = 1$ if $x = \frac{1}{2}$.

The function h is the called entropy function and the equality $H(u(x)) = h(u(x))$ holds for $x \in \mathbb{R}$. Some well-known entropy functions are given as follows:

$h_1(x) = 4x(1-x)$, $h_2(x) = -x\ln x - (1-x)\ln(1-x)$, $h_3(x) = \min\{2x, 2-2x\}$ and

$$h_4(x) = \begin{cases} 2x, & x \in [0, \frac{1}{2}] \\ 2(1-x), & x \in [\frac{1}{2}, 1] \end{cases}.$$

Note that the function h_1 is the logistic function, h_2 is the called Shannon function and h_3 is the tent function.

The probability density function (PDF) for a continuous random variable defined on the interval $[a, b]$ is a non-negative function $p(x)$ such that the integral of $p(x)$ over the entire interval equals 1. In other words, for any subset A of the interval $[a, b]$, the probability of the random variable taking a value in S is given by the integral of over A. Mathematically, this can be expressed as follows [24]:

$$0 \leq \int_{x \in A} p(x)dx \leq 1 \tag{2}$$

The PDF can be used to determine the probability of the random variable taking on a value in any subset of $[a, b]$, and can also be used to calculate expected values, variances, and other statistical properties of the random variable.

If $p(x)$ is any probability density function then the Shannon entropy of $p(x)$ is equal to [26]:

$$H = -\int_{x \in (-\infty, \infty)} p(x)\log_2 p(x)dx. \tag{3}$$

Let us suppose that $u(x)$ be any triangular membership function of fuzzy set u over a real numbers interval $[a, b]$ and

$$\Delta = \int_{x \in Supp\ u} u(x)dx, \tag{4}$$

where the notation $Supp\ u$ is $Supp\ u = \{x : u(x) \geq \lambda, \lambda \in [0, 1]\}$. Then the function

$$P(x) = \frac{1}{\Delta}u(x) \tag{5}$$

is satisfy the conditions of probability density functions. After that, in the following calculations, the function $P(x)$ will be considered the probability density function on the interval $[a, b]$ and the interval $[a, b]$ will be any interval of biomarkers for kidney diseases. Thus the Shannon entropy value on the interval $[a, b]$ will be equal to

$$H_{[a,b]} = -\int_{x \in Supp\ u} P(x)\log_2 P(x)dx. \tag{6}$$

Since Shannon's entropy can be thought of as the measure of "information content" in a variable, in the following section and next section, we will compare the Shannon entropy values of CAF(pM), Scr(μmol/l) and CysC (mg/l) obtained for healthy men and women in different age ranges.

Let u and v be two fuzzy set on any crisp set X. Then the Koczy similarity [27] of fuzzy sets u and v is defined as follows:

$$S(u, v) = \frac{1}{1 + d(u, v)} \tag{7}$$

where $d(u, v) = \max\limits_{i=1,2,3}\{|u_i - v_i|\}$ and according to (1) the u_1, u_2, u_3, v_1, v_2 and v_3 are $u_1 = \lambda_1 - \alpha_1$, $u_2 = \lambda_1$ and $u_3 = \lambda_1 + \beta_1$, $v_1 = \lambda_2 - \alpha_2$, $v_2 = \lambda_2$ and $v_3 = \lambda_2 + \beta_2$. Let $(H_n^i) = \left(-\int_{x \in (-\infty, \infty)} P_n(x)\log_2 P_n(x)dx\right)$,

$(n \in \mathbb{N})$ be the entropy sequence of the i^{th} biomarker of a patient who has undergone a kidney transplant and H^i_{both} be the entropy value calculated for healthy male or female individuals according to i^{th} biomarker. Let's modify the expression given in (7) to provide the following definition.

Definition 2.1. The sequence (H^i_n) is called healing sequence according to i^{th} biomarker that is $i \in \{CAF, Scr, Cys\}$, another word, if i is one of the CAF, Scr, or Cys. Let

$$\lim_n S(H^i_{both}, H^i_n) = \frac{1}{1+\lim_n d(H^i_{both}, H^i_n)} = \begin{cases} \text{Successful transplant}, & \text{if } \lim_n S(H^i_{both}, H^i_n) \in (\frac{1}{2}, 1] \\ \text{Unsuccessful transplant}, & \text{if } \lim_n S(H^i_{both}, H^i_n) \in [0, \frac{1}{2}] \end{cases}. \tag{8}$$

The limit value given in (8) is called the success of transplantation.

