Survival of Highly Sensitized Patients on the Waiting List for Kidney Transplantation at Modena Transplant Center

Giacomo Mori[a], Jessica Plessi[c], Niccolò Morisi[a,c], Laura Tonelli[c], Laura Melara[c], Giuseppe Oliviero[c], Alice Parmigiani[a], Marco Ferrarini[c], Stefano Di Sandro[b,c], and Gabriele Donati[a,b*]

[a]Nephrology, Dialysis, and Kidney Transplant Unit, Azienda Ospedaliero-Universitaria di Modena, Italy; [b]Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, Azienda Ospedaliero-Universitaria di Modena, Italy; and [c]Surgical, Medical, and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine (CHIMOMO), University of Modena and Reggio Emilia, Modena, Italy

ABSTRACT

Background. HLA sensitization plays a pivotal role in kidney transplantation. The presence of anti HLA antibodies strongly limits access to transplantation to subjects on the waiting list, particularly for highly sensitized patients. The aim of this study is to evaluate the waiting time of highly sensitized candidates, when compared with patients with a lower level of sensitization, and the respective survival rates on the waiting list.

Methods. We conducted a single center retrospective observational study stratified according to calculated panel reactive antibodies (cPRAs) in highly sensitized patients (cPRA $\geq$ 80%) and patients with a lower level of sensitization (NH; cPRA $<$ 80%). A total of 911 patients on the waiting list were considered. Survival analysis was performed according to Kaplan Meier, and multivariate analysis was performed with Cox regression. Mortality data were collected only for 222 patients who were residents in the Province of Modena, Italy.

Results. Highly sensitized subjects have a significantly longer waiting time from enrollment to kidney transplantation when compared to patients with a lower level of sensitization, but in our highly sensitized patients the mortality rate resulted slightly lower because of the protective effect of a younger age at enrollment.

Conclusions. Highly sensitized patients wait longer to achieve kidney transplantation, but they do not show worse survival rates, likely because of a younger age at enrollment. These results highlight the importance of innovative strategies to allow access to transplantation to highly sensitive subjects to limit the personal and social cost of a prolonged stay on dialysis.

RENAL transplantation is the best treatment option for end-stage renal disease. However, the success of the transplant is heavily influenced by the recipient's immune response to the graft.

The major histocompatibility complex plays a pivotal role in the definition of self and non-self, and therefore the presence of antibodies against human leukocyte antigen (HLA) in sera of transplant recipients significantly increases the risk of acute and chronic rejection, with detrimental consequences on the outcomes of kidney transplantation (KTX) [1−5]. Nonetheless, subjects with preformed anti-HLA antibodies have reduced opportunities to find a compatible donor, with longer waiting times. As a consequence, deceased kidney donor waiting lists share the burden of accumulation of highly sensitized (HS) patients, for whom standard allocation policies struggle to offer consistent chances of transplantation, highlighting the need for innovative strategies for HS subjects [6].

The aim of this study is to evaluate the waitlist vintage of HS candidates for kidney transplantation, when compared with patients with a lower level of sensitization (NH), and the respective survival rates on the waiting list.

*Address correspondence to Gabriele Donati, CHIMOMO Department, University of Modena and Reggio Emilia, Via del pozzo 71, 41124, Modena, Italy. E-mail: gabriele.donati@unimore.it

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MATERIALS AND METHODS

We conducted a retrospective observational study, considering patients enrolled on the Modena Center KTX waiting list from January 1, 2005, to December 31, 2020. Inclusion criteria were the time of enrollment and age over 18 years. We excluded living kidney donors and simultaneous kidney and liver transplant recipients because of the different timing and criteria for organ allocation. Patients were screened according to the local protocol, absolute contraindications to transplantation included active cancer, severe irreversible heart failure, active infection, severe untreatable aorto-iliac arteriopathy, and decompensated psychiatric disorders.

We considered demographic variables, the waitlist vintage, and the dialysis vintage. Patients were stratified according to calculated Panel Reactive Antibodies (cPRA) in HS (cPRA $\geq$ 80%) and NH patients (cPRA < 80%).

Continuous variables were described in terms of mean or median (Kolmogorov-Smirnov test was applied to verify a normal distribution), and categoric variables as frequency. Comparison between groups was performed with non-parametric tests for independent samples (Mann-Whitney *t* test) and Chi square, when appropriate.

