Clinical outcomes at medium-term follow-up of COVID-19

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Abstract

Background: The long coronavirus disease 2019 (COVID-19) syndrome is defined as persistent physical, cognitive and/or psychological symptoms that continue for more than 12 weeks following the acute illness.

Methods: In all, 2,646 patients were randomly selected from all individuals who were diagnosed with COVID-19. They were interviewed so as to assess the persistence of symptoms and health-related quality of life. Blood investigations were also taken.

Results: The median (interquartile range (IQR)) age was 44 (31–55) years and 48.6% were males. Five per cent had been hospitalised. Follow-up was for a median of 142 days (IQR: 128–161). Twenty-two per cent of the participants claimed that they were feeling worse than they felt before COVID-19. The most common symptoms were anosmia, ageusia, fatigue, shortness of breath, headaches and myalgia. The Short Form-36 questionnaire revealed that 16.4% felt that they were somewhat worse than in the previous year and that hospitalised patients fared worse in all domains except for role-emotional. New-onset diabetes was similar to the rate of undiagnosed diabetes in the background population. Hospitalised patients had significantly higher liver transaminases, fasting plasma glucose, glycated haemoglobin, uric acid, red cell distribution width, mean platelet volume, triglyceride levels and troponin levels but lower estimated glomerular filtration rate and high-density lipoprotein-cholesterol at follow-up.

Conclusions: A significant proportion of patients were symptomatic at a median follow-up of 142 days and felt worse than 1 year previously. Hospitalised patients had more biochemical and haematological abnormalities compared to non-hospitalised ones, suggesting ongoing inflammation in subjects who were more severely affected by the disease.

Introduction

The coronavirus disease 2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It has resulted in significant concern globally in view of its possible multi-organ involvement and especially high fatality rate in elderly patients, immune deficient subjects as well as in those having underlying medical conditions affecting the lungs, the kidneys and the heart being. To date, there have been over 590 million confirmed cases of COVID-19, including over 6.4 million deaths (WHO).[1]

Besides causing an acute illness, it is now recognised that infection by SARS-CoV-2 may result in the long COVID syndrome. This has been defined by the National Institute for Health and Care Excellence of the UK as a set of persistent physical, cognitive and/or psychological symptoms that continue for more than 12 weeks following the acute illness and which are not explained by an alternative diagnosis.[2] In the vast majority, the long COVID syndrome has been studied in small patient cohorts.[3] The largest studies are the ones from Wuhan, China (n = 1,733)[4] and from Bergamo, Italy (n = 767).[5] The former was restricted to hospitalised patients and the latter to patients who were either hospitalised or discharged from the emergency department. Other studies ranged from 33 to 538 subjects.[3]

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The aim of the present study was therefore to investigate the persistence of symptoms in a nationally representative sample of post-COVID patients.

Patients and methods

Individuals who were diagnosed with COVID-19 infection following nasopharyhngeal swabbing in any of the testing centres in Malta between October 2020 and March 2021 were invited to participate in the study. Exclusion criteria included patients with learning disabilities, dementia or inability to give informed consent, subjects younger than 18 years of age and older than 70 years of age, non-Caucasian ethnicity as well as non-Maltese residents who were therefore inaccessible for follow-up. It was decided to exclude patients older than 70 years a priori in view that, with increasing age, there is increased probability of having multiple co-morbidities with associated limited mobility, thus making it difficult to assess the generalised well-being of these patients. Furthermore, most of the domains in the questionnaires utilised assessed the current state of the patient rather than a comparison to a previous state, thus making it more difficult to discern any impact of COVID-19 on the general well-being of subjects more than 70 years of age.

Subjects were interviewed using the 36-Item Short Form Survey (SF-36)[6] and a standardised post-COVID specific questionnaire[7] at around 5 months after having a positive COVID-19 result. Information regarding past medical history, and smoking history was also obtained during the patient interview. The latter was performed through a telephone call.

