The Daily COVID-19 Literature Surveillance Summary

August 13, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Climate

- An author affiliated with the Department of Health & Human Performance at the University of Tennessee presents the 2018 Social Vulnerabilities for the American Indian and Alaska Native people (AIAN) by tribal geographic areas and calls attention to the high risk of contracting COVID-19 and its associated complications among the AIAN people. The author highlights the potential value of utilizing these resources in order to understand the COVID-19 impact on AIAN communities and their ability to recover from the pandemic.

Understanding the Pathology

- A group of pharmacists and toxicologists in Spain discuss neurological invasion by SARS-CoV-2 and the therapeutic potential of high dose melatonin in limiting the neurological impact of the virus namely in its ability to reduce the permeability of the blood brain barrier and counteract neuroinflammation.

Management

- A prospective study of 386 hospitalized patients admitted for COVID-19 in Iran found that the development of cardiac injuries was associated with a four-fold increase in-hospital mortality rate and that preexisting cardiovascular disease, malignancy, hypoxia, leukocytosis and lymphopenia upon presentation were independently associated with an increased risk of developing cardiac injuries.
- Endocrinologists at the University of Michigan observed that severe hyperglycemia and insulin resistance were associated with increased inflammatory markers among two diabetic COVID-19 patients at their facility. The authors share their guidelines and protocols for insulin regimens and monitoring inflammatory markers, suggesting that their protocol may improve glycemic control and, thus, patient outcomes in this population.
- Researchers performed neurological examination and brain imaging on 140 COVID-19 patients admitted to the ICU to investigate the prevalence of delirium and other neurological abnormalities. The findings highlight a high prevalence of neurological abnormalities in COVID-19 patients admitted to the ICU (118/140, 84.3%) and suggest a role for assessing a patient's neurological state to accurately allocate hospital resources and provide proper care to maximize recovery rates.

Adjusting Practice During COVID-19

- A survey conducted by University of Illinois-Chicago Cancer Center among 609 patients with breast cancer found 45% of patients reported cancer treatment delays during the COVID-19 pandemic. Younger patients self-reported greater delays than older patients, with no significant differences found based on race, insurance, site of care, or cancer stage. These delays in cancer treatment for younger patients indicates potential for increased rates of disease progression, mortality, and pain due to delay, highlighting the need for protective processes and managing strategies for this vulnerable population during the pandemic.
- A study compared 30-day complication rates, readmission, and mortality among 183 hip fracture patients at a tertiary care center in Argentina prior to and during the COVID-19 pandemic. Results showed increased time waiting for surgery during the lockdown time period, as well as higher rate of thromboembolic events and a higher mortality rate during the pandemic.

TABLE OF CONTENTS

AMERICAN INDIAN AND ALASKA NATIVE PEOPLE: SOCIAL VULNERABILITY AND COVID-19

Hathaway ED.. J Rural Health. 2020 Aug 3. doi: 10.1111/jrh.12505. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

An author affiliated with the Department of Health & Human Performance at the University of Tennessee presents the 2018 Social Vulnerabilities (SV) for the American Indian and Alaska Native people (AIAN) by tribal geographic areas (Table 1). Given the social vulnerabilities of this group, the author calls attention to the high risk of contracting COVID-19 and its associated complications among the AIAN people. The author highlights the potential value of utilizing SV measures, specifically naming the CDC SV Index as a resource, to understand the COVID-19 impact on AIAN communities and their ability to recover from the pandemic.

FIGURES

Table 1. Social Vulnerability of American Indian and Alaska Native People by Geographic Area

Geographic Region	# of Tracts	% Pov	% Unemp	% PCI	% NoHSDp	% Age 65+	% Age ≤17	% Disabl	% SngPnt
Albuquerque Area Southwest	25	23.1(9.3)	12.1(7.1)	19,137(7,096)	15.3(6.1)	14.2(5.9)	26.5(7.6)	13.7(5.5)	12.6(7.3)
California	88	25.1(16.6)	14.5(12.3)	26,570(24,178)	17.9(13.7)	16.6(16.1)	26.9(13.9)	15.2(7.6)	15.7(13.9)
Great Lakes	54	24.7(12.4)	10.3(6.9)	24,154(14,034)	12.3(6.6)	14.4(7.2)	28.6(8.4)	15.5(5.0)	17.5(9.8)
Great Plains	31	35.3(13.7)	13.8(7.2)	17,120(6,039)	16.4(5.1)	10.2(4.2)	35.5(5.4)	12.8(3.0)	18.2(6.2)
Inter-Tribal Council of Arizona	50	32.1(12.2)	17.3(9.4)	17,250(6,458)	20.7(10.1)	13.3(6.4)	27.7(8.0)	16.8(8.5)	14.3(7.7)
Navajo	38	40.2(7.0)	18.3(7.1)	12,117(1,823)	26.9(7.2)	11.9(2.3)	28.7(3.4)	15.5(4.4)	13.3(3.3)
Northwest	66	21.9(12.2)	11.3(7.7)	23,740(10,365)	15.3(9.8)	15.2(7.7)	25.9(7.5)	17.5(8.0)	13.6(7.7)
Oklahoma Area	16	19.2(12.8)	6.4(3.5)	22,353(6,147)	14.7(9.3)	16.5(5.4)	26.5(8.6)	17.9(3.9)	11.8(10.2)
Rocky Mountain	23	24.3(12.5)	10.0(6.4)	21,313(7,208)	11.2(3.1)	15.2(6.4)	28.8(6.2)	13.9(5.4)	11.3(5.7)
United South & Eastern Tribes	38	30.0(15.2)	13.7(9.8)	20,269(11,425)	19.7(8.7)	11.6(7.9)	31.3(10.2)	15.7(5.8)	19.5(10.0)
All Tribal Areas Average	429	27.5(14.5)	13.2(9.2)	21,235(11,282)	17.3(10.2)	14.2(9.4)	28.3(9.5)	15.6(6.6)	15.2(9.6)
U.S. Average	3141	**15.6(6.5)**	**5.8(2.9)**	**27,036(6,512)**	**13.4(6.3)**	**18.4(4.6)**	**22.4(3.5)**	**15.9(4.4)**	**8.3(2.8)**

