

Comparison of Pregnant and Non-pregnant Women With COVID-19 Infection

Tania Maria Fernandez Hernandez,
Master in Medical Emergencies, Consultant
Pediatrics, The Cuban Hospital, Qatar.

Richard Alexander Sera Blanco,
Master in Medical Emergencies,
Consultant Emergency and Critical Care,
The Cuban Hospital, Qatar.

RICHARDSERABLANCO@GMAIL.COM

Teresa Sandra Erice Rivero,
Master in Integral Woman Attention,
Consultant Obstetrics and Gynecology,
The Cuban Hospital, Qatar.

Oreste Mojena Mojena,
Master in Medical Emergencies, Consultant
Pediatrics, The Cuban Hospital, Qatar.

Reynol Rubiera Jimenez
Master in Medical Emergencies,
Consultant Emergency and Critical Care,
The Cuban Hospital, Qatar.

Daniel Reynaldo Concepcion
Consultant Vascular Surgery,
The Cuban Hospital, Qatar.

***Corresponding Authors:** Richard Alexander Sera Blanco.

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ABSTRACT

Background: Covid-19 infected pregnant women has been reported worst outcome than non-pregnant due to physiological and immunological changes mainly in the third trimester of pregnancy.

Methods: Observational analytic retrospective study with Covid-19 infected 411 women, whose ranges of age were between 18 to 52 years old divided in two groups; 84 pregnant and 327 non-pregnant admitted in The Cuban Hospital of Qatar, since April 1st to June 30th of 2020. It was aimed to compare both groups according to clinical, laboratory, radiological and main outcomes. Analysis of frequencies, Ji Square, Variance and Odds Ratio were performed.

Results: Pregnant tended to be younger and predominated third trimester of pregnancy; obesity, vitamin D deficiency and asymptomatic infection prevailed in pregnant and were significant. Fever and cough were more frequent in non-pregnant. Chest X ray showed Focal Bilateral lesions prevailed in non-pregnant; most of pregnant did not do X rays. D- dimer and alkaline phosphatase were higher in pregnant, alanine amine transferase was higher in non-pregnant. 4 to 7 days of hospital stay

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Citation: Tania Maria Fernandez Hernandez, et al. Comparison of Pregnant and Non-pregnant Women With COVID-19 Infection. Journal of Clinical Medicine and Surgery. 2022;1(1):3.

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predominated in pregnant. Oxygen therapy, moderate and severe respiratory distress and intensive care unit admission were predominant in pregnant. No lethality was observed in pregnant with Covid-19 infection.

Conclusion: Covid-19 pregnant are younger and has higher probability of asymptomatic disease; but they have higher risk of co-morbidities, respiratory failure, intensive care admission and mechanical ventilation; mortality risk is higher in non-pregnant.

Keywords: Covid-19, Infection, Pregnant women, Respiratory distress syndrome, Ventilators.

I. INTRODUCTION

On December of 2019, Wuhan Health Commission in the Hubei province of China notified the World Health Organization (WHO) about 41 cases of pneumonia of unknown etiology [1]. These patients presented with symptoms such as fever, dyspnea, dry cough, and radiological findings showing bilateral lung glassy opacities; they were diagnosed as severe acute respiratory syndrome caused by an RNA Coronavirus 2 (SARS-CoV-2), belonging to the family Coronaviridae [2,3]. More than 80 % of the infections caused by the virus are mild to moderate and many patients were asymptomatic at the time of presentation [4]. The most common clinical findings are fever, dry cough, shortness of breath, myalgia or fatigue, and some patients report characteristic diarrhoea, loss of taste or smell at early stage of infection [5]. The virus may lead to the development of acute respiratory distress syndrome (ARDS) requiring Intensive Care Unit admission and death [5]. Typical laboratory abnormalities of Covid-19 infection mentioned are leukopenia, lymphocytopenia and increased D dimer, especially for severe patients [6]. Radiography and chest CT scan has shown frequent pulmonary consolidation and ground glass patchy infiltrates [7].

It has been considered Covid-19 infection as a special risk for pregnant women which [8]. Taking into account the presence of immunosuppression and associated physiological changes, pregnancy may cause high susceptibility to respiratory pathogens and severe pneumonia, which may require hospitalization in ICU and ventilatory support. It has been stated that clinical characteristics reported in pregnant women with confirmed SARS-CoV-2 infections are similar to those of non-pregnant with same condition [8].

