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More Accurate Organ Recipient Identification Using Survey Informatics of New Age Technologies

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ABSTRACT
Organ transplantation is a miraculous achievement for most of the end-stage diseases caused due to organ failure. Providing the organ to the most accurate recipient is always a challenge. The survival prediction of the recipient based on various health and environmental/infrastructural data (e.g.: live traffic) is not considered in the current selection algorithms, thus reducing the healthy lifespan of the recipient. The objective of this research is to do an in-depth analysis of the historical transplantation data for the organ (kidney) and figure out statistical evidence of various parameters which are affecting the survival time of the organ recipient. Both univariant and covariant analysis (impact in conjunction with other varying parameters) of these data parameters are studied. The result of this study was further analyzed to identify such parameters which vary frequently with time but also impact the predicted survival curve of the recipient. The research focuses on the benefit of new-age technology such as IoT in accurately predicting the most suitable recipient with a longer survival curve. The research ultimately wants to bring out an efficient recipient identification mechanism for organ procurement and transplantation

Keywords: *HLA matching algorithm, Internet of Things, Organ Procurement, Organ Transplantation, Traffic Control.*

1. INTRODUCTION

Organ transplantation is considered the optimal lifesaving approach for most of the end-stage diseases caused due to the malfunctioning of human body organs. The latest advancement in the medical field has greatly increased the success rate of transplantation. A patient without receiving a transplant has only half the survival chance of a person who procures a graft from a cadaveric and has only one-fourth the survival chance than a person who receives an organ from a living donor [1]. Patients who receive organ transplantation, have on an average increased survival chance of 7 years than those patients who are on the waiting list for organ allocation. Effective algorithmic support for decision-making can help in selecting the recipient whose transplantation can increase the survival years [2]. Even though HLA matching is considered as the key factor in deciding the correct recipient from the waiting list, various other factors also have an impact on increasing the median survival time among the recipients who are on the top priority list [3]. The traditional and non-traditional risk factors like age of the donor and the recipient, Body Mass Index (BMI), Cold Ischemia Time (CIT), Warm Ischemia Time (WIT), Duration to the reach transplant center, comorbidities of the recipient are other factors which will influence the success of the transplantation procedure [4]. This research is limited to the patients suffering from End Stage Renal Diseases and on the follow-up data of Kidney transplantation, who has received allograft from both living and deceased donors [5]. This research work focuses on the impact of each of these factors using various statistical analysis tools and then developing a system to reduce the impact of those factors on survival time. Kaplan-Meier model and Cox proportional hazards regression model are extensively used in this research work. The study has been done using the follow-up data collected by the United Network for Organ Sharing (UNOS) performed for Kidney transplantation [6].

Survival rates after transplantation have greatly increased from the early years due to the improvement achieved in the medical fields. Advancements include immunosuppression and antimicrobial agents to reduce the rejection occurring due to the HLA mismatch, imaging methods to reduce the variations due to the difference in donor-recipient matching. As advancement in medical science has reached a plateau, the focus is now on, increasing the long-term survival of the transplant recipients. Various statistical approaches are used to investigate the time taken for the events which occur, post-transplantation of the organ [7].

Timely organ transplantation is one of the most challenging and complex areas of modern medicine. Effective transplantation, after the selection of the right recipient, is greatly influenced by the transportation time especially in the current scenario of untimely and unpredictable situations of traffic conditions. Increased travel time in turn drastically reduces the viability of the organ and reduces the allograft survival rate, leading to an increase in the number of re-transplantations. The cost of transplantation in seriously ill patients is more expensive. Also, there is a higher probability of graft failure in sicker patients, which may eventually lead to re-transplantation [8].

Technology has been making the world a smaller place. Advancement in various areas of wireless sensor-based systems, microcontrollers, healthcare-specific gateways, and cloud-based servers can contribute a vital role in making timely transplantation [9]. This can help to increase the utilization of available healthy organs from the pool that is presently going unused. Internet of Things driven systems can help in identifying the correct recipient and also help in well-timed transplantation particularly for organs like kidney and liver which has only a few hours of preservation time. This research aims to propose an IoT-based organ procurement and distribution system which can bring remarkable improvement in timely procurement, accurate serotyping, and resolving ethical, legal, and clinical issues. It also helps to attain a healthy patient's graft survival [10].

