

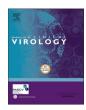
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Journal of Clinical Virology



journal homepage: www.elsevier.com/locate/jcv

Paper from the 21st ESCV meeting

COVID-19 patient characteristics and time to viral clearance: A retrospective observational study in a multiethnic population (United Arab Emirates)

Wael Hafez^{a, b, *}

^a NMC Royal Hospital, 16th Street, Khalifa City, Abu Dhabi, UAE

^b Medical Research Division, Department of Internal Medicine, The National Research Centre, Cairo, Egypt

A R T I C L E I N F O	A B S T R A C T		
Keywords: SARS-CoV-2 COVID-19 Viral clearance Asymptomatic Severity Multi-ethnicity United Arab Emirates	<i>Background:</i> SARS-CoV-2 virus is the causing agent of COVID-19. The factors contributing to delayed viral clearance are still unclear. <i>Methods:</i> We investigated the factors influencing the time to viral clearance in COVID-19 patients using medical records from 1785 adult patients of various ethnicities treated at NMC Royal Hospital in Abu Dhabi, UAE. The Cox-proportional Hazard Model was utilized to identify risk variables for delayed viral clearance, and the Kaplan-Meier plot was used to measure the time to viral clearance among different groups. <i>Results:</i> several factors have been associated with an increased risk of delayed viral clearance, including advanced age ($p = 0.006$), presence of cardiovascular diseases ($p = 0.016$), presentation with upper respiratory tract infection (URTI) ($p = 0.043$), and combined gastrointestinal (GIT) and symptoms (URTI) ($p = 0.006$, $p < 0.001$, respectively). 'The overall median viral clearance time was 24 days. It was 32 days among patients over 60, 21 among those with URTI, GIT symptoms, and asymptomatic, 24 among diabetics, and 46.5 days among cardiovascular patients. The median time till viral clearance was 30 days among severe COVID-19 patients and 39 days among ICU-admitted patients. <i>Conclusions:</i> We concluded that advanced age, cardiovascular comorbidities, disease presentation, and severe COVID-19 outcomes increased the risk of delayed viral clearance and severe to implement an early and comprehensive management strategy to improve the outcome.		

1. Introduction

In December 2019, a series of pneumonia cases of unknown cause was admitted to the hospitals in Wuhan city, China [1]. Later, the causative organism was identified and designated as a severe acute respiratory syndrome–coronavirus-2 (SARS–CoV-2); hence the disease caused by it was called Coronavirus Disease-2019 (COVID-19) [1]. World Health Organization (WHO) declared COVID-19 as a worldwide pandemic in March 2020 [2]; the virus caused an exponential increase of COVID-19 cases and posed a threat to the public health worldwide.

The Centers for Disease Control and Prevention (CDC) recommends that the confirmatory test for SARS-CoV-2 infection is done by the assessment of different nucleic acid targets of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) amplification from a nasopharyngeal specimen [3,4]. Viral clearance and clinical shedding are determined by at least two consecutive negative results from upper respiratory tract specimens [5].

Based on early studies, the median duration of positive RT-PCR results was 20 days, and the absolute duration was 37 days [6]. Delayed viral clearance was documented to up to 111 days [7], while the shortest duration of viral clearance was 3 days [8]. Many factors are associated with prolonged viral shedding, including high viral load leading to severe disease course, prolonged hospitalization, hospital admission to the intensive care unit (ICU), and death [9].

Zheng et al. [9] reported prolonged viral shedding among patients with severe COVID-19 (14–30 days) compared to those with mild symptoms (10–21 days). Additionally, Fang et al. [10], p.147–178 also reported that ICU-admitted patients with COVID-19 had more prolonged

https://doi.org/10.1016/j.jcv.2022.105297

Received 1 March 2022; Received in revised form 18 September 2022; Available online 22 September 2022

1386-6532/© 2022 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

^{*} Corresponding author at: Nmc Royal Hospital, 16 St, P.O. BOX 35233 Khalifa City, Abu Dhabi, UAE. *E-mail address:* Wael.hafez@nmc.ae.

time to viral clearance than those not admitted to the ICU.

A study of 113 hospitalized COVID-19 patients in China showed that prolonged time to viral clearance was greatly associated with the male gender, time from onset of the disease to hospitalization, and invasive mechanical ventilation [11]. Also, Zeng Li et al. [12], p.506–512 reported that prolonged time to viral clearance was associated with other factors, including time from onset to hospitalization, fever, and treatment with corticosteroids. Other studies also reported age as an independent factor for prolonged viral shedding (\geq 65 years) [13]; the median duration of viral shedding was reported as 30 days (41–50 years), 33 days (51–60 years), 34 days (61–70 years) and 34 days (> 70 years) [7].

Prolonged time to SARS-CoV-2 clearance was also observed in patients with several co-morbidities such as immunodeficiency (61 days) [14], hemodialysis patients (24–37 days) [15], and coronary heart disease (21 days) [8].

