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Effects of Coronavirus Disease 2019 and Frailty on Delirium in the Intensive Care Unit: A Propensity Score Analysis

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Abstract

Purpose: The association between frailty and delirium has emerged as a research topic. Neurological symptoms have been reported among patients with coronavirus disease 2019 (COVID-19), but its effects on delirium remain unclear. This study aimed to compare the incidence of delirium between patients with COVID-19 and those without COVID-19, and to evaluate the impact of COVID-19 and frailty on delirium. **Methods:** This retrospective study included patients aged ≥ 20 years who were admitted to our intensive care unit (ICU) between January 2020 and February 2022. An inverse probability of treatment weighting using stabilized inverse propensity scores was adopted to minimize bias. After patient demographics were adjusted, the incidence of delirium, assessed using the Confusion Assessment Method for ICU, was compared between patients with COVID-19 and those without COVID-19. The effects of COVID-19 and the Clinical Frailty Scale score on delirium were analyzed by adjusting some covariates, including the sequential organ failure assessment (SOFA) score, using a generalized estimating equation. **Results:** Among 260 eligible patients, 226 patients were included. The weighted incidence of delirium was 56.9% and 61.9% in patients with and without COVID-19, respectively (p = 0.67). The generalized estimating equation revealed that the odds ratios (95% confidence interval) for COVID-19, the CFS score, and the SOFA score were 1.49 (0.62 - 3.57), 1.46 (1.11 - 1.91), and 1.22 (1.10 - 1.36), respectively. **Conclusion:** CFS and SOFA scores on ICU admission may be associated with delirium, with no significant difference between patients with COVID-19 and those without COVID-19.

Keywords

COVID-19, Delirium, Frailty, Intensive Care Unit, SARS-CoV-2

1. Introduction

Delirium is an acute neurocognitive disorder, characterized by fluctuating disturbances in attention and consciousness [1]. It frequently occurs in patients admitted to the intensive care unit (ICU), and its incidence varies depending on age, comorbidities, and general condition upon admission [2] [3] [4]. The association between frailty, a measure of biological age rather than chronological age, and postoperative delirium among patients in the critical care setting has emerged as a research topic [5] [6].

In 2019, the novel severe acute respiratory syndrome coronavirus-2 caused a pandemic. The main manifestations of coronavirus disease (COVID-19) are fever and respiratory symptoms [7]; however, there have been reports on the development of neurological sequelae, including delirium, among patients with COVID-19 [8] [9] [10]. The reported incidence of delirium in patients with COVID-19 is up to 32%, although the effects of COVID-19 on delirium remain unclear [11] [12]. Delirium risk assessment upon ICU admission improves the quality of care; however, because patients with severe COVID-19 require isolation, it becomes difficult to respond to sudden changes in a timely manner.

It is challenging to conduct randomized control trials to evaluate the effects of COVID-19 on delirium; thus, we aimed to evaluate whether patients with severe COVID-19 had an increased incidence of delirium during their ICU stay using propensity score analysis. We also sought to assess the effects of COVID-19 and frailty on delirium.

2. Material and Methods

2.1. Ethical Approval

This retrospective study was approved by the Institutional Review Board of Nara Medical University, Kashiyama, Nara, Japan (Chairperson. M Toshifumi) on March 30, 2022 (approval number: 3285). The requirement for informed consent was waived because of the retrospective nature of the study.

2.2. Patients

All patients aged ≥ 20 years who were admitted to ICU of our hospital between January 2020 and February 2022 were included in this study. Patients admitted to ICU following surgery were excluded. Meanwhile, patients requiring intensive care upon returning to the general ward after surgery were included. Patients admitted to the cardiac care unit were also excluded.

