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Prevalence and Risk Factors for Mortality among COVID-19 Patients Hospitalized in Karachi City Pakistan

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ABSTRACT

Background: **Corona virus disease (Covid -19) is the most contagious form of the disease of present time. Therefore, the risk factors which proliferate the spread and hinders the better outcome should be identified. There is gross difference in the spread and outcome of covid 19 in different region of the world. There is need to identify these factors in different communities of the globe.**

Material and method: **This is a retrospective observational cohort study of Covid -19 patients admitted during the study period. Institutional and ethical review board permission was taken prior to the study. Univariate and multivariate binary logistic regression was run and odds ratio with 95% confidence intervals were obtained. P value of ≤ 0.05 was considered significant. Outcome variables were recovery and death.**

Results: **There were 840 patients admitted between the study duration, while 704 (83.8%) were included in our study. There were 491(69.7%) males and 213(30.3%) females. The mean age of the population was 54.6±15.5 years. All continuous variables were categorized according to binary outcome (recovered and death) of patients. In Logistic regression analysis we found that patients in age group of 51-65 years died 2.5 time more than patients of age ≤ 50 years. Similarly, the patients within age group of > 65 died 4.5 times higher than ≤ 50 years of age (p<0.001). Male patients died 1.5 times more than females. Among all comorbid conditions HTN had significant effect on death, they died 1.5 times more than normotensive patients. In multivariate logistic regression analysis, the age groups had same significant effect on death when adjusted with other parameters, while effect of gender vanished. Similarly, the effect of HTN was also abolished when other factors were included in analysis.**

Conclusion: **We concluded that there is an urgent need of reevaluation of the traditional risk factors associated with viral epidemic and understanding the changing paradigm of epidemiology emerging out from this epidemic in both developed and developing counties. There is need of more data from developing world to elucidate the risk factors.**

Keywords: risk factors, COVID-19, developing countries, Pakistan, pandemic, outcome.

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I. Introduction

Corona virus disease (COVID-19) is the most contagious form of the disease of present time. The first case was diagnosed in China on 8 December 2019 and within a span of three month was declared a global emergency by WHO [1]. COVID-19 tends to spread symptomatically as well as asymptomatically with approximately 10% of diagnosed cases progress to critical disease [2].

The risk factors were evaluated in different studies, for example in U.K Biobank, analysis of 428,225 patients evaluated for modifiable and non-modifiable risk factors. After multivariable adjustment, modifiable risk factors were found to be high body mass index, smoking, physical fitness, hypertension (HTN), while non-modifiable risk factors were recognized to be older age, male sex, black ethnicity, socioeconomical deprivation, long standing illness and high Cystatin C [3]. In the same way, in other part of Europe prevalence of risk factors calculated among elderly population. The risk factors like HTN, chronic lung disease, cardiovascular disease, cancer, diabetes (DM) and obesity were evaluated. A total of 75.3% of the study population had at least one risk factor for severe COVID-19, 45.9% had at least two factors and 21.2% had at least three risk factors. The prevalence of underlying medical conditions ranged from 4.5% for cancer to 41.4% for HTN, and the region-specific prevalence of having at least three risk factors ranged from 18.9% in Northern Europe to 24.6% in Eastern Europe [4]. In China the risk factors for COVID-19 were recognized to be older age, White cell count, glucose level, fever, and asthma along with female gender in some group of the patients [5]. Similar risk factors were recognized in neighboring countries like Bangladesh and India [6], [7].

Despite the presence of similar risk factors in other part of the world, there is a gross variation in the diagnosis of new cases and cumulative deaths in different region of the world. According to WHO, for example, the cumulative death in Americas and Europe till December 2020 was 872486(47%) and 588770(32%) respectively as compared to Eastern Mediterranean 1220061 (6%) and African region 43592(2%). Similarly, the diagnosis of the cumulative cases were 36 million and 26 million in America and Europe respectively as compared with Eastern Mediterranean 4.9 million and Africa 1.9 million [8]

There might be some other risk factors than the traditional risk factors which were evaluated in above mentioned studies. For instance, countries with high values of disability adjusted life years, lost to cardiovascular diseases, cancer and chronic respiratory disease had highest value of fatality rate. Fatality rate is also found to be positively associated the share of population over 70 years, GDP (Gross domestic product) per capita and level of democracy [9]. Pakistan was thought to be the vulnerable to COVID-19 associated morbidity and mortality due to poor health care system, behavior of population [10]. But all predictions were failed when Pakistan showed a drastic decline in the incidence and mortality due to COVID-19 [11]. There seems a "reverse epidemiology" of COVID risk factors and outcome in the two worlds i.e., developing and developed world. This study examined the risk factors and outcome of COVID-19 infection in a population of a developing country like Pakistan.