Survival analysis was performed according to Kaplan Meier, and multivariate analysis was performed with Cox regression. Mortality data were collected only for people who were residents in the Province of Modena, Italy, because of excessive censored cases in the remaining population.

RESULTS

A total of 911 subjects were considered (Table 1), 114 (12.5%) with cPRA $\geq$ 80%, and 797 (87.5%) with cPRA < 80%. The HS group showed a significantly higher prevalence of female patients (54% vs 32%, $P < .01$) and patients waiting for a second or third transplant (34% vs 6%, $P < .01$), slightly younger (median age at enrollment 47 vs 52 years, $P < 0.01$) than NH patients. Blood group frequency reflected Italian epidemiology, with 0 resulting more frequent in the HS group (53.3% vs 45%, $P < .01$).

Time to Transplant

The median time from enlistment to KTX for the whole population was 656 days (interquartile range [IQR] = 326-1355), with a significant difference between the HS and NH groups (median = 1632 vs 627 days, ratio = 2.6, $P < .01$; Fig 1). A wider difference was noted when considering the time between the start of dialysis and transplantation (3296 vs 1895 days, ratio = 1.8, $P < .01$).

Similar values were noted for the subpopulation residents in the province of Modena, Italy (n = 222; Fig 2A), with a median time from enlistment to transplantation of 1871 vs 1062 days ($P < .05$), and from dialysis start to transplantation of 2829 vs 1678 days (although the latter did not reach statistical significance, with $P = .12$).

To better understand the differences in access to transplantation between the HS and NH groups, a Kaplan Meier curve was plotted for the whole population considering KTX as the event. We can clearly observe how HS subjects have a reduced transplant rate at different follow-up intervals, with curves diverging at 6 months from enrollment. At 3-year follow-up from enlistment, 26% of HS patients vs 47% of NH patients were transplanted, 33% vs 60% at 5 years, and 56% vs 67% at 10 years. In the NH group, more than half of the patients are thus transplanted at 5 years from enlistment, whereas only 33% of HS patients reach this goal. It is interesting to note that at 10 years there is only a small increase in NH transplanted subjects, probably because of significant sensitization, although inferior to the 80% cPRA cutoff. On the other hand, HS patients have a more consistent relative increase in the transplantation rate at 10 years because of the Italian National Program for HS patients which allows an allocation priority of organs retrieved on the Italian territory to subjects with at least 8 years of dialysis or waitlist vintage and a cPRA $\geq$ 90%.

A multivariate Cox regression was performed to evaluate the relative weight of different variables on transplantation rate. A significant model ($P < .05$) was obtained that included cPRA, blood group 0, body mass index (BMI), and dialysis vintage ($P < .05$ for each variable). The cPRA, BMI, and dialysis vintage showed a negative effect on transplantation wait times (hazard ratios [HRs] = 0.996, 0.973, and 0.999). According to the previous literature highly sensitized, obese, and long-vintaged patients receiving dialysis have smaller chances to get transplantation. On the contrary, the 0 group favors earlier transplantation (HR = 1.785), because of minor competition in the allocation process, due to blood group distribution in our country.

Mortality

The Modena Center KTX waiting list is composed of roughly half of the patients who are residents in the Emilia Romagna region of Italy and half from different Italian regions. Of the regional subjects, 80.3% are residents in the Province of Modena. In the majority of cases, death is anticipated by a drop out from the list for clinical reasons (cardiovascular events, infectious episodes, and cancer are among the most relevant ones), causing a loss of registry data on the actual date when the patients eventually died. As a consequence, we performed a mortality analysis only on the population resident in the Province of Modena to reduce censored cases.

The Modena province population considered in the study includes 222 subjects (Table 2), with a median age of 51 years, 35% of female subjects, and a median BMI of 25 kg/m^2. The HS group (cPRA $\geq$ 80%) includes 32 patients (14%), with an inferior median age (47 vs 53 years) and a higher prevalence of female patients (50% vs 33%).

Time to transplant survival analysis shows results similar to the general population (Fig 2A), with a median time from enlisting to transplantation of 1871 vs 1062 days when comparing the HS and NH groups ($P < .05$, ratio = 1.76).

