Journal of Hepatocellular Carcinoma

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RAPID COMMUNICATION

A Comparison of Presentation, Treatment, and Survival After Hepatocellular Carcinoma of Viral and Non-Viral Etiology in Damietta, Egypt, 2007–2019

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Context: The difference in prognosis between patients diagnosed with viral versus non-viral hepatocellular carcinoma (HCC) in Egypt remains unclear.

Methods: We used data from patients diagnosed with HCC between 2007 and 2019 from a large monocentric retrospective cohort at the Damietta Oncology referral center (northern Egypt). Presentation and treatment were compared between viral versus non-viral etiology HCC patients. Survival was compared relying on univariate and multivariate Cox regressions.

Results: Data from 4714 HCC patients were analyzed. Among them, 204 (4.3%) presented with a non-viral etiology. Patients with non-viral versus viral etiology had a similar presentation overall, especially regarding the BCLC stage at HCC diagnosis. After controlling for various individual characteristics, patients with non-viral versus viral etiology had poorer survival (adjusted Hazard Ratio: 1.244; 95% Confidence Interval: 1.069–1.447).

Conclusion: Despite similar features, patients with non-viral- related HCC had poorer survival compared to patients with viral-related HCC.

Keywords: hepatocellular carcinoma, liver cancer, viral etiology, non-viral etiology, survival, epidemiology

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm globally, ranking as the fifth most prevalent form of cancer in males and the seventh in females.[1] The majority of HCC cases are caused by chronic liver disease resulting from infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), representing more than 80% of total cases of HCC.[2]

In some geographical areas, there has been a notable decline in the occurrence of HCC recently. This decline may be linked to the expanding coverage of HBV vaccinations and the introduction of direct-acting antivirals (DAAs) for HCV. Meanwhile, there was a concomitant rise in the incidence of HCC in some Western countries, which could be attributed to the growing incidence of the metabolic syndrome and other related risk factors such as insulin resistance and obesity, and the associated increase in the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD).[3,4]

MASLD is currently considered the most prevalent chronic liver disease, nearly affecting one-third of the adult population worldwide. Moreover, about 3% to 5% of patients with MASLD can progress to metabolic dysfunction-associated steatohepatitis (MASH). Patients diagnosed with MASH are at a higher risk of developing end-stage liver disease and HCC,[4] which currently drives the increasing prevalence of HCC cases attributed to non-viral causes which has been reported in some countries.

Received: 24 January 2024
Accepted: 18 May 2024
Published: 31 May 2024

The unclear prognosis of individuals diagnosed with non-viral HCC compared to those with viral HCC is a topic that needs to be investigated.[5]

The situation of the HCC epidemic is quite specific in Egypt, where HCC is the first most prevalent type of cancer in both sexes.[6] The high prevalence of HCV in Egypt significantly contributes to the increased HCC indices in the country, accounting for more than 90% of all HCC cases.[7] Moreover, over the past years, the Egyptian National Treatment Programs have conducted large HCV testing actions (screening for more than 65 million population over 8 months) and the linked HCC screening activities among those infected with HCV, especially cirrhotic patients.[8,9] These efforts have led to a trend toward HCC diagnosed at earlier stage.[7] However, whether these activities primarily targeted against HCV have impacted differently viral versus non-viral HCC etiology is unknown.

Based on data collected from a monocentric retrospective cohort, this study aimed to compare the presentation and survival outcomes between individuals diagnosed with HCC on top of viral hepatitis and those with HCC and non-viral backgrounds in Egypt.

Methods

Population and Data Collection

We relied on data from a monocentric retrospective study conducted in a tertiary specialized oncology referral center in Damietta, northern Egypt. Recruitment and data collection of this cohort have been previously detailed.[7]

Briefly, the cohort included all patients who presented with a diagnosis of HCC between January 1, 2007, and December 31, 2019. HCC diagnosis and presentation data, including the BCLC staging,[10] were extracted from the patient's medical records. Specifically, HCV status was determined based on the presence of anti-HCV antibodies, while the presence of HBsAg determined HBV status. Using patients' medical records, the primary treatment for HCC was determined according to the highest level of treatment received, ordered as follows: surgical liver resection, curative locoregional therapy (including radiofrequency or microwave ablation and percutaneous ethanol injection), noncurative locoregional therapy (transarterial chemoembolization), and supportive care only. Patients final vital status and date of latest contact were determined following a three-step process relying on data from the patient's medical record, consulting the Egyptian National Cancer Registry,[11] and eventually directly contacting the patient or their next of kin.