The study aimed to investigate different factors associated with time till viral clearance among COVID-19 patients in the multi-ethnic population in United Arab Emirates (UAE).

2. Materials and methods

2.1. Study design and population

This was a retrospective cohort investigation of medical records from COVID-19 patients treated in NMC Royal Hospital, Khalifa City, Abu Dhabi, UAE. The study included 1785 adult COVID-19 patients. The study was conducted on COVID-19 patients treated between 8th April 2020 and 31st June 2020.

The following data were collected from all patients' medical records: demographic and clinical characteristics, laboratory, and radiological findings, administered therapy, and COVID-19 outcomes.

All patients received treatment, whether symptomatic or specific antiviral regimens, as soon as they were diagnosed, on their first visit to the outpatient clinic, or at the time of admission, whenever admitted.

2.2. Virologic investigations

The testing protocol for all patients was based on the national guidelines for clinical management and treatment of COVID-19 in the United Arab Emirates.

Laboratory diagnosis of COVID-19 was done by Solgent's 2019-nCoV RT-PCR kit using nasopharyngeal swab specimens. The Bio-Rad Cycler PCR, USA, and CFX-96 plate reader from Biorad were used for RT-PCR analysis and viral detection according to the manufacturer's instructions. A cycle threshold (CT) value above 40 was defined as a SARS-CoV-2 positive sample [16].

All patients were evaluated at the time of presentation to the outpatient clinic or emergency department, then re-evaluated every 5 days, and the test were repeated for those who became negative after 24 h. The first two consecutive negative RT-PCR test results were considered a sign of viral clearance [17].

Time to viral clearance was defined by the number of days from symptom onset with positive SARS-CoV-2 RT-PCR test results to the persistent first negative of two consecutive negative RT-PCR findings. In addition, we used the world health organization (WHO) classification to classify COVID-19 patients as severe (severe/critical) and non-severe (mild/moderate) [18]. Delayed time to viral clearance was defined as the longer median time to viral clearance of each group of patients when compared to other groups regarding the same risk predictor (There is no reference median time to viral clearance all over the study population). This study was conducted according to the Declaration of Helsinki. All patient identifiers were removed while the data was being processed, and patient privacy was preserved throughout the study. The study was reviewed and approved by Abu Dhabi Health COVID-19 Research Ethics Committee (Ref: DOH/CVDC/2022/1739). As a retrospective study, the

Journal o	of Clinical	Virology	157	(2022)	105297

Table 1

Baseline demographics and clinical presentation of the study population.

Demographics	Sub-categories	Total = 1785Count (%)	
Age category	0–29	412 (23.1)	
	30–39	772 (43.2)	
	40-49	412 (23.1)	
	50–59	154 (8.6)	
	60+	35 (2.0)	
Gender	Female	245 (13.7)	
	Male	1540 (86.3)	
Race	American Indian/Alaska Native	8 (0.4)	
	Asian	1438 (80.6)	
	Black/African American	49 (2.7)	
	White	290 (16.2)	
BMI category	Underweight	36 (2.0)	
	Normal	641 (36.4)	
	Overweight	751 (42.6)	
	Moderate Obesity	258 (14.7)	
	Severe Obesity	59 (3.4)	
	Morbid Obesity	16 (0.9)	
Clinical presentati		10 (0.9)	
Hypertension	No	1744 (97.7)	
riypertension	Yes	41 (2.3)	
Diabetes	No	1737 (97.3)	
mellitus	Yes	48 (2.7)	
Cardiovascular/	No	1772 (99.3)	
chronic kidney	Yes	13 (0.7)	
diseases	165	13 (0.7)	
Pneumonia	No	1077 (63.8)	
(Chest X-ray)	Yes	611 (36.2)	
Main	Asymptomatic	1187 (67.1)	
presentation	GIT	8 (0.5)	
F	URTI	490 (27.7)	
	URTI, GIT	85 (4.8)	
Disease severity	Non-severe	1723 (96.5)	
Discuse severity	Severe	62 (3.5)	
ICU admission	No	1762 (98.7)	
	Yes	23 (1.3)	
Treatment	Azithromycin	81 (4.5)	
ireatment	Hydroxychloroquine	40 (2.2)	
	Hydroxychloroquine +Favipiravir	92 (5.2)	
	Hydroxychloroquine	92 (5.2) 10 (0.6)	
	+Favipiravir+Lopinavir/Ritonavir	10 (0.0)	
		65 (3.6)	
	Hydroxychloroquine + Azithromycin	65 (3.6) 52 (2.9)	
	Hydroxychloroquine + Azithromycin +Favipiravir	52 (2.9)	
		1445 (91.0)	
	Symptomatic only	1445 (81.0)	

BMI: Body mass index; GIT: Gastrointestinal tract; ICU: Intensive care unit; URTI: Upper respiratory tract infection.

informed consent form was not required.