The SF-36 was utilised in the study in view that is a well-studied, frequently used, self-reported health assessment. It originates from the Medical Outcomes Study and is frequently employed as a gauge of an individual's or a population's quality of life. It consists of 36 questions that address eight different areas of health, mainly:

(1) Physical activity restrictions brought on by health issues; (2) social activity restrictions brought on by health or emotional issues; (3) restrictions on routine activities brought on by physical health issues; (4) aches and pains; (5) mental health (psychological distress and well-being); (6) restrictions on routine activities due to emotional issues; (7) vitality (energy and fatigue) and (8) perceptions of general health. Using a scoring key, the scores for the various domains are transformed and combined to get a total score that ranges from poor to high in terms of quality of life.[6]

Biochemical analysis was performed in a randomly selected subgroup of 1,058 patients. Biochemical tests included fasting plasma glucose (FPG), fasting lipid profile, glycated haemoglobin (HbA1c) and N-terminal pro-type B natriuretic peptide (NT-proBNP) levels. Newly diagnosed diabetes was defined as a $FPG \geqslant 7.0$ mmol/L or a $HbA1c \geqslant 6.5\%$ (45 mmol/mol) as recommended by Diabetes UK.[8] The study was approved by the Faculty Research Ethics Committee of the Faculty of Medicine & Surgery of the University of Malta.

Statistical methods

Statistical analysis was performed using IBM SPSS version 23.0. Normality of distribution was assessed using the Kolmogorov–Smirnov test. All continuous data had non-normal distribution and comparisons between hospitalised and non-hospitalised patients were made using the Mann–Whitney U test. To further explore the mechanism of any differences in follow-up blood investigations between hospitalised and non-hospitalised patients, adjustment for possible confounders was made by multiple regression analyses. In model 1, adjustment was made for age and gender. Model 2 was additionally adjusted for cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic respiratory disease and obesity. Model 3 was as for model 2 but additionally adjusted for hyperlipidaemia, atrial fibrillation smoking status and hypertension.

Results

The study included 2,646 participants. These were followed up for a median of 142 days (interquartile range, IQR: 128–161). The median age was 44 (31–55) years and 48.6% were males. Five per cent of the study population was hospitalised in view of severe illness and of these 0.7% were intubated. Table 1 shows the baseline characteristics of the study population. Smokers comprised 16.9% of the population and 10.3% were ex-smokers. 17% suffered from hypertension, 10.7% had hyperlipidaemia, ischaemic heart disease was present in 2.3%, heart failure in 0.6%, obesity in 18%, chronic kidney disease in 0.2%, chronic respiratory disease in 6.9% and type 2 diabetes mellitus in 7.3%.

At a median follow-up of 142 days (IQR: 128–161 days), 22% of the participants claimed that they were feeling worse than they felt before COVID-19, while 77% claimed that their general condition was same to previous; 22.5% reported shortness of breath while 8.4% reported chest pain; fatigue was present in 25.6%, headaches in 19.6% and myalgia in 14.7%. Abnormal taste of food and anosmia were reported in 52.9% and 55.2%, respectively (Figure 1).

With regard to health-related quality of life as assessed by the SF-36 questionnaire, the vast majority (78.8%) of subjects claimed that they felt about the same as the previous year, 16.4% claimed that they were somewhat worse while 1.4% claimed that they were much worse (Figure 2). Figure 3 shows transformed scores of the each of the domains of the SF-36, namely mental health, general health, vitality, bodily pain, social functioning, role-emotional, role-physical and physical functioning. Most of the participants exhibited high scores in all domains, indicating general good health in all sectors. However, on comparing hospitalised as compared to non-hospitalised subjects, it was noted that hospitalised patients fared worse at medium-term follow-up in all domains except for role-emotional (Table 2).

Blood investigations were taken at follow-up in 1,378 participants (52%). Table 3 compares the follow-up biochemical data between hospitalised and non-hospitalised patients. Hospitalised patients had significantly higher

Table 1. Baseline characteristics of study population.

