The healthcare professionals' support towards organ donation. An analysis of current practices, predictors, and consent rates in Apulian hospitals

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Abstract

Introduction. The paper investigates the critical care staff's support towards organ donation by analysing how their attitude, knowledge, confidence, engagement, and training can act as predictors of donation consent rates. Our study focused on hospitals in the Apulia Region, Italy.

Material and methods. The study employs a quantitative methodology based on a survey of healthcare professionals. The rate of consent to organ and tissue donation at the hospital level, given as a ratio of the permissions received to the proposals performed, was extracted from GEDON software related to the year 2019 report. For each Apulian participating hospital, we calculated a median score for each of the five predictors (namely, attitude, knowledge, confidence, engagement, and training) and investigated the association with hospital consent rates.

Results. The results highlight that the engagement of the intensive care units' healthcare personnel stands as the only influential predictor of the consent rate.

Discussion. In Italy's Apulia Region, efforts are needed to increase consent rates for organ donation. Strategies should concentrate on continuous support, as well as specific training of hospital staff involved in the donation process.

INTRODUCTION

Organ donation is a crucial issue in addressing the medical needs of many patients worldwide. The research community is putting efforts into new strategies to expand the availability of organs for transplantation without direct actions on the donor pool through regenerative medicine and organ bioengineering [1-5]. While regenerative medicine technologies aim to repair and regenerate poorly functioning organs [5], these attempts are still far from an actual clinical translation [6-8], and, as of today, there is not a significant impact on

clinical staff nurses

Key words

- medical doctors
- donation
- consent

the number of transplants. Therefore, seeking consent from donors still stands as the only effective strategy to address the medical needs of those waiting for an organ. In Italy, there was an increasing number of organ do-

In Italy, there was an increasing number of organ donations and transplants in 2019. However, the opposition to organ recovery had risen again. The 2019 annual report of the National Transplant Center mentions two sides of the issue: on the one hand, the transplant network showed signs of constant improvement (2019 was the second-best year for the amount of activity, and the donor lists continued to shrink); on the other hand, the **ORIGINAL ARTICLES AND REVIEWS**

availability to donate remained lower than necessary [9]. The most significant fact is the recent increase in potential donors, that is, the subjects in a state of brain death reported by the Intensive Care Units (ICUs) as possible candidates for organ recovery. In 2019, the potential donors were 2,766 as opposed to 2,665 in 2018, with a 3.8% increase as a key indicator of the system's efficiency. The reported numbers allowed the system to absorb the negative consequences of the rate of opposition to organ recovering, which rose from 29.8% in 2018 to 31.2% in 2019. Out of 863 negative responses, most were expressed by the deceased patients' relatives. In 2019, each donation generated 2.5 transplants on average. Therefore, the 1.4% increase in the opposition rate had a cost of missed transplants for 122 patients [9]. With no opposition, in 2019 alone, about 2,200 more transplants would have been carried out. The data on donations confirmed substantial deviations from North to South Italy. With a national average of 22.8 donors per million of the population (PMP), the range varies from 49.5 donors PMP in Tuscany to 8 donors PMP in Sicily. General data on the southern regions look worrying and highly negative, showing opposition rates 15-20 points above the national average, with the peak in Sicily (49.6%) and Calabria (49.4%, +7.9% compared with 2018) [9].

Until the end of 2020, Italy required the so-called "explicit consent" for the donation of organs and tissues. Therefore, it was essential to verify the existence of a declaration expressed in life or the non-opposition of the family members [10-12]. The Ministry of Health recently amended Law 91/99, regulating the principle of "tacit approval". As of December 2020, the reform introduced tacit consent. Namely, adults will all be considered potential donors if they did not oppose during their life, so, in the absence of explicit refusal. The declaration of relatives who have the right to express the willingness of the donor is always taken into consideration even if there are no declarations of will manifested in life by the donor. Despite the introduction of the new norm, the Italian system has experienced a worrying increase in opposition rates.

The low donation rate in the Apulia region is associated with a high opposition rate [13]. Different factors can influence donation rates. One of the most important barriers to organ donation is the refusal of the family members, namely the custodians of the deceased's will, influenced by the family's cultural characteristics. Therefore, in the donation process, nurses and medical doctors' active participation and support towards donation represent crucial aspects during the identification and reporting phase. In particular, the health professionals' attitude, knowledge, confidence, engagement, and training can impact donation rates. Thus far, few studies have evaluated the connections among these elements. Several studies highlight that the team's attitude and knowledge dedicated to donation can impact the rate of consensus among family members [14, 15].