2.3. Data management and statistical analysis

All data were supplied for statistical analysis with R Software version 3.5.2 (2018–12–20) – "Eggshell Igloo" after discussing the Protocol, the purpose of the study, and data collection and verification. Normally distributed quantitative data were summarized as mean \pm standard deviation (SD) and range, or median and interquartile range when the data were not normally distributed. While qualitative data were summarized as frequency (n) and percentage (%). A Kaplan-Meier plot was conducted for univariate analysis to assess the time to viral clearance among different groups of patients. For Multivariate analysis, a Cox regression model to estimate the hazard ratio was performed. All tests were bilateral, with a P-value < 0.05 considered as statistical significance.

3. Results

3.1. Baseline demographic characteristics of study population

The study was conducted on 1785 adult COVID-19 patients. Asians

Table 2

Univariate and adjusted hazard ratios from cox proportional hazard model after adjusting for confounders.

Overall survival		HR (univariable) ¹ HR (95% CI)	P - value	HR (multivariable) ¹ HR (95% CI)	P - value
Gender:	Female	_	_	_	
	Male	1.06 (0.89–1.26)	0.506	1.03 (0.84–1.26)	0.77
Diabetes Mellitus (DM):	Not Diabetic	_	_	_	
	Diabetic	0.48 (0.34–0.69)	<0.001	0.86 (0.57–1.29)	0.463
Cardiovascular Diseases:	Absent	-	_	-	
	Present	0.29 (0.15–0.56)	<0.001	0.40 (0.19–0.85)	0.016
Chest X-ray (Pneumonia):	No Pneumonia	-	_	-	
v • •	Pneumonia	0.91 (0.80–1.03)	0.127	1.06 (0.92–1.21)	0.439
Patients' First Presentation:	Asymptomatic	-	-	-	
	GIT symptoms	0.78 (0.33–1.89)	0.589	0.80 (0.32-2.02)	0.641
	URTI symptoms	1.23 (1.07–1.40)	0.003	1.20 (1.01–1.42)	0.043
	URTI, GIT symptoms	0.46 (0.35–0.61)	<0.001	2.15 (1.18–3.91)	0.012
COVID-19 Symptoms:	Normal Smell and Taste	-	_	-	
	Loss of Smell and Taste	1.38 (0.90–2.13)	0.143	1.07 (0.65–1.77)	0.784
Disease Severity:	Not-Severe	_	-	-	
	Severe	0.33 (0.24–0.46)	<0.001	0.26 (0.13–0.52)	<0.001
ICU Admission:	Not ICU Admitted	-	-	-	
	ICU Admitted	0.23 (0.13–0.40)	<0.001	0.38 (0.19–0.76)	0.006
Race/ Ethnicity:	American Indian/Alaska Native	_		_	
	Asian	0.30 (0.10-0.93)	0.036	0.30 (0.07-1.23)	0.093
	Black/African American	0.26 (0.08–0.86)	0.027	0.31 (0.07-1.30)	0.109
	White	0.27 (0.08–0.83)	0.023	0.30 (0.07–1.25)	0.099
	0.00				
Age Category:	0-29		-		0 510
	30–39	0.99 (0.85–1.16)	0.924	0.95 (0.80–1.12)	0.518
	40-49	0.95 (0.80–1.14)	0.588	0.95 (0.78–1.15)	0.565
	50–59	0.84 (0.66–1.06)	0.138	0.92 (0.71–1.19)	0.529
	60+	0.36 (0.23–0.57)	<0.001	0.51 (0.31–0.82)	0.006
HR = Hazard Ratio, CI = Confid	ence Interval				

BMI: Body mass index; GIT: Gastrointestinal tract; ICU: Intensive care unit; URTI: Upper respiratory tract infection.

represented the highest percentage (80.6%) of the total study population. The majority of our population is aged between 30 and 39 years old (43.2%), and males (86.3%). The body mass index of 42.6% of patients was overweight or normal (36.4%). The presence of co-morbidities was not common among our study population. Regarding COVID-19 clinical presentation and outcomes, pneumonia affected 36.2% of our study population. However, 67.1% of patients were asymptomatic. Here, COVID-19 was mostly not severe (96.5%), and only 32 patients (1.3%) were admitted to the ICU. And most of the study population (81%) received symptomatic treatment only (Table 1).

3.2. Factors associated with delayed viral clearance among COVID-19 patients

The Cox-proportional Hazard Model showed that patients above 60 had an increased risk for prolonged viral clearance by 51% (p = 0.006). There was a 60% reduction in the risk of delayed viral clearance among COVID-19 patients without cardiovascular problems (p = 0.016). While upper respiratory tract infections (URTI) were associated with a 20% increased risk (p = 0.043), and the risk was elevated to more than twice (HR = 2.15) if the patient was suffering from URTI and gastrointestinal tract (GIT) symptoms simultaneously during his first presentation (p = 0.012).

Several COVID-19 outcomes were also associated with increased risk for prolonged viral clearance, including ICU admission (62%) (p = 0.006) and severity of COVID-19 (74%) (P < 0.001) (Table 2). In contrast, several factors did not increase the risk of viral persistence, including gender, ethnicity, loss of taste and sensation, presence of pneumonia, and body mass index (BMI) (Table 2).