2.3. Covariates

The baseline data included age, sex, body mass index (BMI), comorbidities (symptomatic stroke, chronic heart failure, ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation, chronic lung disease, chronic kidney disease, hematologic disease, connective tissue disease, hepatic disease), presence of a solid cancer, and daily use of benzodiazepines before hospitalization. The frailty status and

general condition upon ICU admission were evaluated using the Clinical Frailty Scale (CFS) and Sequential Organ Failure Assessment (SOFA) score, respectively [13] [14]. The CFS score is a numerical assessment tool for frailty, ranging from 1 (very fit) to 9 (terminally ill) [13], and it is routinely used in our ICU. Additionally, medical conditions requiring intensive care were assessed and classified into eight categories: COVID-19, neurological disease, cardiac failure, respiratory failure, digestive disease, blood disease, infection, and kidney disease. All data were obtained by reviewing the relevant medical records.

2.4. Assessment of Delirium

Delirium was assessed in ICU thrice daily. The patient's level of sedation or agitation was first assessed using the Richmond Assessment Sedation Scale (RASS), with scores ranging from −5 (unarousable) to +4 (combative) [15]. The presence of delirium was then assessed, using the Confusion Assessment Method for ICU (CAM-ICU), in patients with a RASS score of ≥−3 [16]. The CAM-ICU consists of the following four parts; 1) mental status, 2) inattention, 3) consciousness, and 4) disorganized thinking. Then, delirium is considered to be present if patients have positive reactions to 1), 2), and 3), or if patients have positive reactions to 1) and 2) and a negative reaction to 3), then a positive reaction to 4).

2.5. Outcomes

The primary outcome assessed in this study was the overall incidence of delirium, defined according to CAM-ICU. In our primary outcome, recurrent episodes were not considered. Delirium was defined as at least one positive result during the ICU stay. The secondary outcome was the delirium positivity rate, which was calculated by dividing the number of positive CAM-ICU results by the number of CAM-ICU evaluations.

2.6. Statistics

The data are presented as mean (standard deviation) or number (percentage). Univariate analysis was performed using the unpaired t-test or Fisher's exact test.

Patients with or without COVID-19 cannot be randomly assigned; moreover, risk factors vary among ICU patients with COVID-19 and those without COVID-19. Thus, the inverse probability of treatment weighting (IPTW) method, which uses stabilized inverse propensity scores, was adopted to minimize bias and maintain the sample size. To derive the propensity score for the presence or absence of COVID-19, a logistic regression model was developed. The independent variables presented before the occurrence of COVID-19 included age, sex, BMI, symptomatic stroke, chronic heart failure, ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation, chronic lung disease, chronic kidney disease, hematologic disease, connective tissue disease, hepatic disease, solid cancer, and benzodiazepine intake before hospitalization. Standardized mean differences were used to assess the balance among covariates. A value greater than 0.1 indicated an

imbalance [17]. The generalized estimating equation (GEE) was adopted to compare the outcomes of interest between patients with COVID-19 and those without COVID-19. In GEE models, covariates with a standardized mean difference of ≥0.1 after IPTW, as well as the CFS and SOFA scores, which are covariates decided after the occurrence of COVID-19, were adjusted. Age, which was the most significant factor for delirium, was also included as a covariate in the GEE models. All data were analyzed using SPSS (version 22.0; IBM Inc., Armonk, NY, USA) and an RMS package for R, version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). A P-value of <0.05 indicated statistical significance. The sample size was dependent on the study period, which started when the first patient with COVID-19 was admitted to ICU.

3. Results

Among 260 eligible patients, 226 had complete data and were included in the analysis (**Figure 1**). There were 130 patients with COVID-19, three patients with neurological disease, seven patients with cardiac failure, 42 patients with respiratory failure aside from COVID-19, 18 patients with digestive disease, four patients with hematologic disease, 19 patients with an infection, and three patients with kidney disease.

The mean age was 66.9 years old, and the mean values of the CFS and SOFA scores upon ICU admission were 5.9 and 8.1, respectively (**Table 1**). Based on the IPTW, only chronic heart failure and connective tissue disease had a standardized mean difference of ≥0.1 (**Table 2**).

The weighted incidences of delirium were 56.9% and 61.9% among patients with and without COVID-19, respectively (p = 0.67). The GEE (probability distribution; binomial distribution and link function; Logit) yielded the CFS scores (odds ratio [OR]: 1.46, 95% confidence interval [CI]: 1.11 - 1.91), SOFA scores (OR: 1.22, 95% CI: 1.10 - 1.36), and presence of COVID-19 (OR: 1.49, 95% CI: 0.62 - 3.57) (**Table 3**).