When considering death, instead of KTX, as the event ending follow-up, Kaplan Meier curves (Fig 2B) show a significantly

Table 1. Overall Population Characteristics, HS (cPRA ≥ 80%) Vs No Patients With an NH (cPRA < 80%).

Overall Population	HS	NH	TOTAL	*p* Value
Patients, n	114 (12.5%)	797 (87.5%)	911	
Age at listing, years, median	47 (39-55)	51 (43-59)	50 (42-59)	$p < .01$ (Mann-Whitney)
Gender, M/F	M 52 (46%) F 62 (55%)	M 544 (68%) F 253 (32%)	M 596 (65%) F 315 (35%)	$p < .01$ (χ^2 test)
Blood group				
A	- 33 (29%)	- 319 (40%)	- 352 (39%)	$p = .14$ (χ^2 test)
B	- 15 (13%)	- 87 (11%)	- 102 (11%)	
AB	- 5 (4.3%)	- 29 (4%)	- 34 (4%)	
0	- 61 (53.5%)	- 358 (45%)	- 419 (46%)	
Rhesus factor				
Positive	-98 (86%)	-696 (87%)	- 794 (87%)	$p = .44$ (χ^2 test)
Negative	-16 (14%)	-86 (11%)	- 102 (11%)	
Unknown	- 1 (0.1%)	-14 (2%)	- 15 (2%)	
BMI (kg/m^2, median, IQR)	22.7 (20.9-24.5)	24.3 (21.9-27.0)	24.1 (21.7-26.8)	$p < .01$ (Mann-Whitney)
N on dialysis at listing	112 (98.2%)	788 (98.8%)	900 (98.7%)	$p = .9$ (χ^2 test)
N pre-emptive at listing	2 (1.8%)	9 (1.2%)	11 (1.3%)	$p = .5$ (χ^2 test)
N listed for second or third transplant	39 (34%)	48 (6%)	87 (9.5%)	$p < .01$ (χ^2 test)
cPRA (%, median, IQR)	96.5 (86-100)	3 (0-8)	3 (0-23)	$p < .05$ (Mann-Whitney)
Days on the waiting list (median, IQR)	1632 (381-2423)	627 (321-1230)	656 (326-1355)	$p < .01$ (χ^2 test)
N transplanted				
3-y follow-up	30 (26%)	377 (47%)	407 (45%)	$p < .05$ (χ^2 test)
5-y follow-up	38 (33%)	477 (60%)	515 (56.5%)	
10-y follow-up	64 (56%)	536 (67%)	600 (65.8%)	
Total	67 (59%)	538 (67.5%)	605 (66.4%)	
Dialysis vintage until KTX (days, median, IQR)	3296 (1892-4465)	1895 (992-3807)	1972 (1023-4019)	$p < .01$ (χ^2 test)

BMI, body mass index; cPRA, calculated panel reactive antibodies; HS, highly sensitive; IQR, interquartile range; KTX, kidney transplant; NH, lower level of sensitization.

better survival for the HS group ($P < .001$), although the curves have a similar slope and a small absolute difference in survival at 10 years.

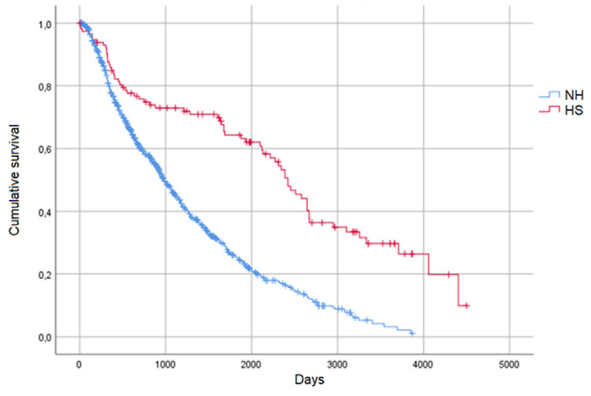

Fig 1. Overall population: time (days) from enlisting to transplantation. HS (cPRA ≥ 80%) vs patients with an NH (cPRA < 80%), $p < .01$. cPRA, calculated panel reactive antibodies; HS, highly sensitive; NH, lower level of sensitization.

