

ORIGINAL ARTICLE

PERSISTENCE OF FATIGUE AMONG COVID-19 SURVIVORS IN BANGLADESH: A TWO-MONTH AFTER FOLLOW-UP STUDY

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Abstract:

Background: A limited number of studies have exclusively assessed fatigue among post-COVID patients. Our study aimed to assess the persistence and associations of fatigue among COVID-19 survivors after two months of recovery from their primary illness. **Methods:** During hospital admission from August to September, 2020, a total of 400 patients were diagnosed to be suffering from fatigue using Chalder fatigue scale. After obtaining informed written consent, patients were followed up two months later over telephone. A total of 332 participants participated in the interview (63 patients could not be traced and another 5 patient died within two months). Patients were asked to categorize their present fatigue condition based on a simplified questionnaire developed for telephone interview. **Results:** Among study participants, 62.9% (n=207) were found to be still suffering from fatigue two months after their hospital discharge. A significant association of fatigue was found with age (p=0.000), hypertension (RR: 1.51; CI: 1.15-1.99; p=0.002), diabetes mellitus (RR: 1.45; CI: 1.08-1.95; p=0.010), ischemic heart disease (RR: 2.04; CI: 1.15-3.64; p=0.011), on admission SpO₂ (p=0.000), on admission serum ferritin (p=0.000), d-dimer (p=0.000), CRP (p=0.000), and Hb% (p=0.019). Binary logistic regression model revealed significant association of age and on-admission SpO₂ with persistence of fatigue. **Conclusions:** Fatigue is a highly prevalent symptom among the COVID-19 survivors with significant association between fatigue and patients clinical and laboratory markers.

Keywords: COVID-19, SARS-CoV-2, fatigue, Bangladesh, post-COVID

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Introduction:

As documented in cases with other viral infections, it is expected that a good portion of COVID-19 survivors will suffer from some form of post-COVID fatigue. However, the researchers and the community are still in the dark about the prevalence of post-COVID-19 fatigue and associated factors for

the persistent symptoms. Chronic tiredness is the most common manifestation of fatigue. The fatigue may be reported as muscle weakness, slowed reflexes and responses, impaired decision-making and judgment, dizziness, sleep disturbance, and a majority of these remain undiagnosed (Perin et al., 2020; Griffith & Zarrouf, 2008). It usually settles after

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2 or 3 weeks of viral illness; however, it can linger for weeks or months in some people. The exact mechanism of fatigue is unknown and multifactorial theories are well accepted (Cho et al., 2006; Tanriverdi et al., 2007).

The long term consequence of Severe Acute Respiratory Syndrome (SARS caused by the novel coronavirus SARS-CoV) that emerged from South East Asia in early 2003 was assessed in a Toronto study. It showed a good percentage of survivors experienced fatigue even after one year of the initial infection (Moldofsky & Patcai, 20211). In a similar follow-up study in Hong Kong, over 40% of respondents from 233 SARS survivors reported a chronic fatigue problem 40 months after infection (Lam et al., 2009). During the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak, a longitudinal study revealed that many MERS survivors suffered from chronic fatigue even more than one year after the outbreak in South Korea. The prevalence rate of CFS was about 32.7% at 18 months after the MERS outbreak (Lee et al., 2019).

The study on fatigue syndrome among COVID-19 survivors is limited. A recent study in Ireland assessed the prevalence of fatigue in patients recovered from the acute phase of COVID-19 illness using the Chalder Fatigue Score (CFQ-11); more than half of affected people were reported to have persistent fatigue (67/128; 52.3%) at the median of 10 weeks after initial COVID-19 symptoms (Townsend et al., 2020). This was a small study and involved both admitted and non-admitted COVID patients. We wanted to assess if the Irish study's result is replicated in more extensive research in Bangladesh. Moreover, our study also aimed to look into other associations and predictors of post-COVID 19 fatigues, which were not evaluated in most other studies.