As some authors highlight [16], the family's decisions are influenced by the training of the healthcare staff, their intervention, and the satisfaction with the relationship and communication carried on with the family and caregivers throughout the hospitalization [17]. Other authors state that healthcare professionals need to transfer unequivocal messages to the family members [18] to understand brain death and the irreversible cessation of all vital functions [19]. Moreover, the healthcare professionals' knowledge and attitude [20] about organ donation are essential for planning awareness-raising activities, which impact donation rates [21, 22].

Generally, studies show that healthcare professionals' support towards organ donation can influence their dedication. If healthcare professionals do believe in the value of organ donation, they will be keener on translating their beliefs to the donor's family [23]. The process of organ donation is widely managed by the nursing staff [24], and the identification of potential donors is considered a nursing activity. Given the importance of the nursing staff's role, they need proper training to understand the importance of the process and fully satisfy the donors and their families' health needs [25, 26].

Starting from these premises, in our paper, we aim at evaluating the attitude, knowledge, confidence, engagement, and training of healthcare professionals dedicated to the donation of organs and tissues and correlating these factors with the hospital-level donation consensus rates. Attitude is considered as the participants' will to be organ and tissue donors, the sharing of choice to donate with the closest family members, and the certainty that brain death corresponds to a person's death. Knowledge is measured as the existence of internal hospital processes, the presence of formal guidelines, and standardized procedures for ascertaining brain death and obtaining consent. Confidence analyzes how comfortable the healthcare workers feel in situations of identification and care of a potential donor, explanation about brain death, acquisition of the related consent, and care of the relationship with the relatives during the phase of the grief. Engagement stands as a significant predictor for evaluating the local transplant coordinator's capability to involve the whole ICU team during all the phases of the donation process. Training, intended as the practice of the staff working in ICUs, refers to the training courses attended and detects the needs concerning the phases of identification and care of a potential donor, communication about severe brain damage to the closest family member, explanation of brain death, and acquisition of the consent. Following the differences in donation rates in Italy's various areas, we focus our analysis on the hospitals in a southern region, Apulia, with high opposition rates, involving its Donation and Transplant Network.

MATERIALS AND METHODS

This multicenter study involved physicians and nursing staff in all ICUs in Apulia by completing an online questionnaire using Google Forms. No identifying data were collected (like name, surname, and so on). An invitation was sent to the transplant coordinator of each institution, who later shared the request with the hospital's direction office and later with the ICU staff. The Regional coordinator office followed up the invitation by telephone to ensure that the request was taken into high consideration. Most institutions replied without the need to be recalled. The survey evaluated the attitude, knowledge, confidence, training, and engagement of healthcare professionals within the donation network. In the survey, the 26 hospitals that operate in the Apulia Region were investigated.

Data collection tool – survey

A literature review allowed choosing the tool of a Swiss multicenter study by Keel *et al.* [14]. The authors employed a survey composed of 40 closed-ended questions and two open-ended questions. Keel's survey was selected since it was used in a country where the hospital organization of donations and the consent system are similar to the Italian ones, with the opposition rates below 50%, like Apulian ones. Moreover, the questionnaire was submitted to both medical doctors and nursing staff devoted to the donation activity. The data obtained were associated with the actual consent rate in the examined hospitals.

The original questionnaire was not validated, still authorized by CNDO, the Swiss National Committee for Organ Donation [14]. Starting from Keel's survey, the Italian version was validated before the investigation. The CVI-I (Content Validity Index of the items) was calculated to evaluate the validity of the content. Construct validity was investigated through an EFA (Exploratory factor analysis). Cronbach's alpha (α) coefficient was used to examine the internal consistency of each factor on the scale, Spearman's rho coefficient to test its stability.

To associate the results of the questionnaire about the critical care staff's attitudes with the consent rates, we used the reports of Apulian Regional Transplant Coordination Center in 2019 [13], extrapolated by GEDON, a web-based application used for the management of the reports on potential organ donors. GEDON provides an advanced tool for the communication of all clinical data related to a potential organ donor, among the CR (Intensive Care Center), CRT (Regional Transplant Coordination Center), CT (Transplant Center), LT (Tissue Typing Laboratory), CNTO (National Transplant Center Operative Italy), and SIT (Transplant Information System) units.