II. Material and Method

This is a retrospective observational cohort study of COVID-19 patients admitted in COVID-19 unit of Indus Hospital Karachi from 1st of March 2020 to 30th of Sep 2020. We included patients of all ages and the diagnosis of COVID-19 was made by RT-PCR, performed through nasopharyngeal extraction of viral specimen. Permission from the institutional ethical review committee was taken prior to conduction of study. History, clinical examination, laboratory investigations, and ultrasound imaging of the kidneys was acquired from the Health Management Information System (HMIS) record of the patients. Data was collected on a structured proforma which included variables like age, gender, comorbid conditions, clinical presentation, hemodynamic status, and lab parameters. Outcome variables were recovery, and death.

Statistical analysis: The data was entered and analyzed in IBM SPSS version 21. Cleaning and coding of data was done prior to analysis. Mean±Std were computed for continuous variables, while categorical parameters were expressed in frequencies with percentages. Cross tabulation was done to see the distribution of variables according to outcome of disease, then to see the observe amount of effect of parameters on outcome of COVID patients, univariate and multivariate binary logistic regression was run and odds ratio with 95% confidence intervals were obtained. P value of $\leq$ 0.05 was considered significant.

III. Results

There were 840 patients admitted between March to 30 September 2020, while 704 (83.8%) were included in our study. Male were 491(69.7%), while 213(30.3%) were female (Fig. 1).

The mean age of our patients was 54.6±15.5 years with the minimum of 1 years and maximum of 95 years and males were predominant 491(69.7%). The most common symptom of COVID was shortness of breath 520(74%) while the most prevalent sign was fever 211(30%) (Table I).

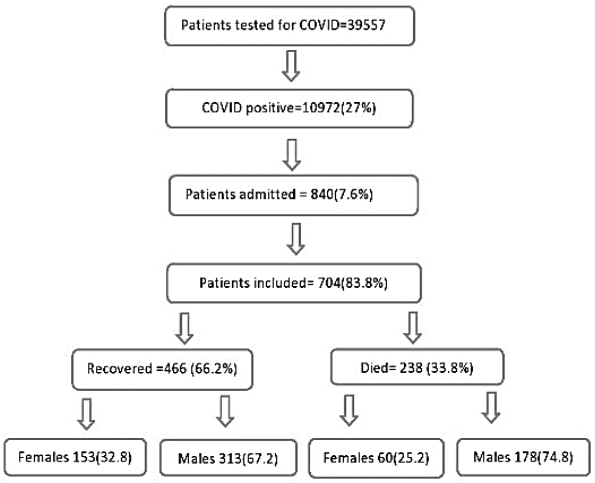

Fig. 1. Distribution of population.

TABLE I: DEMOGRAPHIC AND CLINICAL PARAMETERS OF PATIENTS = 704

Variables	Mean ± std/n (%)
Age	54.6±15.5
Male/Female	491(69.7)/213(30.3)
Pulse(beats/min)	90 ± 19.4
Systolic BP (mm of Hg)	129.4 ± 22.6
Diastolic BP (mm of Hg)	75.2 ± 14
RR (breaths/min)	24.4 ± 6.1
Fever	211(30)
SOB	520(74)
Cough	307(45)
Oliguria	136((19.3)
Confusion	89(12.6)
Drowsiness	84(11.9)
Edema	67(9.5)
Vomiting	56(8)
volume depletion	38(5.4)
Anorexia	34(4.8)
Nausea	34(4.8)
Seizures	6(0.9)
ACEI/ARB	85(12.1)
Aspirin	199(28.3)
Statins	153(21.7)

BP Blood pressure, RR Respiratory rate, SOB Shortness of breath, ACEI Angiotensin converting enzyme inhibitor, ARB Angiotensin receptor blocker.