Patient characteristics (*n* = 2,646)	Values
Hypertension (*n* (%))	451 (17%)
Hyperlipidaemia (*n* (%))	284 (10.7%)
Ischaemic heart disease (*n* (%))	60 (2.3%)
Cerebrovascular accident/transient ischaemic attack (*n* (%))	14 (0.5%)
Peripheral vascular disease (*n* (%))	7 (0.3%)
Heart failure (*n* (%))	15 (0.6%)
Type 1 diabetes mellitus (*n* (%))	9 (0.3%)
Type 2 diabetes mellitus (*n* (%))	194 (7%)
Atrial fibrillation (*n* (%))	18 (0.7%)
Chronic kidney disease (*n* (%))	5 (0.2%)
Obesity BMI > 30 (*n* (%))	477 (18%)
Chronic respiratory disease (*n* (%))	184 (7%)
Dialysis (*n* (%))	2 (0.1%)
Liver cirrhosis (*n* (%))	2 (0.1%)
Immunosuppressants (*n* (%))	12 (0.5%)
Pregnancy (*n* (%))	32 (1.2%)
Smokers:ex-smokers:non-smokers (*n* (%))	448 (16.9%):274 (10.3%):1,922 (72.7%)

BMI: body mass index; eGFR: estimated glomerular filtration rate.

Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m^2.

Figure 1. Symptoms reported by patients at a median follow-up of 142 days (IQR: 128–161 days) as assessed by the post-COVID-specific questionnaire (Carvalho-Schneider C). IQR: interquartile range; SOB: shortness of breath.

alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), FPG, HbA1c, uric acid, red cell distribution width (RDW), mean platelet volume (MPV), triglyceride levels and troponin levels but lower high-density lipoprotein (HDL)-cholesterol estimated glomerular filtration rate at follow-up. There were no differences in NT-proBNP levels. Multivariate analysis was consequently performed to adjust for possible confounders. Results obtained are outlined in Table 4. RDW, MPV, triglyceride, GGT and FPG were significant in all models; uric acid and troponin levels were statistically significant in models 1 and 2.

New-onset diabetes, as assessed from both FPG and HbA1c levels at follow-up, was diagnosed in 50 patients (4.7%, 95% confidence interval: 3.5–6.2%). Seven of the cases of newly diagnosed diabetes occurred in patients who had been hospitalised (5.3%).

Discussion

Our data show that approximately one-fifth of subjects were still significantly debilitated in the medium-term following COVID-19. Most common persistent symptoms were abnormal sense of smell and taste. A significant proportion (22.5%) still reported shortness of breath. These are significant findings, especially when one considers that our cohort was randomly selected from all COVID-19 patients, of which 95% were not hospitalised.

With regard health-related quality of life, the SF-36 was utilised. This is a well-validated and extensively used questionnaire.[9,10] Here it was noted that, at 5-month follow-up period, subjects who had been previously hospitalised for COVID-19 still fared generally worse with regard overall well-being, vitality, bodily pain, physical and social functioning together with mental health.
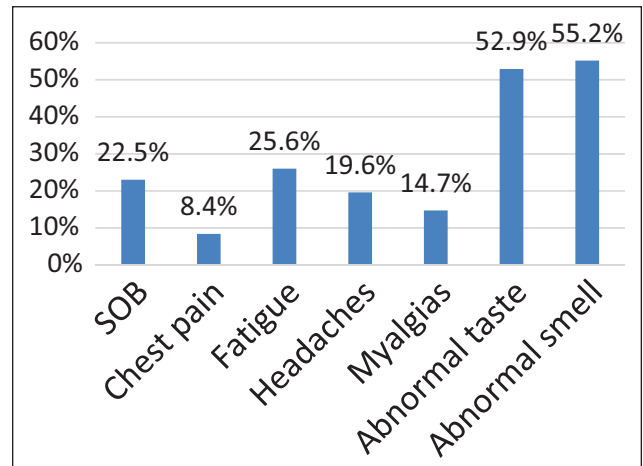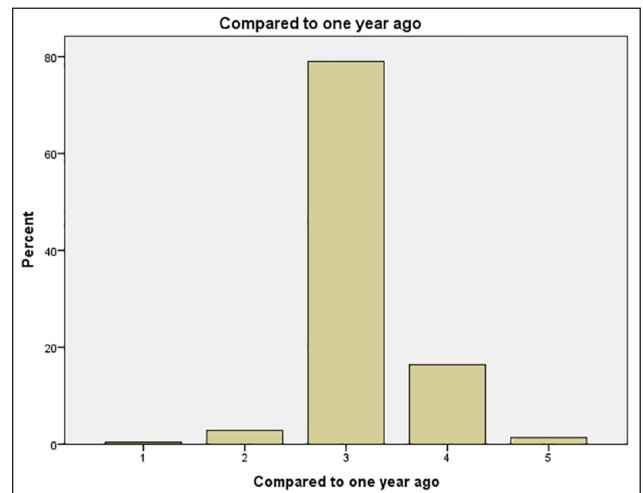

