The high mental health burden of "Long COVID" and its association with on-going physical and respiratory symptoms in all adults discharged from hospital

To the Editor:

During previous severe coronavirus outbreaks, 15% of survivors suffered from depression and 33% from post-traumatic stress disorder (PTSD) at a mean follow-up of 22.6 and 32.2 months, respectively [1]. A recent systematic review identified that whilst physical symptoms receive most attention, the effects of coronavirus disease 2019 (COVID-19) upon mental health may be equally important [2]. One meta-analysis estimated the prevalence of depression and PTSD in the general public during this pandemic at 24% and 15%, respectively [3]. In adults with pre-existing asthma and COPD, the prevalence of depression and PTSD was 31.5% and 11.3%, respectively [4]. For patients with acute COVID-19 infection, this increased to 42% for depression and 96% for symptoms consistent with PTSD [3].

There are little data on psychiatric ill-health in adults recovering from COVID-19, especially in those with symptoms weeks to months after their initial infection, or "Long COVID" [5]. One study suggested these adults are more likely to be diagnosed with psychiatric conditions, with an estimated incidence of mood disorders of 9.9%. However, this was suggested to be under-estimated as it relied on reporting *via* electronic health data rather than active screening of symptoms [6].

We investigated the mental health burden in adults discharged from hospital with COVID-19 and explored factors that contribute to this.

We established a virtual follow-up service (methodology and questionnaire previously reported [7]) for all adults discharged from hospital with a clinical diagnosis of COVID-19 (with or without positive swabs). Our cohort included adults treated in the emergency department, inpatient wards and intensive care. We screened for psychological morbidity using the Patient Health Questionnaire 2-item (PHQ-2) for depression and Trauma Screening Questionnaire (TSQ) for PTSD; these are brief but have good diagnostic sensitivity [8, 9]. Adults with positive scores (PHQ-2 $\geqslant$3/6 and TSQ $\geqslant$6/10) were provided a referral link to local psychology services.

We consecutively sampled and included in our analysis all adults who consented to follow-up. A power calculation was not undertaken due to the observational nature of the study. In line with national guidance for such work, our research was exempt from the need for institutional review board approval [10]. Non-parametric data were compared with Mann–Whitney U-test and categorical data with Chi-squared test. Logistic regression analysis was performed to review the multivariate association between different factors. All tests of significance were two-tailed. p-values $\leqslant$0.05 were considered statistically significant.

As of 22 May 2020, our hospitals had discharged 1050 adults with COVID-19. After excluding patients who died or were clinically inappropriate for follow-up, 90% (n=946) received virtual follow-up at a median of 65 days (interquartile range (IQR) 37.5–92.5). Efforts to follow-up all patients included using translation services, ensuring results were representative of the hospital population.

760 (80.3%) completed the consultation (mean±SD age 60.7±16.3 years); 60.2% were male and 48.4% of black or minority ethnic (BAME) background. Table 1 summarises our follow up outcomes.

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Adults discharged from hospital with COVID-19 may experience "Long COVID", where mental health symptoms are significant and linked to physical symptoms such as breathlessness. Clinicians should use brief screening questionnaires to support their recovery. https://bit.ly/3d22SJM

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TABLE 1 Demographics and results from virtual follow-up of patients with and without positive Patient Health Questionnaire 2-item (PHQ-2) and Trauma Screening Questionnaire (TSQ) scores