Geographic Region	% Minrty	% LimEng	% MUnit	% Mobile	% Crowd	% NoVeh	% GroupQ	% UnInsur
Albuquerque Area Southwest	85.3(22.4)	1.8(1.9)	0.3(0.6)	22.6(9.0)	7.9(7.0)	8.3(4.8)	0.5(0.7)	20.2(10.4)
California	79.0(24.3)	2.8(8.2)	1.5(4.5)	23.1(21.3)	8.4(11.1)	8.2(8.1)	0.4(2.4)	20.5(14.8)
Great Lakes	60.3(29.5)	0.4(0.9)	3.5(4.7)	9.7(8.2)	4.0(3.7)	11.2(9.2)	1.1(1.9)	14.5(11.0)
Great Plains	77.8(19.4)	0.8(1.3)	3.2(3.2)	17.1(10.3)	12.7(9.1)	9.8(5.6)	1.1(1.3)	27.0(9.0)
Inter-Tribal Council of Arizona	85.3(22.8)	1.6(2.4)	0.6(1.1)	20.2(17.5)	7.6(7.6)	11.8(10.2)	0.9(2.1)	21.5(9.5)
Navajo	98.4(1.2)	6.3(3.4)	0.3(0.6)	21.2(6.6)	17.4(5.0)	14.4(4.4)	0.5(1.0)	24.0(6.9)
Northwest	60.4(28.8)	2.0(4.0)	3.7(10.5)	14.1(10.3)	5.9(4.9)	7.5(8.3)	0.9(2.3)	14.9(7.4)
Oklahoma Area	49.2(30.4)	1.4(3.5)	0.8(1.2)	13.4(9.2)	3.4(3.3)	5.3(4.1)	1.8(4.9)	15.3(6.8)
Rocky Mountain	55.6(29.0)	0.5(0.7)	1.5(2.0)	16.5(9.5)	6.5(5.2)	6.0(4.3)	2.4(3.5)	24.5(11.2)
United South & Eastern Tribes	85.5(14.1)	1.0(1.5)	3.2(8.6)	13.8(13.6)	7.1(9.1)	12.2(9.3)	0.7(1.3)	26.7(19.3)
All Tribal Areas Average	74.8(27.3)	2.0(4.6)	2.1(5.7)	17.5(14.0)	8.0(8.4)	9.7(8.2)	0.9(2.2)	20.3(12.4)
U.S. Average	**22.5(20.2)**	**1.7(2.8)**	**4.7(5.7)**	**12.9(9.6)**	**2.4(2.4)**	**6.4(4.5)**	**2.5(4.6)**	**10.1(5.1)**

Presented as Mean(SD)
# of Tracts: Number of census tracts (subdivisions of counties) for Tribal Areas and Number of Counties for U.S. Average
% Pov: Percentage of persons below poverty estimate
% Unemp: Unemployment Rate estimate
% PCI: Per capita income estimate, 2014-2018 American Community Survey
% NoHSDp: Percentage of persons with no high school diploma (age 25+) estimate
% Age 65+: Percentage of persons age 65+
% Age ≤17: Percentage of persons age ≤17
% Disabl: Percentage of civilian noninstitutionalized population with a disability estimate, 2014-2018 American Community Survey
% SngPnt: Percentage of single parent households with children under 18 estimate, 2014-2018 American Community Survey
% Minrty: Percentage minority (all persons except white, non-Hispanic) estimate, 2014-2018 American Community Survey
% LimEng: Percentage of persons (age 5+) who speak English "less than well" estimate, 2014-2018 American Community Survey
% MUnit: Percentage of housing in structures with 10 or more units estimate
% Mobile: Percentage of mobile homes estimate
% Crowd: Percentage of occupied housing units with more people than rooms estimate
% NoVeh: Percentage of households with no vehicle available estimate
% GroupQ: Percentage of persons in institutionalized group quarters estimate, 2014-2018 American Community Survey
% Uninsur: Percentage uninsured in the total civilian noninstitutionalized population estimate, 2014-2018 American Community Survey

CORONAVIRUS DISEASE 2019 (COVID-19) AND ITS NEUROINVASIVE CAPACITY: IS IT TIME FOR MELATONIN?

Romero A, Ramos E, López-Muñoz F, Gil-Martín E, Escames G, Reiter RJ.. Cell Mol Neurobiol. 2020 Aug 9. doi: 10.1007/s10571-020-00938-8. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

This literature review by authors affiliated with multiple scientific and medical backgrounds investigates the therapeutic potential of melatonin to counteract COVID-19 neuroinvasion. Based on their observations (illustrated below), the authors urge providers to consider melatonin's use as a COVID-19 treatment due to its low risk and potential efficacy, although the authors acknowledge challenges to this treatment (precise dosing, low oral bioavailability, etc).

SUMMARY

The authors review and discussion includes, but is not limited to, the following:
- the high safety profile of melatonin
- the possibly neuroprotective abilities of melatonin, namely in restoring the integrity of the Blood Brain Barrier (BBB) by limiting permeability
-potential targets of melatonin against SARS-CoV-2 infection in the CNS (Figure 2)
-the possible ability of melatonin to help maintain mitochondrial function
- the ability of melatonin to activate astrocytes and microglia, providing protection and counteracting neuroinflammation.

ABSTRACT

The world faces an exceptional new public health concern caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), subsequently termed the coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). Although the clinical symptoms mostly have been characterized, the scientific community still doesn t know how SARS-CoV-2 successfully reaches and spreads throughout the central nervous system (CNS) inducing brain damage. The recent detection of SARS-CoV-2 in the cerebrospinal fluid (CSF) and in frontal lobe sections from postmortem examination has confirmed the presence of the virus in neural tissue. This finding reveals a new direction in the search for a neurotherapeutic strategy in the COVID-19 patients with underlying diseases. Here, we discuss the COVID-19 outbreak in a neuroinvasiveness context and suggest the therapeutic use of high doses of melatonin, which may favorably modulate the immune response and neuroinflammation caused by SARS-CoV-2. However, clinical trials elucidating the efficacy of melatonin in the prevention and clinical management in the COVID-19 patients should be actively encouraged.

FIGURES

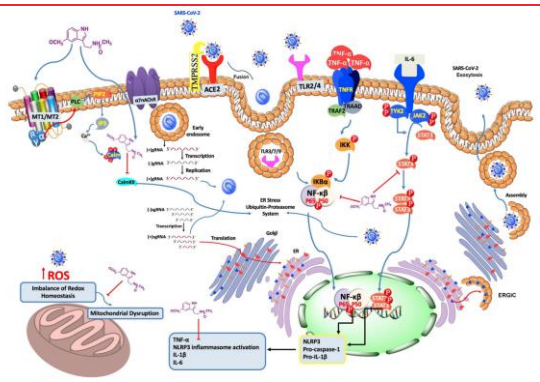

Fig. 2 Hypothetical diagram of the possible targets where melatonin may act against SARS-CoV-2 infection in the CNS. SARS-CoV-2 enters neuronal cells through ACE2, as the receptor binding domain, and TMPRSS2 for spike protein (s protein) priming. Next, SARSCoV-2 nucleocapsid triggers clathrin-mediated endocytosis enhancing cytoplasm release. Subsequently, the single negative strand RNA [(−)gRNA] synthesized from (+)gRNA template is used to replicate more copies of viral RNAs. Afterwards, subgenomic RNAs (sgRNAs) synthesized from the (+)gRNA template encode viral structural and accessory proteins, which are subsequently assembled with newly synthesized viral RNAs in the ER and Golgi, followed by budding into