Methods

This prospective cohort study was conducted at DMCH, a 2600 bedded public hospital and the largest tertiary COVID-19 treatment center in Bangladesh with a dedicated 500 bed COVID unit. After obtaining the ethics committee approval from DMCH, all COVID-19 patients admitted from July to August 2020, who were able to give informed consent, were enrolled for the "Clinical and Epidemiological Study of Hospitalized COVID-19 cases in Bangladesh." During hospital stay and discharge, patients were

diagnosed as suffering from fatigue with the help of a structured questionnaire; Chadler fatigue scale for fatigue. Total 11 questionnaire for evaluation for fatigue 1. Do you have problems with tiredness? 2. Do you need to rest more? 3. Do you feel sleepy or drowsy? 4. Do you have problems starting things? 5. Do you lack energy? 6. Do you have less strength in your muscles? 7. Do you feel weak? 8. Do you have difficulties concentrating? 9. Do you make slips of the tongue when speaking? 10. Do you find it more difficult to find the right word? 11. How is your memory? All questions were scored in "Likert" style 0=better than usual, 1=no worse than usual, 2= worse than usual & 3=much worse than usual with a range from 0 to 33.

Finally, patients were broadly allocated into two groups—"patients suffering from fatigue" and "patients NOT suffering from fatigue" based on their scores. A total of 400 patients from this study pool were diagnosed as suffering fatigue during the time of their hospital discharge, and they all were offered to participate in a telephonic conversation 2 months after their discharge from the hospital. During follow up interview through telephone after 2 months, we again asked question regarding Chadler scale were categorized as "still suffering from fatigue." Or "NOT suffering from fatigue". After 2 months of their discharge, we tried to contact enrolled participants on three consecutive days. If not answered, we left a message for them inviting them for a telephonic conversation at their chosen time. Despite that, a total of 63 patients could not be followed up and data of five patients were missing as they expired after their release from the hospital. Therefore, the final statistical analysis was performed on 332 patients.

Inclusion criteria:

- Patients admitted to DMCH with moderate to severe COVID symptoms according to the World Health Organization (WHO) and national guideline classification of COVID-19 severity.
- A positive PCR (real time reverse transcriptase-polymerase chain reaction for SARS, CoV-2) test result within the past 7 days.
- Patients diagnosed as suffering from some form of fatigue by Chadler fatigue scale.
- Patients meeting the WHO criteria for discharge from hospital for quarantine at home (no fever

for three consecutive days, improvement in other symptoms) were eligible for our study and were followed up after 2 months.

Exclusion criteria:

- Patients not interested in a follow up session through a telephone conversation.
- Patient diagnosed as “NOT suffering from fatigue.”
- Patient lost to follow up.
- Patient who died within eight weeks of hospital discharge.

Data collection: Patients’ information such as age, gender, smoking history, comorbidities, SpO₂, and results from common baseline investigations (e.g., Hb%, complete blood count [CBC], CRP, serum ferritin, and serum D dimer), usually advised to COVID-19 patients admitted in DMCH, were collected from the hospital registry as well as the epidemiological study data. After 2 months, all eligible participants were contacted by phone and were asked to answer a dedicated set of questionnaires. Interviews were conducted by trained physicians and data were stored in Microsoft Excel within a password protected laptop. A total of 400 hospitalized COVID-19 patients diagnosed as suffering from some form of fatigue using the Chadler scale. Informed written consent obtained from patients regarding follow-up study after two months (n=400) Patients contacted through telephone after two months of their discharge from the hospital Total 332 patients finally participating in the study 63 patients did not respond even after repeated contact and Five patients died during the next two months (total exclusion: n=68)

Statistical analysis: All statistical analysis was performed using R programming language. The categorical variables were represented with the number of cases and their percentages. Median and interquartile ranges were calculated for continuous variables. The p value was set less than 0.05 for all statistical tests. For the analysis, participants were divided into two groups —“patients suffering from fatigue” and patients not suffering from fatigue.” Wilcoxon rank sum test and χ^2 test of independence were conducted to identify the significant variables responsible for the dependent outcome, persistence of fatigue after 2 months of hospital discharge. With the Wilcoxon rank sum test and χ^2 test of independence, there is no scope for finding out the significance of any variable. Adjusting all other variables, ordinal logistic regression was done to solve

this issue. Binary logistic regression was employed to determine the predictor variable for binary outcome sleep disturbance while adjusting for covariates like age, gender, D-dimer, and so forth. In the ordinal logistic regression, all variables were used as the initial model but performing stepwise regression with the smallest akaike information criterion, and the final model was chosen. Repeated K fold cross validation was done for measuring the accuracy of logistic regression to both train the model and obtain a less biased estimate of prediction error than the direct estimate. Results were presented as odds ratios (OR) with corresponding 95% CI and p values.