TABLE II: DISTRIBUTION OF AGE, GENDER, COMORBID, COMPLICATIONS AND TREATMENT ACCORDING TO OUTCOME OF COVID-19 PATIENTS

Variables		Recovered 466(66.2%)	Died 238(33.8%)	Total
Age(years)	≤50	200(42.9)	47(19.7)	247(35.1)
	51-65	189(40.6)	113(47.5)	302(42.9)
	>65	77(16.5)	78(32.8)	155(22)
Gender	Male	313(67.2)	178(74.8)	491(69.7)
	Female	153(32.8)	60(25.2)	213(30.3)
Comorbid				
Diabetes mellitus	Yes	196(42.1)	116(48.7)	312(44.3)
	No	270(57.9)	122(51.3)	392(55.7)
Hypertension	Yes	265(56.9)	158(66.4)	423(60.1)
	No	201(43.1)	80(36.6)	281(39.9)
Ischemic heart disease	Yes	76(16.3)	52(21.8)	128(18.2)
	No	390(83.7)	186(78.2)	576(81.8)
Complications				
Acute kidney injury	Yes	61(13.1)	147(61.8)	208(29.5)
	No	405(86.9)	91(38.2)	496(70.5)
Acute coronary syndrome	Yes	13(2.8)	15(6.3)	28(4)
	No	453(97.2)	223(93.7)	676(96)
Congestive cardiac failure	Yes	19(4.1)	16(6.7)	35(5)
	No	447(95.9)	222(93.3)	669(95)
Peripheral vascular disease	Yes	7(1.5)	7(2.9)	14(2)
	No	459(98.5)	231(97.1)	690(98)
Thromboembolic event	Yes	12(2.6)	21(8.8)	33(4.7)
	No	454(97.4)	217(91.2)	671(95.3)
Treatment				
Methylprednisolone	Yes	315(67.6)	198(83.2)	513(72.9)
	No	151(32.4)	40(16.8)	191(27.1)
Remdesivir	Yes	67(14.4)	63(26.5)	130(18.5)
	No	399(85.6)	175(73.5)	574(81.5)
Tocilizumab	Yes	61(13.1)	79(33.2)	140(19.9)
	No	405(86.9)	159(66.8)	564(80.1)
Hydroxychloroquine	Yes	62(13.3)	41(17.2)	103(14.6)
	No	404(86.7)	197(82.2)	601(85.4)
Vasopressin	Yes	16(3.4)	184(76.5)	198(28.1)
	No	450(96.6)	56(23.5)	506(71.9)
Ventilatory support	Yes	15(3.2)	170(71.4)	185(26.3)
	No	451(96.8)	68(28.6)	519(73.7)
Hemodialysis support	Yes	86(18.5)	70(29.4)	156(22.2)
	No	38(81.5)	168(70.6)	548(77.8)

For analysis purpose, we categorized all continuous variables and obtained their frequencies according to binary outcome (recovered and death) of patients, suffering from COVID-19. We observed that majority of patients belonged to age group of 51-65 years 302(42.9%) and hence majority of patients who died were from the same age group 113(47.5%). Similarly male patients were more in number 491(69.7%) and they encountered death more than female patients 178(74.8%) vs 60(25.2%), respectively. The most common comorbid was HTN 423(60.1%) in our patients and these patients were more prone to death than normotensive 66.4% vs 36.6%. Acute kidney injury (AKI) was the most prevailing complication of COVID-19 in our cohort 208(29.5%) and these patients suffered death more as compared to patients without AKI and other complications 147(61.8). Patients were treated with different medications according to their clinical status and progression of disease. Methylprednisolone was given to 513(72.9%) patients in which 315 recovered while 198 died. while remaining of the treatment like Remdesivir, Tocilizumab and Hydroxychloroquine were given to a smaller number of patients. Patients who developed severe or critical disease and required support in the form vasopressors, ventilator and hemodialysis succumbed to death more as compared to those who did not need these supports 184(76.5%), 170(71.4%) and 70(29.4%), respectively (Table II).