the lumen of the ERGIC to form new virions. Then, virus particles are transported in secretory vesicles to the plasma membrane and released by exocytosis. Furthermore, the entry of SARS-CoV-2 into neuronal cells may dysregulate mitochondrial metabolism increasing ROS and leading to the induction of endoplasmic reticulum stress. In this regard, melatonin's high difusibility allows it to enter in neuronal cells, it binds to CaM and may act on the Ca2+/CaMKII system, regulating the expression of ACE2, modulating the linking between endoplasmic reticulum stress and infammatory response and scavenging ROS. However, in both MT1/MT2 and α7nAChR receptors, melatonin-mediated signaling may infuence in reduced SARS-CoV-2 entry. When SARS-CoV-2 infects the CNS, it triggers the release of pro-infammatory cytokines. (i) TNF-α, which acts by binding to TNFR receptor recruiting TRADD. This protein binds to TRAF2 to phosphorylate and activate the IKK. Then, IKK complex phosphorylates IKBα, resulting in the translocation of NF-κB to the nucleus, where it targets many coding genes for mediators of infammatory responses. (ii) IL-6 induces gene activation in response to cytokine receptor stimulation. STAT3 proteins dimerize and translocate to the nucleus. JAK2/STAT3 signaling is a crucial link acting as a pivotal mediator of neuroinfammation. (iii) The binding of SARS-CoV-2 to the TLR (TLR3/7/9) upregulates the pro-infammatory transcription factor NF-κB and causes the release of pro-IL-1β which is cleaved by caspase-1, followed by NLRP3 infammasome activation. Consequently, melatonin may revert these pro-infammatory efects by inhibiting the JAK2/STAT3 signaling pathway and NF-κB translocation. In addition, as an anti-infammatory agent, melatonin inhibits the activation of NLRP3 infammasome. Stimulation (blue colored) or inhibition (red colored) by melatonin and SARS-CoV-2 are also shown. Organelles/structures were not drawn to scale

IN ANIMAL MODELS

DELAYED SEVERE CYTOKINE STORM AND IMMUNE CELL INFILTRATION IN SARS-COV-2-INFECTED AGED CHINESE RHESUS MACAQUES

Song TZ, Zheng HY, Han JB, Jin L, Yang X, Liu FL, Luo RH, Tian RR, Cai HR, Feng XL, Liu C, Li MH, Zheng YT.. Zool Res. 2020 Aug 7:1-10. doi: 10.24272/j.issn.2095-8137.2020.202. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Authors affiliated with Kumming Institute of Zoology and the Affiliated Drum Tower Hospital of Nanjing University conducted an animal study on healthy young Chinese rhesus macaques (ChRMs) and older ChRMs inoculated with SARS-CoV-2 virus. They found lowered T cell counts, a stronger cytokine storm and a delayed immune response in the older ChRMs (Figure 3). Further, viral titer differences were not significant between the two groups, possibly suggesting that severe inflammation may contribute more to COVID-19 pathogenesis in the aged ChRMs rather than high viral titers. The authors suggest that these findings could help understand the poor outcomes of old patients with COVID-19 compared to young patients.

ABSTRACT

As of June 2020, Coronavirus Disease 2019 (COVID-19) has killed an estimated 440?000 people worldwide, 74% of whom were aged >=65 years, making age the most significant risk factor for death caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To examine the effect of age on death, we established a SARS-CoV-2 infection model in Chinese rhesus macaques (Macaca mulatta) of varied ages. Results indicated that infected young macaques manifested impaired respiratory function, active viral replication, severe lung damage, and infiltration of CD11b + and CD8 + cells in lungs at one-week post infection (wpi), but also recovered rapidly at 2 wpi. In contrast, aged macaques demonstrated delayed immune responses with a more severe cytokine storm, increased infiltration of CD11b + cells, and persistent infiltration of CD8 + cells in the lungs at 2 wpi. In addition, peripheral blood T cells from aged macaques showed greater inflammation and chemotaxis, but weaker antiviral functions than that in cells from young macaques. Thus, the delayed but more severe cytokine storm and higher immune cell infiltration may explain the poorer prognosis of older aged patients suffering SARS-CoV-2 infection.

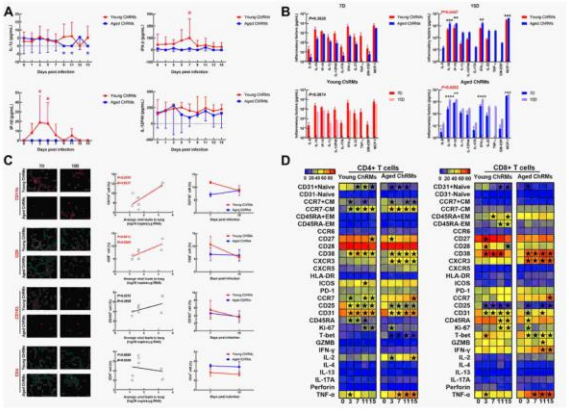

Figure 3. Immune responses in young and aged ChRMs during SARS-CoV-2 infection
A: Concentrations of cytokines in plasma. B: Concentrations of cytokines in lung tissue. C: Immunofluorescence staining of immune cells in lungs. D: Characteristics of CD4+ T and CD8+ T cells in peripheral blood. *: 0.01 less than P less than 0.05; **: 0.001less than P equal too or less than 0.01; ***: 0.0001 less than P equal to or less than 0.001; ****: P less than 0.0001. star: P less than 0.05.

THE ASSOCIATION BETWEEN CARDIAC INJURY AND OUTCOMES IN HOSPITALIZED PATIENTS WITH COVID-19

Karbalai Saleh S, Oraii A, Soleimani A, Hadadi A, Shajari Z, Montazeri M, Moradi H, Talebpour M, Sadat Naseri A, Balali P, Akhbari M, Ashraf H.. Intern Emerg Med. 2020 Aug 9. doi: 10.1007/s11739-020-02466-1. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A prospective study of 386 hospitalized patients admitted for COVID-19 at Sina Hospital in Iran from March to May, 2020 found that the development of cardiac injuries was associated with an increased in-hospital mortality rate when compared to patients without cardiac injury (40.9% vs 11.1%; p value less than 0.001). Further, preexisting cardiovascular disease, malignancy, hypoxia, leukocytosis and lymphopenia upon presentation were independently associated with an increased risk of developing cardiac injuries (Table 4). The authors suggest that further investigation into the mechanisms underlying cardiac injury in SARS-CoV-2 infection should be performed.