Results:

Table-I
Characteristics of participant

Characteristic	N = 332
Sex	
Male	218 (66%)
Female	114 (34%)
Age (Years)	50 (37, 60)
Smoker	62 (19%)
SPO ₂ (%) at admission	88.0 (85.0, 91.0)
Hypertension	151 (45%)
Diabetes mellitus	136 (41%)
Ischemic heart disease	57 (17%)
Asthma	44 (13%)
Chronic obstructive pulmonary disease	23 (6.9%)
Chronic kidney disease	20 (6.0%)
Malignancy	2 (0.6%)

Data from a total of 332 participants were analyzed. Male patients were overly represented with a total of 66% (n=218) participants and remaining 34.3% (n=114) were female. Results reveal, most patients were hypoxic during admission at the hospital for COVID-19, with a median SPO₂ of 88.0 % (85.0, 91.0). Diabetes mellitus (41%, n=136) and hypertension (45.4%, n=151) were two of the most prevalent comorbidities found among participants. On interview, 62.9% (n=207) had been suffering from some form of fatigue, and only 37% (n=125) of participants were free from initial fatigue and were back to their pre-hospital admission level activities(Table-I)

Table-II
Significant variables which are associated with Fatigue

Characteristic	Present, N = 207	Absent, N = 120	p-value
Age (Years)	53 (42, 61)	42 (32, 53)	<0.001
Sex			0.090
Male	143 (69%)	71 (59%)	
Female	64 (31%)	49 (41%)	
Body weight (Kg)	68 (62, 74)	64 (60, 69)	0.002
Smoker	44 (21%)	15 (12%)	0.066
Hypertension	108 (52%)	39 (32%)	<0.001
Diabetes mellitus	96 (46%)	38 (32%)	0.013
Asthma	25 (12%)	19 (16%)	0.4
SPO2 (%) on admission	87.0 (85.0, 89.5)	90.0 (87.0, 92.0)	<0.001
Serum Ferritin at admission	423 (256, 780)	248 (132, 436)	<0.001
Serum D dimer at admission	1.00 (0.50, 1.50)	0.58 (0.43, 1.00)	<0.001
Ischemic heart disease	44 (21%)	12 (10%)	0.014
Chronic obstructive pulmonary disease	17 (8.2%)	4 (3.3%)	0.13
Chronic kidney disease	14 (6.8%)	5 (4.2%)	0.5
Neutrophils (%)	5.3 (3.3, 8.4)	4.5 (3.0, 6.9)	0.091

Table II showed that Age, Sex, Body weight, Smoking status, Presence of hypertension, Presence of diabetes, admission SPO2, admission serum Ferritin, serum D dimer, Neutrophils % and Ischemic heart disease these were significantly associated with fatigue.

On testing, statistically significant association was observed between fatigue and age (p=0.000),

hypertension (RR: 1.51; CI: 1.15-1.99; p=0.002), diabetes mellitus (RR: 1.45; CI: 1.08-1.95; p=0.010), ischemic heart disease (RR: 2.04; CI: 1.15-3.64; p=0.011), on admission SpO2 (p=0.000), on admission serum ferritin (p=0.000), d-dimer (p=0.000), CRP (p=0.000), and Hb% (p=0.019) (Table-III).

Table-III
Contributing Demographic, clinical and laboratory variables for fatigue

Variables	Fatigue Present (n=207)	Fatigue Absent (n=125)	p-value	Reference Value	RR (95% CI)
Age (Years), median (IQR)	53 (41, 61)	43 (32, 53)	0.000		
Gender					
Male, n (%)	143 (69.1%)	75 (60%)	0.091	Male	1.15 (0.97-1.36)
Female, n (%)	64 (30.9%)	50 (40%)			
Smoker, n (%)	44 (21.3%)	19 (15.2%)	0.173	Yes	1.39 (0.86-2.28)
HTN, n (%)	108 (52.2%)	43 (34.4%)	0.002	Yes	1.51 (1.15-1.99)
DM, n (%)	96 (46.4%)	40 (32%)	0.010	Yes	1.45 (1.08-1.95)
Asthma, n (%)	25 (12.1%)	19 (15.2%)	0.416	Yes	0.795 (0.46-1.38)
IHD, n (%)	44 (21.3%)	13 (10.4%)	0.011	Yes	2.04 (1.15-3.64)
COPD, n (%)	17 (8.2%)	6 (4.8%)	0.235	Yes	1.71 (0.68-4.63)
CKD, n (%)	14 (6.8%)	6 (4.8%)	0.466	Yes	1.40 (0.56-3.57)
SpO ₂ (%), median (IQR)	87 (85, 90)	90 (86, 92)	0.000		
Serum Ferritin, median (IQR)	423 (256,799)	301 (132, 539)	0.000		
D-dimer, median (IQR)	1 (0.5, 1.5)	0.61 (0.43, 1.02)	0.000		
CRP, median (IQR)	19 (10, 29)	12 (6, 20)	0.000		
Hb%, median (IQR)	11.5 (10.6, 13)	12.1 (11.1, 13.1)	0.019		
Neutrophils (%), median (IQR)	81.6 (72.6, 85)	79 (72, 84)	0.050		
Lymphocyte (%), median (IQR)	15 (10, 23)	17 (11.5, 24.5)	0.138		