The transplantation process is a costly procedure and the failure of which has to be treated as a serious issue [11]. There are many reasons for the transplantation failure such as the health profile of the donor, health profile of the recipient at the time of transplantation, time taken to transplant organs after procuring the organ, etc. Providing the organ to the most accurate recipient is always a challenge. Most of the time an organ is allocated just by selecting the recipient based on their position in the organ waiting list maintained by the government or private organizations. A very mediocre matching algorithm is also used for the identification of the recipient. The survival prediction of the recipient based on various health and environmental/infrastructural data (e.g.: live traffic) is not considered in this selection process thus reducing the healthy lifespan of the recipient [12].

1.1. Objective

The objective of this research is to do an in-depth analysis of the historical transplantation data for the organ (kidney) and figure out statistical evidence of various parameters which are affecting the survival time of the organ recipient. Both individual impact and simultaneous impact (impact in conjunction with other varying parameters) of these data parameters are studied. Results of this study were further analysed to identify such parameters which vary frequently with time but also impact the predicted survival curve of the recipient. The research focuses on the benefit of new-age technology such as IoT in accurately predicting the most suitable recipient with a longer survival curve.

The research ultimately brings out an efficient recipient identification mechanism for organ procurement and transplantation. Research also wants to pave ways in bringing better transparency in recipient identification by using technologies like IoT and blockchain. A system based on these technologies is expected to make recipient selection traceable and transparent to all the stakeholders participating in the organ procurement and transplantation process.

The research also focuses on the impact of the infrastructure (e.g.: travel time to the transplantation centre) of the country, on the healthy lifespan of the recipient.

2. RELATED WORKS

Transplants are one of the most miraculous achievements of modern medicine whereas transplantation is one of the most challenging and complex areas of modern medicine. Organ transplantation is the process of surgically transferring a donated organ into a patient with end-stage organ failure. The number of patients waiting for organ transplantation in the United States alone has surpassed 123,175. Every hour adds at least six patients to the organ waiting list [13]. At present, out of the 1, 50,000 patients requiring kidney transplants across India, only 200 get kidneys by way of donations from the deceased [14]. To achieve successful transplantation and improve the utilization of the available organ, it is important to reduce the time taken for the retrieval of the organ and transplantation of the same. The organ which is donated will be viable for transplantation only for a few hours [15]. This time varies from 4 to 24 hours based on the organ type. This is especially true for organs like the kidney, heart, and liver, which have only a few hours of preservation time. A significant amount of time is taken by many of the pre and post procurement procedures like the serotyping of the donor and the recipient, assessment of the organ, estimation of transplant candidate’s immunological risk by the physician, transplant transportation, and other bioethical and legal issues regarding the transplantation.

Donor and recipient matching algorithms are of great importance to understand the mismatch to reduce the allorecognition and immunity of the transplant [16]. HLA typing, age, BMI, and various other body parameters of the recipient and the donor along with the location information are the various inputs given to the system. The graft outcome and transplant rejection due to immunity are greatly affected by the disparity in these factors.

HLA matching is not a very significant factor in determining the correct recipient if allograft is from a living donor. While there is a linear relationship between HLA mismatch and patient survival if it is from a deceased donor. If there is a risk of 13% with 1 mismatch, it has a higher risk of 64% of allograft failure with 6 mismatches [17]. The increasing number of HLA mismatches, especially those of HLA-A, HLA-B and HLA-DR loci of the transplant candidates has to be greatly considered to reduce the immunological risk leading to failed graft and patient survival rates. As HLA-typing is considered a crucial component in allocating kidneys from a deceased donor for a successful graft and patient survival, HLA-typing has evolved greatly from serological-based typing to molecular HLA-typing and solid-phase anti-HLA-antibody-detection assays [18]. Independent of the year of transplantation and the immunosuppression used, the association between HLA mismatches and graft rejection seems to be more for transplantation from deceased donors than from live donors.

Recent analysis and statistical studies carried out using the UNOS data show that the significance of donor age is much above the potential factors like HLA-mismatching, in determining the graft and patient survival. This has led to a paradigm shift in the kidney allocation algorithm which was predominantly based on HLA-matching to focus on other factors like donor age. Further studies have shown that the recipient age along with the donor age is an important factor determining the outcome of the organ transplantation [19].