It may not always be possible to obtain a sequence using the entropy values obtained for a biomarker. In this case, using a sequence that has terms close in value to the terms of the obtained entropy sequence can be a solution. The (H^i_n) sequences used here will be taken as a sequence of real numbers that are approximately equal to the terms of the actual entropy sequence. As an example of the use of Definition 2.1, we will give the following case study:

3 A Case Study

In the [19], the intervals of serum levels of biomarkers among healthy subjects of different age and sex groups are given by Yu et al. in Table 1 and in Table 2. In this study the valuable data which obtained by Yu et al. will play a fundamental role.

Table 1: Serum levels of biomarkers among healthy subjects of different age and sex groups

Age of Groups	Gender	Numbers	CAF (pM)	Scr(μumol/l))	Sys C(mg/l)
18-34 Years	Male	25	131.2 ±71.6	110.6 ± 11.8	0.78 ±0.10
	Female	29	120.3 ± 56.1	89.3 ± 7.0	0.70 ± 0.09
	Both	54	125.3 ±63.3	99.2 ± 14.3	0.74 ± 0.10
35-49 Years	Male	25	138.6 ± 34.8	104.8 ± 13.7	0.77 ± 0.08
	Female	31	117.5 ±44.6	82.7 ±9.8	0.65 ± 0.10
	Both	56	126.9 ± 41.5	92.6± 16.0	0.70 ± 0.11
50-64 Years	Male	25	149.1±49.8	108.6 ±13.3	0.91± 0.22
	Female	19	202.6± 42.9	94.7 ± 11.3	0.82 ± 0.15
	Both	44	172.2 ± 53.6	102.6 ± 14.2	0.87 ± 0.20
≥65 Years	Male	22	154.1 ± 47.3	112.0 ± 12.6	1.09± 0.32
	Female	24	192.3 ± 53.3	91.8 ±13.7	0.91 ± 0.14
	Both	46	174.1 ± 53.6	101.5 ±16.5	1.00± 0.26

In this paper continuous data were expressed as mean ± standard deviation (SD) or median (minimum; maximum). That is, the means of the notation $a \pm b$ is the real number a is denotes arithmetic mean and the real number b is denotes standard deviation. In our calculations by using $a \pm b$ we will obtain support of fuzzy sets and these supports will denote $[a-b, a+b]$.

Again, in [19], Yu et al. have observed that time course changes in Serum CAF, Creatinine, eGFR (CKD-EPI), Cystatin C and NGAL in patients undergoing kidney transplantation and these changes are given in Table 2. If we compare the data in Table 1 and Table 2, we can observe that there is a certain variation

Table 2: Time course changes in serum CAF, creatinine, eGFR (CKD-EPI), cystatin C and NGAL in patients undergoing kidney transplantation.

	Before Tx	1 day after	2 days after	6 months after
Serum CAF (pM)	921.7 (618.1, 1508.8)	360.4 (85.9, 1291.3)*	164.1 (6.8, 977.3)*	164.8 (74.3, 338.0)*
Creatinine (lmol/l)	845.5 (476.0, 1856.0)	365.0 (115.0, 1254.0)*	204.5 (80.0, 1275.0)*	144.0 (67.0, 320.0)*
eGFR (ml/min/173 m2)	5.8 (2.6, 11.1)	17.4 (4.2, 58.2)*	35.2 (4.2,8 8.3)*	52.6 (20.1, 121.7)*
Cystatin C (mg/l)	5.49 (1.00, 12.00)	2.00 (1.00, 4.18)*	2.00 (1.00, 4.47)*	1.42 (0.77, 3.60)*
NGAL (ng/ml)	911.0 (305.3, 1783.2)	201.1 (71.0, 654.1)*	158.9 (52.5, 994.4)*	93.1 (11.9, 186.5)*

in the values. However, they do not provide us with information about the uncertainties contained in these variations. Therefore, it is necessary to calculate their entropies to determine these uncertainties. This will be performed in this study. If you need to more information about the notations in Table 1 and Table 2, you can see [19].