3.3. Viral clearance and patients characteristics and main presentation

Among 1785 COVID-19 patients included in our study, only 14 patients suffered from delayed viral clearance. The median time (IQR) to viral clearance among the study population was (median: 24 days, IQR (17:32); 95% CI: (23–25)).

There were 412 younger than 29 years, 772 aged from 30 to 39 years, 412 aged from 40 to 49 years, 154 aged from 50 to 59 years, and 35 patients were older than 60 years old. The median time to viral clearance was significantly longer (P = 0.0001) among COVID-19 patients older than 60 years old (median (IQR) = 32 days (21:60)), and shorter in patients aged from 40 to 49 years (median= (IQR) = 22 days (16:32)). (Fig. 1).

Among the study population, there were 1187 asymptomatic patients, 8 with GIT symptoms only, 490 with URTI, and 85 patients with both URTI and GIT symptoms. The median time (IQR) was significantly shorter among patients with URTI symptoms (median = 21 days, IQR: (15:30), p < 0.001). In contrast, the median time (IQR) to viral clearance was longer among asymptomatic patients (median time = 25 days, IQR: (18:33)) or those with GIT symptoms (median = 25 days, IQR: (24:44))

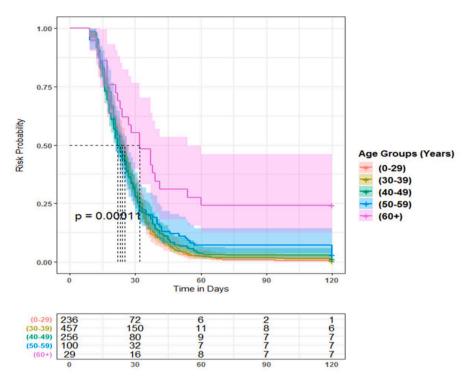


Fig. 1. Kaplan Meier estimate stratified by age.

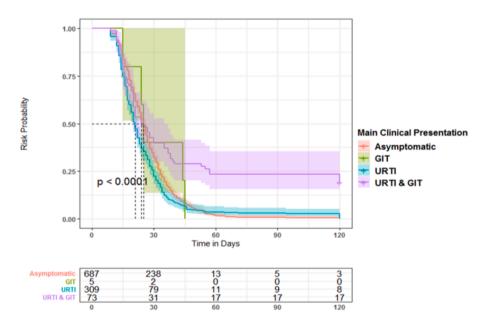


Fig. 2. Kaplan Meier estimate stratified by clinical presentation.

(Fig. 2).

3.4. Viral clearance and the presence of co-morbidities

Delayed viral clearance was observed among 7 patients with diabetes and 7 non-diabetic COVID-19 patients. The median time to viral clearance was 24 days and 22 days among non-diabetic and diabetic COVID-19 patients, respectively (Fig. 3).

Among 1772 patients without cardiovascular diseases, 11 were suffering from delayed viral clearance, and 3 out of 10 COVID-19 patients who were suffering from cardiovascular diseases showed delayed viral clearance. The median time (IQR) to viral clearance among patients without cardiovascular diseases was 24 days (17:32). In comparison, the median time (IQR) to viral clearance was significantly longer among patients with cardiovascular diseases, 46.5 days (29.00: Inf) (p < 0.001) (Fig. 4).

3.5. Viral clearance and COVID-19 outcomes

Time till viral clearance was further examined based on COVID-19 outcomes. ICU admission was considered one of the main causes of the prolonged median time to viral clearance. Among 23 patients admitted to ICU, 14 patients experienced viral clearance with median (IQR) time to viral clearance 39 days, which was longer than the median

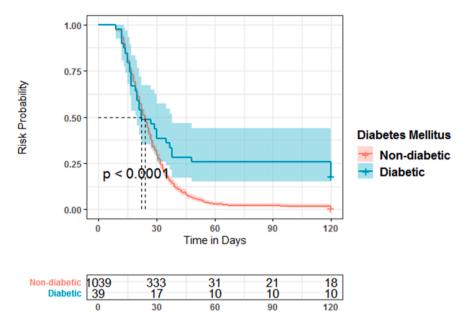


Fig. 3. Kaplan Meier estimate stratified by presence of diabetes mellitus.

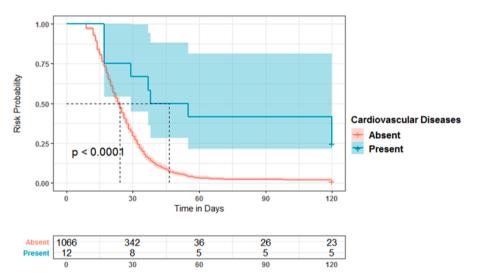


Fig. 4. Kaplan Meier estimate stratified by presence of cardiovascular diseases.