Another important factor that has a greater impact on the survival outcome is the Cold Ischemia Time (CIT). An increased graft failure is observed for the kidney transplantation from deceased donor kidney with a CIT greater than 12 hours. The risk of death-censored graft failure is significantly more if the CIT is greater than 22 hours. The risk hazard is elevated if the kidney is from a donor of age greater than 60 years old. The influence of CIT was so significant that it has led to the debate on the opinion on whether the allocation has to be based on of histocompatibility of human leukocyte antigen or given more importance on making lesser cold ischemia time for reducing the risk of graft failure [10]. The follow-up of renal transplantation with a CIT in 3 groups in 10-year gap showed that the risk of graft failure was statistically significant for CIT greater than 36 hours than those between 16 hours and 36 hours respectively [20].

Several studies for finding the impact of various factors influencing the ischemia time, prolonged hospitalisation, complications in surgery, and more frequent admission in intensive care units of the ESRD recipients. Obesity defined by BMI of the patients had a major impact on transplant consideration including the selection of the candidate, waiting list priority management also in predicting the outcome before and after transplantation. The World Health Organisation has defined BMI >=30 as obese BMI and those lower than 30 are considered as non-obese [21]. Recipients with obese BMI are found to have greater complications than those with lower BMI.

Other factors which affect the post-transplantation success rate include comorbidities that have to be monitored on a real-time basis include diabetes and heart failure. The number of ESRD patients with high comorbidity is increasing significantly at the transplantation centres. An increased death censored graft failure both pre and post transplantation is associated with patients with high comorbidity [22]. Statistical analysis showed that comorbidities like heart failure and cerebrovascular diseases are highly associated with increased mortality risk of deceased donor kidney transplant.

An IoT-based system can effectively reduce process delay of both the pre and post organ procurement process. Tracking of the organ during the transportation of the organ can be monitored and controlled by an IoT-based system. The emergence of the Internet of Things equipped with sensors can transmit concurrent data related to this towards a single repository in the cloud server. The details of the registered patients along with the real-time health data from a variety of sensors can be stored in cloud-based servers. These servers eventually can be used to analyse the data using various matching techniques and complex algorithms for a more specific, flexible, and robust means of high-resolution HLA typing and serotyping. These analysed data are then shared through wireless connectivity with medical professionals who can make appropriate decisions. RFID-based ambulance systems that are fitted with GPS capabilities alongside various other sensors can relay data about the vehicle’s location and current progress which can be used for the transportation of the organs without any delay [23]. The efficiency of such an IoT-based system heavily depends on the algorithms which correlate and analyse the collected data through IoT sensors and clinical information systems.

3. ANALYSIS OF ORGAN TRANSPLANTATION AND FOLLOWUP DATA

A study was carried out on the transplant follow-up data of the kidney transplantation dataset of the United Network of Organ Sharing (UNOS) consisting of deidentified patient-level information of all the renal transplantation carried out between January 1st, 1999 and 12th December 2004.

The time to death of a patient after organ transplantation, the time between the transplantation, and graft failure, the time between transplantation and re-transplantation and the relapse-free survival time between the transplantation and the recurrence of the disease are the four events that are particularly considered to investigate for the survival analysis. Univariate analysis of HLA histocompatibility, donor age, recipient age, Ischemia time, recipient BMI and other commodities has been done using survival curves to understand their impact on survival prognosis. Kaplan-Meier plots are used to visualize the impact of each categorical variable in determining the variation of the time for a particular event to occur, by ignoring the impact of other factors [24].

Survival probability can be used to find the probability that an individual survives from the time of transplantation to a specified future time t. The hazard function can be used to find the probability that an individual who is under observation at a time t, has encountered an event. Survival analysis using Cox proportional hazard regression can assess the effect of several risk factors simultaneously on survival time by the covariates which potentially affect the prognosis of the recipient [25].