4 The Entropies of Serum CAF, Creatinine and Cystatin C in Patients Undergoing Kidney Transplantation

In this section, the biomarker intervals will convert into fuzzy sets according to age and sex using appropriate membership functions and determined their entropies values. Afterwards, obtained entropy values will be evaluated based on their magnitudes to determine the chaotic state contained in the biomarker intervals.

According to Table 1, CAF values for individuals who are male and aged between 18-34 are given in the interval $[59.6, 202.8]$. According to this, for males and aged between 18-34, the membership function of the CAF, $CAF_{(18-34)M}(x)$, is equal to

$$CAF_{(18-34)M}(x) = \begin{cases} \frac{x-59.6}{131.2-59.6}, & x \in [59.6, 131.2] \\ \frac{202.8-x}{202.2-131.2}, & x \in (131.2, 202.8] \\ 0, & \text{otherwise} \end{cases}. \tag{9}$$

If we consider equality (4) then we see that $\Delta = 71.6$. From equality (5) we obtain that the probability density function of CAF for individuals who are male and aged between 18-34 as follows:

$$P_{CAF(18-34)M}(x) = \frac{1}{\Delta} CAF_{(18-34)M}(x) = \begin{cases} \frac{x-59.6}{5126.56}, & x \in [59.6, 131.2] \\ \frac{202.8-x}{5126.56}, & x \in (131.2, 202.8] \\ 0, & \text{otherwise} \end{cases}. \tag{10}$$

The function $P_{(18-34)M}(x)$ given in (11) satisfies the conditions of the probability density function which it given in (2). Thus, the entropy of the CAF for individuals who are male and aged between 18-34 is computed as follows:

$$H_{CAF(18-34)M} = -\int_{x \in Supp\ CAF(18-34)M} P_{(18-34)M}(x) \log_2 P_{(18-34)M}(x) dx = 6.88324.$$

Similarly to above, since $\Delta = \frac{1}{56.1}$;

$$P_{CAF(18-34)F}(x) = \frac{1}{\Delta} CAF_{(18-34)F}(x) = \begin{cases} \frac{x-64.2}{3147.21}, & x \in [64.2, 120.3] \\ \frac{176.4-x}{3147.21}, & x \in (120.3, 176.4] \\ 0, & \text{otherwise} \end{cases}. \tag{11}$$

and the Shannon entropy of the CAF for individuals who are female and aged between 18-34 is

$$H_{CAF(18-34)F} = -\int_{x\in Supp\ CAF(18-34)F} P_{(18-34)F}(x)\log_2 P_{(18-34)F}(x)dx = 6.53128.$$

For individuals who are male and female and aged between 18-34 according to data of [19], similar calculations can made for Scr(μumol/l) and Sys C(mg/l), it can be seen that $H_{Scr(18-34)M} = 4.28206$, $H_{Scr(18-34)F} = 3.5287$. The $H_{Cys(18-34)M} = -2.60058$ and $H_{Cys(18-34)F} = -2.75258$. The Shannon entropies of Scr(μumol/l) and Sys C(mg/l) can be calculated for other age groups with similar calculations. These are given in Table 3 as a table. The term in the expression 6.46551 represents a very small imaginary component, which may

Table 3: Shannon entropy of biomarkers among healthy subjects of different age and sex groups

Age of Groups	Gender	Shannon Entropy of CAF (pM)	Shannon Entropy of Scr(μumol/l)	Shannon Entropy of Sys C(mg/l)
18-34 Years	Male	6.88324	4.28206	-2.60058
	Female	6.53128	3.5287	−2.75258
	Both	6.70548	4.55929	-2.60076
35-49 Years	Male	5.84236	4.49745	-2.92251
	Female	3.81713	4.01413	-2.70018
	Both	6.09639	4.72135	-2.46308
50-64 Years	Male	4.50536	4.4547	-1.46308
	Female	6.14425	3.63403	-2.01562
	Both	6.46551	4.54917	-1.60058
≥65 Years	Male	6.28512	4.3767	-0.922509
	Female	6.45741	4.49745	-2.11515
	Both	6.46551	4.76574	-1.22207

arise due to rounding errors or other computational reasons. Therefore, the real part of the result should be considered as 6.46 to evaluate the Shannon entropy. This is very important: Entropy is a concept that measures the uncertainty of a probability distribution. If a negative Shannon entropy is obtained, it is indicated that this may be due to the characteristics of the probability distribution. For example, if the sum of probabilities is not equal to 1 or if there is an inverse relationship between the probabilities, a negative entropy can be obtained. This indicates that the distribution is regular and predictable, and the information content is low. If the entropy value is 0, the distribution becomes completely predictable, and there is no uncertainty.