Statistical Analysis

All eligible patients were considered for inclusion if they had both a non-missing date of diagnosis and a date of latest notice. HCC etiology was defined based on HCV and HBV statuses, with viral etiology defined as HCV, HBV, or dual infection. Patients with both HCV and HBV negative statuses were thereafter referred to as "non-viral etiology". Patients with missing or inconclusive results for HCV or HBV serology were excluded from the analysis.

Categorical variables were represented as percentages, while continuous variables were described using the median along with the 25th and 75th percentiles. General and clinical characteristics at HCC diagnosis were compared across etiology using the Student test for continuous variables and the Chi-square test (or the exact Fisher test when the effectives were small) for categorical variables. We used the Kaplan–Meier method to construct survival curves. Additionally, the Log rank test was also used to assess survival differences in univariate analysis. We first tested the assumption of proportional hazards using the Schoenfeld residual test before applying the Cox regression model in univariate and multivariate analysis. The multivariable analysis focused on variables that can be assessed upon diagnosis. The BCLC stage was entered into the model in order to capture disease progression, but other variables related to tumor characteristics were disregarded in order to prevent collinearities in the explicative variables. Hazard ratios (HR) were reported together with 95% confidence intervals (CI). All analyses were conducted using the R statistical software (version 4.3.1).

Results

We accessed the medical files of 5210 eligible patients. Among them, 5096 (97.8%) had a non-missing date of diagnosis and the date of the latest notice. A total of 4714 patients had a non-missing etiology (n=393 missing etiology), representing 90.5% of the eligible sample that was eventually included in the statistical analysis.

Among patients with non-missing etiology, the HCC etiology was distributed as follows: 4316 were HCV (91.6%), 154 were HBV (3.3%), 40 were co-infected with HBV-HCV (0.8%), and 204 had no evidence for HBV or HCV infection (4.3%). This represented 4510 (95.7%) patients with viral etiology and 204 (4.3%) with non-viral etiology. Only 3 patients (<0.1%) reported any alcohol consumption.

Table 1 describes the presentation of the patients, overall and per etiology. Most of the patients' general and clinical characteristics were similar between patients with a viral vs non-viral etiology, with some exceptions. Patients with a non-viral HCC were slightly older than patients with a viral etiology (63 vs 60 years old in median, respectively, p=0.0029); they were less likely to present with a history of gastroesophageal varices (10.9% vs 16.7%, p = 0.0311), with

Table 1 General and Clinical Characteristics of Patients Diagnosed with HCC (Damietta, 2007–2019), Overall and by Etiology

		Overall	Etiology		P-value
		N = 4714	Viral N = 4510	Non-Viral N= 204	
General characteristics					
Sex	Male Female	3650 (77.4%) 1064 (22.6%)	3498 (77.6%) 1012 (22.4%)	152 (74.5%) 52 (25.5%)	0.3079
Area of residence	Urban Rural NA	1192 (25.3%) 3518 (74.7%) NA: 4	1137 (25.2%) 3369 (74.8%) NA: 4	55 (27.0%) 149 (73.0%) NA: 0	0.5788
Year of HCC diagnosis	<2014 2014–2019	2165 (45.9%) 2549 (54.1%)	2081 (46.1%) 2429 (53.9%)	84 (41.2%) 120 (58.8%)	0.1639
Age at 1st visit in DOC	Median [Q25-Q75] NA	61 [55–67] 4	60 [55.00–67.00] 4	63.00 [56.00–69.00] 0	0.0029
Tobacco consumption	No Yes NA	3038 (64.6%) 1664 (35.4%) NA: 12	2916 (64.8%) 1583 (35.2%) NA: 11	122 (60.1%) 81 (39.9%) NA: 1	0.1693
Clinical characteristics					
Hypertension	No Yes NA	3559 (76.5%) 1094 (23.5%) NA: 61	3406 (76.4%) 1050 (23.6%) NA: 54	153 (77.7%) 44 (22.3%) NA: 7	0.6907
Diabetes	No Yes NA	3440 (73.9%) 1214 (26.1%) NA: 60	3295 (73.9%) 1162 (26.1%) NA: 53	145 (73.6%) 52 (26.4%) NA: 7	0.9191
History of gastroesophageal varices	No Yes NA	3717 (83.5%) 732 (16.5%) NA: 265	3538 (83.3%) 710 (16.7%) NA: 262	179 (89.1%) 22 (10.9%) NA: 3	0.0311
Ascites	No Yes NA	2785 (59.3%) 1914 (40.7%) NA: 15	2649 (58.9%) 1849 (41.1%) NA: 12	136 (67.7%) 65 (32.3%) NA: 3	0.0133

(*Continued*)

Table 1 (Continued).