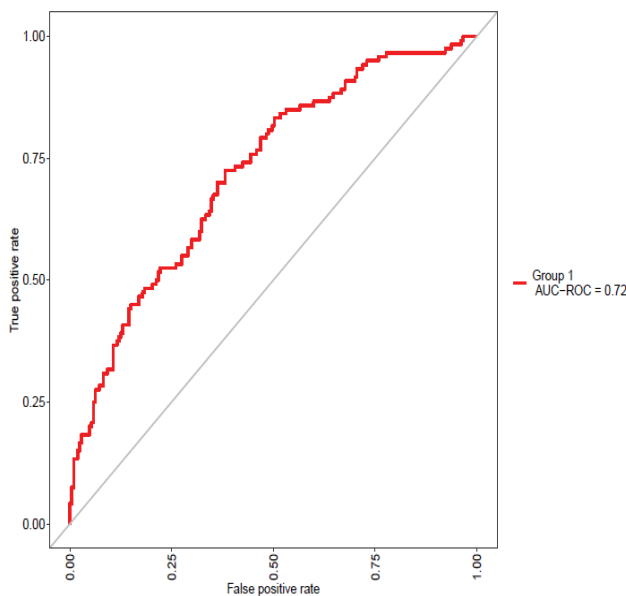
Table-IV
Statistically significant variables on binary logistic regression model

Variables	B.	S.E.	Wald	p-value	OR	95% CI Lower	95% CI Upper
Age (Years)	-.036	.011	10.558	.001	0.964	0.943	0.986
SPO2 (%)	.062	.028	4.924	.026	1.064	1.007	1.124

Variables were then tested on a binary logistic regression model and only age (OR: 0.964; 95%CI: 0.94-0.98; p= 0.001) and on-admission SpO2 (OR: 1.064; 95% CI: 1.01-1.12; p=0.026) had statistically significant contribution to the model Table IV.

Using Repeated K fold cross validation method we have found that the prediction performance of the model is around 72%.

Image 2 RUC curve for fatigue



Discussion:

In our study, the overall prevalence of fatigue persistence among the COVID survivors was 62.9%. Townsend et al. reported that more than half of COVID-19 survivors reported fatigue, even after ten weeks later, regardless of their initial infection's seriousness (Townsend et al., 2020). In another study, fatigue (55%) was the most common reported symptom among post-COVID patients who recovered from acute illness (Garrigues et al., 2020). The Italian study by Carfi et al. (2020) also had a similar result, with 53% (143 COVID-19 patients) reporting fatigue after a mean of 60 days of the first COVID-19 symptom. Locally, in a study conducted among physicians at Dhaka Medical College Hospital, fatigue level was found to be higher among SARS-CoV-2

infected individuals compared to control group. But, interestingly, no association could be established between fatigue and pre-existing co-morbidities, which are in stark contrast to our findings (Hasan et al., 2020). Another study conducted at same institution among post-COVID patients after one month, found 70% of study participants to be suffering from some form of fatigue (Mahmud et al., 2021).

On binary logistic regression, negative association was found between age and fatigue level. While the older age group is vulnerable to post-COVID complications, younger age groups are not immune to after effects of COVID-19. In a prospective Norwegian study, 21% of young people aged 16-30, isolating at home were still suffering from fatigue 6-months after their initial infection (Blomberg et al., 2021). Hence, while the association between age and fatigue level needs to be further evaluated, young people, contrary to popular belief, are highly susceptible to post-COVID complications like fatigue.