In some cases, a negative entropy result can be a realistic outcome. For example, if a group of items in a dataset exhibits a more distinct characteristic than all other items, then the probability distribution for that group may have a lower entropy and this entropy could be negative. Therefore, negative entropy in the table may not be perceived as a problem.

5 The Shannon Entropy of Reference Ranges and Healing Sequences for Serum c-terminal Agrin Fragment Used as a Biomarker for Kidney Function in Kidney Recipients

In the [19] (see, Table 3), the values of CAF, Scr and $Cys\ C$ have given as a table for the baseline characteristics of kidney transplants. According to Table 3. of Yu et al., Serum CAF (pM) takes the value in the interval $[618.1, 1508.8]$ before Tx, takes the value of $[85.9, 1291.3]$ after one days, takes the value of $[6.8, 977.3]$ after two days and the takes value of [74.3, 338.0] after six months. Similarly, Creatinine (μmol/l) takes the value of in the interval [476.0, 1856.0] before Tx, the value of $[115.0, 1254.0]$ after one days, the value of

$[80.0, 1275.0]$ after two days and the value of $[67.0, 320.0]$ after six months and Cystatin C (mg/l) takes the value of in the interval $[1.00, 12.00]$ before Tx, the value of $[1.00, 4.18]$ after one days, the value of $[1.00, 4.47]$ after two days and the value of $[0.77, 3.60]$ after six months, where Tx denotes transplantation.

Similarly to Section 4, we can construct membership functions of the Serum CAF (pM), Creatinine, Cystatin C after we can obtain probability density functions and using these functions we can calculate Shannon entropy of kidney recipients.

According to data of [19], Serum CAF (pM) takes the value of in the interval [618.1, 1508.8] before Tx. According to this, the membership function Serum CAF (pM) before Tx, $CAF_{Tx}(x)$, is equal to

$$CAF_{Tx}(x) = \begin{cases} \frac{x-618.1}{1063.45-618.1}, & x \in [618.1, 1063.45] \\ \frac{1508.8-x}{1508.8-1063,45}, & x \in (1063, 45, 1508.8] \\ 0, & \text{otherwise} \end{cases}. \tag{12}$$

If we consider equality (4) then we see that $\Delta = 445.35$. From equality (5) we obtain that the probability density function of CAF for individuals who are male and aged between 18-34 as follows:

$$P_{CAF_{Tx}}(x) = \frac{1}{\Delta} CAF_{Tx}(x) = \begin{cases} \frac{x-618.1}{198336,6225}, & x \in [618.1, 1063.45] \\ \frac{1508.8-x}{198336,6225}, & x \in (1063.45, 1508.8] \\ 0, & \text{otherwise} \end{cases}. \tag{13}$$

The function $P_{CAF_{Tx}}(x)$ with given in (13) satisfies the conditions of the probability density function which is given in (2). Thus, the entropy of the CAF_{Tx} is computed as follows:

$$H_{CAF_{Tx}} = -\int_{x \in Supp\ P_{CAF_{Tx}}} P_{CAF_{Tx}}(x) \log_2 P_{CAF_{Tx}}(x) dx = 9.52014.$$

Similarly to above, the entropy values of the CAF, Scr and Sys are given in Table 4 .

Table 4: Healing entropy values for various biomarkers

	The Entropy Values according to Days after Transplantation				
Biomarkers	1.Day	2. Day	...	180.Day	...
CAF	9.95664	9.94393	...	7.7641	...
Scr	9.8749	9.9441	...	7.70434	...
Cys	1.39037	9.94414	...	1.22215	...

Now, we can determine the success of the transplantation of the kidney using the healing sequence which it given in Definition (2.1).