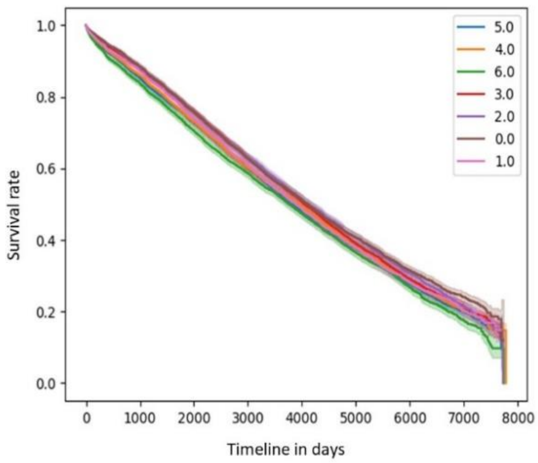

Figure 1 Impact of HLA Match in the outcomes of kidney transplantation.

The analysis was carried out on the 64302 patient details focusing on the 6 mismatch levels, without considering the HLA-A, B, and DR loci. Kaplan-Meier plots were used to visualize survival curves. As can be seen from the plot in Figure 1, recipients having HLA mismatch <=2, are seen to have a longer duration of life than those with a higher mismatch. A donor-recipient having a mismatch level 6 is having only a 20-percentage chance to live for 7000 days.

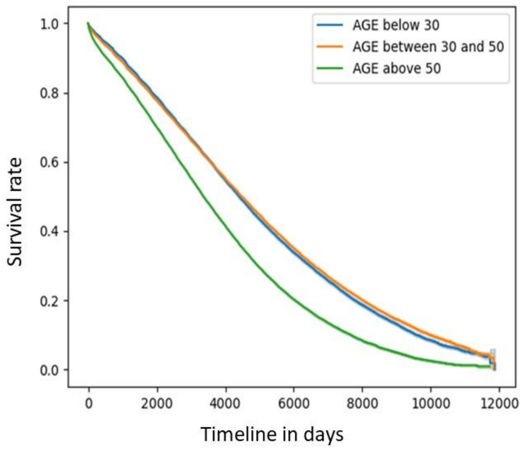

Figure 2 Impact of donor age in the outcomes of kidney transplantation

The same dataset was taken to study the effect of donor age on the transplantation of the kidney, using Kaplan-Meier plots to visualize survival curves. From the plot in Figure 2, it can be seen that donor age is an important factor in determining the success of the transplantation. Donor age has a greater impact on the chances of graft outcome and patient survival years [26]. Age 30 can be considered as median value, as it can be seen that if the donor is of age greater than 30 years the recipient is shown to have a shorter life span than those between 30 and 50years. However, the study to reduce the impact of donor age, if the recipient is also in the same age group is considered for further work.

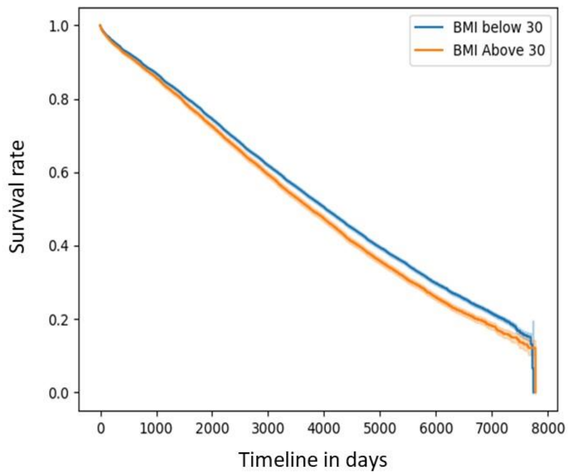

Figure 3 Impact of Recipient BMI in the outcomes of kidney transplantation

Kaplan-Meier plots were used to visualize survival curves for the impact of donor Body Mass Index on the graft and the patient survival rate [27]. Donors of BMI greater than 30, which is considered as the median value, clearly indicating lesser chances of survival than those below 30 [28]. This can be seen in Figure 3.

The median of Cold Ischemia Time (CIT) is considered as 16.2 hours for the kidney. Kaplan-Meier plots were used to visualize survival curves for the recipients who procured Kidney and the transplantation is done within 10 hours. As can be seen from the survival curves in Figure 4, CIT has a major impact in predicting the graft and patient survival than those transplants which took more time.