Figure 2. General health of the study participants as compared to the previous year, as assessed via the SF-26 questionnaire (1: much better than previous year; 2: somewhat better than previous year; 3: same as previous year; 4: somewhat worse than previous year; 5: much worse than previous year).

Of concern is our finding that, not only do hospitalised patients fare worse on the SF-36 questionnaire, but this is also accompanied by significantly higher ALP and GGT levels. Importantly, this difference persisted even after adjustment for potential confounders, such as diabetes and obesity. This is important since both diabetes and obesity are known risk factors for more serious COVID-19 and also predispose to hepatic steatosis. Liver injury has been previously reported in the acute COVID-19 phase[11,12] and has been associated with worse clinical outcomes in the acute phase.[13,14] Although we cannot exclude residual confounders, our data suggest that there may be persistent ongoing liver injury in the medium-term in the more severe COVID-19 patients. This merits further study.
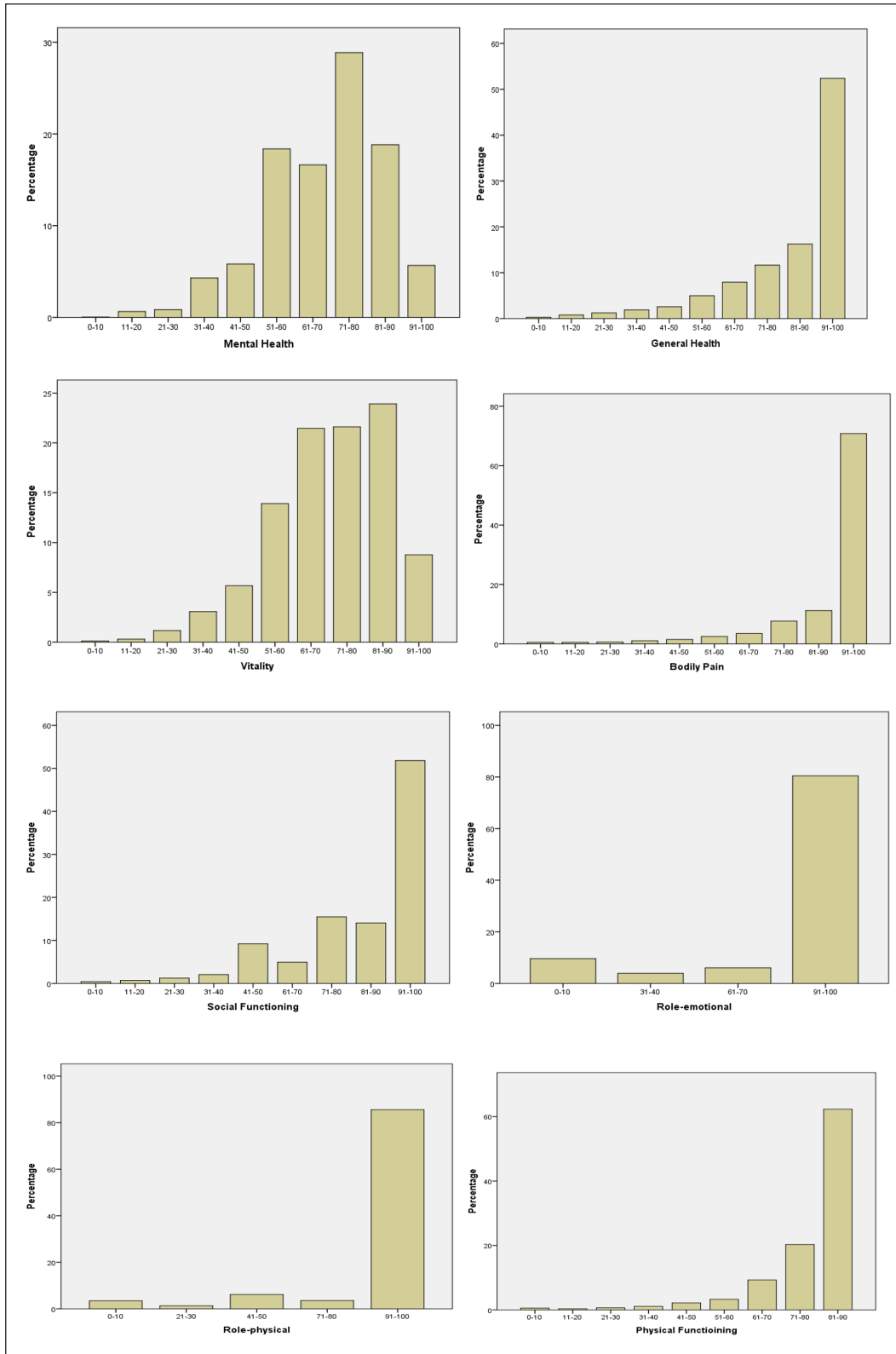
Figure 3. Percentage of subjects within each transformed score range of the individual domains of the 36-Item Short Form Survey (SF-36).