The study was approved by the CRT in Apulia. According to Italian laws, non-interventional studies do not necessarily require approval by an ethics committee. The survey participants were exclusively healthcare professionals, with voluntary participation. No significant identifying information about the participants is possible. The study was conducted following the principles of the Declaration of Helsinki.

Statistical analysis

For each Apulian hospital involved, we first calculated the consent rate as the ratio between the consents received and the proposals made. For each predictor (attitude, knowledge, confidence, engagement, and training), some questions (ranging from a minimum of two to a maximum of four) were formulated, with a score assigned to each answer, as shown in *Table 1*. For each question, the sum of the responses received was calculated, with the average of these scores representing the value of the predictor. A descriptive analysis was carried out by evaluating the answers based on the variability of the professional category (medical doctor or nurse). Attitude, knowledge, confidence, engagement, and training were investigated through a variable number of questions (from two to four) with dichotomous answers, with n = 1 assigned for each positive response.

Regarding the predictor engagement, depending on the number of cases in which the healthcare professional was involved in the donation activities, a score of 0 was assigned in case of no involvement, 2 if involved 1 to 3 times, 5 if involved 4 to 6 times and 8 for more than 6 times. The overall score of each predictor is represented by the average of the scores obtained. A pool of questions was also created to collect data relating to the socio-demographic characteristics of the sample: hospital and operating unit, role, gender, age, years of professional experience.

Later, the consent rates were associated with the predictors. Then, the hospital differences were compared using an ANOVA. As a homoskedasticity test, Bartlett was used, with a p-value = 0.2218>0.05. Following the test, we could claim that the variances were homogeneous, as the homoskedasticity hypothesis was true. We then applied the ANOVA method with a p-value = 0.02425<0.05, so we rejected the null hypothesis. The averages of the average scores per area were not statistically equal. Finally, we used the post hoc test to look for which areas had statistically different means.

The statistical analysis was performed using the software R [27]. We carried out an association among the predictors to estimate the set association, ranging between -1 and +1. Later, we associated the variables with the consent rate by conducting a regression analysis of the significance rate of the predictors for the consent rate, with a p-value set at <0.005.

The following *Table 2* reports the numbers of Apulia per ICU in 2019. With 102 donation proposals made, 44 refused and 58 accepted, with an opposition rate of 43.14%.

The opposition rate was calculated based on the proc.7 indicator (established by the CNTO), which relates the number of proposals made / the number of consents/oppositions obtained.

Descriptive analysis of the target population

The questionnaire was sent to all Apulian hospitals, equipped with a neurosurgery and stroke-unit neurology department, involved in the regional network of transplants that regularly carry out brain death and organ and tissue removal activities.

553 participants in 22 Apulian hospitals completed the questionnaire correctly. Four hospitals declined to participate. The sample consisted of 189 medical doctors (34.2%) and 364 nurses (65.8%). The medical personnel comprise 49.7% women and 50.3% men, whereas the nursing staff members are represented by 43.7% women and 56.3% men. Of the sample, 35.3% (split into 22.1% nurses and 13.2% medical doctors) belong to the 35-44 age range, followed by 31.1% within the 45-54 age range. 45.6% of the participants claim professional experience ranging between 11 and 20 years, and 29.1% have more than 20 years of service.

RESULTS

The attitude of the healthcare staff towards organ and tissue donation is overwhelmingly positive (*Figure 1*). Of the sample, 99% of the participants declared in favour of donation. However, only 7.4% (27) of the nursing staff and 7.9% (15) of the medical staff state that they would donate, but with restrictions, their organs after death. Moreover, 5.5% (20) of the nursing staff and 7.9% (15) of the medical staff do not seem to agree that brain death corresponds to the person's death.

Analysis of Apulian territory

The Apulia Region was divided into three macroareas, distinguished by the geographical criterion and the population density, thus grouping the hospitals accordingly. The number of hospitals in each area is homogeneously distributed for the population hosted. The regional coordination of Transplants for Apulia has carried out these subdivisions based on the neurosurgery and neurology stroke-unit departments' presence, guaranteeing a right and equitable distribution.