		Overall	Etiology		P-value
		N = 4714	Viral N = 4510	Non-Viral N= 204	
Encephalopathy	No Yes NA	4408 (94.2%) 273 (5.8%) NA: 33	4212 (94.0%) 268 (6.0%) NA: 30	196 (97.5%) 5 (2.5%) NA: 3	0.0386
Imaging system used	CT Scan MRI Both NA	4521 (95.9%) 105 (2.2%) 50 (1.1%) NA: 38	4328 (96.0%) 99 (2.2%) 47 (1.0%) NA: 36	193 (94.6%) 6 (2.9%) 3 (1.5%) NA: 2	0.8150
Clinical characteristics					
Hepatic focal lesion (HFL) number	1 2 3 >3 (multifocal) NA	2069 (45.3%) 559 (12.2%) 112 (2.5%) 1829 (40.0%) NA: 145	1980 (45.3%) 528 (12.1%) 108 (2.5%) 1754 (40.1%) NA: 140	89 (44.7%) 31 (15.6%) 4 (2.0%) 75 (37.7%) NA: 5	0.5001
Vascular invasion	No Yes NA	3717 (83.5%) 732 (16.5%) NA: 265	3380 (76.1%) 1061 (23.9%) NA: 69	153 (75.7%) 49 (24.3%) NA: 2	0.9049
Distant metastasis	No Yes NA	3771 (81.6%) 851 (18.4%) NA: 92	3613 (81.7%) 807 (18.3%) NA: 90	158 (78.2%) 44 (21.8%) NA: 2	0.2063
Child-Pugh score	A B C NA	1727 (36.9%) 1769 (37.8%) 1178 (25.2%) NA: 40	1656 (37.0%) 1686 (37.7%) 1132 (25.3%) NA: 36	71 (35.5%) 83 (41.5%) 46 (23.0%) NA: 4	0.5332
ECOG Stage	0 1 2 3 4 NA	98 (2.1%) 1349 (29.5%) 1872 (41.0%) 1216 (26.6%) 31 (0.7%) NA: 148	96 (2.2%) 1296 (29.6%) 1797 (41.1%) 1152 (26.4%) 30 (0.7%) NA: 139	2 (1.0%) 53 (27.2%) 75 (38.5%) 64 (32.8%) 1 (0.5%) NA: 9	0.2967
BCLC stage at diagnosis	0/A B C D NA	766 (16.7%) 711 (15.5%) 1353 (29.5%) 1755 (38.3%) NA: 129	736 (16.8%) 681 (15.5%) 1286 (29.3%) 1686 (38.4%) NA: 121	30 (15.3%) 30 (15.3%) 67 (34.2%) 69 (35.2%) NA: 8	0.5189

ascites (32.3% vs 41.1%, p=0.0133) and with encephalopathy (2.5% vs 6%, p=0.0386). Patients from both groups did not differ significantly regarding the ECOG stage, Child-Pugh score, or BCLC stage at HCC diagnosis. Laboratory values at diagnosis were affected by a substantial rate of missing values, but overall, there was no major difference between HCC etiologies except for prothrombin concentration (p=0.0305, Supplementary Table 1).