Each patient was evaluated for an average of 20.7 times throughout a mean ICU stay of 10.3 days. The weighted delirium positivity rates were 25.1% and 20.8% among patients with and without COVID-19, respectively (p = 0.46). GEE (probability distribution; normal distribution and link function; Logit) revealed that the CFS (risk ratio (RR): 1.28, 95% CI: 1.03 - 1.58) and SOFA scores (RR: 1.07, 95% CI: 1.02 - 1.13) were associated with the secondary outcome, whereas the presence of COVID-19 was not statistically significant (RR: 1.17, 95% CI: 0.77 - 1.75) (**Table 4**).

4. Discussion

This retrospective analysis included 226 patients with a mean age of 66 years. Based on the propensity scores, the weighted incidence of delirium among ICU patients with COVID-19 was 56.9%. The difference in the weighted incidence of delirium between patients with COVID-19 and those without COVID-19 was not statistically significant. Additionally, the CFS and SOFA scores were asso-

ciated with the incidence of delirium and the delirium positivity rate after adjusting for confounders, including the presence of COVID-19.

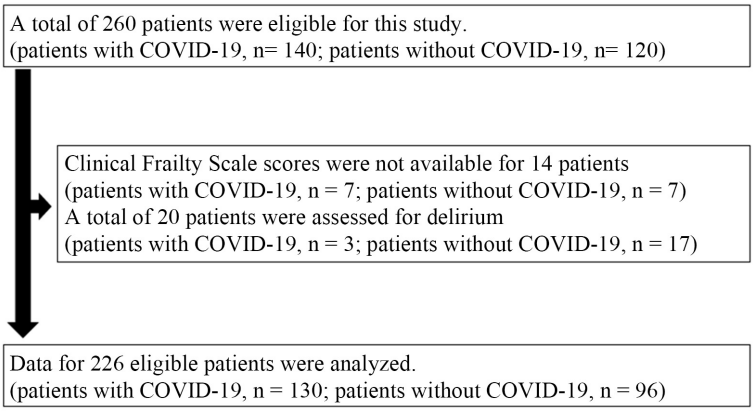

Figure 1. Study flowchart. COVID-19, coronavirus disease 2019. Twenty patients were not assessed for delirium for the following reasons: death, n = 19; transfer to general ward without recovery of consciousness, n = 2; and lack of assessment before transfer to the general ward, n = 1.

Table 1. Patient demographics before inverse probability of treatment weighting, with their Clinical Frailty Scale and Sequential Organ Failure Assessment scores.

	Total (n = 226)	No COVID-19 (n = 96)	COVID-19 (n = 130)	p-value	SMD
Age (years)	66.9 (14.1)	69.3 (13.6)	65.0 (14.3)	0.02	0.30
Female	66 (29.2)	34 (35.4)	32 (24.6)	0.1	0.23
Body mass index (kg/m^2)	23.9 (5.2)	22.4 (4.8)	25.1 (5.2)	<0.001	0.53
Symptomatic stroke	22 (9.7)	16 (16.7)	6 (4.6)	0.003	0.39
Chronic heart failure	15 (6.6)	11 (11.5)	4 (3.1)	0.01	0.32
Ischemic heart disease	28 (12.4)	11 (11.5)	17 (13.1)	0.83	0.04
Hypertension	115 (50.9)	55 (57.3)	60 (46.2)	0.1	0.22
Diabetes mellitus	67 (29.6)	24 (25.0)	43 (33.1)	0.23	0.17
Atrial fibrillation	15 (6.6)	8 (8.3)	7 (5.4)	0.42	0.11
Chronic lung disease	47 (20.8)	26 (27.1)	21 (16.2)	0.04	0.26
Chronic kidney disease	36 (15.9)	21 (21.9)	15 (11.5)	0.04	0.26
Hematologic disease	12 (5.3)	10 (10.4)	2 (1.5)	0.005	0.38
Connective tissue disease	15 (6.6)	11 (11.5)	4 (3.1)	0.01	0.32
Hepatic failure	20 (8.8)	12 (12.5)	8 (6.2)	0.1	0.22
Solid cancer	55 (24.3)	40 (41.7)	15 (11.5)	<0.001	0.72
Benzodiazepines before hospitalization	17 (7.5)	7 (7.3)	10 (7.7)	1	0.01
CFS score	5.9 (1.4)	6.4 (0.9)	5.6 (1.6)	<0.001	0.58
SOFA score	8.1 (4.0)	9.9 (4.4)	6.8 (3.2)	<0.001	0.80