ABSTRACT

In this study, we aimed to assess the association between development of cardiac injury and short-term mortality as well as poor in-hospital outcomes in hospitalized patients with COVID-19. In this prospective, single-center study, we enrolled hospitalized patients with laboratory-confirmed COVID-19 and highly suspicious patients with compatible chest computed tomography features. Cardiac injury was defined as a rise of serum high sensitivity cardiac Troponin-I level above 99th percentile (men: > 26 ng/mL, women: > 11 ng/mL). A total of 386 hospitalized patients with COVID-19 were included. Cardiac injury was present among 115 (29.8%) of the study population. The development of cardiac injury was significantly associated with a higher in-hospital mortality rate compared to those with normal troponin levels (40.9% vs 11.1%, p value < 0.001). It was shown that patients with cardiac injury had a significantly lower survival rate after a median follow-up of 18 days from symptom onset (p log-rank < 0.001). It was further demonstrated in the multivariable analysis that cardiac injury could possibly increase the risk of short-term mortality in hospitalized patients with COVID-19 (HR = 1.811, p-value = 0.023). Additionally, preexisting cardiovascular disease, malignancy, blood oxygen saturation < 90%, leukocytosis, and lymphopenia at presentation were independently associated with a greater risk of developing cardiac injury. Development of cardiac injury in hospitalized patients with COVID-19 was significantly associated with higher rates of in-hospital mortality and poor in-hospital outcomes. Additionally, it was shown that development of cardiac injury was associated with a lower short-term survival rate compared to patients without myocardial damage and could independently increase the risk of short-term mortality by nearly two-fold.

FIGURES

	Odds ratio	95% confidence interval	*p*-value
Age (per 1 year increase)	1.018	0.998–1.038	0.073
Cardiovascular disease[a]	2.019	1.008–4.045	0.047
Malignancy	3.802	1.109–13.035	0.034
CVA/TIA	2.162	0.564–8.289	0.261
Previous ACEI/ARB use	0.948	0.459–1.955	0.884
Blood O_2 saturation < 90%	2.541	1.473–4.383	0.001
WBC > 10,000 × 10^9/L	2.743	1.446–5.205	0.002
Lymphocyte < 1000 × 10^9/L	2.924	1.632–5.238	< 0.001
C-reactive protein	0.999	0.994–1.004	0.706

CVA cerebrovascular accident, *TIA* transient ischemic attack, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, O_2 oxygen, *WBC* white blood cell

[a] Cardiovascular disease includes hypertension, coronary heart disease, or congestive heart failure

Table 4 Multivariable logistic regression analysis of predictors of cardiac injury in hospitalized patients with COVID-19

MANAGING HYPERGLYCEMIA IN THE COVID-19 INFLAMMATORY STORM

Gianchandani R, Esfandiari NH, Ang L, Iyengar J, Knotts S, Choksi P, Pop-Busui R.. Diabetes. 2020 Aug 10:dbi200022. doi: 10.2337/dbi20-0022. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Endocrinologists at the University of Michigan observe that severe hyperglycemia and insulin resistance were associated with increased inflammatory markers (D-dimers, IL-6, triglycerides, procalcitonin, etc) among two diabetic COVID-19 patients at their facility. Figure 1A and 1B). The authors share their guidelines and protocols (Table 1, 2) for insulin regimens and monitoring inflammatory markers, suggesting that their protocol may improve glycemic control and, thus, patient outcomes in this population.

ABSTRACT

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) is now at global pandemic levels causing significant morbidity and mortality. Patients with diabetes are particularly vulnerable and more likely to get severe complications when infected with this virus. Although the information continues to emerge, here we provide our perspective on initial outcomes observed in hospitalized patients with diabetes and the potential role played by the proinflammatory metabolic state in these patients that promotes fertile ground for the virus' inflammatory surge, resulting in severe insulin resistance and severe hyperglycemia. The rapidly evolving renal failure, hypotension, pressor and steroid use, and variable nutritional support further complicates their management. Thus, timely implementation of glucose management protocols addressing these complex scenarios while also following COVID-19-related trajectories in inflammatory biomarkers and being cognizant of the health care provider exposure may substantially affect morbidity and mortality.

FIGURES

Table 1—Initial subcutaneous insulin dosing guideline for critically ill COVID-19 patients admitted with high glucose

BG 200–250 mg/dL*: see details of treatment and titration in Table 2				
a	**START SLIDING SCALE REGULAR** insulin: moderate to high dose scale			**MONITORING**
b	**ADD SCHEDULED REGULAR INSULIN** every 6 h if uncontrolled with scale or if tube feeds started			BG check every 6 h
c	**ADD BASAL INSULIN GLARGINE for patients with the following:**			
	• T1DM (70% of home dose for eGFR >50 and 50% for eGFR <50 to **avoid DKA**)			
	• T2DM on home insulin (25–50% basal dose) or >2 drugs			
	• Uncontrolled glucose on regular insulin alone: use 0.1–0.3 units/kg daily (below)			
	• NPH may be appropriate basal for patients on steroids			
BG 250–350 mg/dL: START SCHEDULED SUBCUTANEOUS INSULIN				
		HIGH SENSITIVITY **No known diabetes, known DM with** renal failure (eGFR<30), insulin naive, mild disease*	**MODERATE SENSITIVITY** **Known DM,** renal failure (eGFR 30–50), intermediate disease course**	**LOW SENSITIVITY** **Known DM,** renal function (eGFR >50), steroids, severe disease***
Type of insulin		**Insulin dose (units/kg)**		
BASAL#	**Glargine daily: noon or 6 P.M.**	0.1 units/kg/day	0.15–0.2 units/kg/day	0.3 units/kg/day
BOLUS	**Scheduled regular insulin every 6 h**	**Approximate start doses (units/kg every 6 h); use clinical judgement**		
	No tube feeds	0.1	0.15	0.2
	Low rate tube feeds (≤25 cc/h)	0.1–0.125	0.1–0.15	0.2–0.25
	High rate tube feeds (≥25 cc/h)	0.15	0.2	0.3
SCALE	**Regular insulin every 6 h**	Moderate	Moderate	High
FOLLOW TRENDS IN INFLAMMATORY MARKERS: PROCALCITONIN, D-DIMER, hsCRP, AND TRIGLYCERIDES TO GUIDE IN UPWARD or DOWNWARD TITRATION OF INSULIN DOSE				
BG >350 mg/dL: INSULIN INFUSION NOT INITIATED or VARIABLE INFUSION RATES HARD TO TRANSITION				
Regular insulin	**BG (mg/dL)**	**Give subcutaneous regular insulin dosed as below:**		**MONITORING**
1st dose	350–450	0.2 units/kg		After 2 h
	>450	0.3 units/kg		
2nd dose	250–350	None		After 4 h
	350–450	Give 50% original dose		
	>450	Redose original dose calculated in 1		
3rd dose	<250	Maintain current dose + add low dose sliding scale		After 6 h
	250–350	Increase current dose 10% + add moderate dose sliding scale		
	350–450	Increase current dose 20% + add moderate dose sliding scale		
	>450	Increase current dose 30% + add moderate dose sliding scale		
≥4 doses	Titrate dose in 3 as per BG and order as scheduled regular			Every 6 h
BASAL INSULIN: #as above				
BG >350 mg/dL: TRANSITIONING FROM INSULIN INFUSION WITHIN A FEW HOURS VERY QUICKLY WITH SUBCUTANEOUS REGULAR INSULIN				
REGULAR insulin	**BG (mg/dL)**			**MONITORING**
1st dose	Calculate average hourly drip rate for 2 h			After 2 h
	Multiply average hourly drip rate × 3			
	Give that dose as subcutaneous regular insulin stat; **stop insulin drip**			
2nd dose	<70: hypoglycemia protocol			After 4 h
	70–150: reduce dose by 50%			
	150–350: no intervention			
	>350: repeat original dose of regular insulin			
3rd dose	<70: hypoglycemia protocol			After 6 h
	70–150: reduce dose by 50% + add moderate dose sliding scale			
	150–350: continue original dose + add moderate dose sliding scale			
	>350: increase original dose by 50% + add high dose sliding scale			
≥4 doses	Titrate dose in 3 as per BG and order as scheduled regular			Every 6 h
BASAL INSULIN: #as above				
BG >450 mg/dL: SHORT DURATION OF INSULIN INFUSION TILL DRIP RATE STABILIZES				