Across patients with BCLC stage B, C, or D at diagnosis, we did not observe a large difference in offered treatment options according to etiology (Figure 1). However, among patients diagnosed at BCLC stage 0/A, we observed a more significant proportion of patients receiving surgical resection among non-viral versus viral etiology (32.1% vs 11.0%,

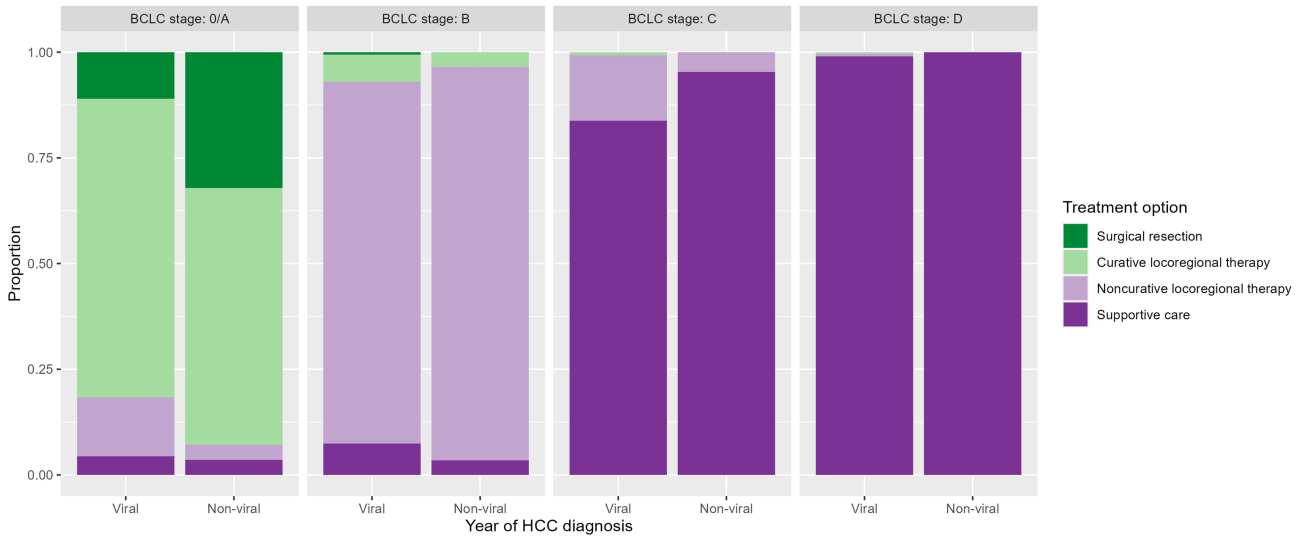

Figure 1 Treatment option per BCLC stage and HCC etiology.

Fisher's exact test p=0.011). For the 689 patients who received curative therapy and who had a non-missing follow-up time, HCC-recurrence-free survival did not significantly differ between HCC etiology (Supplementary Figure 1, p = 0.83).

The median survival after HCC diagnosis was 6.2 months for non-viral etiology vs 8.1 months for viral etiology, with a log-rank p-value (p=0.0086), suggesting a significantly lower survival among the former (Table 2 and Figure 2). Both survival curve shapes and Schoenfeld residuals (p=0.27) suggested that the assumption of proportional hazards was valid.

In the multivariate analysis, we observed that survival was negatively associated with age and with advanced BCLC stages at diagnosis (Table 3). Hypertension was positively associated with survival (adjusted Hazard Ratio, aHR=0.922, 95% Confidence interval, CI: 0.852–0.997). Lastly, a non-viral HCC etiology was associated with poorer survival (aHR=1.244, 95% CI: 1.069–1.447).

Discussion

In this retrospective, monocentric cohort study of patients diagnosed with HCC in northern Egypt, we observed that a small proportion, <5%, of HCC could be attributable to non-viral etiology. The presentation of non-viral etiology patients was similar to those with viral etiology, especially regarding the BCLC stage. However, we observed that among patients diagnosed at an early stage of the disease (BCLC stage 0/A), those with a non-viral etiology did benefit significantly more frequently from surgical resection than those with viral etiology. HCC-recurrence-free survival did not differ across etiology among those who benefited from curative treatment. When analysing survival, we observed that patients with a non-viral etiology acknowledged a slightly but significantly higher mortality risk than those with a viral etiology. This higher mortality risk for non-viral etiology remained significant after adjusting for other characteristics.