Values are reported as mean (standardized difference) or number (%). COVID-19, coronavirus disease 2019; CFS, Clinical Frailty Scale; SOFA, Sequential Organ Failure Assessment.

Table 2. Mean or percentage values after inverse probability of treatment weighting.

	No COVID-19 (n = 96)	COVID-19 (n = 130)	SMD
Age (years, mean)	68.3	67.2	0.07
Female (%)	34.3	32.4	0.04
Body mass index (kg/m^2, mean)	23.7	24.1	0.08
Symptomatic stroke (%)	9.6	7.6	0.07
Chronic heart failure (%)	6.1	3.9	0.10
Ischemic heart disease (%)	13.8	11.3	0.07
Hypertension (%)	50.2	52.9	0.05
Diabetes mellitus (%)	26.6	25.2	0.03
Atrial fibrillation (%)	5.3	5.4	0.01
Chronic lung disease (%)	23.5	25.6	0.04
Chronic kidney disease (%)	21.3	20.4	0.02
Hematologic disease (%)	5.3	5	0.01
Connective tissue disease (%)	6.4	10.2	0.13
Hepatic failure (%)	8.9	7	0.06
Solid cancer (%)	26.1	29.6	0.08
Benzodiazepines before hospitalization (%)	5.4	6.8	0.05

Values are reported as mean (standardized difference) or number (%). COVID-19, coronavirus disease 2019; SMD, standardized mean difference.

Table 3. Adjusted odds ratio associated with delirium after inverse probability of treatment weighting.

	Odds ratio	95% confidence interval	p-value
COVID-19	1.49	0.62 - 3.57	0.36
Chronic heart failure	0.83	0.26 - 2.65	0.75
Connective tissue disease	0.49	0.11 - 2.20	0.35
Age	1.01	0.98 - 1.04	0.36
CFS score	1.46	1.11 - 1.91	0.005
SOFA score	1.22	1.10 - 1.36	<0.001

COVID-19, coronavirus disease 2019; CFS, Clinical Frailty Scale, SOFA, Sequential Organ Failure Assessment Delirium was defined by at least one positive Confusion Assessment Method for the Intensive Care Unit result during the intensive care unit stay.

Neuroinflammation, which is strongly influenced by systemic inflammation, is contributed to the development of delirium [18]. Patients requiring intensive care have high levels of systemic inflammation, which may be related to the high incidence of delirium in the ICU. In fact, more than 50% patients experienced at least one episode of delirium during their ICU stay. This incidence was similar to previously reported rates of 51% and 57% [12] [19]. However, the incidence

Table 4. Adjusted risk ratios associated with the delirium positivity ratio after inverse probability of treatment weighting.

	Risk ratio	95% confidence interval	p-value
COVID-19	1.17	0.77 - 1.75	0.44
Chronic heart failure	0.68	0.30 - 1.50	0.34
Connective tissue disease	0.96	0.48 - 1.91	0.91
Age	1.01	0.99 - 1.02	0.09
CFS score	1.28	1.03 - 1.58	0.02
SOFA score	1.07	1.02 - 1.13	0.002

COVID-19, coronavirus infectious disease 2019; CFS, Clinical Frailty Scale; SOFA, Sequential Organ Failure Assessment. The delirium positivity ratio was calculated by dividing the number of positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) results by the number of CAM-ICU evaluations.

varied among studies because of differences in the baseline characteristics of the included patients. There was no significant difference in the incidence of delirium between patients with COVID-19 and those without COVID-19. Based on this, other factors were more likely involved in the development of delirium among patients admitted to the ICU.