Our majority of patients who died had high TLC 182(76.5%) in contrast to those who had normal count 56(16.4%). Likewise, high number of patients had lymphopenia 594(85.4%) and therefore more death was observed in those who had low lymphocyte count 221(37.2%) than those who had normal counts 17(7.1%). Similarly, low albumin was more prevalent in COVID patients 499(63.8%), among patients who died, 199(83.6%) were hypoalbuminic as compared to the patients with normal level 39(16.4%). Low bicarbonate levels were also more frequently observed in this group of patients as 482(68.5%) and 184(77.3%) patients died in comparison with those who had high or normal bicarbonate levels (Table III). All laboratory parameters related to COVID-19 infection were raised in our patients and the patients who died of COVID had more raised levels of Lactate dehydrogenase (LDH), C-reactive protein (CRP), Ferritin and D-Dimer (Table III).

In Logistic regression analysis we found that patients in age group of 51-65 years died 2.5 time more than patients of age ≤ 50 years. Similarly, the patients within age group of >65 died 4.5 times higher than ≤ 50 years of age ($p<0.001$). Male patients died 1.5 times more than females. Among all comorbid conditions HTN had significant effect on death, they died 1.5 times more than normotensive patients. Acute kidney injury was the most dreadful complication with COVID-19 infection, as the death was 10.7 times more in patients with AKI than with non-AKI ($P<0.001$). Similarly, patients who suffered with acute coronary syndrome (ACS) and thromboembolic event (TEE) died 2.3 and 3.7 times more, respectively. Patients with sepsis (TLC >11000) died 5.2 times more than the patients with normal leucocyte count ($p<0.0001$).In the same way, low level of platelets, lymphocytes and albumin had 2.9,3.2 and 4.4 times, respectively died more than the patients who had normal range of these labs ($p<0.001$).Electrolytes disturbance also had an impact on mortality as we found that patients who had hypernatremia, hyperkalemia, hypobicarbonatemia (acidosis) and hyperbicarbonatemia (alkalosis) died 17.4,4.4,2.5 and 2 times more, respectively than those who had normal levels of

these electrolytes (p<0.001). Patients with high levels of LDH, Ferritin, D-Dimer and Procalcitonin had 11.2, 3.6, 6.7 and 4.1 times more death, respectively (p<0.001). To adjust the independent effect of variables on outcome of COVID-19 we did multivariate logistic regression analysis and kept all these variables in final model and found that age groups had same significant effect on death when adjusted with other parameters, while effect of gender vanished. Similarly, the effect of HTN was also abolished when other factors were included in analysis.

TABLE III: FREQUENCY OF LAB PARAMETERS ACCORDING TO OUTCOME OF COVID-19 PATIENTS

Laboratory variables		Recovered 466(66.2%)	Died 238(33.8%)	Total
Hemoglobin (gm/dl)	<12	180(38.6)	101(42.4)	281(39.9)
	≥12	286(61.4)	137(57.6)	423(60.1)
Total leucocyte count	>11	180(38.6)	182(76.5)	362(51.4)
	≤11	28(61.4)	56(16.4)	342(48.6)
Platelets	<150	57(12.2)	68(28.6)	125(17.8)
	≥150	409(87.9)	170(71.4)	579(82.2)
Lymphocyte count	<20%	373(80)	221(37.2)	594(84.4)
	≥20%	93(20)	17(7.1)	111(15.6)
Albumin(gm/dl)	<3.5	250(53.6)	199(83.6)	499(63.8)
	≥3.5	216(46.4)	39(16.4)	255(36.2)
Sodium (meq/L)	Eunatremia	330(70.8)	131(55)	461(65.5)
	Hyponatremia	126(27)	38(16)	164(23.3)
	Hypernatremia	10(2.1)	69(29)	79(11.2)
Potassium (meq/L)	Normokalemia	407(87.3)	166(69.7)	573(81.4)
	Hyperkalemia	36(7.7)	64(26.9)	100(14.2)
	Hypokalemia	23(4.9)	8(3.4)	31(4.4)
Bicarbonate (meq/L)	Normal	115(24.7)	28(11.8)	143(20.3)
	Low	298(63.9)	184(77.3)	482(68.5)
	High	53(11.4)	26(10.9)	79(11.2)
Lactate dehydrogenase (u/l)	<250	51(10.9)	5(2.1)	56(8)
	250-500	259(55.6)	62(26.1)	321(45.6)
	>500	156(33.5)	171(71.8)	327(46.4)
C reactive protein(mg/L)	>10	427(91.6)	224(94.1)	651(92.5)
	≤10	39(8.4)	14(5.9)	53(7.5)
Ferritin(ng/ml)	>250	403(86.5)	228(95.8)	631(89.6)
	≤250	63(13.5)	10(4.2)	73(10.4)
D-Dimer	>0.4	294(63.1)	219(92)	513(72.9)
	≤0.4	172(36.9)	19(8)	191(27.1)
Procalcitonin(ng/ml)	>0.49	193(41.4)	177(74.4)	370(52.6)
	≤0.49	273(58.6)	61(25.6)	334(47.4)