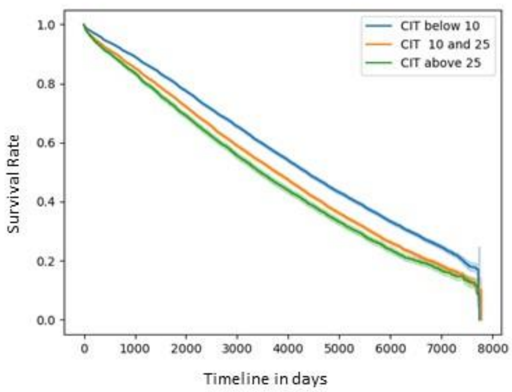

Figure 4 Impact of Cold Ischemia Time

As seen from the above survival analysis based on univariate (Kaplan-Meier) gives the direct dependency of that variate for survival, however, this analysis ignores the dependency of the impact of the other variates at the same time. Moreover, univariate analysis is more accurate when the variable is more categorical (e.g.: HLA mismatch 1 against HLA mismatch 6). These models have some limitations when the variate is more quantitative (e.g.: age of the recipient or Cold Ischemia Time).

A multivariate survival analysis that works for both categorical variables and quantitative variables is seen to be more beneficial in checking the overall impact of all the variates on recipient survival. Cox proportional hazards regression analysis is used in this research for the multivariate survival analysis. This method gives the simultaneous impact of multiple variates (risk factors) on survival.

The simultaneous impacts of the following risk factors are analyzed in this research

1. Age of the recipient
2. Age of the donor
3. Number of HLA mismatches
4. BMI of the recipient at the time of organ transmission
5. Cold ischemia time for the kidney

Using the data analysis framework, a hazard ratio graph is generated as shown in Figure 5.

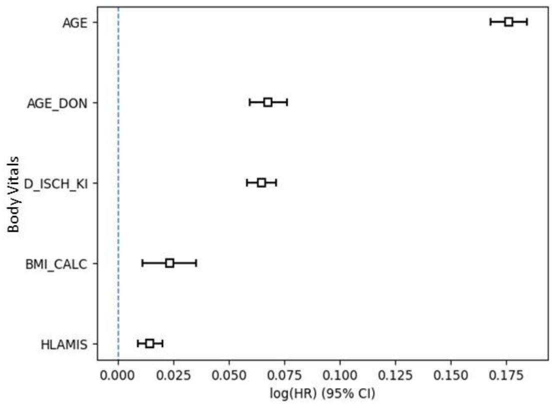

Figure 5 Hazard Ratio using Cox Regression Model

Cox Regression Summary, depicted in Figure 7, displays the p-values, hazard ratios, and 95% confidence intervals for the hazard ratios for each of the health data parameters considered for the analysis. The p-value for recipient age is <0.005 and HR is 1.19, indicating a strong relationship between the recipient age and increased risk of death. The p-value for CIT is <0.005 and HR is 1.07, indicating a considerably strong relationship between the CIT and increased risk of death.

As evident from the summary analysis, the z value (z = coef/se(coef)) is high for age (both recipient and donor) and cold ischemia time. This indicates that with the increases of these values there is an increased risk for the recipient's survival. Also, the regression coefficients are all positive values, which indicates all the parameters considered impact adversely on the survival timeline. The hazard ratio is higher for recipient and donor age and cold ischemia time and then followed by HLA mismatch and BMI of the recipient. A Box Graph is used to depict the Hazard Ratio using Cox Regression Model. Figure 5, shows the upper and lower confidence level of regression coefficients.

4. ALGORITHMS

A survival prediction model is developed by training the Cox Proportional-Hazards Model with 65000 de-identified patient data from the UNOS database consisting of the renal transplantation data carried out between January 1st, 1999 and 12th December 2004. The dataset selected so that there is significant survival time after the transplantation date (15 – 20 years). Null values are filtered, the dataset is organized into groups based on the recipient and donor parameters based on the criteria. The trained Cox proportional hazard model with 65000 recipient data which is used in the previous analysis.

The analysis is applied to the patient sample to see the predicted survival curve. The patient sample (recipients) details with residing city details given in Table 1 are selected for the analysis.