As specified in *Table 1*, for each of the analyzed predictors with a favourable answer, we created a score for the dimension and calculated the average for each hospital. Moreover, we calculated the average score of the consent for each area, comparing and describing eventual intra-regional differences.

After aggregating the survey results, we could observe interesting differences among the macro-areas. In particular, we analyzed the predictors for each area singularly.

Regarding *attitude*, generally positive, the Central Area shows the most favourable attitude, with a value of 1, followed by the Southern Area with 0.96, and lastly, the Northern Area with 0.80.

Regarding *knowledge*, we observed that the Central Area has the highest value with 0.85, followed by the Southern Area with 0.78 and the Northern Area with 0.51 (*Figure 2*).

Confidence shows similar results, with no area obtaining significantly higher scores.

Concerning *engagement*, in a significant way, the Central Area (with 1.56) and the Southern Area (with 1.47) prevail over the Northern Area (with 0.75).

Regarding the predictor *training*, the Central Area obtained the highest value (0.74), followed by the Southern Area (0.67) and the Northern Area (0.57).

We can state that knowledge and engagement are the predictors that significantly differ among the three areas.

The Northern Area assumes a significant value compared to the other two areas, as reported in *Table 3*. In our study, such an area ends up being the most virtuous one within the Apulian transplant network.

Even though the Northern Area has earned the lowest scores for all the predictors examined in the present study, it has registered a 76.19% consent on organ donation. This area has 8 ICUs, but only 4 ICUs reported potential donors in 2019, with 21 donation proposals and 16 permissions.

The Central Area registered an increased procurement activity, even with a consent rate of 55.32%. In this area, 10 ICUs exist, but the reporting activity was carried out only in 5 of them. Specifically, 47 donation proposals were made, obtaining 26 consents. Based on the predictors' analysis, this area stands as the most productive in terms of the personnel's engagement and knowledge.

In the Southern Area, with 8 ICUs, a consent rate of 47.06% was registered. Of the 34 donation proposals, 16 consents were obtained, considering that 7 ICUs prepared the reports on potential donors.



Figure 1

Attitude toward donation healthcare professionals.

Table 1

Survey and predictor cutoff of donation

Dimension	Positive answer	Score
<i>Attitude</i> What is your general attitude towards organ and tissue donation for transplants? Would you donate your organs after death? Does brain death correspond to death?	Yes or Yes with restrictions	0-3
<i>Knowledge</i> Does your hospital have standardized procedures for the donation process? Does your hospital have standardized guidelines for obtaining consent for organ donation?	Yes	0-2
Confidence Do you feel comfortable in the following situation: Explaining to relatives about brain death? Do you feel comfortable in the following situation: Formulating the proposal for organ donation to family members? Do you feel comfortable in the following situation: Accompanying and supporting relatives during their bereavement?	Yes	0-3
Engagement Please indicate the number of cases in which you have been involved in the past year: Reporting of severe brain damage to next of kin Please indicate the number of cases in which you have been involved in the past year: Explaining to relatives about brain death Please indicate the number of cases in which you have been involved in the past year: Formulating the proposal for organ donation to family members In your opinion, what moment do you think is more appropriate to address the issue of organ donation with relatives? (choose one answer)	-	None = 0 1-3 = 2 4-6 = 5 >6 = 8
<i>Training</i> Have you ever received training in the concept of brain death Have you ever received communication skills training (including bereavement management) in the donation process	Yes	0-2

We conducted an analysis of linear association among the single predictors to estimate the set association, ranging between -1 and +1. The associations are displayed in *Figure 3*, and some of them are significant. Attitude has a 43% association with knowledge, 24% with confidence, and 21% with engagement. Confidence has a 59% association with engagement and 25% with training. While engagement assumes a 30% association with training and 18% with consent, the latter predictor is worthy of an in-depth analysis as the only one associated with consent.

We performed a regression analysis by setting a 95% confidence interval for the association among the variables to the consensus rate, with P-value of P<0.005 of the significance rate of the predictors on the consensus.

Next, we analyzed the linear regression model among all the predictors and the consent rate to assess their statistical significance (*Table 2*). Our analysis of the association between the consent rates for donation and the survey scores has identified the healthcare personnel's



Figure 2 Intra-regional differences in the scores.