Taking into account the data in Table 4, we can write the healing sequences of CAF as $(H_n^{CAF}) = (6.68 + 3.27e^{(-0.2116(n-1))})$ for kidney transplantation. The value of H_{both}^{CAF} is 6.4332 by taking the arithmetic average of the sum of the "both" values of CAF in Table 3. In this case,

$$\frac{1}{2} < \lim_n S(H_{both}^{CAF}, H_n^{CAF}) = \frac{1}{1 + \lim_n d(6.4332, H_n^{CAF})} \leq 1, \tag{14}$$

where d denotes the natural metric on real numbers set.

Again, taking into account the data in Table 4, we can write the healing sequences of Scr as $(H_n^{Scr}) = (4.55 + (9.94 - 4.55)/(1 + (n-1)/59)$ for kidney transplantation. The value of H_{both}^{Scr} is 4.642 by taking the arithmetic average of the sum of the "both" values of Scr in Table 3. In this case,

$$\frac{1}{2} < \lim_n S(H_{both}^{Scr}, H_n^{Scr}) = \frac{1}{1 + \lim_n d(4.642, H_n^{Scr})} \leq 1. \tag{15}$$

Due to Definition 2.1, the meaning of (14) and (15) are that the kidney transplant is successful according to healing sequences $(H_n^{CAF}) = (6.68 + 3.27e^{(-0.2116(n-1))})$ and $(H_n^{Scr}) = (4.55 + (9.94 - 4.55)/(1 + (n-1)/59)$. Furthermore, the (14) and (15) give us the result that the transplants of kidney transplant recipients, who were the subject of the research of Yu et al. in [19], were successful.

It is note that the healing sequence is obtained differently for each biomarker. These sequences will also vary from patient to patient. Therefore, a healing sequence should be obtained according to the patient under observation. Sometimes it may not be possible to obtain a healing sequence.

A similar calculation can also be made for Sys. However, I could not obtain an improvement sequence for Sys. I will address this as a separate problem in another study.

6 Discussions

We will consider full part and three decimals of the Shannon entropy values of the biomarkers CAF, Scr and Cys C which they have given in Table 3 and are discussed as follows:

6.1 Discussions for Table 3

The discussions can be summarized as follows:

1. For the age group of 18-34 years, the Shannon entropy value provides valuable insights into the uncertainty associated with the CAF (pM) interval, as indicated in Table 1. The entropy value, being significantly greater than 1 for all sex types, suggests that there is a substantial amount of variability in CAF levels within this age range. This variability could be attributed to various factors such as individual differences, lifestyle choices, and underlying health conditions.

   A Shannon entropy value greater than 1 implies that the distribution of CAF levels within the specified age group is widely spread, leading to a higher degree of uncertainty. In practical terms, this means that within the 18-34 age range, kidney transplant patients may exhibit diverse CAF concentrations, making it challenging to draw definitive conclusions solely based on these values. The observation of high entropy underscores the importance of further investigation to understand the underlying factors contributing to this variability in CAF levels. It also emphasizes the need for additional studies involving larger and more diverse patient populations to validate these findings and establish more robust reference ranges for CAF in kidney transplant recipients. Moreover, healthcare professionals should be cautious while interpreting CAF levels in young adult patients, considering the significant uncertainty associated with the biomarker's values in this specific age group. The use of complementary diagnostic tools and the integration of patient-specific data may be essential in making accurate clinical decisions and evaluating kidney function effectively in young kidney transplant recipients.

   In conclusion, the Shannon entropy analysis highlights the considerable uncertainty in CAF levels among kidney transplant patients aged 18-34 years. This finding encourages further research to enhance our understanding of this phenomenon and underscores the importance of personalized and comprehensive approaches when evaluating kidney function in this particular age group.

2. For the age group of 18-34 years, the Shannon entropy values for the intervals of Scr (μmol/l) and Sys C (mg/l) in kidney transplant patients (Table 1) reveals a substantial degree of uncertainty across all sex types. These high entropy values suggest considerable variability in serum creatinine and systemic C levels within this specific age range. Such pronounced uncertainty underscores the complexity of kidney function in young transplant recipients, emphasizing the importance of careful monitoring and tailored medical interventions to address the diverse needs and responses observed in this demographic. Further research and analysis of these biomarkers' fluctuations can potentially lead to enhanced strategies

for managing kidney transplant patients within this age category and improving their overall health outcomes.