At the beginning of the pandemic, Chen et al [9], reported that pregnant women with Covid-19 had fever, cough, myalgia, sore throat, malaise, gastrointestinal symptoms and shortness of breath upon admission. Elevated C-reactive protein, lymphopenia, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were the main laboratory findings. Most of them showed ground-glass shadows in Chest CT scans. Other authors [10] had stated that incidences of fever, cough and positive chest CT findings in pregnant women with COVID-19 are less than those in the normal population with Covid-19, but the rate of preterm labor is higher among pregnant with Covid-19 than among pregnant without SARS-Cov2.

Pereira et al [11], demonstrated in a study of pregnant women admitted with Covid-19 infection that one-third developed pneumonia. In spite of 5 % presented a critical state, no renal or cardiac failures or maternal deaths were reported; most of them had a favorable clinical course. Covid-19 infection may be associated with an increased risk of premature rupture of membranes, preterm delivery, fetal tachycardia, and fetal distress.

As the reviewed medical literature shows some conflicting evidence in regard with the characteristics of SARS-Cov2 infection in pregnant women; the aim of this study was to compare clinical, laboratory, radiology and outcomes of pregnant and non-pregnant women infected by Covid-19 virus.

II. PATIENTS AND METHODS

It was performed a retrospective observational analytic study with 411 women divided in two groups, 84 pregnant and 327 non-pregnant with range of age between 18 and 52 years; admitted in The Dukhan Hospital of Qatar with the diagnosis of Covid-19 infection, from April 2nd to June 30th of 2020. It was considered as a case-control type study, taking into account the pregnancy as an event and Covid-19 infection as a common condition. Main objective comprised a comparison of clinical, laboratory, radiological and outcome findings during hospital stay. Data were collected from the medical record department by responsible of the investigation. Pregnant and non-pregnant were compared according to the following variables; age, gestational age, co-morbidities, symptoms, chest X ray (CXR) findings; main laboratory results including leukocytes, D-dimer, alkaline phosphatase (ALK), alanine amine transferase (ALT), aspartate amine transferase (AST), ferritin, creatinine, lactic dehydrogenase (LDH) and creatinine. Oxygen therapy, presence of acute respiratory distress syndrome (ARDS), use of non-invasive (NINV) and invasive (INVV) mechanical ventilation, intensive care unit (ICU) admission and lethality were compared too. As an inclusion criterion for the study, it was considered the presence of a positive Polymerase Chain Reaction (PCR) test for Covid-19 virus, being the patients symptomatic or not.

Statistical analysis was performed with IBM SPSS Statistics statistical software (v26.0 Armonk, New York, USA). It was applied an analysis of relative and absolute frequencies for all variables. Analysis of variance (ANOVA) was done for continues variables and Ji square was done for nominal and categorical variables, applying the Fischer exact test. Odds Ratio with confidence intervals were calculated according to MedCalc on line calculator [12], and results were highlighted for pregnant. It was considered an alfa significance level of 95 %, if it was the case, 99 % was emphasized. This study was approved by Qatar Research Medical Counsel under number MRC-01-20-1032.

Obtaining the informed consent was waived, as all data were retrospectively recorded and no risk procedure, treatment or intervention was performed in any patient. It was respected patient confidentiality and the information obtained will be used only for advice and development of health systems.

III. RESULTS

Age groups depicted in TABLE 1 showed a prevalence of 25 to 34 years with 159 cases (38.7 %); pregnant predominated over non-pregnant and there was a statistically significant relation between pregnant state and distribution of age groups ($p < 0.05$; 95 % CI).

Table 1: Distribution of age groups.

Age (years)	Pregnant		Not Pregnant		Total	
	#	%	#	%	#	%

18 to 24	19	22,6	25	7,6	44	10,7
25 to 34	45	53,6	114	34,9	159	38,7
35 to 44	20	23,8	117	35,8	137	33,3
45 to 52	-	-	70	21,4	70	17
Total	84	20,4	327	79,6	411	100

Source: medical record. $p < 0.05$; 95

Distribution of gestational age in pregnant showed 24 or more weeks prevailed with 54 (64 %), followed by 12 to 24 weeks with 21 (25 %) and less than 12 weeks had only 9 cases (11 %).