To better understand which variables impacted on this result, we performed Cox regression. A multivariate Cox regression (including age at listing, BMI, presence of cardiovascular, neoplastic or infectious comorbidities, PRA, blood group, type of dialysis, and HIV status) was performed with a significant result ($P = .012$). Among the selected variables, only age at listing and blood group were individually significant, so we simplified the regression. Including only age at listing and blood group, the model retained statistical significance ($P < .01$), with older age (expB = 1.115) and group B (expB = 16.5 compared to group 0) being associated with worse survival. In the absence of a direct relationship between immunization status and clinical fitness, this result could be an expression of the homogeneous standards of evaluation of kidney transplant candidates in our center, with a comparable distribution of cardiovascular, oncologic, and infectious comorbidities among HS and NS subjects (Table 2 shows the frequencies, without statistical significance). On the other hand, group B is rare in Italy, so the lower chances of getting a transplant could explain the worse measured survival, but the relatively small size of the considered sample does not allow to draw definitive conclusions.

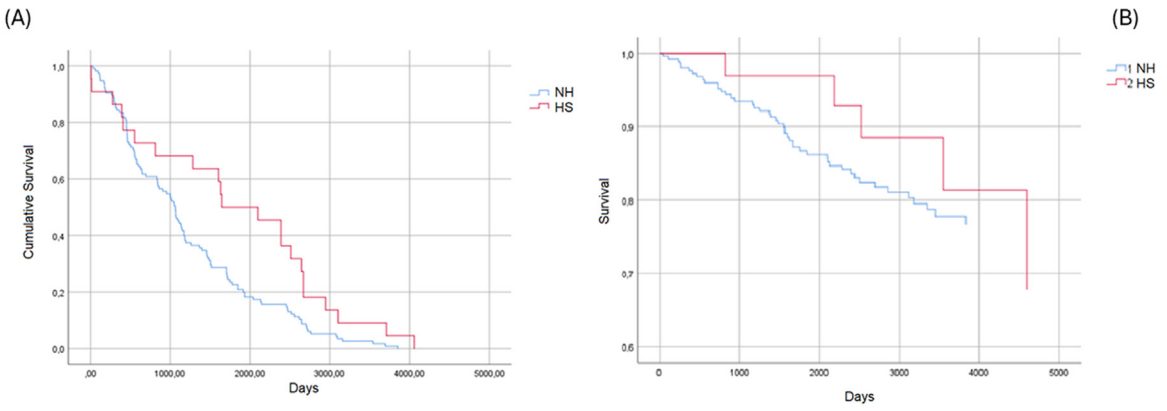

Fig 2. Modena province population survival analysis. HS (cPRA ≥ 80%) vs patients with an NH (cPRA < 80%). Time (days) from enlisting to transplantation **(A)**, $p < .05$. Time (days) from listing to death **(B)**, $p < .001$. cPRA, calculated panel reactive antibodies; HS, highly sensitive; NH, lower level of sensitization.

Table 2. Modena Province Population Characteristics: HS (cPRA ≥ 80%) Vs Patients With an NH (cPRA < 80%)

Modena population	HS	NH	TOTAL	*p* Value
Patients, n	32 (14%)	190 (86%)	222	
Age at listing (years, median, IQR)	47 (37-56)	53 (44-60)	51 (43-59)	$p < .05$ (χ^2 test)
Gender, M/F	M 16 (50%) F 16 (50%)	M 129 (67%) F 61 (33%)	M 145 (65%) F 77 (35%)	$p < .05$ (χ^2 test)
BMI (kg/m^2, median, IQR)	23 (21-26)	25 (22-27)	25 (22-27)	$p = 0.5$ (Mann-Whitney test)
Comorbidities				
Diabetes	1 (3.2%)	23 (12.1%)	24 (10.8%)	$p = .17$
Cardiovascular	17 (53.1%)	111 (58.4%)	128 (57.6%)	$p = .31$
Previous cancer	8 (25%)	31 (16.3%)	39 (17.6%)	$p = .23$ (χ^2 test)
N listed for second or third transplant	8 (25%)	12 (6%)	20 (9%)	$p < .05$ (χ^2 test)
Type of dialysis:				
Hemodialysis	24 (75%)	140 (73%)	164 (73.9%)	$p = .95$
Peritoneal dialysis	8 (25%)	50 (26.3%)	58 (26.1%)	(χ^2 test)
cPRA (%, median, IQR)	91 (84-99)	3 (0-10)	3 (0-35)	$p < .05$ (Mann-Whitney test)
Days on the waiting list (median, IQR)	1871 (618-2663)	1062 (471-1716)	1072 (462-1914)	$p < .05$ (Mantel Cox test)
N Transplanted 15 y follow-up	22 (68%)	115 (61%)	137 (62%)	$p = .6$ (χ^2 test)
Dialysis vintage until KTX (days, median, IQR)	2829 (1977-4208)	1678 (978-2617)	1871(1011-3562)	$p = .12$ (Mantel Cox test)
N Deaths	5 (15%)	46 (25%)	51 (23%)	$p = .3$ (χ^2 test)
Causes of death:				
Cardiovascular events	2 (40%)	11 (23.9%)	13 (25.4%)	$p = .4$ (CVE vs Cancer)
Cerebrovascular events	0	4 (8.7%)	4 (7.8%)	(χ^2 test)
Cancer	3 (60%)	7 (15.2%)	10 (19.6%)	
Infectious	0	5 (10.8%)	5 (9.8%)	
Unknown	0	19 (41.3%)	19 (37.3%)	