3. For the 35-49 years, the Shannon entropy value indicates that the interval of CAF(PM), which is given Table 1, contains a large amount of uncertainty as it is much greater than 1 for all sex types.

4. In the 35-49 years age group, the Shannon entropy value reveals a notable level of uncertainty within the intervals of Scr (μumol/l) and Sys C (mg/l), as presented in Table 1, across all sex types. The entropy value, significantly greater than 1, suggests substantial variability in the levels of serum creatinine (Scr) and serum C (Sys C) biomarkers among kidney transplant patients within this specific age range. This finding indicates that kidney function and other related physiological processes represented by these biomarkers exhibit diverse and complex patterns in individuals aged 35-49 years.

   The observed high entropy underscores the importance of carefully monitoring kidney function and related health parameters in this particular age group of kidney transplant recipients. The variability in Scr and Sys C levels may be influenced by various factors, such as lifestyle, comorbidities, and response to immunosuppressive medications. Therefore, healthcare professionals must take these fluctuations into account when designing personalized treatment plans and assessing the overall health status of patients within this age category.

5. In the 50-64 years age group, the Shannon entropy value highlights significant uncertainty within the intervals of CAF (pM), as reported in Table 1, across all sex types. The entropy value, being much greater than 1, suggests substantial variability in the levels of CAF biomarkers in kidney transplant patients within this specific age range. This finding implies that kidney function and neuromuscular junction (NMJ) dysfunction, which the CAF biomarker represents, may exhibit diverse patterns and responses in this demographic.

   The observed high entropy underscores the complexity and heterogeneity of kidney-related health conditions in individuals aged 50-64 who have undergone kidney transplantation. It also emphasizes the need for precise and individualized monitoring and treatment strategies to manage the varying health challenges that may arise in this age category.

6. For the 50-64 years, the Shannon entropy value indicates that the intervals of Scr(μumol/l) and Sys C(mg/l), which are given in Table 1, contains a large amount of uncertainty as it is much greater than 1 for all sex type.

Shannon entropy is generally used as a measure of uncertainty in an information source. If the entropy of CAF or other biomarkers is greater than 1; it usually indicates uncertainty in that source. This may also suggest that the information source is less predictable or more complex. However, this is only a general interpretation and more context are needed for a more accurate interpretation.

6.2 Discussions for Results of Section 5

Considering the insights gained from this section, the initial measurements taken during the early days of kidney transplantation reveal a highly intricate state of kidney function, as indicated by the remarkably high values of entropy. This finding suggests that the biomarkers used to assess kidney function, as reported by Yu and other researchers in [19], exhibit a significant degree of chaos and variability within their respective ranges. The heightened entropy values imply that kidney transplant recipients experience considerable fluctuations and unpredictability in these biomarkers during the immediate post-transplant period.

As patients progress through the post-transplant period and undergo proper medical management, a notable transformation occurs. The once chaotic state of kidney function gradually stabilizes, as reflected

by a decrease in the entropy values over time. This reduction in entropy signifies a trend toward greater regularity and predictability in the levels of biomarkers associated with kidney function.

The decreasing entropy values can be attributed to various factors, such as the healing and recovery process of the transplanted kidney, the adjustment of immunosuppressive medications, and the body's adaptation to the new organ. As the transplanted kidney becomes integrated into the recipient's body and begins to function optimally, the overall dynamics of kidney-related biomarkers tend to stabilize, leading to a less chaotic state.

The observed trend of decreasing entropy over time is promising and reinforces the significance of continuous monitoring and medical intervention during the early phases of kidney transplantation. By closely observing the changes in entropy values and biomarker levels, healthcare professionals can better understand the trajectory of kidney function recovery and identify potential complications or abnormalities that may require timely intervention.

Furthermore, this knowledge could pave the way for refining post-transplant care protocols and developing personalized treatment strategies tailored to individual patients. By promoting the transition from a chaotic to a more stable state of kidney function, healthcare providers can enhance the long-term success of kidney transplantations and improve the overall quality of life for transplant recipients.

In conclusion, the fluctuations in entropy values during the early post-transplant period highlight the complexity and dynamic nature of kidney function. The subsequent decrease in entropy underscores the positive evolution of kidney function over time, offering hope for improved patient outcomes and reinforcing the importance of meticulous monitoring and care throughout the kidney transplantation journey.