ASAP, as soon as possible; BG, blood glucose; DKA, diabetes ketoacidosis; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); PTA, prior to admission; T1DM, patients with type 1 diabetes; T2DM, patients with type 2 diabetes. *Mild disease: intubated without pressor support. **Intermediate disease: intubated with stable ventilator settings and stable pressor support. ***Severe disease: variable and multiple pressor requirements for hypotension and increasing ventilator settings to maintain adequate oxygenation.

Table 2

	DETAILED TREATMENT GUIDANCE BG 200–250 mg/dL	
1.	**NO PRIOR KNOWN DIABETES or KNOWN DIABETES ON <2 ORAL AGENTS**	**MONITORING**
	• Check HbA_{1c} if none available in last 3 months	Check BG every 6 h
a	**Start sliding scale** regular insulin: moderate to high dose and escalate scale if BG >250 mg/dL	
b	**Add scheduled regular insulin every 6 h** if TF initiated (see above for regular insulin dosing based on eGFR and hourly TF rate) + scale	
c	**Add scheduled regular insulin if BG remains>250 mg/dL +** scale even if no TF initiated	
2.	**KNOWN DIABETES PRIOR TO ADMISSION**	Check BG every 6 h
	• Check HbA_{1c} if none available in last 3 months	
a	**T1DM** NPO: **add basal insulin glargine** ASAP (to **avoid DKA**): use 70% of home dose if eGFR >50 and 50% if eGFR <50 **+ scale**	
b	**T1DM on insulin pump and has supplies:** if feasible, continue basal insulin via pump (use increased temporary basal rate if needed); **rare use in ICU so calculate total basal as in a**	
c	**T1DM + TF:** continue basal insulin (to prevent DKA) and add **scheduled regular insulin for TF every 6 h** (guidance above based on eGFR and TF rate) + scale	
d	**T2DM NPO:** on regimen that included insulin prior to admission: start 25–50% basal dose + scale	
e	**T2DM on insulin PTA + TF:** start 25–50% basal dose and regular insulin for TFcoverage every 6 h; see above for dose calculations + scale	

BG, blood glucose; DKA, diabetes ketoacidosis; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); HbA_{1c}, hemoglobin A_{1c}; NPO, nothing by mouth; PTA, prior to admission; T1DM, patients with type 1 diabetes; T2DM, patients with type 2 diabetes; TF, tube feeding.

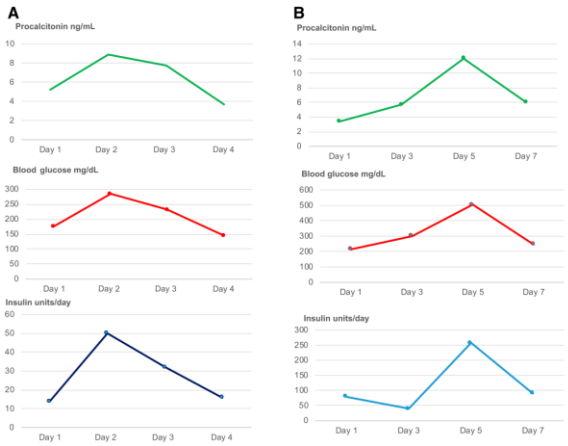

Figure 1—Examples of randomly selected patients admitted with COVID-19–related pneumonia, acute respiratory distress syndrome, and important surges in inflammatory biomarkers who developed severe hyperglycemia in the presence of cytokine storm. Data are shown for procalcitonin, blood glucose levels, and insulin requirement during the acute inflammatory surge in two randomly selected patients: patient A, well controlled prior to admission on oral antiglycemic agents, and patient B, requiring prior insulin

NEUROLOGY

DELIRIUM AND ENCEPHALOPATHY IN SEVERE COVID-19: A COHORT ANALYSIS OF ICU PATIENTS

Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, Studer A, Radosavljevic M, Kummerlen C, Monnier A, Boulay C, Fafi-Kremer S, Castelain V, Ohana M, Anheim M, Schneider F, Meziani F.. Crit Care. 2020 Aug 8;24(1):491. doi: 10.1186/s13054-020-03200-1.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Researchers performed a cohort study of 140 COVID-19 patients diagnosed by RT-PCR admitted into one of two ICU units in Strasbourg University Hospital between March 3rd, 2020 and May 5th, 2020 to investigate the prevalence of delirium and other neurological abnormalities and the impact that a patient's neurological state had on the necessity for mechanical ventilation and length of ICU stay. Additionally, authors performed brain magnetic resonance imaging (MRI's), electroencephalograms (EEGs), and cerebrospinal fluid (CSF) analysis on different subsets of patients with delirium and/or neurological abnormalities. The findings highlight a high prevalence of neurological abnormalities in COVID-19 patients admitted to the ICU (118/140, 84.3%) and suggest a role for assessing a patient's neurological state to accurately allocate hospital resources and provide proper care to maximize recovery rates.