Main comorbidities depicted in TABLE 2 exposed a predominance of obesity in both groups with 89 patients (21.7 %); according to observations it prevailed in pregnant and they had a statistically significant higher risk of obesity (OR 3.9; 95 % CI 2.3-6.5, $p < 0.0001$) than non-pregnant. Vitamin D deficiency had the second incidence having 58 patients (14.1%), it predominated in pregnant, and they had a statistically significant higher risk for vitamin D deficiency (OR 6.5; 95 % CI 3.6-11.8; $p < 0.0001$) than non-pregnant. Other co-morbidities had lesser incidence and didn't showed higher risk in covid19 infected pregnant. It was observed a statistically significant lesser risk of hypertension in pregnant (OR 0.2; 95 % CI 0.005-0.6; $p = 0.004$) than non-pregnant.

A total of 183 (44.5 %) patients had symptoms (see TABLE 2), and they were prevalent in non- pregnant with 151 cases (46.2 %). Symptomatic disease had a non-statistically significant 30 % of lesser risk in pregnant (OR 0.7; 95 % CI 0.4-1.2; $p = 0.18$) compared to non-pregnant. Fever (42.1%), sore throat (32.6 %) and myalgia (31.9 %) had the highest prevalence and they predominated in non-pregnant. Rest of the symptoms had lower incidence; although sore throat, chest pain and diarrhea showed a statistically significant reduced risk of presentation in pregnant.

CXR findings reflexed in TABLE 3 showed Focal Bilateral lesions were predominant having 92 patients (22.4 %), in which non-pregnant prevailed. Nevertheless, pregnant had a non-significant 40 % reduction risk of presentation for this finding (OR 0.6; 95 % CI 0.3-1.2; $p=0.16$). Not Done CXR had the second incidence with 82 patients (20 %); pregnant predominated and they had a very statistically significant higher risk of presentation (OR 34.6; 95 % CI 18.2-65.8, $p < 0.001$). Diffuse Unilateral, Diffuse Bilateral and Not Findings demonstrated statistically significant reduced risk of presentation in pregnant.

Hospital length of stay shown in TABLE 5 demonstrated 4 to 7 days was more frequent in pregnant and they had a statistically significant higher probability (OR 1.8; 95 % CI 1.1-2.9; $p = 0,01$) for this condition. 1 to 3, 8 to 14 and more than 14 days were more frequent in non-pregnant, and they had a non-significant reduced risk in pregnant. Mean D dimer and ALK were higher for pregnant (see TABLE 4) and both showed statistically significant difference ($p < 0.001$). Mean ALT value was higher in non-pregnant and was statistically significant ($p = 0.005$). Rest of laboratory determinations had no statistically significant difference among pregnant and non-pregnant.

Table 2: Distribution of main co-morbidities and symptoms.

Co- morbidities	Pregnant(84)		Non- Pregnant (327)		Total (411)		OR and Cifor pregnant			p value
	#	%	#	%	#	%	OR	Inf	Sup	
Obesity**	36	42,4	53	16,3	89	21,7	3,9	2,3	6,5	< 0,0001**
Vitamin D** deficiency	31	36,5	27	8,3	58	14,1	6,5	3,6	11,8	< 0,0001**
Diabetes mellitus	12	14,1	68	20,9	80	19,5	0,7	0,3	1,2	0,2
Bronchial Asthma	3	3,5	11	3,4	14	3,4	1,1	0,3	3,9	0,9
Hipertension	3	3,5	58	17,8	61	14,9	0,2	0,05	0,6	0,004**
Collagen	1	1,2	11	3,4	12	2,9	0,3	0,04	2,7	0,3
Steroids	1	1,2	2	0,6	3	0,7	1,9	0,2	21,8	0,6
Symptoms										
	#	%	#	%	#	%	OR	Inf	Sup	P value
Yes	32	38,1	151	46,2	183	44,5	0,7	0,4	1,2	0,18
No	52	61,9	176	53,8	228	55,5	1,3	0,85	2,3	0,18
Fever	27	32,1	146	44,6	173	42,1	0,6	0,4	1	0,03
Myalgia	22	26,2	109	33,3	131	31,9	0,7	0,4	1,2	0,21
Cough	16	19	71	21,7	87	21,2	0,8	0,5	1,5	0,59
Sore Throat	15	17,9	119	36,4	134	32,6	0,4	0,2	0,7	0,001**
Rhinorrhea	12	14,3	54	16,5	66	16,1	0,8	0,4	1,7	0,62
Chest pain	11	13,1	79	24,2	90	21,9	0,5	0,2	0,9	0,03**
Abdominal pain	10	11,9	59	18	69	16,8	0,6	0,3	1,3	0,18
SOB	14	16,7	67	20,5	75	18,2	0,7	0,4	1,4	0,43
Diarrhea	8	9,5	70	21,4	78	19	0,4	0,2	0,8	0,01**