6.3 The Disadvantages of This Study

The entropy values, in this calculation, maybe depend

1. to measure devices and individuals,
2. to conditions of the environment,
3. to alimentation of people,
4. results may change from one region to an other region
5. entropy values may depend on the species of the person.

Converting reference ranges to fuzzy sets and calculating Shannon entropy can be used to confirm a diagnostic method or identify a disease. However, these data are only a part of the picture. These data should be considered in conjunction with many other factors such as disease symptoms, medical history, medication use, age, gender and genetic factors.

Therefore, a more comprehensive data analysis is necessary to collect, model, and interpret data more accurately. This analysis may include data mining techniques, artificial intelligence methods, and other mathematical and statistical tools to obtain more comprehensive results. In general, it has been concluded that combining biomarkers such as Scaf with mathematical techniques such as fuzzy sets and Shannon entropy can provide a valuable understanding of the diagnosis and treatment of kidney diseases; advanced research can lead to the development of more effective diagnostic and treatment approaches for kidney diseases.

7 Conclusion

The Shannon entropy, discussed in this article, can be used to measure the disorder in the tissue; high entropy values indicate the disorder is high, while low entropy values indicate that more order. This information

can help machine learning algorithms be more successful in recognition or classification tasks by better understanding of the structure of the tissue.

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References

[1] Rutkowska D, Starczewski A. Fuzzy inference neural networks and their applications to medical diagnosis. In: Szczepaniak PS, Lisboa PJG, Kacprzyk J. (eds.) *Fuzzy systems in medicine*. Heidelberg. Germany: Physica-Verlag HD; 2000. p.503518.

[2] Şengönül M, Kayaduman K, Zararsız Z, Atpınar S. The entropies of the sequences of fuzzy sets and applications of entropy to cardiography. *International Journal of Mathematical Modelling & Computations*. 2016; 6(2): 159-173.

[3] Şengönül M. An application of fuzzy sets to veterinary medicine. *Theory & Applications of Mathematics & Computer Science*. 2016; 6(1): 1-12.

[4] Huang QM, Tong XJ, Zeng S, Wang WK. Digital image resolution and entropy. *2007 International Conference on Machine Learning and Cybernetics, 01.10. 2007*. Hong Kong. China: IEEE, 2007. p.15741577. DOI: https://doi.org/10.1109/ICMLC.2007.4370396

[5] Bardossy A. Blinowska A. Fuzzy reasoning in pacemaker control. In: Szczepaniak PS, Lisboa PJG, Kacprzyk J. (eds.) *Fuzzy systems in medicine*. Heidelberg. Germany: Physica-Verlag HD; 2000. p.451466.

[6] Linkens DA, Abbod MF, Backory JK, Shieh JS. Closed-loop control of anaesthesia using fuzzy logic. In: Szczepaniak PS, Lisboa PJG, Kacprzyk J. (eds.) *Fuzzy systems in medicine.* Heidelberg. Germany: Physica-Verlag HD; 2000. p.467483.

[7] Li X, Zhao Z, Cheng HD. Fuzzy entropy threshold to breast cancer detection. *Information Sciences-Applications.* 1995; 4(1): 49-56. DOI: https://doi.org/10.1016/1069-0115(94)00019-X.

[8] Murugesan G, Ahmed TI, Bhola J, et al. Fuzzy logic-based systems for the diagnosis of chronic kidney disease. *BioMed Research International*. 2022; Article ID 2653665, 15 pages. DOI: https://doi.org/10.1155/2022/2653665

[9] Hamedan F, Orooji A, Sanadgol H, Sheikhtaheri A. Clinical decision support system to predict chronic kidney disease: A fuzzy expert system approach. *International journal of medical informatics.* 2020; 138: 104-134. DOI: https://doi.org/10.1016/j.ijmedinf.2020.104134

[10] Norouzi J, Yadollahpour A, Mirbagheri SA, et al. Predicting renal failure progression in chronic kidney disease using integrated intelligent fuzzy expert system. *Computational and Mathematical Methods in Medicine*. 2016(3):1-9. DOI: https://doi.org/10.1155/2016/6080814

[11] Czogala E, Leski J. Entropy and energy measures of fuzziness in ecg signal processing, In: Szczepaniak PS, Lisboa PJG, Kacprzyk J. (eds.) *Fuzzy systems in medicine*. Heidelberg. Germany: Physica-Verlag HD; 2000. p.227245.