TABLE IV: AMOUNT OF EFFECT OF VARIABLES ON DEATH OF COVID PATIENTS

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI Lower-Upper	p value	Odds ratio	95% CI Lower- Upper	p value
Age 51-65 years	2.5	1.7-3.8	<0.001	2	1.1-3.6	0.024
Age >65 years	4.3	2.8-6.7	<0.001	3.2	1.6-6.4	0.001
Male	1.5	1.01-2.1	0.035	1.2	0.68-2.1	0.54
Diabetes mellitus	1.3	0.96-1.8	0.092	0.9	0.55-1.5	0.695
Hypertension	1.5	0.08-2.1	0.015	1.1	0.62-1.8	0.845
Ischemic heart disease	1.4	0.97-2.1	0.072	0.84	0.44-1.6	0.599
Acute kidney injury	10.7	7.4-15.6	<0.001	4	2.4-6.8	<0.001
Acute coronary syndrome	2.3	1.1-5	0.028	3.9	1.3-11.7	0.015
Congestive cardiac failure	1.7	0.86-3.4	0.13	0.48	0.17-1.3	0.152
Peripheral vascular disease	2	0.69-5.7	0.204	0.5	0.11-2.4	0.381
Thromboembolic event	3.7	1.8-7.6	<0.001	2.7	0.85-8.6	0.093
Hemoglobin <12mg/dl	1.2	0.85-1.6	0.329	0.76	0.45-1.3	0.329
Total leucocyte count >11g/dl	5.2	3.6-7.4	<0.001	2.8	1.7-4.7	<0.001
Platelets <150	2.9	1.9-4.3	<0.001	1.8	0.97-3.5	0.061
Lymphocyte count <20%	3.2	1.9-5.6	<0.001	2.1	0.88-4.9	0.095
Albumin <3.5g/dl	4.4	3-6.5	<0.001	3.6	2.1-6.4	<0.001
Hyponatremia	0.76	0.5-1.2	0.195	0.32	0.17-0.59	<0.001
Hypernatremia	17.4	8.7-34	<0.001	3.9	1.7-8.7	0.001
Hypokalemia	0.85	0.37-1.9	0.705	1.8	0.58-5.3	0.316
Hyperkalemia	4.4	2.8-6.8	<0.001	2.2	1.1-4.3	0.025
Hypobicarbonatemia	2.5	1.6-3.9	<0.001	1.8	0.94-3.5	0.075
Hyperbicarbonatemia	2	1.1-3.8	0.025	1.6	0.64-4.2	0.304
Lactate dehydrogenase250- 500 U/L	2.4	0.94-6.4	0.068	2.9	0.86-9.9	0.085
Lactate dehydrogenase >500 U/L	11.2	4.4-28.7	<0.001	7.7	2.3-26.3	0.001
C reactive Protein >10	1.5	078-2.75	0.239	1	0.39-2.7	0.97
Ferritin >250	3.6	1.8-7.1	<0.001	0.69	0.25-1.9	0.47
D Dimer >0.49	6.7	4.1-11.2	<0.001	2.6	1.3-5.1	0.006
Procalcitonin >0.5	4.1	2.9-5.8	<0.001	2.4	1.5-4	0.001

Reference categories: Age<50 years, Female, Absence of comorbid and complications,Hb≥12,TLC≤11,Platelet≥150,Lymphocyte count≥20%,Albumin≥3.5,Eunatremia,Normokalemia,NormalBicarb,LDH<250,CRP≤10,Ferrittin≤250,Dimer≤0.49,Procalcitonin≤0.4