The GEE revealed that the CFS and SOFA scores upon ICU admission were significant indicators for the development of delirium, which is in line with the results of previous studies [6] [20]. Frail patients were reportedly more susceptible to stress, which results in inflammation, and they might be more likely to become delirious [18] [21]. Furthermore, the SOFA score reflects organ damage, and high SOFA scores would indicate a highly inflammatory state, which might induce delirium.

This study had some limitations. First, factors after ICU admission were not assessed. Sedatives and mechanical ventilation also affected the development of delirium; however, these were difficult to include as factors because delirium was assessed multiple times. Most importantly, these were not included because this study aimed to assess the risk at the time of admission. Second, a prolonged ICU stay increases the risk of delirium. However, this issue was addressed in the study by calculating the delirium positivity rate. Third, inflammatory were not measured in this study. General condition at ICU admission was measured using SOFA score. Since inflammation is a contributing factor to delirium, different results could have been obtained if inflammation levels had been assessed; however, measurement of inflammatory cytokines is not common in clinical practice, and c-reaction protein does not necessarily reflect inflammation in viral diseases, thus the familiar SOFA score was chosen. Finally, the generalizability of our findings is limited because this was a single-center study.

5. Conclusion

The findings of this study suggest that delirium frequently occurs among patients

requiring intensive care, regardless of their COVID-19 status. Moreover, the CFS and SOFA scores on ICU admission were associated with the occurrence of delirium and delirium positivity rate. Medical staff, including clinicians and nurses, who provide care to COVID-19 patients could respond to delirium during ICU management by screening them in the same way they do for non-COVID-19 patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Roy, M., Rivest, M.P., Namian, D. and Moreau, N. (2019) The Critical Reception of the DSM-5: Towards a Typology of Audiences. *Public Understanding of Science*, **28**, 932-948. https://doi.org/10.1177/0963662519868969

[2] Rood, P., Huisman-de Waal, G., Vermeulen, H., Schoonhoven. L., Pickkers, P., *et al.* (2018) Effect of Organisational Factors on the Variation in Incidence of Delirium in Intensive Care Unit Patients: A Systematic Review and Meta-Regression Analysis. *Australian Critical Care*, **31**, 180-187. https://doi.org/10.1016/j.aucc.2018.02.002

[3] Kotfis, K., Marra, A. and Ely, E.W. (2018) ICU Delirium—A Diagnostic and Therapeutic Challenge in the Intensive Care Unit. *Anaesthesiology Intensive Therapy*, **50**, 160-167. https://doi.org/10.5603/AIT.a2018.0011

[4] Kooken, R.W.J., van den Berg, M., Slooter, A.J.C., Pop-Purceleanu, M. and van den Boogaard, M. (2021) Factors Associated with a Persistent Delirium in the Intensive Care Unit: A Retrospective Cohort Study. *Journal of Critical Care*, **66**, 132-137. https://doi.org/10.1016/j.jcrc.2021.09.001

[5] Gracie, T.J., Caufield-Noll, C., Wang, N.Y. and Sieber, F.E. (2021) The Association of Preoperative Frailty and Postoperative Delirium: A Meta-Analysis. *Anesthesia & Analgesia*, **133**, 314-323. https://doi.org/10.1213/ANE.0000000000005609

[6] Darvall, J.N., Bellomo, R., Paul, E., Bailey, M., Young, P.J., *et al.* (2021) Routine Frailty Screening in Critical Illness: A Population-Based Cohort Study in Australia and New Zealand. *Chest*, **160**, 1292-1303. https://doi.org/10.1016/j.chest.2021.05.049

[7] Koh, J., Shah, S.U., Chua, P.E.Y., Gui, H. and Pang, J. (2020) Epidemiological and Clinical Characteristics of Cases During the Early Phase of COVID-19 Pandemic: A Systematic Review and Meta-Analysis. *Frontiers in Medicine* (*Lausanne*), **7**, 295. https://doi.org/10.3389/fmed.2020.00295

[8] Helms, J., Kremer, S. and Meziani F. (2020) More on Neurologic Features in Severe SARS-CoV-2 Infection. Reply. *The New England Journal of Medicine*, **382**, e110. https://doi.org/10.1056/NEJMc2015132