Source: medical record. **p < 0.05; CI 95%

OR: Odd ratio. CI: Confidence interval. Inf: inferior. Sup: Superior. SOB: shortness of breath.

A total of 26 patients (6.3 %) needed oxygen therapy (see TABLE 6) and it was prevalent in pregnant. ARDS was present in 13 patients (3.2 %); it prevailed in pregnant and they had a non-statistically significant higher risk (OR 2.5; 95 % CI 0.8-7.9; p = 0.1) for this complication. Severe ARDS predominated in pregnant, and they had a non-significant higher risk. 11 women (2.7 %) were connected to non-invasive and invasive ventilation; pregnant predominated 4 (4.8 %) and had a non-significant higher risk. Use of INVV prevailed with 9 cases (2.2 %); it was predominant in pregnant and they had a non-significant higher risk. ICU admission prevailed in pregnant with 8 (9.5 %), but they had a non-significant higher risk for this condition. Only 1 non-pregnant patient died, which represented 0.2 % of the total sample.

Table 3: Chest X ray findings.

Chest X ray	Pregnant(n=84)		No pregnant (n=327)		Total (n=411)		OR and CI forpregnant			
	#	%	#	%	#	%	OR	Inf	Sup	p value
Focal unilateral	-	-	17	5,2	17	4,1	0,1	0,006	1,7	0,11
Diffuse Unilateral	1	1,2	92	28,1	93	22,6	0,03	0,004	0,2	0,0006**
Focal bilateral	14	16,7	78	23,9	92	22,4	0,6	0,3	1,2	0,16
Diffuse bilateral	4	4,8	48	14,7	52	12,7	0,3	0,1	0,8	0,02**
Not findings	5	6	70	21,4	75	18,2	0,2	0,1	0,6	0,002**
Not done	60	71,4	22	6,7	82	20	34,6	18,2	65,8	<0,001**

Source: medical record. **p < 0.05; CI 95% OR: Odd ratio. CI: Confidence interval. Inf: inferiorlimit. Sup: Superior limit.

Table 4: Main clinical laboratory results.

Lab Tests	Pregnant(n=84)		Non-pregnant(n=327)		p value
	mean	CI	mean	CI	
Leukocyte	7,9	7,2-8,6	7,8	7-8,6	0,93
Creatinine	41,2	33,9-48,4	49,2	47,1-51,2	0,04
LDH	174,6	156,9-192,4	189	171,7-206,1	0,4
D Dimer	1,44	1,13-1,75	0,7	0,6-0,8	<0,001**
AST	20,7	17,8-23,6	25,8	23,2-28,3	0,06
ALT	17,5	13,7-21,3	29,3	25,4-33,3	0,005**
ALK	100,4	87,8-113,1	68,8	63,5-74,1	<0,001**
Bilirubin	7,4	5,8-8,9	7,4	6,3-8,5	0,94
Ferritin	108,3	42,1-174,5	146,4	122-170,7	0,19

Source: medical record. **p < 0.01; CI 99% CI: Confidence interval. Inf: inferior limit. Sup:Superior limit. LDH: lactic dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALK: alkaline phosphatase.

Table 5: Hospital length of stay.