(IQR) among 1757 COVID-19 patients who were not admitted to the ICU (median time = 24 days, IQR: (17:32)), while the remaining 9 patients did not achieve viral clearance and died (p < 0.001) (Fig. 5). However, there was no statistically significant difference between ICU-admitted patients who achieved viral clearance compared to those who did not achieve viral clearance regarding their demographic or clinical characteristics (Table 3).

There were 62 severe and 1723 non-severe COVID-19 patients included. Kaplan-Meier analysis showed a statistically significant difference in time to viral clearance between both groups (median time = 30 days, IQR: (18:120), vs. median time = 24 days, IQR: (17: 32), p < 0.001) for severe and non-severe patients respectively) (Fig. 6).

4. Discussion

The current study investigated different factors influencing the time to viral clearance of SARS-CoV-2. The findings revealed an increased risk of delayed viral clearance in patients over the age of 65, those with cardiovascular comorbidities, those with mixed URTI and GIT symptoms, severe COVID-19 patients, and ICU-admitted patients. Besides, the median time to viral clearance was significantly longer among those patients.

Our findings are consistent in the literature; the median time till viral clearance among our study population was 24 days which is similar to that observed by Wei et al. [16], p.2131–2133 in Wuhan city (23.5 days) and Bennasrallah et al. [17], p.463–469 (20 days).

On the other hand, While Xu et al. [11], p.799–806 reported that the median time for viral detection since the onset of symptoms of the disease was 17 days, Shu et al. [21] reported the median time was 16 days, and Li et al. [12], p.506–512 reported the median time was 11 days. The heterogeneity of patients in terms of delayed hospital admission, treatments administered, and initiation time of viral detection, in addition to the interval between and performing the PCR for the SARS COV-2 test could explain these differences.

Our study revealed that advanced age was associated with an increased risk of prolonged time to viral clearance, which is consistent with previous studies [19,22,23]. This could be attributed to the decline of T cell functions and proliferation with increasing age resulting in

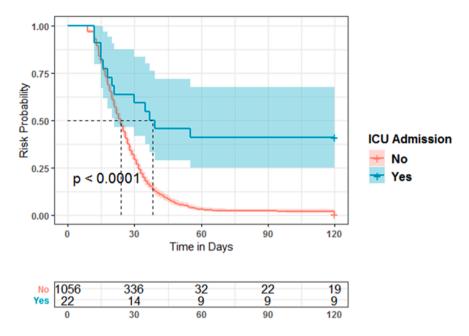


Fig. 5. Kaplan Meier Estimate stratified by ICU admission.

Table 3

Comparative analysis between ICU-admitted patients who experienced viral clearance or not regarding demographics and clinical presentation among ICU admitted patients.

Demographics	Total ICU admitted = 23	Viral clearance	Viral clearance		
		No9 (39.1%)	Yes14 (60.9%)		
Age categories	0–29	0 (0.0)	0 (0.0)	0.522	
	30–39	1 (11.1)	3 (21.4)		
	40-49	2 (22.2)	6 (42.9)		
	50-59	2 (22.2)	3 (21.4)		
	60+	4 (44.4)	2 (14.3)		
Gender	Female	2 (22.2)	0 (0.0)	0.142	
	Male	7 (77.8)	14 (100.0)		
Race	American Indian/Alaska Native	0 (0.0)	0 (0.0)	0.366	
	Asian	6 (66.7)	11 (78.6)		
	Black/African American	2 (22.2)	0 (0.0)		
	White	1 (11.1)	3 (21.4)		
BMI categories	Underweight	0 (0.0)	1 (7.1)	0.553	
Ū	Normal	1 (11.1)	4 (28.6)		
	Overweight	4 (44.4)	3 (21.4)		
	Moderate Obesity	4 (44.4)	4 (28.6)		
	Severe Obesity	0 (0.0)	2 (14.3)		
	Morbid Obesity	0 (0.0)	0 (0.0)		
Clinical presentation					
Hypertension	No	4 (44.4)	11 (78.6)	0.179	
	Yes	5 (55.6)	3 (21.4)		
Diabetes mellitus	No	5 (55.6)	9 (64.3)	1.0	
	Yes	4 (44.4)	5 (35.7)		
Cardiovascular/chronic kidney disease	No	7 (77.8)	11 (78.6)	1.0	
·····	Yes	2 (22.2)	3 (21.4)		
Pneumonia (Chest-x-ray)	No	0 (0.0)	0 (0.0)	1.0	
	Yes	9 (100.0)	14 (100.0)		
Main presentation	Asymptomatic	0 (0.0)	0 (0.0)	1.0	
•	GIT Symptoms	0 (0.0)	0 (0.0)		
	URTI Symptoms	0 (0.0)	0 (0.0)		
	URTI, GIT Symptoms	9 (100.0)	14 (100.0)		
Disease severity	Non-severe	0 (0.0)	2 (14.3)	0.502	
,	Severe	9 (100.0)	12 (85.7)		
Treatment	Hydroxychloroquine+ Favipiravir	4 (44.4)	5 (35.7)	0.719	
	Hydroxychloroquine +Favipiravir+Lopinavir/Ritonavir	2 (22.2)	1 (7.1)		
	Hydroxychloroquine + Azithromycin +Favipiravir	2 (22.2)	5 (35.7)		
	Symptomatic only	1 (11.1)	1 (7.1)		
	Hydroxychloroquine +Azithromycin	0 (0.0)	2 (14.3)		

BMI: Body mass index; GIT:Gastrointestinal tract; ICU: Intensive care unit; URTI: Upper respiratory tract infection.