BMI, body mass index; cPRA, calculated panel reactive antibodies; CVE, cardiovascular events; HS, highly sensitive; IQR, interquartile range; KTX, kidney transplant; NH, lower level of sensitization.

DISCUSSION

The Italian Kidney Allocation System operates at two levels: regional and national. Patients on the list are considered for donors procured in the specific region of registration; each candidate can be registered in a maximum of two Italian regions. Until 2020, each region had its own allocation algorithm, which was then unified under the Italian National Kidney Allocation Algorithm (INKA).

In Emilia Romagna, the Italian region where our center is located, the order of recipients for allocation has been defined considering the blood group (identical), age difference between the donor and the recipient, year of dialysis, time on the waiting list, and HLA match. Urgency criteria (malfunctioning vascular access and recent ileal neobladder) are in place that start regionally and can be extended nationally after 3 months, allowing access to all available Italian donors. As to expanded criteria donors, there is no allocation difference between HS and NH patients. After 8 years on the waiting list and a peak PRA > 90%, patients have access to the National Hyperimmune Program (NHP), which allows the allocation of donors found throughout Italy, with compatible blood groups and no minimum HLA compatibility requirement. Expanded criteria donors are not offered for these patients on the NHP. The average waiting time from enrollment to transplantation is 3 years, even after enrollment in the NHP.

Our data describe the impact of HLA sensitization, measured by cPRA, on access to kidney transplantation and on survival of waitlisted patients at the Modena Transplant Center.

The term HS refers to a subject with a high level of preformed anti-HLA antibodies, as a consequence of previous exposure to non-self-tissues, such as pregnancy, blood transfusions, or previous transplants. The degree of sensitization is usually expressed as PRA. In the original works by Terasaki, PRA was obtained by incubating the lymphocytes of 10 to 40 randomly chosen donors with the serum of each recipient. The presence of cytotoxic antibodies directly relates to a positive crossmatch; thus PRA describes the frequency of positive cross matches that could be expected for a specific patient against a chosen population [7]. Although highly specific, this methodology is poorly sensitive, and, for this reason, it has been now substituted by cPRA, which estimates the likelihood of finding a suitable donor based on the prevalence in the recipient's serum of unacceptable anti-HLA antibodies against the reference population (eg, a cPRA of 90% describes the presence of anti-HLA antibodies in the patient's serum against 90% of potential donors), demonstrated with flow cytometry or solid phase assays [8,9]. The definition of unacceptable antibodies can vary among transplant centers, it is usually based on a Median Fluorescence Intensity (MFI) between 1000 and 5000 (3000 in the Modena Center), although even weaker values seem to have an impact on long term outcomes [10−12].

As a consequence, every subject with a PRA over 0% can be considered HS, but there is not a unanimous consensus about the threshold for the definition of HS.

In the United States, according to Organ Procurement and Transplantation Network policies, a patient with a cPRA greater than 98% is considered highly sensitized, although for donors with a Kidney Donor Profile Index less than or equal to 20%, cPRA strata are taken into consideration (0-20; 21-79; 80-98; 99; and 100%), suggesting 80% as a cutoff value for broad sensitization [13]. In Europe, reference values vary between transplant centers and allocation systems. For instance, the Eurotransplant kidney allocation policy considers patients with a cPRA equal or greater than 85% as HS [14]. In Italy, a subject with a cPRA equal or greater than 80% is considered HS and, since 2009, eligible for priority allocation through the NHP when waiting on the list for more than 10 years. This policy was updated in 2014, reducing the minimum waiting time to 8 years, and again in 2017 by switching the sensitization criteria to a maximum cPRA over 90% [15].