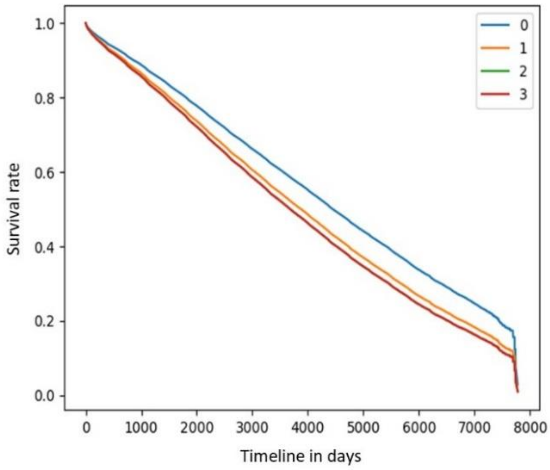

Figure 6 Survival graph when the recipient is in different cities

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%
AGE	0.18	1.19	0.00	0.17	0.18	1.18	1.20
AGE_DON	0.07	1.07	0.00	0.06	0.08	1.06	1.08
COLD_ISCH_KI	0.06	1.07	0.00	0.06	0.07	1.06	1.07
HLAMIS	0.01	1.01	0.00	0.01	0.02	1.01	1.02
BMI_CALC	0.02	1.02	0.01	0.01	0.04	1.01	1.04

	z	p	-log2(p)
AGE	42.19	<0.005	inf
AGE_DON	15.56	<0.005	179.00
COLD_ISCH_KI	19.69	<0.005	284.18
HLAMIS	5.23	<0.005	22.52
BMI_CALC	3.81	<0.005	12.80

Figure 7 Cox Regression Summary

Table 1. Sample patients for analysis with residing city details

PT_CODE (RECIPIENT IDENTIFIER)	AGE	AGE_DON	Location	HLAMIS	BMI_CALC	DAYSWAIT_ALLOC
Recipient 0	43	41	Hosur	2	20	100
Recipient 1	42	45	Hyderbad	2	22	200
Recipient 2	55	58	Pune	2	23	300
Recipient 3	75	72	Pune	2	23	400

The Survival graph for each recipient is depicted as shown in Figure 6. As expected, Recipient 0 with all health data parameters in acceptable range gives the best survival and Recipient 3 with all the data parameters in more hazard range gives the worst survival prediction.

5. COMPARATIVE ANALYSIS- IOT BASED PREDICTIVE MODEL VS EXISTING METHOD

As seen from the study so far, it is very clear that the time duration taken by the organ and organ recipient to reach the transplantation center plays an important role in the healthy survival time of the recipient. Because the duration by which the recipient reaches the transplant center directly adds to the cold ischemia time of the organ. Another important factor which affects the overall survival time of the recipient is the vital health parameter of the recipient such as BMI, Blood pressure, glucose level at the time of transplantation. IoT-based framework to predict the cold ischemia time based on the travel time between the recipient's current location and the transplant center location is found to be very helpful to identify the most ideal recipient from the pool of high priority receivers in the organ waiting list.

The proposed IoT-based framework includes the trained Cox proportional hazard model. The travel time between the recipient location and transplant center is directly added as the cold ischemia time. Google APIs (Google Map API Python) is used for calculating live travel time to the transplant center. The travel time calculator module is integrated with the IoT framework.

As seen from the survival graph in Figure 6, the IoT-based predictive model selects the recipient 0 as the best candidate for transplantation planned in Bengaluru. Recipient 0 has 15 to 20% predicted survival chances than the recipient 3.

In the absence of the predictive model, Recipient 3 would have been selected by default for organ transplantation due to the high waiting period in the organ waiting list.

6. CONCLUSIONS

As seen from the analysis survival rate is higher if the age of recipient and donor is lower. The higher the HLA matching the higher will be the survival rate. Lower the BMI better the survival rate. Also, lower the cold ischemia time then better will be the survival rate.

When the various parameters are analysed for the simultaneous impact on the survival rate, the recipient age has the maximum influence on the survival rate. This is followed by donor age, cold ischemia time, HLA mismatch, and BMI of the recipient respectively

IoT-based prediction model derived in this research seems to be selecting the most ideal recipient from the waiting list.

AUTHORS' CONTRIBUTIONS

The author Benita Jose Chalissery, conceived the presented idea, developed the theory, and performed the computations.

The authors V. Asha, B. Meenakshi Sundaram verified the analytical methods and encouraged them to verify the findings of this work. All authors discussed the results and contributed to the final manuscript.

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