Our cohort demonstrated a significant prevalence of HCC associated with viral etiologies, accounting for 95.7% of cases. In contrast, non-viral etiologies accounted for 4.3% of cases, which closely aligns with most reports from Egypt, where viral hepatitis, especially HCV, is the leading risk factor for HCC. In a report published by Shaker et al in Egypt, non-viral causes of HCC were reported in 3.5% of a large cohort of 1313 patients.[12] A later study conducted in Egypt, which investigated a smaller

Table 2 Median, 6-, 12- and 24-Month Survival, per HCC Etiology

HCC Etiology	Median Survival Time (Months)	6-Month Survival	12-Month Survival	24-Month Survival
Viral (N=4510)	8.1 (7.8–8.4)	59% (57–60)	38% (36–39)	17% (16–19)
Non-viral (N=204)	6.2 (4.4–8.4)	51% (44–58)	35% (29–43)	15% (10–21)

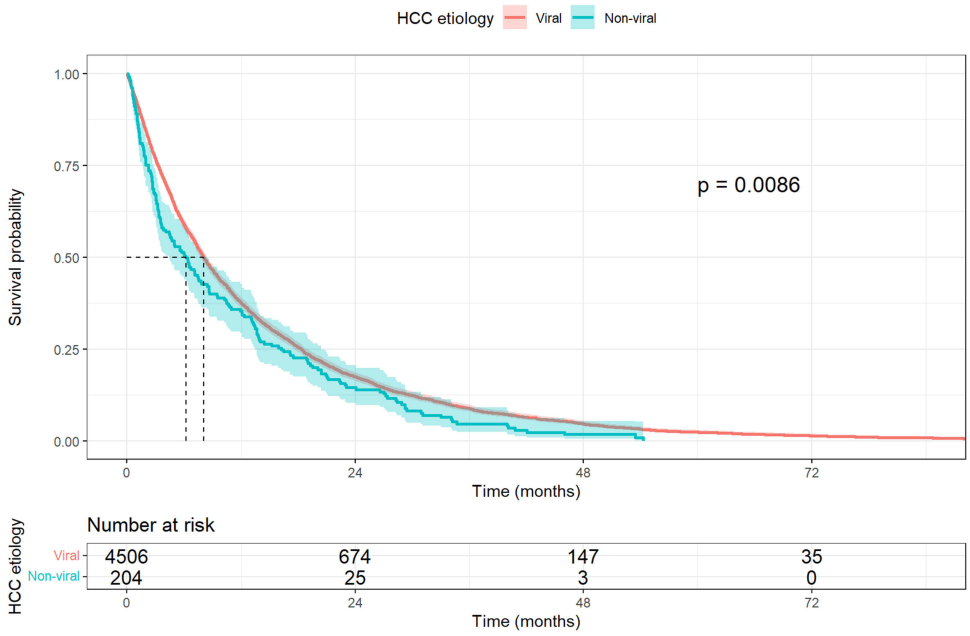

Figure 2 Kaplan-Meier survival curves after HCC diagnosis, per etiology.

group of patients, found a lower prevalence of non-viral causes of HCC, accounting for around 1.88% of cases.[13] Moreover, the present studies found that the recent Egyptian National Treatment Programs targeting HCV elimination have not yielded to a significant change in the relative contribution of viral versus non-viral etiologies in the HCC epidemic. Worldwide, the non-viral causes of HCC represent a more considerable proportion of HCC etiologies compared to what is reported in Egypt. This difference may be attributed to the relatively low rates of alcohol consumption in Egypt, which can be related to cultural and religious factors. For example, the prevalence of alcohol-related HCC in Europe can reach up to 33%,[14] and in the United States, it can reach up to 23%,[15] while studies reported a percentage between 15% and 30% in Japan.[16] The non-viral causes of HCC in Egypt remain to be clearly identified, particularly as type-2 diabetes and tobacco consumption did not significantly differ between etiology groups. However, previous Egyptian studies reported association with pesticides exposure and heavy smoking,[17] and research about the non-viral causes of HCC deserves further efforts.

The median age of patients diagnosed with non-viral HCC was somewhat higher than those with a viral etiology, with median ages of 63 and 60. This finding aligns with previous research conducted in Korea, where the mean age of patients

Table 3 Crude and Multi-Adjusted Cox Regression Model for Survival After HCC Diagnosis