[9] Alkeridy, W.A., Almaghlouth, I., Alrashed, R., Alayed, K., Binkhamis, K., *et al.* (2020) A Unique Presentation of Delirium in a Patient with Otherwise Asymptomatic COVID-19. *Journal of the American Geriatrics Society*, **68**, 1382-1384.

https://doi.org/10.1111/jgs.16536

[10] Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., *et al.* (2020) Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology*, **77**, 683-690. https://doi.org/10.1001/jamaneurol.2020.1127

[11] Shao, S.C., Lai, C.C., Chen, Y.H., Chen, Y.C., Hung, M.J., *et al.* (2021) Prevalence, Incidence and Mortality of Delirium in Patients with COVID-19: A Systematic Review and Meta-Analysis. *Age Ageing*, **50**, 1445-1453. https://doi.org/10.1093/ageing/afab103

[12] Jäckel, M., Aicher, N., Biever, P.M., Heine, L., Bemtgen, X., *et al.* (2021) Delirium in Critically Ill Patients with and without COVID-19: A Retrospective Analysis. *Journal of Clinical Medicine*, **10**, 4412. https://doi.org/10.3390/jcm10194412

[13] Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Meneilly, G.S., Knip, A. and Tessier, D. (2013) Diabetes in the Elderly. *The Canadian Journal of Diabetes*, **37**, S184-S190. https://doi.org/10.1016/j.jcjd.2013.01.045

[14] Vincent, J.L., de Mendonça, A., Cantraine, F., Moreno, R., Takala, J., *et al.* (1998) Use of the SOFA Score to Assess the Incidence of Organ Dysfunction/Failure in Intensive Care Units: Results of a Multicenter, Prospective Study. Working Group on "Sepsis-Related Problems" of the European Society of Intensive Care Medicine. *Critical Care Medicine*, **26**, 1793-1800. https://doi.org/10.1097/00003246-199811000-00016

[15] Sessler, C.N., Gosnell, M.S., Grap, M.J., Brophy, G.M., O'Neal, P.V., *et al.* (2002) The Richmond Agitation-Sedation Scale: Validity and Reliability in Adult Intensive Care Unit Patients. *American Journal of Respiratory and Critical Care Medicine*, **166**, 1338-1344. https://doi.org/10.1164/rccm.2107138

[16] Ely, E.W., Inouye, S.K., Bernard, G.R., Gordon, S., Francis, J., *et al.* (2001) Delirium in Mechanically Ventilated Patients: Validity and Reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA*, **286**, 2703-2710. https://doi.org/10.1001/jama.286.21.2703

[17] Austin, P.C. (2009) Using the Standardized Difference to Compare the Prevalence of a Binary Variable between Two Groups in Observational Research. *Communications in Statistics—Simulation and Computation*, **38**, 1228-1234. https://doi.org/10.1080/03610910902859574

[18] Fried, L.P., Ferrucci, L., Darer, J., Williamson, J.D. and Anderson, G. (2004) Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *The Journals of Gerontology Series A Biological Sciences and Medical Sciences*, **59**, 255-263. https://doi.org/10.1093/gerona/59.3.M255

[19] Williamson, C.A., Faiver, L., Nguyen, A.M., Ottenhoff, L. and Rajajee V. (2022) Incidence, Predictors and Outcomes of Delirium in Critically Ill Patients with COVID-19. *Neurohospitalist*, **12**, 31-37. https://doi.org/10.1177/19418744211034815

[20] Rahimi-Bashar, F., Abolhasani, G., Manouchehrian, N., Jiryaee, N., Vahedian-Azimi, A., *et al.* (2021) Incidence and Risk Factors of Delirium in the Intensive Care Unit: A Prospective Cohort. *BioMed Research International*, **2021**, Article ID: 6219678. https://doi.org/10.1155/2021/6219678

[21] Klein, R.S. (2022) Mechanisms of Coronavirus Infectious Disease 2019-Related Neurologic Diseases. *Current Opinion in Neurology*, **35**, 392-398. https://doi.org/10.1097/WCO.0000000000001049