Statistically significant association was found between fatigue level and diabetes mellitus, on admission SpO2, hypertension, and ischemic heart disease. Previous studies indicate, diabetes mellitus and cardiac functioning status are common and independent predictors of fatigue among affected individuals (Kalra&Sahay, 2018; Fritschi& Quinn, 2010; Nelesen et al., 2008). Hence, our study findings perfectly complement previous researches on fatigue and its associated variables.

Among clinical and laboratory markers, fatigue was statistically associated with on admission SpO2, Hb%, serum ferritin, d-dimer, and CRP level. The relationship between Hb% and fatigue is previously documented in numerous studies where patients with lower Hb% tend to suffer from higher fatigue level (Holzner et al., 2002; Jacobsen et al., 2004). CRP, d-dimer, and serum ferritin are markers of acute infection in COVID-19 and previous studies indicate towards a strong association among these biomarkers and prevalence of fatigue (Vaucher et al., 2012; Cho et al., 2009; Townsend et al., 2021).

Limitations:

Our single-Centre study has several limitations. Our study is longitudinal and assessed participants over the telephone, which the patients' judgment could have influenced. Finally, this study was not free from the probability of bias, as the subjects had been familiar with the idea of post-COVID fatigue and other symptoms.

Recommendations:

Further studies in large cohorts will be required to assess fatigue subgroups and the potential complex factors at play. We also suggest that it is now time to consider managing this post-COVID syndrome and advocate early analysis of multi-disciplinary fatigue management strategies.

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The authors report no conflict of interest.

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Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

Data availability statement: Data used to write up the manuscript are freely available.

Abbreviation: DM = diabetes mellitus, IHD = ischemic heart disease, HTN= Hypertension, COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease. SpO2 (O2 saturation), d-dimer, ferritin, CRP, Hb%, lymphocyte and neutrophils were measured on admission day. All p-values were derived by Pearson's chi-square test

Note: RR: Relative Risk; CI: Confidence Interval; IQR: Interquartile Range

Normal range: Hb% (men: 13.5-17.5 gm/dl; female: 12-15.4 gm/dl); CRP (0-5 mg/L); serum ferritin (male: 20-250 ngm/ml; female: 10-120 ngm/ml); d-dimer: (d" 0.5 µgm/ml)

Author contribution:

Conceptualization: MKI, MMH, MRA

Methodology: MKI, MRA, MRR

Data collection: MMS, Mohammad MH, MKI

Data analysis: MMAM

Writing first draft: MKI, MMH

Writing- editing and revision: MMAM

Supervision: MRA, MRR

References:

1. Perin, R., Riste, L., Hann, M., Walther, A., Mukherjee, A., Heald, A. (2020). Into the looking glass: Post-viral syndrome post COVID-19. *Medical Hypotheses*, 144. <https://dx.doi.org/10.1016%2Fj.mehy.2020.110055>
2. Griffith, J.P., Zarrouf, F.A. (2008). A systematic review of chronic fatigue syndrome: don't assume it's depression. *The Primary Care Companion to the Journal of Clinical Psychiatry*, 10(2), 120-128. <https://dx.doi.org/10.4088%2Fpcc.v10n0206>
3. Cho, H.J., Skowera, A., Cleare, A., Simon, W. (2006). Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. *Current Opinion in Psychiatry*, 19(1), 67-73. <https://doi.org/10.1097/01.yco.0000194370.40062.b0>
4. Tanriverdi, F., Karaca, Z., Unluhizarci, K., Kelestimur, F. (2007). The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. *Stress*, 10(1):13-25. <https://doi.org/10.1080/10253890601130823>
5. Moldofsky, H., Patcai, J. (2011). Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurology*, 11:37. <https://doi.org/10.1186/1471-2377-11-37>
6. Lam, M.H., Wing, Y.K., Yu, M.W., Leung, C. M., Ma, R.C.W., Kong, A.P.S., et al. (2009). Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *JAMA Internal Medicine*. 169(22), 2142-2147. <https://doi.org/10.1001/archinternmed.2009.384>
7. Lee, S.H., Shin, H.S., Park, H.Y., Kim, J. L., Lee, J.J., Lee, H., et al. (2019). Depression as a mediator of chronic fatigue and post-traumatic stress symptoms in Middle East Respiratory Syndrome survivors. *Psychiatry Investigation*, 16(1), 59-64. <https://dx.doi.org/10.30773%2Fpi.2018.10.22.3>
8. Townsend, L., Dyer, A.H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., et al. (2020). Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*, 15(11):e0240784. <https://doi.org/10.1371/journal.pone.0240784>
9. Tenforde, M.W., Kim, S.S., Lindsell, C.J., Rose, E. B., Shapiro, N.I., Files, C., et al. (2020) Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March–June 2020. *Morbidity and Mortality Weekly Report (MMWR)*, 69, 993-998. <http://dx.doi.org/10.15585/mmwr.mm6930e1>
10. Garrigues, E., Janvier, P., Kherabi, Y., Bot, A.L., Hamon, A., Gouze, H., et al. (2020). Post-discharge