RDW and MPV were also significantly higher in hospitalised compared to non-hospitalised patients in monovariate analysis. This statistical difference persisted after adjustment for potential confounders in all the three models. RDW is a strong marker for cardiovascular disease including myocardial scar burden,[15] fatal cardiovascular events[16] and all-cause mortality.[17] It has also been associated with diabetic kidney disease.[18] Likewise MPV is associated with cardiovascular disease[19,20] and mortality.[21] Other authors have reported that MPV rise[22] and high RDW[23–26] in hospitalised COVID patients predict increased mortality. Our data show that hospitalised patients continue

Table 2. Health-related quality of life as assessed by SF-36 in hospitalised and non-hospitalised patients 5 months after COVID-19.

Scale	Non-hospitalised patient (n = 2,510)	Hospitalised patient (n = 134)	p Value
Physical functioning	85 (80–85)	80 (60–85)	<**0.001**
Role-physical	100 (100–100)	100 (75–100)	<**0.001**
Bodily pain	100 (84–100)	100 (72.5–100)	<**0.001**
General health	92 (77–97)	82 (62–92)	<**0.001**
Vitality	75 (65–8 5)	70 (60–83.75)	**0.002**
Social functioning	100 (75–100)	87.5 (62.5–100)	<**0.001**
Role-emotional	100 (100–100)	100 (100–100)	0.1
Mental health	72 (60–80)	76 (64–84)	**0.009**

IQR: interquartile range.
Significant *p* values are marked in bold. Data are presented as median (IQR).

Table 3. Biochemical and haematological data at follow-up.

Variable	Non-hospitalised patient (n = 1,291)	Hospitalised patient (n = 87)	p Value
WCC, $\times 10^9$/L	6.61 (5.6–7.84)	6.76 (5.8–8.36)	0.14
Hb, g/dL	14.15 (13.2–15.3)	14.1 (13–15.35)	0.72
Platelets, $\times 10^9$/L	264 (224–310.5)	257 (219–312.5)	0.64
RDW, %	12.9 (12.3–13.5)	13.2 (12.6–14.05)	**0.002**
MPV, fL	10.8 (10.3–10.8)	10.6 (10–11)	**0.003**
eGFR, mL/min/1.73 m^2	92 (80–104)	83 (70.25–99.75)	**0.002**
Total cholesterol, mmol/L	4.97 (4.29–5.69)	4.95 (4.04–5.73)	0.3
HDL-cholesterol, mmol/L	1.44 (1.19–1.74)	1.31 (1.02–1.55)	<**0.001**
Total: HDL-cholesterol	3.41 (2.78–4.23)	3.64 (2.89–4.74)	**0.04**
LDL-cholesterol, mmol/L	2.88 (2.28–3.58)	2.72 (1.94–3.39)	0.12
Non-HDL-cholesterol, mmol/L	3.43 (2.77–4.18)	3.38 (2.63–4.32)	0.94
Triglyceride, mmol/L	1.12 (0.82–1.63)	1.52 (1.06–2.08)	<**0.001**
AST, U/L	22 (18–27)	22 (18–25)	0.65
ALP, U/L	69 (56.75–85)	78 (66.75–94.5)	<**0.001**
ALT, U/L	18 (13–27)	21 (15–30.5)	0.13
GGT, U/L	20 (14–32)	30.5 (21.75–53)	<**0.001**
Bilirubin, umol/L	8.2 (6–11.1)	7.55 (5.33–10.15)	0.13
Albumin, g/L	46 (44–48)	45 (42.05–47)	**0.001**
FPG, mmol/L	5.04 (4.64–5.57)	5.57 (4.99–8.07)	<**0.001**
HbA1c, %	5.4 (5.1–5.7)	5.9 (5.3–7.3)	<**0.001**
Uric acid, umol/L	288 (234–347)	326 (279.5–382)	<**0.001**
Vitamin D, ng/mL	19 (14–26)	19 (16–27)	0.3
NT-proBNP, pg/mL	37 (17–63)	33.5 (14.25–127.5)	0.6
Troponin T, ng/L	4 (3–6)	8 (4.5–13)	<**0.001**