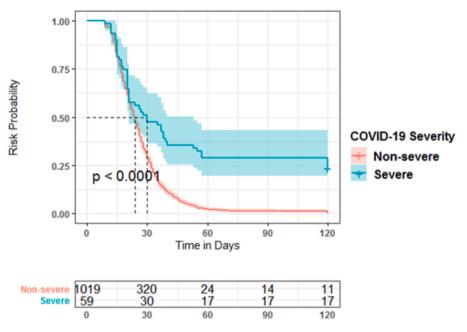


Fig. 6. Kaplan Meier estimate stratified by severity of COVID-19.

decreased control of viral replication and viral clearance. In contrast to our finding, Bennasrallah et al. [17], p.463–469 reported that viral clearance was not significantly different among advanced-aged patients, suggesting other factors such as the presence of co-morbidities could influence the effect of advanced age on time till viral clearance. This assumption is strengthened by our observation, as the presence of cardiovascular disease or diabetes was significantly associated with a longer time to viral clearance. Additionally, A previous study showed a high prevalence of cardiovascular diseases among those aged 45 - 74[24]. Also, several risk factors for cardiovascular diseases were identified including, lifestyle, obesity, age, gender, and the presence of other co-morbidities such as diabetes, and hypertension [25,26]. These findings suggest the presence of many interplaying factors that should be considered cautiously during interpreting the results. So, further controlled studies are needed.

The significant elongation in the time till viral clearance among cardiovascular disease patients was also observed in Fu et al. [8], p.2–4, which reported coronary heart disease as an independent risk factor for viral shedding. Several studies also showed that hypertensive patients usually suffer from prolonged viral shedding [11,21]. Diabetes mellitus was associated with increased risk for viral persistence based on the univariate analysis but not the multivariate. Diabetic patients also showed a significantly longer duration for viral clearance when compared with nondiabetic patients. However, Li et al. [12], p.506–512 and Bhattacharya et al. [23] showed a non-significant correlation between diabetes and viral shedding. And Hirai et al. [19], p.864–868 showed a significant association between diabetes and a shorter time till viral clearance. Still, the association between different clinical and sociodemographic characteristics of patients is unclear and requires further controlled investigations.

Here, gender was not associated with an increased risk of viral persistence, which is consistent with the findings of several studies [12, 20]. However, few studies observed a significant correlation between the male gender and prolonged time till viral clearance [11,27]. This could be due to male predominance in these reports. The advanced cellular and humoral reactions could be the reason behind improved viral clearance among females [28].

Our study identified presentation with URTI and GIT symptoms as a risk factor for viral persistence. Also, A substantial number of our cohort was asymptomatic. Interestingly, they showed a significantly longer time until viral clearance. Previous reports had reported higher viral load in asymptomatic COVID-19 patients, and it decreased slowly compared with symptomatic patients [22,29]. However, the positivity of viral detection does not always confirm transmissibility and being infectious; also, false-positive results could occur. Identifying asymptomatic patients and their characteristics is very important to understand the transmission dynamics of the virus and the implantation of public health measures.

Disease Severity and ICU admission were significantly associated with an increased risk of delayed viral clearance. In Xu et al.'s study [11], p.799–806, the severity of COVID-19 at admission was significantly associated with prolonged viral shedding. Time to viral clearance was also shorter among patients with mild symptoms compared with severe symptoms [22]. Zhou et al. [6], p.1054–1062 also reported prolonged time till viral clearance among severe and critically ill COVID-19 patients. These observations are highly important for deciding the duration of antivirals administration and The recommendations of the duration of patient isolation.

In our previous study, we examined the impact of different COVID-19 treatment protocols, including azithromycin, favipiravir, lopinavir/ ritonavir and hydroxychloroquine on disease outcomes which included the time to viral clearance and the results showed no significant effect of different antivirals on the time till viral clearance [30]. These findings were also reported in other studies by Hong et al., Liu et al. and Cheng et al. [31–33]. These findings suggest that the antiviral treatments have no clinical utility regarding the time till viral clearance among COVID-19 patients.

Because the number of patients included was reasonable, and the study group was multi-ethnic, this study has the power of a multi-center study. Our study has some limitations, including that viral detection was conducted by a qualitative assay and from nasopharyngeal swabs only and not from feces, blood, or sputum. Previous reports showed a higher viral load in patients' excretions than in respiratory samples [34]. We did not include the history of exposure of asymptomatic patients. Also, viral detection by RT-PCR does not necessarily determine the infectibility of the patients, and false results could be obtained.