- persistent symptoms and health-related quality of life after hospitalisation for COVID-19. *Journal of Infection*, 81(6), e4-e6. <https://dx.doi.org/10.1016%2Fj.jinf.2020.08.029>
11. Carfi A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. (2020). Persistent symptoms in patients after acute COVID-19. *JAMA*, 324(6), 603-605. <https://doi.org/10.1001/jama.2020.12603>
 12. Hasan, A.T.M.H., Islam, M.S., Khan, N., Munna, N. H., CHoton, W. R., Arefin, M.K., et al. (2020) Assessment of post SARS CoV 2 fatigue among physicians working in COVID designated hospitals in Dhaka, Bangladesh. medRxiv. <https://doi.org/10.1101/2021.02.08.21251352>
 13. Mahmud, R., Rahman, M.M., Rassel, M.A., Monayem, F.B., Sayeed, S.K.J., Islam, M.S., et al. (2021). Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLoS One*, 16(4), e0249644. <https://doi.org/10.1371/journal.pone.0249644>
 14. Blomberg, B., Mohn, K.G.I., Brokstad, K.A., Zhou, F., Linchausen, D.W., Hansen, B., et al. (2021). Long COVID in a prospective cohort of home-isolated patients. *Nature Medicine*. <https://doi.org/10.1038/s41591-021-01433-3>
 15. Kalra, S., Sahay, R. (2018). Diabetes Fatigue Syndrome. *Diabetes Therapeutics*, 9(4), 1421-1429. <https://dx.doi.org/10.1007%2Fs13300-018-0453-x>
 16. Fritschi, C., Quinn, L. (2010). Fatigue in patients with diabetes: A review. *Journal of Psychosomatic Research*, 69(1), 33-41. <https://dx.doi.org/10.1016%2Fj.jpsychores.2010.01.021>
 17. Nelesen, R., Dar, Y., Thomas, K., Dimsdale, J.E. (2008). The relationship between fatigue and cardiac functioning. *Achieves of Internal Medicine*, 168(9), 943-949. <https://dx.doi.org/10.1001%2Farchinte.168.9.943>
 18. Holzner, B., Kemmler, G., Greil, R., Kopp, M., Zeimet, A., Raderer, M., et al. (2002). The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Annals of Oncology*, 13(6), 965-973. <https://doi.org/10.1093/annonc/mdf122>
 19. Jacobsen, P.B., Garland, L.L., Booth-Jones, M., Donovan, K.A., Thors, C.L., Winters, E., et al. (2004). Relationship of hemoglobin levels to fatigue and cognitive functioning among cancer patients receiving chemotherapy. *Journal of Pain and Symptom Management*, 28(1), 7-18. <https://doi.org/10.1016/j.jpainsymman.2003.11.002>
 20. Vaucher, P., Druais, P., Waldvogel, S., Favrat, B. (2012). Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial. *CMAJ*, 184(11):1247-1254. <https://dx.doi.org/10.1503%2Fcmaj.110950>
 21. Cho, H.J., Seeman, T.E., Bower, J.E., Kiefe, C.I., Irwin, M.R. (2009). Prospective association between C-Reactive Protein and fatigue in the coronary artery risk development in young adults study. *Biological Psychiatry*, 66(9), 871-878. <https://dx.doi.org/10.1016%2Fj.biopsycho.2009.06.008>
 22. Townsend L, Fogarty H, Dyer A, Martin-Loeches, I., Bannan, C., Nadarajan, P., et al. (2021). Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. *Journal of Thrombosis and Haemostasis*, 19(4), 1064-1070. <https://doi.org/10.1111/jth.15267>