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; GGT: gamma glutamyl transferase; Hb: haemoglobin; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MPV: mean platelet volume; NT-proBNP: N-terminal pro-type B natriuretic peptide; RDW: red cell distribution width; WCC: white cell count.
Significant *p* values are marked in bold. Data are median (IQR). Significant *p* values are marked in bold.

to have higher RDW and MPV in the medium-term follow-up, even after adjusting for various confounders including cardiovascular disease, chronic kidney disease, diabetes, obesity and hypertension at baseline. Therefore, there is the possibility that COVID-19 might lead to elevation of RDW. We do not have baseline RDW levels and therefore our data do not allow us to make definitive conclusions. However, this possibility merits further study as it might be an indicator of future cardiovascular disease in severe COVID-19.

Troponin levels together with other cardiac biomarkers are established prognostic indicators in acute COVID-19,[27–29] but few authors have investigated their role in the post-COVID syndrome. We found higher troponin T levels in hospitalised patients compared to non-hospitalised ones in monovariate analysis and in models 1 and 2. Statistical significance was lost in model 3, in which additional adjustment was made for hyperlipidaemia, atrial fibrillation, smoking status and hypertension. This suggests that the observed difference might be mediated by

Table 4. Biochemical and haematological data for hospitalised patients at follow-up after adjustment for possible confounders.

Factor	Model 1 p value	Model 2 p value	Model 3 p value
RDW, %	0.001	0.01	0.01
MPV, fL	0.02	0.02	0.02
eGFR, mL/min/1.73 m²	0.3	0.62	0.58
HDL-cholesterol, mmol/L	0.09	0.03	0.05
Triglyceride, mmol/L	0.01	0.02	0.01
ALP, U/L	0.16	0.14	0.011
GGT, U/L	<0.001	0.01	0.01
FPG, mmol/L	<0.001	<0.001	<0.001
Uric acid, umol/L	0.01	0.04	0.09
Troponin T, ng/L	<0.001	0.04	0.08

ALP: alkaline phosphatase; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; GGT: gamma glutamyl transferase; HDL: high-density lipoprotein; MPV: mean platelet volume; RDW: red cell distribution width.
In Model 1, adjustment is made for age and sex.
In Model 2, adjustment is made for age, sex, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic respiratory disease and obesity.
In Model 3, adjustment is made for age, sex, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic respiratory disease, obesity, hyperlipidaemia, atrial fibrillation smoking status and hypertension.

the confounding effect of these parameters. However, it is also possible that significance was lost due to diminished statistical power when including more variables. This requires further study.