Hospital length of stay(days)	Pregnant(n=84)		Non- pregnant (n=327)		Total (n=411)		OR and Clfor Pregnant			
	#	%	#	%	#	%	OR	Inf	Sup	p value
1 to 3	23	27,4	119	36,4	142	34,5	0,6	0,4	1,1	0,1
4 to 7	47	56	134	41	181	44	1,8	1,1	2,9	0,01**
8 to 14	12	14,3	60	18,3	72	17,5	0,7	0,4	1,4	0,4
More than 14	2	2,4	14	4,3	16	3,9	0,5	0,1	2,4	0,4

Source: medical record. **p < 0.05; CI 95% CI: Confidence interval. Inf: inferior limit. Sup: Superior limit.

Table 6: Oxygen therapy, ARDS severity, non-invasive ventilation and invasive ventilation.

Variables		Pregnant(n=84)		Non pregnant(n=327)		Total (n=411)		OR and CI for Pregnant			P value
		#	%	#	%	#	%	OR	Inf	Sup	
Oxygen therapy		9	10,7	17	5,2	26	6,3	2,2	1	5,2	0,06
ARDS	Mild	1	1,2	1	0,3	2	0,5	3,9	0,2	63,4	0,3
	Moderate	1	1,2	3	0,9	4	1	1,3	0,1	12,7	0,8
	Severe	3	3,6	4	1,2	7	1,7	2,9	0,7	13,6	0,2
	Total	5	6	8	2,4	13	3,2	2,5	0,8	7,9	0,1
Ventilation	NINV	1	1,2	1	0,3	2	0,5	3,9	0,2	63,4	0,3
	INVV	3	3,6	6	1,8	9	2,2	2	0,5	8	0,3
	Total	4	4,8	7	2,1	11	2,7	2,3	0,6	8	0,2
ICU admission		8	9,5	14	4,3	22	5,3	2,3	0,9	5,8	0,06
Lethality		-	-	1	0,3	1	0,2	1,3	0,05	31,9	0,9

Source: medical record. p > 0.05; CI 95% OR: Odds ratio. CI: Confidence interval. Inf: Inferior limit. Sup: Superior limit.

ICU: intensive care unit. NINV: non-invasive ventilation. INVV: invasive ventilation.

IV. DISCUSSION

The present study compared 84 pregnant and 327 non-pregnant women admitted in the hospital with Covid-19 infection with ages ranging from 18 to 52 years considered as a fertile period; 25 to 34 years was the most frequent range of age in which pregnant women predominated; similar fact was reported by the investigation of Qaedan et al [13], whose demonstrated that pregnant women with Covid-19 infection tended to be younger and had more co-morbidities.

De la Gatta et al [14] and Elçi et al [15], have found a predominance of third trimester in pregnant Covid-19 infected patients, issue alike to this investigation in which most of pregnant women admitted had a gestational age of 24 weeks or more. Factors associated to increased risk of infection during pregnancy are well known [16], and this issue has called the attention of others investigators. Factors like swelled respiratory tract make the virus transmitted by droplets and aerosols more easily inhaled and difficult to remove [16]. Changes in reproductive hormones, decreased immune system response, associated to increased angiotensin-converting enzyme (ACE)-2 receptor for SARS-Cov2 virus during pregnancy have been proven [17,18]. It can be considered third trimester as the highest risk for Covid19 infection as physiological and immune changes reach its highest acme in this period.

Obesity was found as a significant co-morbidity in Covid-19 infected pregnant women of this investigation. In the reports of Villar et al [19], and Leila et al [20], overweight and obesity predominated in Covid-19 pregnant women, similar finding quoted in this study, although other maternal co- morbidities like age more than 35 years, diabetes mellitus, hypertension, gestational

hypertension, preeclampsia, HELLP syndrome and asthma were addressed by those authors, but these did not have any significant presence in this enquiry. Vitamin D deficiency has been reported as an important co-morbidity in Covid-19 pregnant by Yalcin et al [21], issue alike to this study too. Zainel et al [22], has reported high rates of obesity and vitamin D deficiency in a population of Qatar, fact to take into account to analysing the true burden of these co-morbidities, as all women included in this investigation came from Middle East and this factor may be reflexed in the sample studied. Obesity [23,24], and vitamin D deficiency [25], have been well stated as significant risks factors for Covid-19 infection and worst outcomes in maternal patients, a observation that support our findings. In this study predominated asymptomatic Covid-19 infection in pregnant and non-pregnant; symptoms were more frequent in non-pregnant women. A systematic review and metanalysis by Gao et al [10], show fever (51%) and cough (31%) as predominant symptoms at admission in Covid19 pregnant women, figures higher than this inquiry. In another systematic review Della Gatta et al [14], reported dry cough and fever as most frequent clinical findings, affecting nearly 50 % of pregnant, a proportion higher than observed in this investigation too. Prevalence of asymptomatic disease derived from those observations might be linked with the characteristic immune response during pregnancy mentioned before [16-18].