For the sake of our study, we thus set a cPRA cutoff value of 80% to distinguish between HS and NS subjects.

The degree of sensitization is directly linked to the time spent on the waiting list. The higher the cPRA of the recipient the longer the waiting time, which can be multiplied by a factor of up to 4 for HS patients [11]. A prolonged stay on dialysis determines an increased HR of drop out for clinical deterioration, although data on mortality after being canceled from the waiting list are frequently missing, because dropped-out patients are lost to follow-up by the transplant centers [16].

HS patients with cPRA ≥ 80% have significantly reduced yearly transplantation ratios unless they are favored by specific allocation policies [17]. The European experience demonstrated how donor pool restriction based on unacceptable antigens, which aims to avoid positive crossmatch in recipients with preformed anti-HLA antibodies, ensures better outcomes and lower rejection rates [18,19]. On the other hand, it can be a disadvantage in terms of waiting time for HS patients with fewer matching options [20]. As an inevitable consequence, broadly HS patients' prevalence increases over the years on the waiting list. Within Eurotransplant candidates with a cPRA ≥ 85%, it increased from 2% to 5.6% from 2011 to 2019 [21]. In Italy, according to the National Transplant Center reports, 304 active patients on the kidney waiting list had a cPRA > 80% and a dialysis vintage of at least 8 years (4.7% of the total listed population) at the end of 2017 [15,22].

Our results are consistent with literature, HS subjects have a longer waiting time before reaching the goal of transplantation, that can be quantified as 1.75 times higher after 3 years of follow up, and 2.6 times higher after 5 years. A longer waiting time associates with an inferior transplantation rate, about −45% at 3 years of follow up. This translates into a significantly higher dialysis vintage for HS patients (median = 9 vs 5.1 years), and reduced access to transplantation despite a favorable score for higher cPRA in the allocation algorithm and dedicated programs for HS subjects.

We did not observe higher mortality in the HS group, despite a greater amount of time spent on dialysis. In our study, these patients are more frequently female patients (because of the impact of pregnancy on the immunological status) and younger (a more reactive immune system relates to a higher risk of sensitization), therefore exposed to reduced cardiovascular risk, that could justify the improved survival that, according to our data,

seem to vary by approximately 6% per year of age at enrollment.

HS subjects are, in other words, prone to longer survival on the waiting list and, consequently, to a longer dialysis vintage. This phenomenon translates into an individual burden and a social cost, in terms of health care expenses and a reduction in the active workforce. HLA sensitization transforms individuals otherwise fit for KTX into long waiters, with the prospect of a progressive deterioration of their clinical conditions and life quality [23,24].

CONCLUSIONS

In conclusion, it is clear that HS is a population that deserves the highest commitment in terms of resources and strategies to favor an improvement in transplantation rates, with a significant impact on the wellbeing of the individual and of the community. The first goal is surely an early referral to a KTX center for young end-stage kidney disease affected subjects, the second step in line would be a strong commitment to living kidney donation, which allows more effective desensitization strategies (eg, AB0 incompatible KTX) and access to kidney paired donation programs [25]. When these targets are missed or unreachable, there is room left for innovative desensitization strategies (eg, imlifidase), which are, at the moment, affected by heavy costs that could be eventually overcome by the avoided years on dialysis [26].

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ETHICAL STATEMENT

The study was approved by the Area Vasta Emilia Nord (AVEN) Ethical Committee no. 335/2022/OSS/AOUMO SIRER ID 4362.

AUTHOR CONTRIBUTIONS

GM substantially contributed to the conception and design of the work, analysis, and interpretation of the data for the work and to its drafting. JP substantially contributed to data analysis and drafting. LT, LM, GO, AP, and MF substantially contributed to the acquisition of the data for the work and to its drafting. NM substantially contributed to statistics and data analysis. SDS substantially contributed to the critical revision of the work for important intellectual content. GD substantially contributed to the conception of the work, to its critical revision for important intellectual content and to the final approval of the paper. All the authors gave final approval of the published version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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