Variable	PHQ-2		p-value	TSQ		p-value
	Negative	Positive		Negative	Positive	
Total patients n	622	105		680	80	
Demographics						
Age	60.5±16.1	59.7±16.1	0.65	61.2±16.5	57.0±13.2	0.03
Female	243 (39.1%)	48 (45.7%)	0.20	259 (38.1%)	43 (53.8%)	0.007
Black, Asian and minority ethnic	289/606 (47.7%)	50/100 (50.0%)	0.69	316/657 (48.1%)	36/75 (48.0%)	0.99
Comorbidities						
Clinical frailty (Rockwood) score (out of 9)	2 (2–3)	2 (2–4)	0.50	2 (2–4)	2 (2–3)	0.07
Diabetes	144/576 (25.0%)	27/97 (27.8%)	0.55	161/625 (25.8%)	20/76 (26.3%)	0.92
Any cardiovascular disease	280/585 (47.9%)	47/99 (47.5%)	0.94	314/636 (49.4%)	33/76 (43.4%)	0.33
Chronic respiratory disease	107/585 (18.3%)	26/99 (26.3%)	0.06	120/636 (18.9%)	20/76 (26.3%)	0.12
Chronic kidney disease	70/579 (12.1%)	15/97 (15.5%)	0.35	81/630 (12.9%)	8/74 (10.8%)	0.62
Depression	16/585 (2.7%)	18/99 (18.2%)	<0.001	27/636 (4.2%)	9/76 (11.8%)	0.004
Anxiety	9/584 (1.5%)	11/99 (11.1%)	<0.001	16/635 (2.5%)	6/76 (7.9%)	0.01
Admission data						
Total number of symptoms (out of 14)[#]	4 (3–5)	5 (3–6)	0.03	4 (3–5)	5 (3–6)	<0.001
Discharged following ED assessment	93 (15.0%)	16 (15.2%)	0.94	100 (14.7%)	11 (13.8%)	0.81
Admitted to intensive care unit	72/487 (14.8%)	16/83 (19.3%)	0.30	78 (11.5%)	12 (15.0%)	0.43
Length of stay days	7 (4–11)	7 (3–15)	0.44	7 (4–12)	7 (3–13)	0.70
Follow-up data						
Any persistent symptoms	259/620 (41.8%)	84/105 (80.0%)	<0.001	286/667 (42.9%)	71/80 (88.8%)	<0.001
Non-improved breathlessness	126/567 (22.2%)	14/97 (14.4%)	0.08	135/603 (22.4%)	10/73 (13.7%)	0.09
MRC breathlessness scale	1 (1–2)	3 (2–3.75)	<0.001	1 (1–2)	3 (2–3.5)	<0.001
Non-improved cough	157/567 (27.7%)	32/98 (32.7%)	0.31	174/603 (28.9%)	19/74 (25.7%)	0.57
Non-improved fatigue	90/564 (16.0%)	28/97 (28.9%)	0.002	101/598 (16.9%)	19/74 (25.7%)	0.06
Non-improved sleep quality	220/559 (39.4%)	46/96 (47.9%)	0.12	233/593 (39.3%)	37/73 (50.7%)	0.06
Myalgia	106/619 (17.1%)	49/104 (47.1%)	<0.001	120/667 (18.0%)	40/79 (50.6%)	<0.001
Anorexia	37/620 (6.0%)	22/104 (21.2%)	<0.001	40/668 (6.0%)	22/79 (27.8%)	<0.001
Confusion or "fuzzy head"	57/619 (9.2%)	46/104 (44.2%)	<0.001	65/667 (9.7%)	42/79 (53.2%)	<0.001
Persistent symptom burden (out of 10)[¶]	0 (0–1)	2 (1–3.75)	<0.001	0 (0–1)	3 (1–4)	<0.001
How close to 100%	90 (80–100)	70 (60–80)	<0.001	90.0 (80–100)	70.0 (60–80)	<0.001
Back to work	174/302 (57.6%)	18/50 (36.0%)	0.004	174/308 (56.5%)	18/48 (37.5%)	0.01

Data are presented as mean±SD or median (interquartile range), unless otherwise indicated. [#]: symptoms included were cough, dyspnoea, chest pain, sore throat, rhinitis, fever, fatigue, myalgia, headache, anorexia, anosmia, diarrhoea, abdominal pain, confusion; [¶]: symptoms included were myalgia, anosmia, chest pain, chest tightness, confusion, diarrhoea, abdominal pain, anorexia, peripheral oedema, focal weakness. ED: emergency department; MRC: Medical Research Council.

47.0% (n=357) of adults had persisting physical and psychiatric symptoms. 105 (14.4%) and 80 (10.5%) adults screened positive for depression and PTSD, respectively. Pre-existing depression and anxiety were associated with positive PHQ-2 (18.2% *versus* 2.7%; 11.1% *versus* 1.5%; both p<0.001) and TSQ (11.8% *versus* 4.2%, p=0.004; 7.9% *versus* 2.5%, p=0.01). No other comorbidity was associated with positive PHQ-2 or TSQ.

Adults with positive PHQ-2 and TSQ were significantly more likely to experience persistent symptoms (PHQ-2 80.0% *versus* 41.8%, TSQ 88.8% *versus* 42.9%; both p<0.001). In particular, they were likely to have ongoing physical symptoms of breathlessness, myalgia, anorexia and confusion (all p<0.001). They were also less likely to have returned to work (PHQ-2 36.0% *versus* 57.6%, p=0.004; TSQ 37.5% *versus* 56.5%, p=0.01).