SUMMARY

Specific findings included:
1. One hundred and eighteen patients (84.3%) presented with delirium and/or other neurological abnormalities such as diffuse enhanced, polykinetic tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes. These patients required longer mechanical ventilation use and a longer ICU stay compared to COVID-19 patients without delirium and/or other neurological abnormalities (Table 2).
2. Unspecified abnormalities indicative of confusion and sedation were seen on 26 of 42 EEGs performed on patients presenting with delirium and/or neurological abnormalities.
3. Brain MRI showed enhancement of subarachnoid spaces in 17 of 28 patients (60.7%); intraparenchymal, predominantly white matter abnormalities in eight of 28 patients (28.6%); white matter microhemorrhages in seven of 28 patients (25%); and perfusion abnormalities in 17 of 26 patients (65.4%) (Figure 2).
4. CSF analysis revealed abnormalities in 18 of 25 patients (72%) including elevated CSF immunoglobin G, protein, and interleukin-6 levels in nine patients and oligoclonal bands associated with a mirror pattern in 13 patients, indicating potential inflammatory processes (Table 3).

ABSTRACT

BACKGROUND: Neurotropism of SARS-CoV-2 and its neurological manifestations have now been confirmed. We aimed at describing delirium and neurological symptoms of COVID-19 in ICU patients. METHODS: We conducted a bicentric cohort study in two French ICUs of Strasbourg University Hospital. All the 150 patients referred for acute respiratory distress syndrome due to SARS-CoV-2 between March 3 and May 5, 2020, were included at their admission. Ten patients (6.7%) were excluded because they remained under neuromuscular blockers during their entire ICU stay. Neurological examination, including CAM-ICU, and cerebrospinal fluid analysis, electroencephalography, and magnetic resonance imaging (MRI) were performed in some of the patients with delirium and/or abnormal neurological examination. The primary endpoint was to describe the incidence of delirium and/or abnormal neurological examination. The secondary endpoints were to describe the characteristics of delirium, to compare the duration of invasive mechanical ventilation and ICU length of stay in patients with and without delirium and/or abnormal neurological symptoms. RESULTS: The 140 patients were aged in median of 62 [IQR 52; 70] years old, with a median SAPSII of 49 [IQR 37; 64] points. Neurological examination was normal in 22 patients (15.7%). One hundred eighteen patients (84.3%) developed a delirium with a combination of acute attention, awareness, and cognition disturbances. Eighty-eight patients (69.3%) presented an unexpected state of agitation despite high infusion rates of sedative treatments and neuroleptics, and 89 (63.6%) patients had corticospinal tract signs. Brain MRI performed in 28 patients demonstrated enhancement of subarachnoid spaces in 17/28 patients (60.7%), intraparenchymal, predominantly white matter abnormalities in 8 patients, and perfusion abnormalities in 17/26 patients (65.4%). The 42 electroencephalograms mostly revealed unspecific abnormalities or diffuse, especially bifrontal, slow activity. Cerebrospinal fluid examination revealed inflammatory disturbances in 18/28 patients, including oligoclonal bands with mirror pattern and elevated IL-6. The CSF RT-PCR SARS-CoV-2 was positive in one patient. The delirium/neurological symptoms in COVID-19 patients were responsible for longer mechanical ventilation compared to the patients without delirium/neurological symptoms. Delirium/neurological symptoms could be secondary to systemic inflammatory reaction to SARS-CoV-2. CONCLUSIONS AND RELEVANCE: Delirium/neurological symptoms in COVID-19 patients are a major issue in ICUs, especially in the context of insufficient human and material resources. TRIAL REGISTRATION: NA.

FIGURES

	All patients ($n = 140$)	No delirium and normal neurological examination ($N = 22$)	Delirium and/or abnormal neurological examination ($N = 118$)	p
Invasive mechanical ventilation				
Duration (days)—median [IQR]	13 [9; 23]	9 [5; 17]	14 [10; 25]	0.011
Auto-extubation with immediate reintubation—n (%)	11 (7.9)	0 (0.0)	11 (9.3)	0.211
ICU stay				
ICU mortality—n (%)	21 (15.0)	2 (9.1)	19 (16.1)	0.634
Length of stay (days)—median [IQR]	15 [10; 25]	10 [6; 21]	15 [11; 25]	0.017
Sedative treatments				
Midazolam—n (%)	121 (86.4)	18 (81.8)	103 (87.3)	0.691
Midazolam (days)—median [IQR]	6 [3; 12]	4 [1; 9]	7 [4; 12]	0.095
Sufentanil—n (%)	138 (98.6)	20 (90.9)	118 (100)	0.047
Sufentanil—median [IQR]	10 [5; 15]	6 [1; 9]	11 [6; 16]	0.004
Propofol—n (%)	83 (59.3)	8 (36.4)	75 (63.6)	0.017
Propofol—median [IQR]	2 [0; 6]	0 [0; 3]	2 [0; 7]	0.027

Table 2. Outcome of the patients

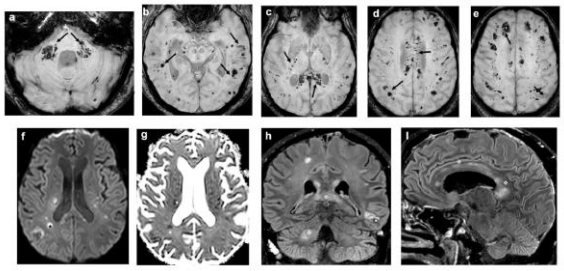

Figure 2. Axial SWI (a-e), axial diffusion (f), apparent diffusion coefficient (ADC) (g), coronal (h), sagittal (i), FLAIR-weighted MR images: multiple infra and supratentorial white matter microhemorrhages (arrows), associated with FLAIR (cross) and diffusion (star) hyperintensities