296

Table 2

Activity report on organ donation in 2019 in Apulia Region

Intensive Care Units in Apulia	Proposals made	e Oppositions		Consents	Hospital consent =	
	n.	n.	%	n.	consents/proposals made %	
Foggia	6	2	33.33	4	66.67	
San Giovanni Rotondo 1	1	0	0.00	1	0.00	
San Giovanni Rotondo 2	2	1	50.00	1	50.00	
San Severo	0	0	0.00	0	0.00	
Cerignola	0	0	0.00	0	0.00	
Andria	12	2	16.67	10	83.33	
Barletta	0	0	0.00	0	0.00	
Bisceglie	0	0	0.00	0	0.00	
Bari Policlinico 1	21	9	942.86	12	57.14	
Bari Policlinico 2	14	5	35.71	9	64.29	
Bari Di Venere	6	5	83.33	1	16.67	
Bari San Paolo	0	0	0.00	0	0.00	
Bari Giovanni XII	0	0	0 0.00	0	0.00	
Bari Mater Dei	0	0	0.00	0	0.00	
Acquaviva	5	1	20.00	4	80.00	
Altamura	1	1	100.00	0	0.00	
Castellana	0	0	0.00	0	0.00	
Monopoli	0	0	0.00	0	0.00	
Brindisi	3	2	66.67	1	33.33	
Taranto	15	4	26.67	11	73.33	
Lecce	11	8	72.73	3	27.27	
Casarano	1	1	100.00	0	0.00	
Tricase	2	2	100.00	0	0.00	
Scorrano	0	0	0.00	0	0.00	
Gallipoli	1	0	0.00	1	100.00	
Città di Lecce	1	1	100.00	0	0.00	
Total	102	44	M 43.14	58	M 25.09	

engagement in ICUs as the only influential predictive factor of the consent rate, with a statistical significance of p<0.00006. The healthcare personnel's engagement stood as the strongest predictor of the consent rate. An increase in the score of the healthcare professionals' engagement led to the probability of a 5.24% increase in the consent rate (*Table 4*).

Moreover, training and knowledge obtained positive scores, even if not significant. A previous study highlights that specific training in the context of organ and tissue donation increases the probability of consent [28]. Our study confirms the need to increase the specific training of health professionals who appear sensitive to the topic to create a "culture of donation" among the team members.

In contrast, attitude and confidence have proven to

be negative, in line with previous studies [29, 30], which report that behaving in an impersonal way with the family members and being too self-confident are perceived by the family in a negative way and therefore leads to a low probability of obtaining the family's consent.

DISCUSSION

The healthcare professional who has been appointed to explain brain death and formulate the subsequent donation proposal to the deceased's family must assume an empathetic attitude, dedicating the needed time through simple communication and knowledge translation [20, 31-33]. Several studies showed that the healthcare personnel's sensitive and compassionate approach to the family is associated with higher consent rates [34-36]. Other studies emphasize that obtaining

Table 3

Statistical difference of the predictors to donation between the North, the Center and the South of the Apulia Region

	Difference	p-value	Significance	LCL	UCL
North - Central	-0.37043592	0.0120	*	-0.6546435	-0.08622839
North - South	-0.32096430	0.0279	*	-0.6051718	-0.03675677
Central - South	0.04947163	0.7267		-0.2347359	0.33367915

LCL: lower control limit; UCL: upper control limit.

297



Figure 3 Association of consent-predictor rates.

"non-opposition" is not only influenced by the person who formulates the donation proposal but also by the approach and the sufficient time to understand the information and make a decision, as perceived by the family [37]. Therefore, the combination of these parameters can contribute to predicting consent rates. However, the predictors should be considered collectively to observe how the independent variables (attitude, knowledge, confidence, engagement, and training) are associated with the dependent variable (consent rate).

Ours stands as the first study conducted in the Apulia region in Italy to investigate the association between the consent rates for organ donation and the attitude, knowledge, confidence, engagement, and training of the medical and nursing personnel in ICUs. The survey has highlighted that the majority of healthcare professionals are in favour of organ donation.

The general analysis shows that engagement is the strongest predictor of consent. The differences in the regional areas should be explored to observe the predictors of interest. Despite their positive attitude toward donation, the healthcare personnel in the Northern Area showed lower scores than their colleagues in the other areas in terms of knowledge, confidence, engagement, and training. The reasons may be related to a territorial issue associated with the local Health Agencies' policies. It may be that such Health Agencies had not invested in organ donation as one of the main objectives of the modern healthcare system.