Positive PHQ-2 and TSQ scores were more common in adults with more physical symptoms on admission (PHQ-2: 5 symptoms (IQR 3–6) *versus* 4 symptoms (IQR 3–5), p=0.03; TSQ: 5 symptoms (IQR 3–6) *versus* 4 symptoms (IQR 3–5), p<0.001; as pre-defined from a list of 14 symptoms) and follow-up (PHQ-2: 2 symptoms (IQR 1–3.75) *versus* 0 symptoms (IQR 0–1); TSQ: 3 symptoms (IQR 1–4) *versus* 0 symptoms (IQR 0–1), both p<0.001; as pre-defined from a list of 10 symptoms).

No significant differences were seen in PHQ-2 or TSQ scores for patients discharged from the emergency department *versus* inpatient wards, or in patients requiring positive airway pressure or intensive care unit treatment *versus* general care.

Logistic regression analysis was undertaken to clarify possible confounders between positive PHQ-2 and TSQ and the above factors. When adjusting for demographics, comorbidities and symptoms, adults with increased symptoms at admission and follow-up remained more likely to have positive PHQ-2 and TSQ; no other significant factors were unmasked. Adults with pre-existing diagnoses of depression and anxiety remained more likely to have positive PHQ-2 but not TSQ.

In summary, amongst adults attending hospital services for COVID-19, there is significant mental health burden at follow-up; 13.8% and 10.5% screened positive for depression and PTSD, respectively, at a median of 9 weeks after discharge. This is not dissimilar to the prevalence derived from electronic health data [6].

An association between ethnicity and COVID-19 infection is reported [11]. Our sample had a higher proportion of adults from BAME backgrounds compared to the demography of our local population. Ethnicity was neither associated with prevalence of psychiatric symptoms nor confounded the association of these symptoms with other risks. However, uptake of mental health services by adults of BAME backgrounds may be affected by well-recognised, important factors [11]. This has public health implications for the management of adults from BAME backgrounds suffering with "Long COVID".

Our data demonstrate that adults with pre-existing depression and anxiety were likely to have positive PHQ-2 and TSQ at follow-up. When adjusting for psychiatric comorbidity, there remained an increased likelihood of depression but not PTSD. This may be due to their pre-existing psychiatric disease, but the association between mental health and COVID-19 is complicated. Psychiatric disease is an independent risk factor for COVID-19, though the explanation for this remains uncertain [6]. In practice, this population is likely to be vulnerable and would certainly benefit from additional support during recovery.

Psychiatric ill-health at follow-up was associated with persistent physical symptoms, such as breathlessness and myalgia. This may be bidirectional: ongoing physical symptoms could lead to psychiatric ill-health and conversely increased mental health burden may present as physical symptoms. Additionally, the SARS-CoV-2 virus may directly cause psychiatric morbidity through cerebral infection or hyperinflammation [2]. Recovery in Long COVID is multi-faceted and we recommend mental health screening to support patients holistically.

There was no association between severity of acute COVID-19 infection and psychiatric morbidity at follow-up, suggesting that all adults, even those with initially limited healthcare interaction, may be at equal risk. Considering the large numbers of adults affected, there is a need to establish robust follow-up and rehabilitation services. Given the association between psychiatric ill-health and inability to return to work, this would support societal and economic recovery through improved functional outcomes.

We believe our data are representative of our patient population, as we actively screened for symptoms in all patients. We included a diverse range of patients with different comorbidities and disease severity. Our multivariate analysis was able to account for possible confounding factors.

Our limitations include not screening for psychiatric ill-health on presentation; thus, we cannot directly compare the prevalence of psychiatric disease pre- and post-infection with COVID-19. Our data cannot sufficiently explain the complex interaction between pre-existing psychiatric illness and current mental health burden. Our data focused on identifying psychological morbidity, but adults infected with COVID-19 may experience positive psychological change and post-traumatic growth [12]. This may mediate psychological morbidity and is interesting to consider for future work by following up the same patients over time.

In summary, adults with "Long COVID" are likely to be referred to healthcare professionals specialising in respiratory or rehabilitation medicine. We advocate using brief mental health screening questionnaires to identify psychological needs and support the recovery of patients who may be far from "back to normal" physically and mentally.

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