	All patients (*n* = 25)
CSF analysis—median [IQR]	
Nucleated cell count (cells/mm^3)—*normal range < 5*	1 [0; 2]
CSF protein level (g/L)—*normal range 0.15–0.45 g/L*	0.33 [0.26; 0.59]
CSF glucose level (g/L)	0.89 [0.75; 1.28]
CSF lactate level (mmol/L)—*normal range 1.2–2.1 mmol/L*	1.29 [1.09; 1.80]
CSF IgG level (mg/L)—*normal range 10–34 mg/L*	32.3 [19.2; 50.3]
CSF albumin level (mg/L)—*normal range 130–350 mg/L*	184 [121; 308]
Albumin ratio CSF/serum X 10^3—*normal range < 8.5*	7.5 [5.8; 11.6]
CSF Interleukin-6 level (pg/mL)—*normal range < 13 pg/mL*	8.9 [2.7; 13.5]
CSF Interleukin-10 level (pg/mL)—*normal range < 3 pg/mL*	0.0 [0.0; 0.1]
CSF Interferon gamma (pg/mL)—*normal range < 80 pg/mL*	0.6 [0.4; 0.7]
CSF abnormalities—number of patients (%)	
Abnormal CSF analysis	18 (72.0)
Elevated nucleated cell count	3 (12.0)
Elevated CSF protein levels	8 (32.0)
Elevated CSF albumin level	5 (20.0)
Elevated albumin ratio CSF/serum	4 (16.0)
Elevated CSF IgG	9 (36.0)
Oligoclonal bands with mirror pattern	13 (52.0)
Elevated interleukin-6 level	7 (28.0)
Elevated interleukin-10 level	2 (8.0)
Elevated interferon gamma level	0 (0.0)
Positive SARS-CoV-2 RT-PCR in CSF	1 (4.0)

CSF cerebrospinal fluid, *RT-PCR* real-time reverse transcriptase polymerase chain reaction

Table 3. Cerebrospinal fluid analysis

HEMATOLOGY AND ONCOLOGY

PATIENT-REPORTED TREATMENT DELAYS IN BREAST CANCER CARE DURING THE COVID-19 PANDEMIC

Papautsky EL, Hamlish T.. Breast Cancer Res Treat. 2020 Aug 9. doi: 10.1007/s10549-020-05828-7. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A survey conducted by University of Illinois-Chicago Cancer Center in April 2020 among patients with breast cancer (n=609 surveyed) found 45% of patients reported cancer treatment delays during the COVID-19 pandemic. Younger patients self-reported greater delays than older patients (Figure 1), with no significant differences found based on race, insurance, site of care, or cancer stage (Figure 2). These delays in cancer treatment for younger patients indicates potential for increased rates of disease progression, mortality, and pain due to delay, highlighting the need for protective processes and managing strategies for this vulnerable population during the pandemic.

ABSTRACT

PURPOSE: The coronavirus disease (COVID-19) pandemic has had a profound impact on cancer care in the US Guidelines focused on the management of COVID-19, rather than healthcare needs of breast cancer patients requiring access to crucial services. This US survey of breast cancer survivors characterizes treatment delays early period in the pandemic. METHODS: We developed a survey and administered it to 609 adult breast cancer survivors in the US. We used snowball sampling with invitations distributed via social media. We used logistic regression to select a model of delay from a pool of independent variables including race, cancer stage, site of care, health insurance, and age. We used descriptive statistics to characterize delay types. RESULTS: Forty-four percent of participants reported cancer care treatment delays during the pandemic. Delays in all aspects of cancer care and treatment were reported. The only variable which had a significant effect was age (97 (.95, 99), $p < 0.001$) with younger respondents (M = 45.94, SD = 10.31) reporting a higher incidence of delays than older respondents (M = 48.98, SD = 11.10). There was no significant effect for race, insurance, site of care, or cancer stage. CONCLUSIONS: Our findings reveal a pervasive impact of COVID-19 on breast cancer care and a gap in disaster preparedness that leaves cancer survivors at risk for poor outcomes. Delays are critical to capture and characterize to help cancer providers and healthcare systems develop effective and patient-tailored processes and strategies to manage cases during the current pandemic wave, subsequent waves, and future disasters.

FIGURES

Table 1 (continued)

			Delay				95% CI for Exp(β)	
			No	Yes	Sig	Exp(β)	Lower	Upper
Current cancer stage	Stage 0	Count	23	18	0.36	1.80	0.51	6.36
		%	56%	44%				
	Stage 1	Count	81	68	0.20	2.10	0.67	6.59
		%	54%	46%				
	Stage 2	Count	95	82	0.20	2.12	0.68	6.61
		%	54%	46%				
	Stage 3	Count	46	36	0.36	1.75	0.53	5.75
		%	56%	44%				
	Stage 4	Count	75	54	0.29	1.87	0.59	5.96
		%	58%	42%				
	Not sure/don't know	Count	13	5	NA	NA	NA	NA
		%	72%	28%				
	Total	Count	333	263				
		%	56%	44%				

Note: Total counts may differ slightly based on missing data

Figure 1: Age distribution and descriptive statistics in sample of respondents.

Breast Cancer Research and Treatment

Table 1 Characteristics of respondents who experienced delays compared with those who did not (*n* = 554)

			Delay				95% CI for Exp(β)	
			No	Yes	Sig	Exp(β)	Lower	Upper
Race	American Indian or Alaska Native	Count	2	1	0.81	0.66	0.02	19.40
		%	67%	33%				
	Asian	Count	7	7	0.82	0.78	0.09	6.71
		%	50%	50%				
	Native Hawaiian or Pacific Islander	Count	2	1	0.64	0.48	0.02	10.86
		%	67%	33%				
	Black	Count	66	37	0.51	0.52	0.08	3.53
		%	64%	36%				
	White	Count	238	204	0.80	0.79	0.12	5.11
		%	54%	46%				
	Total	Count	317	253				
		%	56%	44%				
Site of care	University/Academic Medical Center	Count	142	127	0.17	1.69	0.80	3.57
		%	53%	47%				
	Physician's Office	Count	95	60	0.75	1.14	0.52	2.49
		%	61%	39%				
	Veterans affairs hospital	Count	1	1	0.76	1.58	0.08	30.98
		%	50%	50%				
	Community hospital	Count	69	56	0.45	1.36	0.61	3.03
		%	55%	45%				
	Cancer Center	Count	24	13	0.13	4.17	0.66	26.21
		%	65%	35%				
	Total	Count	333	265				
		%	56%	44%				
Insurance	Insurance through my job	Count	215	183	0.96	0.98	0.53	1.81
		%	54%	46%				
	Private insurance that I purchase on my own	Count	20	18	0.88	1.07	0.44	2.58
		%	53%	47%				
	Public insurance (Medicaid, Medicare)	Count	57	32	0.70	1.16	0.54	2.51
		%	64%	36%				
	None	Count	4	3	NA	NA	NA	NA
		%	57%	43%				
	Other	Count	35	28	0.79	1.34	0.15	12.04
		%	56%	44%				
	Total	Count	331	264				
		%	56%	44%				

Table 1 - Characteristics of respondents who experienced delays compared with those who did not (n=554).