Variable	Categories	Univariate Analysis			Multivariate Analysis		
		cHR	95% CI	P-value	aHR	95% CI	P-value
Etiology	Non-viral vs viral	1.216	[1.052–1.406]	0.0081	1.244	[1.069–1.447]	0.0047
Sex	Female vs Male	0.838	[0.779–0.901]	$<10^{-3}$	0.97	[0.899–1.046]	0.4231
Year of diagnosis	2014–2019 vs <2014	0.983	[0.924–1.045]	0.5754	-		
Area of residence	Rural vs urban	1.094	[1.020–1.173]	0.0116	0.986	[0.917–1.059]	0.6936
Age	10y increase	1.158	[1.117–1.200]	$<10^{-3}$	1.104	[1.065–1.144]	$<10^{-3}$
Hypertension	Yes vs no	0.824	[0.766–0.886]	$<10^{-3}$	0.922	[0.852–0.997]	0.0418
Diabetes	Yes vs no	0.907	[0.847–0.972]	0.0057	1.023	[0.951–1.100]	0.5414
BCLC stage at diagnosis	B vs 0/A	1.85	[1.649–2.076]	$<10^{-3}$	1.822	[1.621–2.048]	$<10^{-3}$
	C vs 0/A	3.532	[3.185–3.917]		3.466	[3.121–3.849]	
	D vs 0/A	5.685	[5.139–6.289]		5.657	[5.102–6.273]	

Abbreviations: cHR, crude Hazard Ratio; aHR, adjusted Hazard Ratio; CI, confidence interval.

with non-viral HCC was reported to be 67.3 years, which was older than patients with viral HCC who had a mean age of 61.[18] However, this difference was not constant across the literature, as Noda et al reported the lack of statistically significant differences in age between viral and non-viral HCC cohorts.[19]

Regarding prognostic markers, there were no significant differences between patients from both groups regarding the ECOG stage, Child-Pugh score, or BCLC stage at the time of HCC diagnosis. These findings align with the study conducted by Hatanaka et al, particularly concerning the Child-Pugh score.[20] In addition, Weinmann et al observed no statistically significant distinctions between individuals diagnosed with HCC associated with NASH and those with HCC caused by other factors, including viral causes.[21] Moreover, non-invasive methods are currently under development for the prognosis of HCC, but are not used yet in the context of Egypt.[22]

A comparative analysis of laboratory tests showed that there was no statistically significant difference between the two groups. Nevertheless, individuals diagnosed with non-viral HCC had a comparatively elevated platelet count. This might be attributed to thrombocytopenia being considered an extra-hepatic symptom of HCV, irrespective of cirrhosis.[23] Contrary to prior findings, Hatanaka et al presented divergent data indicating that individuals with non-viral HCC had notably reduced levels of liver enzymes compared to those with viral HCC. Furthermore, no statistically significant change was seen concerning platelet count.[20]

One of the main objectives of this communication was to identify any differences in the survival between the two groups. The median survival after the diagnosis of HCC was found to be 6.2 months for cases with non-viral etiology, whereas those with viral etiology had a median survival of 8.1 months. These findings support the outcomes obtained in several other studies regarding survival.[19–21,24] Therefore, it is suggested that individuals diagnosed with non-viral HCC have a notably poorer survival rate than those with a viral etiology. This could be attributed to the fact that HCC surveillance is less successful in patients with non-viral HCC compared to those with viral HCC. Additionally, tools for maintaining liver functions, like antiviral treatments in case of viral HCC, are not available for patients with non-viral cases. The findings of this study provide strong evidence about the significance of early diagnosis of HCC in patients with non-viral liver diseases. Furthermore, it underscores the need to implement efficient strategies for identifying high-risk patients with non-viral liver disease prone to developing HCC. This will enable the timely initiation of HCC surveillance procedures.

In conclusion, the present studies suggested that the share of non-viral etiology in the Egyptian HCC epidemic has remained stable over the past 15 years. Individuals diagnosed with non-viral-related HCC and those with viral-related HCC commonly show similar features. Nevertheless, as previously reported in studies conducted in other settings, individuals afflicted with a non-viral etiology have significantly lower median survival rates.

Data Sharing Statement

Data related to this study are available upon a reasonable request through an Email to the corresponding author.

Ethical Clearance

This study received approval from the Research Ethics Committee for Human Subject Research at Air Force Specialized Hospital and from the Egyptian Ministry of Health on 31st July 2019 and on October, 9th 2019, respectively. The data collected were anonymised and retrospective in nature, therefore the requirement for informed consent has been waived by both ethics committees. The study complies with the Declaration of Helsinki.

Funding

This research has been funded by the Pasteur Foundation US. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the article.

Disclosure

The authors declare no competing interests in this work.

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