We observed that the Central Area obtained higher scores in all five predictors, particularly in engagement and training. It should be emphasized that the Central Area is the territorial headquarter of the CRT. We may presume that the presence of the Apulian CRT's headquarter offices at the Policlinic University Hospital of Bari may easily affect the professionals who are directly involved. Eventual best practices carried on from an organizational perspective in training or dealing with the healthcare staff devoted to transplants should then be recognized and shared with the other regional hospitals, especially those with less favourable outcomes.

The analysis of the Southern Area highlights acceptable levels of confidence. However, also in this case, it is not confirmed by the scores of the other predictors that in some way remain similar to those in the Northern Area. Several studies show that where there are many hospitals that are under the jurisdiction of the same Local Health Agency, the coordination of the extended area should be present [14].

In our study, the consent rate is significantly and positively associated with the engagement of healthcare professionals. Moreover, it is observed that the consent rate is higher if the knowledge and training of the medical doctors and the nurses show a favourable inclination toward organ donation. Indeed, those professionals who are already sensitive towards the topic are the ones undergoing training. Nurses and medical doctors play an essential role in the family's final decision. Therefore, being perceived as close to the family, they should provide simple and understandable information [37, 38]. Thus, the professionals' lesser propensity to the donation may influence the family to withhold their consent to donate [39]. It is crucial that the professionals involved in this process are conveniently trained and know the communicative and relational dynamics, being able to use their soft skills by employing a simple language to adequately translate knowledge to the family members in charge of the decision [18, 31, 36]. Moreover, our study confirms that healthcare professionals involved in organ and tissue donation activities should have continuous support in their specific training oriented to acquiring a practical knowledge of the whole process and increase self-confidence. It is essential that the professionals' support towards donation raises the awareness of the population so that the number of oppositions decreases. Further research av-

Table 4

Comparative analysis of predictors to donation

Coefficients					
Estimate Standard Error t value Pr(> t)					
(Intercept)	346.519	77.589	4.466	9.68e-06***	
Attitude	-82.886	89.451	-0.927	0.3545	
Knowledge	107.014	45.971	2.328	0.0203*	
Confidence	-50.273	44.453	-1.131	0.2586	
Engagement	52.427	13.031	4.023	6.54e-05***	
Training	0.1364	39.516	0.035	0.9725	

Significance codes: 0'***'0.001'**'0.01'*'0.05".0.1''1

Residual Standard Error: 34.67 on 547 degrees of freedom, Multiple R-squared: 0.04239, Adjusted R-squared: 0.03364, F-statistic: 4.843 on 5 and 547 DF, p-value: 0.0002416.

enues include in-depth qualitative studies, for instance, interviewing the family members who consented to the donation to deepen which reasons fostered them to do so, measuring the real impact of the healthcare staff's support and counselling.

Our article has several limitations. One significant limitation is connected to the possible presence of other variables that could influence the consent rates. Such variables may include a strong and hardly influenceable cultural belief of the family, the changing in the common feeling towards donation, the shock following the death of a dear one, especially if unexpected or sudden, like a car accident. Moreover, it would be interesting to include other Italian regions, especially those located in the northern and central areas, to compare results and strategies.

Some practical and policy implications emerge from this study, especially a call for policymakers and hospital managers to provide an extension of training programs for both nursing and medical students but also residents and professionals in their lifelong learning education to improve their expertise to deal with such topic. A collaboration with, for instance, the psychologists of the hospital may be welcome, as it proved to be successful in other cases and clinical disciplines, like oncology [40, 41]. It is necessary to set up adequate training, em-

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ploying pioneering informative, communicative, softskill-based tools, leading healthcare professionals to get precise information and a positive attitude in handling the matter. Moreover, common strategies should be employed in all educational settings. While information should be spread even at very early stages, like primary or secondary schools, such topics should be intensified and deepen at healthcare university degrees, to transfer and share the proper knowledge to the nurses and medical doctors-to-be.

Authorship

FR, CMS, ML, and GV conceived the idea of the study. FR and CMS developed the theory and performed the computations. FR had oversight and leadership responsibility for the research activity planning and execution. FR, CMS, and FDM wrote the first draft of the manuscript. ML, GV, LG, AP, and LC critically reviewed and amended the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest statement

The Authors have no conflict of interests to declare.

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