SURGICAL SUBSPECIALTIES

ORTHOPEDICS

PROLONGED SOCIAL LOCKDOWN DURING COVID-19 PANDEMIC AND HIP FRACTURE EPIDEMIOLOGY

Slullitel PA, Lucero CM, Soruco ML, Barla JD, Benchimol JA, Boietti BR, Zanotti G, Comba F, Taype-Zamboni DR, Carabelli GS, Piccaluga F, Sancineto CF, Diehl M, Buttaro MA; HipFEIR [Hip Fracture in the Elderly – Institutional Register] Study Group.. Int Orthop. 2020 Aug 8. doi: 10.1007/s00264-020-04769-6. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

This retrospective study assessed 183 hip fracture patients at a tertiary care center in Argentina from December 2019 to May 2020, analyzing 30-day complication rates, readmission, and mortality, in order to determine differences in this patient population before COVID-19, termed "pre-COVID time" (PCT) and after prolonged mandatory lockdown, termed "COVID time" (CT). Results showed increased time waiting for surgery during the lockdown time period (Figure 1), as well as higher rate of thromboembolic events in the CT group (Table 3) and a higher mortality rate in the CT group (Table 3). Results also revealed no significant difference in patient demographics (Table 1), except for worse scores on the pre-operative Charlson Comorbidity Index (CCI), UCLA activity scale, and frailty index in CT patients, suggesting CT patients have more comorbidities, are less active, and are more frail, which could explain the higher mortality rate in this group.

ABSTRACT

PURPOSE: To analyse the impact of prolonged mandatory lockdown due to COVID-19 on hip fracture epidemiology. METHODS: Retrospective case-control study of 160 hip fractures operated upon between December 2019 and May 2020. Based on the date of declaration of national lockdown, the cohort was separated into two groups: 'pre-COVID time' (PCT), including 86 patients, and 'COVID time' (CT), consisting of 74 patients. All CT patients tested negative for SARS-CoV-2. Patients were stratified based on demographic characteristics. Outcome measures were 30-day complications, readmissions and mortality. A logistic regression model was run to evaluate factors associated with mortality. RESULTS: Age, female/male ratio, body mass index and American Society of Anaesthesia score were similar between both groups ($p > 0.05$). CT patients had a higher percentage of Charlson >= 5 and Rockwood Frailty Index >= 5 scores ($p < 0.05$) as well as lower UCLA and Instrumental Activities of Daily Living scores ($p < 0.05$). This translated into a higher hemiarthroplasty/total hip arthroplasty ratio during CT ($p = 0.04$). Thromboembolic disease was higher during CT ($p = 0.02$). Readmissions (all negative for SARS-CoV-2) were similar between both groups ($p = 0.34$). Eight (10.8%) casualties were detected in the CT group, whereas no deaths were seen

in the control group. Logistic regression showed that frailer (p = 0.006, OR 10.46, 95%CI 8.95-16.1), less active (p = 0.018, OR 2.45, 95%CI 1.45-2.72) and those with a thromboembolic event (p = 0.005, OR 30, 95%CI 11-42) had a higher risk of mortality. CONCLUSION: Despite testing negative for SARS-CoV-2, CT patients were less active and frailer than PCT patients, depicting an epidemiological shift that was associated with higher mortality rate.

FIGURES

Variable	Total cohort ($N = 160$)	Pre-COVID time fractures ($N = 86$)	COVID time fractures ($N = 74$)	p value
Median age (IQR)	86 (79–91)	86 (78–90)	86 (80–91)	0.83
Female patients (%)	132 (82.5%)	67 (78%)	65 (88%)	0.1
Median BMI (IQR)	24.5 (22–27)	24 (21.7–26.6)	24.5 (22.3–27.3)	0.11
Median time (hours) to rRT-PCR (IQR)	–	–	6 (3–19)	–
ASA score (%)				
I–II	34 (21.3%)	22 (25.6%)	12 (16.2%)	
III–IV	126 (78.7%)	64 (74.4%)	62 (84%)	0.15
CCI (%)				
Mild	4 (2.5%)	3 (3.5%)	1 (1.3%)	
Moderate	44 (27.5%)	31 (36%)	13 (17.6%)	
Severe	111 (69.4%)	52 (60.5%)	59 (79.7%)	0.03
Median UCLA scale (IQR)	3 (2–4)	3 (2–4)	2 (2–3)	0.037
Median IADL score (IQR)	4 (2–6)	5 (3–6)	3 (1.75–4)	0.001
Rockwood Frailty Score ≥ 5 (%)	74 (46.3%)	32 (37.2%)	42 (56.8%)	0.013

BMI, body mass index; *rRT-PCR*, reverse transcriptase-polymerase chain reaction; *IQR*, interquartile range; *ASA*, American Society of Anesthesia; *CCI*, Charlson Comorbidity Index; *UCLA*, University of California Los Angeles Activity scale; *IADL*, Instrumented Activities of Daily Living

Table 1. Demographic data of the series divided by group.

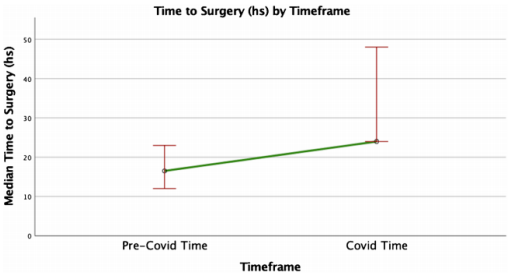

Figure 1. Graph showing median time to surgery for hip fracture resolution during pre-COVID and COVID timeframes with their corresponding 95%CIs.

Variable	Total cohort ($N = 160$)	Pre-COVID time fractures ($N = 86$)	COVID time fractures ($N = 74$)	p value
Intraoperative periprosthetic fracture	3 (1.88%)	1 (1.16%)	2 (2.7%)	0.43
Dislocation (%)	1 (0.63%)	0	1 (1.35%)	0.34
Surgical site infection (%)	2 (1.25%)	2 (2.32%)	0	0.45
Thromboembolic disease (%)	5 (3.13%)	0	5 (6.75%)	0.014
Readmission (%)	15 (9.38%)	7 (8.1%)	8 (10.8%)	0.56
FUO		1	2	
Cholecystitis		0	1	
Ischemic stroke		0	1	
		1	1 (deceased)	
LGB		0	1	
PDD		2	2	
LRTI		2	0	
PJI		1	0	
CHF				
Mortality (%)	8 (5%)	0	8 (10.8%)	0.002

FUO, fever of unknown origin; *LGB*, low gastrointestinal bleeding; *PDD*, psychiatric disorder decompensation; *LRTI*, lower respiratory tract infection; *PJI*, periprosthetic joint infection; *CHF*, congestive heart failure

Table 3. Complications, readmissions and mortality outcomes divided by group.

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