5. Conclusion

In summary, we identified several factors associated with prolonged

time to viral clearance, including advanced age, asymptomatic presentation, URTI and GIT symptoms, cardiovascular diseases, ICU admission, and COVID-19 severity. It is recommended to conduct large studies including larger number of populations to understand the dynamics of SARS-CoV-2 infection and clearance and guide public health measures and planning

All authors declare no competing financial interests

Disclosure statement The author declares no conflict of interest.

Ethics approval

This study was accompanied based on the Declaration of Helsinki. All patient identifiers were removed while the data was being processed, and patient privacy was preserved throughout the study. The study was reviewed and approved by Abu Dhabi Health COVID-19 Research Ethics Committee (Ref: DOH/CVDC/2022/1739). As a retrospective study, the informed consent form was not required.

Informed consent statement

The study was reviewed and approved by Abu Dhabi Health COVID-19 Research Ethics Committee (Ref: DOH/CVDC/2022/1739). As a retrospective study, the informed consent form was not required.

Data availability statement

Data can be available upon request from the first and corresponding author.

Author contribution

Conceptualization, W.H.; methodology, W.H.; data analysis and interpretation, W.H.; writing—review and editing, W.H.; supervision, W.H.; project administration, W.H.

Funding

No funding was received.

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.

Acknowledgements

I would like to express my sincere gratitude to Prakash Janardan for his motivation, enthusiasm, and continuous support of our work. Immeasurable appreciation and deepest gratitude for the help and support are extended to Dr. Rita Vassena, and the Nmc NMC Clinical Research team, Gayathri Rahul, Veeranna Shivakala, Shailendra Singh, and Rohit Dusane for their help and great advice. We would like to express our gratitude to the Medical Agency for Research and Statistics (MARS)for their editorial support.

References

- J. She, J. Jiang, L. Ye, L. Hu, C. Bai, Y. Song, 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies, Clin. Transl. Med. 9 (1) (2020), https://doi.org/10.1186/s40169-020-00271-z.
- [2] WHO, "WHO Director-General's Opening Remarks At the Media Briefing on COVID-19 - 11 March 2020 - World Health Organization," World Heal. Organ., 2020.