In this inquiry Focal Bilateral lesions prevailed in non-pregnant and Not Done CXR predominated in more than 70 % of pregnant, both results were statistically significant. Carrasco et al [26], reported predominant Focal Bilateral infiltrates in a sample of 105 pregnant, an issue alike to this study; but Not Done affected nearly 50 % of pregnant, a lesser figure than this inquiry. Less than 30 % of Covid-19 pregnant admitted in our hospital had done CXR, an issue related with a specific policy stated by Hamad Medical Corporation of Qatar, in which “pregnant woman shall not be exposed to radiation, unless life-saving and informed consent shall be required”. In this study about tenth of pregnant developed severe Covid-19 pneumonia and all were discharge, a fact that support a more conservative approach in exposing pregnant and her fetus to unnecessary radiation. It has been reported [7] CXR may be normal in almost 50 % of Covid-19 patients, a figure found higher than this investigation, in which No Findings reached 20 % of the sample. Chest CT scan yields more sensitivity and specificity for the diagnosis of Covid-19 pneumonia [7], but it was never done to pregnant in this study.

This investigation showed mean D-dimer and ALK were significantly higher for pregnant, a similar result in terms of D-dimer to Wang et al [7], but they found levels of leukocytes and neutrophils were significantly higher too. Mean ALT value was higher in non-pregnant in this study, a fact alike has been reported [7], but those authors described urea and creatinine were significantly elevated in non-pregnant too. Other inflammatory markers measured in this study like leukocytes and ferritin did not have any significant difference between pregnant and non-pregnant women.

4 to 7 days of hospital stay predominated, and it had a significant higher probability of presentation in pregnant; meanwhile non-pregnant had longer hospital stay in this investigation. Comparable results obtained other authors [13,8], as they have found a predominant asymptomatic disease and shorter hospital stay in Covid-19 pregnant.

Pregnant had a non-significant higher risk of using oxygen therapy, ARDS and mechanical ventilation than non-pregnant in this study, no mortality was observed in pregnant. Yan et al [2,9], published pregnant with Covid-19 infection confirmed had

almost 10 % of ICU admission, figure comparable to this investigation in which there was a non-statistically significant higher risk for pregnant. Figures of NINV in pregnant reported by those authors [2,9], was ten times superior than this study and a systematic review of Karimi et al [30] shows a mortality rate of 1.3 % in Covid-19 pregnant, different from this report in which no pregnant died. Lack of mortality in our investigation is attributed to the proper application of triage, classification and organized protocols for the management and treatment of pregnant with Covid19 infection that Qatar Ministry of Health has instituted since the beginning of the pandemic in December of 2019.

This investigation lacked analysis of maternal complications because there weren't observe during the period studied, and they had no any impact on the outcome of the pregnant women included, issue that may suppose a weakness for this study. Nonetheless, this aspect should be clarified in future inquiries about the real burden caused by Covid-19 infection on pregnant women and their new-borns.

V. CONCLUSION

As a final conclusion, in this investigation was observed Covid-19 infected pregnant trend to be younger and predominate third trimester of pregnancy. Pregnant have higher risk of co-morbidities, higher probability of asymptomatic infection and less done CXR. In spite of having higher risk of oxygen therapy, respiratory distress and ICU admission, pregnant shows a very low risk of mortality.

VI. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

VII. ACKNOWLEDGEMENT

TM and RA prepared the first draft of the manuscript and they made critical revisions to the paper and responded the reviewers and critically reviewed manuscript. TS, OM and DR collaborated in conceptualizing, designing and preparing the data base of the study. RA and RR collaborated in statistical analyzing, editing and critically reviewed manuscript; All authors wrote, reviewed and approved the final draft of manuscript.

VIII. ETHICAL STATEMENT

This is an observational, retrospective, analytic study where no risk procedure or administration of substance were done. So, informed consent was waived.

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