Triglyceride levels at follow-up were noted to be statistically higher in hospitalised patients as compared to non-hospitalised ones; this persisted following adjustment in all three models. On the other hand, HDL-cholesterol was found to be statistically significantly lower in hospitalised after adjustment only in model 2 with borderline significance in model 3. Likewise, uric acid was found to be statistically significant following adjustment in models 1 and 2 while FPG was very highly significant in all three models. All these four factors, namely triglyceride, HDL-cholesterol, FPG and uric acid levels are markers of metabolic disease. Interestingly, a 12-year follow-up of subjects who had recovered from the previous coronavirus illness, SARS, revealed that subjects who had been previously infected by SARS experienced a higher incidence of derangements in lipid profile, altered glucose metabolism as well as cardiovascular problems as compared to volunteers who were matched for age and body mass index.[30] Furthermore, a recent study carried out by Barman et al.[31] in COVID-19 patients showed that temporal changes in lipid parameters before and after COVID-19 may be associated with mortality and in-hospital adverse outcomes. This is in keeping with the findings of Masana et al.[32] who showed that low HDL-cholesterol and high triglyceride concentrations measured before or during hospitalisation are strong predictors of a severe COVID-19; the authors suggest that these could be sensitive markers of inflammation. The current study goes a step further in showing that lower HDL and higher triglyceride levels persist in hospitalised patients as compared to non-hospitalised patients at

5-month follow-up period, possibly suggesting ongoing inflammation that could contribute to the long-COVID syndrome and the lower values obtained in the SF-36 questionnaire.

The rate of newly diagnosed diabetes was 4.7%, with a confidence interval of 3.5%–6.2%. This is similar to the rate of undiagnosed diabetes in this age group in the Maltese population.[33] There have been various reports of new-onset diabetes after COVID-19.[34] Our data suggest that previous reports of new-onset diabetes may have been driven by previously undiagnosed diabetes or that any diabetogenic effects of COVID-19 may be transitory. It should be noted that most studies either did not report the date of detection of newly diagnosed diabetes or the diagnosis was made within a few days of COVID-19.[34] In some studies, the definition of new-onset diabetes was based solely on high plasma glucose[35]; such results could be explained by acute stress hyperglycaemia. Only two studies required patients to have a HbA1c > 6.5% in addition to high plasma glucose to be classified as new-onset diabetes.[36] This decreases, though it does not abolish, the possibility that patients with previously undiagnosed diabetes be misclassified as being new-onset.[8] In our study, biochemical tests were done after a median follow-up of 142 days after COVID-19 and hence we have eliminated the possibility of acute stress hyperglycaemia. Furthermore, none of the previous studies compared the rate of diabetes with the rate of undiagnosed diabetes in the background population. However, it should be noted that most previous studies have studied hospitalised patients[35–37] and it is therefore also possible that only severe COVID-19 is associated with increased diabetes risk. This is supported by our finding that both plasma glucose and HbA1c were higher in hospitalised patients compared to non-hospitalised ones after 5 months, even after adjustment of possible confounders such as diabetes, obesity, hypertension and cardiovascular disease (Table 4). Postulated mechanisms for COVID-induced diabetes include increase in ACE-2 resulting in insulin resistance[38] and decreased pancreatic β-cell function.[39] Another postulated mechanism is destruction of β-cells by the SARS-CoV2.[40]

Strengths and limitations

A major strength of the study is that a reasonably large cohort ($n = 2{,}646$), which is larger than most other studies, was followed up post-COVID. Another strength is that our patients were randomly selected from a list of subjects who tested positive for SARS-CoV-2. This is a more unbiased selection than recruiting only patients requiring hospitalisation. We cannot, of course, exclude that more mildly symptomatic or asymptomatic patients did not subject themselves to swabbing and were therefore missed. However, very vigorous contact tracing was being implemented in our country at the time. This should have minimised such bias.

With regard to limitations, our study was limited to Caucasian subjects. This is in view that the Maltese population is largely of Caucasian origin and therefore other ethnic groups would have been inadequately represented for meaningful analyses. Since there may be racial differences in the

frequency and severity of the long COVID syndrome, it would be relevant that other races are studied by other authors.

Conclusion

We found that a significant proportion of post-COVID patients were symptomatic at a median follow-up of 142 days and felt worse than 1 year previously. Hospitalised patients had more deranged lipid and liver parameters as well as elevated RDW and MPV compared to non-hospitalised ones, suggesting ongoing inflammation in subjects who were more severely affected by the disease. It will be important to investigate whether these differences remain after longer follow-up and whether there is persistent liver or cardiac injury. Further studies should also study other populations and ethnic groups.

Declaration of conflicting interests

Funding

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