Among all complications AKI and ACS had remain significant effect in multivariate analysis to, although odds ratio of AKI decreased from 10.7 to 4.0. On the contrary, the odds ratio of ACS was increased up to 3.9 times. The odds ratio of high total leucocyte count (TLC) and low albumin also decreased in adjusted model but retained their significant effect on death. On the other hand, low platelets and lymphopenia lost their significant impact on outcome in multivariate analysis. Both hypernatremia and hyperkalemia had significant impact on death in multivariate model too, although their odds ratio were decreased. On the other hand, bicarbonate lost its effect on outcome of patients in adjusted analysis. Patients with high levels of LDH, D-Dimer and Procalcitonin maintained their significant impact on death in adjusted analysis, while effect of Ferritin was eliminated when adjusted with other factors (Table IV.)

IV. Discussion

This is the first study from this country presenting the risk factors for COVID-19 admitted in Indus hospital Karachi, a tertiary care hospital. There is a vast difference in the incidence, prevalence and case fatality rate observed in the two economically divided worlds (the developing and the developed world). The possible explanation could be the differences in factors like social behavior, concept of hygiene emerged in the western countries and expropriation of health from physician to state over the last 200 years after industrialization and development [12]-[14].

In our population females were less effected, admitted and faced death as compared to males, as observed in other studies too, although this effect was lost in adjusted analysis [15]. There are many hypotheses for this gender difference for the predilection of COVID-19 in males and protection for the females. Firstly, in comparison with innate and acquired immunity, females have higher counts of CD4+ T cells, more vigorous CD8+ T cell cytotoxic projection, and increased production of immunoglobulin from B cell compared to males. Secondly, females produce more interferon type I. Thirdly, the X chromosomes contain many immune related genes and lastly, there is an effect of estradiol enhancement on immune system [16]. But the effect of all these factors in our population is hard to predict as overall health status of female in our society is not according to the definition of health by WHO [17]. On the other hand, social behavior like hand washing was also thought to be a cause of low prevalence of COVID-19 in females, as it is an observation that hand washing is mostly practiced by female in a natural setting [18]. The social practice of hand washing before and after meal and after using washroom along with offering prayers which need not only washing of hand, but cleaning of nose and throat might have protective effect in Muslim community like Pakistan [19], [20].

Among the co-morbid condition, we found hypertension played an important role in increasing mortality. In a meta-analysis of 71 studies comprising 216,843 patients' hypertension was significantly associated with death. We did not find any association of DM, IHD, and CCF with mortality [15]. Patients who were complicated with acute kidney injury in our population showed devastating outcome and acute kidney injury in COVID-19 patients recognized as predictor [21], [22].

Effect of treatment was also not very encouraging in our patients. Methylprednisolone, Remdesivir, Tocilizumab and Hydroxychloroquine were used in different patients according to the WHO and local guidelines. The overall impact of treatment was not supportive in improving the survival, also concluded recently in a large, randomized trial [23].

Among laboratory parameters we found a significant effect of high TLC and low lymphocyte count, low albumin high LDH on mortality, but in multivariate analysis AKI and ACS high TLC, low albumin, hypernatremia, and hyperkalemia were significantly associated with bad outcome. This effect was also observed in other studies [24].

Our study has few limitations because of its observational nature and retrospective data collection, although the sample size is adequate, and no other data is published with this number from this country. The impact of COVID-19 is severe all around the world but surprisingly it affected the developed nations more gravely than the developing countries. The possible explanation could be the different epidemiological factors observed during the epidemic, as we mentioned, rich economy, high GDP, high education, concept of hygiene does not prove to provide protection from epidemic [9], [12]. The epidemiology and demography of COVID-19 is different in this population. Therefore, despite the presence of the traditional risk factors which were thought will deteriorate the outcome of the disease in this population, the mortality was not as high as we are still observing in the western population.

V. Conclusion

We concluded that there is a dire need of reassessing the traditional risk factors associated with viral epidemic and understanding the changing paradigm of epidemiology emerging out from this epidemic in both developed and developing counties. There is an obligation to have more data from developing world to elucidate the risk factors, so that people and countries can protect themselves with this new dynamic of disease spread observed in corona pandemic.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures

The authors declare that they have no conflict of interest.

COMPLIANCE WITH ETHICS GUIDELINES

We have received a waiver of consent from the institutional review board (IRD_IRB_2020_04_017).

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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