- [3] V.M. Corman, et al., Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR, Eurosurveillance 25 (3) (2020), https://doi.org/10.2807/1560-7917. FS.2020.25.3.2000045.
- [4] "Interim guidelines for clinical specimens for COVID-19 | CDC," 2020. https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html (accessed May 30, 2021).
- [5] Eurosurveillance Editorial Team, Latest updates on COVID-19 from the European Centre for disease prevention and control, Euro Surveill 25 (6) (2020), https://doi. org/10.2807/1560-7917.ES.2020.25.6.2002131.
- [6] F. Zhou, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.
- [7] C. Zhou, et al., Impact of age on duration of viral RNA shedding in patients with COVID-19, Aging (Albany. NY). 12 (22) (2020) 22399–22404, https://doi.org/ 10.18632/aging.104114.
- [8] Y. Fu, et al., Risk factors for viral RNA shedding in COVID-19 patients, Eur. Respir. J. 56 (1) (2020) 2–4, https://doi.org/10.1183/13993003.01190-2020.
- [9] S. Zheng, et al., Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study, BMJ 369 (2020), https://doi.org/10.1136/bmj.m1443. Apr.
- [10] Z. Fang, Y. Zhang, C. Hang, J. Ai, S. Li, W. Zhang, Comparisons of viral shedding time of SARS-CoV-2 of different samples in ICU and non-ICU patients, J. Infect. 81 (1) (2020) 147–178, https://doi.org/10.1016/j.jinf.2020.03.013.
- [11] K. Xu, et al., Factors associated with prolonged viral RNA shedding in patients with coronavirus disease 2019 (COVID-19), Clin. Infect. Dis. 71 (15) (2020) 799–806, https://doi.org/10.1093/cid/ciaa351. Aug.
- [12] T.Z. Li, et al., Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19, J. Med. Virol. 93 (1) (2021) 506–512, https://doi.org/10.1002/jmv.26280. Jan.
- [13] K. Wang, et al., Differences of severe acute respiratory syndrome coronavirus 2 shedding duration in sputum and nasopharyngeal swab specimens among adult inpatients with coronavirus disease 2019, Chest 158 (5) (2020) 1876–1884, https://doi.org/10.1016/j.chest.2020.06.015.
- [14] A.M. McKie, T.P.W. Jones, C. Sykes, Prolonged viral shedding in an immunocompetent patient with COVID-19, BMJ Case Rep 13 (10) (2020) 1–4, https://doi.org/10.1136/bcr-2020-237357.
- [15] S. Otsubo et al., "Prolonged shedding of SARS-CoV-2 in COVID-19 infected hemodialysis patients," Wiley, vol. 25, no. 3, pp. 356–358, 2021, doi: 10.1111/ 1744-9987.13566.
- [16] "DiaPlexQ ™ Novel Coronavirus (2019-nCoV) Detection Kit INSTRUCTIONS FOR USE (IFU)," 2020.
- [17] United Arab Emirates Ministry of Health and Prevention, "National guidelines for clinical management and treatment of COVID-19".
- [18] "Clinical Managment of COVID-19—Intterim Guidance. 2020.," 2020. https: //www.google.com/url?sa=t&rct=j&q=&esrc=s&source=we b&cd=&cad=tja&uact=3&ved=2ahUKEwiD8On8jID3AhVDXRoKHcrIBOgQFn oECAsQAQ&url=https%3A%2F%2Fapps.who.int%2Firis%2Fbistream%2Fhandle %2F10665%2F332196%2FWHO-2019-nCoV-clinical-2020.5-eng.pdf&usg =AOvVaw3KM (accessed Apr. 25, 2022).
- [19] C.J. Wei, X.X. Hu, G.M. Ye, J.M. Yang, Z.S. Cheng, X.H. Wang, Time and risk factors of viral clearance in COVID-19 patients, Chin. Med. J. (Engl). 134 (17) (2021), https://doi.org/10.1097/CM9.00000000001467.
- [20] C. Bennasrallah, et al., Factors associated with a prolonged negative conversion of viral RNA in patients with COVID-19, Int. J. Infect. Dis. 105 (2021), https://doi. org/10.1016/j.ijid.2021.02.089.
- [21] H.M. Shu, et al., Factors influencing viral clearance in mild COVID-19 and clinical characteristics of asymptomatic patients, Biomed Res. Int. 2021 (2021), https:// doi.org/10.1155/2021/5909612.
- [22] N. Hirai, et al., Factors associated with viral clearance periods from patients with COVID-19: a retrospective observational cohort study, J. Infect. Chemother. 27 (6) (2021), https://doi.org/10.1016/j.jiac.2021.02.015.
- [23] B. Bhattacharya, et al., SARS-CoV-2 RT-PCR profile in 298 Indian COVID-19 patients: a retrospective observational study, Pathog. Dis. 79 (1) (2021), https:// doi.org/10.1093/femspd/ftaa064.
- [24] M. Noale, F. Limongi, S. Maggi, Epidemiology of cardiovascular diseases in the elderly, Adv. Exp. Med. Biol. 1216 (2020) 29–38, https://doi.org/10.1007/978-3-030-33330-0_4/TABLES/2.
- [25] A.A. Alsheikh-Ali, et al., Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East cardiovascular epidemiological (ACE) study, PLoS One 9 (8) (2014), https://doi.org/10.1371/JOURNAL.PONE.0102830. Aug.
- [26] S. Al-Shamsi, D. Regmi, R.D. Govender, Incidence of cardiovascular disease and its associated risk factors in at-risk men and women in the United Arab Emirates: a 9year retrospective cohort study, BMC Cardiovasc. Disord. 19 (1) (2019), https:// doi.org/10.1186/S12872-019-1131-2. Jun.
- [27] M. Khan, H. Khan, S. Khan, M. Nawaz, Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study, J. Med. Microbiol. 69 (8) (2020), https:// doi.org/10.1099/jmm.0.001231.
- [28] A. Bouman, M.Jan Heineman, M.M. Faas, Sex hormones and the immune response in humans, Hum. Reproduct. Update 11 (4) (2005), https://doi.org/10.1093/ humupd/dmi008.
- [29] S. Lee, et al., Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea, JAMA Intern. Med. 180 (11) (2020), https://doi. org/10.1001/jamainternmed.2020.3862.

W. Hafez

- [30] W. Hafez, H. Saleh, Z. Al Baha, M. Tariq, S. Hamdan, S. Ahmed, Antiviral used among non-severe COVID-19 cases in relation to time till viral clearance: a retrospective cohort study, Antibiot 11 (4) (2022) 498, https://doi.org/10.3390/ ANTIBIOTICS11040498. 2022, Vol. 11, Page 498Apr.
- [31] W. Hong, et al., Use of combined treatment of 3rd-generation cephalosporin, azithromycin and antiviral agents on moderate SARs-CoV-2 patients in South Korea: a retrospective cohort study, PLoS One 17 (5) (2022), e0267645, https:// doi.org/10.1371/JOURNAL.PONE.0267645. May.
- [32] W.Da Liu, et al., Experience of the use of hydroxychloroquine on patients with COVID-19: a perspective on viral load and cytokine kinetics, J. Formos. Med.

Assoc. 120 (5) (2021) 1269–1273, https://doi.org/10.1016/J.JFMA.2020.08.022. May.

- [33] C.Y. Cheng, et al., Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 shedding in patients with mild pneumonia in Taiwan, J. Microbiol. Immunol. Infect. 53 (3) (2020) 488–492, https://doi.org/10.1016/J.JMII.2020.03.032. Jun.
- [34] W. Zhang, et al., Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes, Emerg. Microbes Infect. 9 (1) (2020), https://doi.org/10.1080/22221751.2020.1729071.