[12] Rakus-Andersson E, Zettervall H. *Different Approaches to Operations on Continuous Fuzzy Numbers.* Warszawa. EXIT Publishing House; 2008.

[13] Çekim Tunç S, Kılınç G, Şengönül M, Kayaduman K. Logistic entropy of bone mineral density at diabetes and nondiabetes and new type visualizations. *Annals of Fuzzy Mathematics and Informatics*. 2022; (24)3: 271-280. DOI: https://doi.org/10.30948/afmi.2022.24.3.271

[14] Bloch I. Fusion of Numerical and Structural Image Information in Medical Imaging in the Framework of Fuzzy Sets . In: Szczepaniak PS, Lisboa PJG, Kacprzyk J. (eds.) *Fuzzy systems in medicine*. Heidelberg. Germany: Physica-Verlag HD; 2000. p.429447.

[15] Taherkhani N, Sepehri MM, Khasha R, Shafaghi Sh. Ranking patients on the kidney transplant waiting list based on fuzzy inference system. *BMC Nephrology*. 2022; 23(1): 1-14. DOI: https://doi.org/10.1186/s12882-022-02662-5

[16] Kılınç G. Logistic Entropy of Trabecular Bone Score in SLE Patients and New Type Visualizations, *Computational and Mathematical Methods in Medicine*, vol. 2022, Article ID 3292249, 8 pages, 2022. DOI: https://doi.org/10.1155/2022/3292249

[17] Clinical Pharmacology&Therapeutics. Commentary: Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. https://doi.org/10.1067/mcp.2001.113989 [Accessed 20 April 2023].

[18] Monti E, Sarto F, Sartori R, et al. C-terminal agrin fragment as a biomarker of muscle wasting and weakness: A narrative review. *Journal of Cachexia, Sarcopenia and Muscle*. 2023; 14(2): 730-744. DOI: https://doi.org/10.1002/jcsm.13189

[19] Yu D, Li HX, Liu Y, et al. The reference intervals for serum c-terminal agrin fragment in healthy individuals and as a biomarker for renal function in kidney transplant recipients. *Journal of Clinical Laboratory Analysis*. 2017; 31(3): e22059. DOI: 10.1002/jcla.22059

[20] Woroniecki RP, Schnaper HW. Progression of glomerular and tubular disease in pediatrics. *Seminars in Nephrology*. 2009; 29(4): 412-424. DOI: https://doi.org/10.1016/j.semnephrol.2009.03.016

[21] Sadegh K, Zadeh AL. The Construction of Fuzziness. In: Seising R, Tabacchi ME (eds) *Fuzziness and Medicine:Philosophical Reflections and Application Systems in Health Care.* Verlag Berlin Heidelberg. Germany: Springer; 2013.

[22] Zadeh LA. Fuzzy sets. *Information and Control*. 1965; 8(3): 338-353. DOI: http://dx.doi.org/10.1016/S0019-9958(65)90241-X

[23] De Luca A, Termini S. A definition of a nonprobabilistic entropy in the setting of fuzzy sets theory. *Information and Control*. 1972; 20: 301-312. DOI: https://doi.org/10.1016/S0019-9958(72)90199-4

[24] Wang WJ, Chui CH. The entropy change of fuzzy numbers with arithmetic operations. *Fuzzy Sets and Systems*. 1999; 103(3): 357-366. DOI: https://doi.org/10.1016/S0165-0114(99)80001-3

[25] Zimmermann HJ. *Fuzzy Set Theory-and Its Applications.* Boston: Kluwer Academic Publishers; 1996.

[26] Good IJ. *The Estimation of Probabilities: An Essay on Modern Bayesian Methods*. Cambridge: The MIT Press Publishing; 1965.

[27] Johanyák ZC, Kovács S. Distance based similarity measures of fuzzy sets. In: *3rd Slovakian-Hungarian Joint Symposium on Applied Machine Intelligence, 2122 January 2005,* Herl'any. Slovakia: Slovak Artificial Intelligence Society; 2005. p.265276.

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