ORIGINAL ARTICLE

Baseline Glycemic Status and Outcome of Persons with Type 2 Diabetes with COVID-19 Infections: A Single-Center Retrospective Study

Marion Sarigumba, Jimmy Aragon, Ma. Princess Kanapi

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Makati Medical Center, Makati City, Philippines

Abstract

Introduction. The coexistence of two global pandemics, COVID-19 and type 2 diabetes mellitus, has been implicated with worse prognosis. The association of diabetes and worse outcome in viral infections stems from the detrimental effect of hyperglycemia to the control of viremia and different components of the host response. This study aimed to describe the epidemiological and clinical characteristics of confirmed COVID-19 patients and establish the association of baseline glycemic status and COVID-19 outcomes among persons with type 2 diabetes.

Methodology. A single center, retrospective study among adult persons with type 2 diabetes diagnosed with COVID-19 in Makati Medical Center from March 1 to August 31, 2020. A total of 156 medical records (26%) out of 584 confirmed cases were reviewed. Data were collected on diabetes status, comorbid conditions and laboratory findings. Both Cox proportional hazards models and logistic regression models were fitted. To assess the factors associated with mortality as a dichotomous endpoint (died/survived), binary logistic regression was performed. On the other hand, a time-to-mortality analysis was performed using Cox regression. For the effect estimate, we refer to hazard ratios in the Cox proportional hazards model and odds ratios in the logistic regression models. All analyses were adjusted for age and sex and two models were additionally adjusted for any presence of comorbidity.

Results. A total of 156 COVID-19 patients with diabetes were analyzed. Upon admission, 13% were in diabetic ketosis, 4% were in a state of DKA, and 2% had hypoglycemia. About 5%, 33%, 26%, and 36% of patients had mild, moderate, severe, and critical COVID-19, respectively. Between non-survivors and survivors, the latter group were significantly younger in age (*p*<.003) and had less ICU admissions (*p*<.001). Although DKA status upon admission seemed to result in increased odds of non-survival (cOR 5.8 [95% CI 1.1-30.7]), no other feature in the glycemic history was significantly associated with mortality outcome after having adjusted for age and sex. Death in this study was limited to patients with severe or critical disease.

Conclusion. The risk of mortality is five times greater among patients admitted with diabetic ketoacidosis. The incidence of complications were also significantly greater and mortality was limited to patients with severe or critical disease.

Key words: Diabetes mellitus, Coronavirus

INTRODUCTION

Severe respiratory infections have posed serious hazards to global health. In the last two decades, there have been documented major outbreaks of two beta coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. These have caused fatal pneumonia with mortality rates as high as 10% and 36%, respectively. In December 2019, a novel coronavirus, subsequently named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) was discovered in Wuhan, Hubei Province, China that caused clusters of pneumonia cases in the locality. The disease it causes is called COVID-19. Due to rapid sustained human-to-human transmission, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020. This formidable outbreak in many cities in China, expanding internationally, led to the escalation to a pandemic on March 11, 2020.[1]

The pathophysiological mechanisms underlying this condition are still not fully understood, but it has been observed that most severe and fatal cases with COVID-19 have occurred in the elderly or in patients with underlying comorbidities, particularly cardiovascular diseases, diabetes mellitus, chronic lung and renal disease, hypertension and cancer.[2-5] According to one Chinese meta-analysis with 1527 patients, the most prevalent cardiovascular metabolic abnormalities associated with COVID-19 include hypertension (17.1%, 95% CI 9.9-24.4%) and cardio-cerebrovascular disease (16.4%, 95% CI 6.6-26.1%), followed by diabetes (9.7%, 95% CI 6.9-12.5%). It showed that those with diabetes or hypertension had a 2-fold increase in risk of severe disease or requiring intensive care unit (ICU) admission.[6]

Corresponding author: Marion B. Sarigumba, MD
Section of Endocrinology, Diabetes and Metabolism,
Department of Medicine Makati Medical Center
No. 2 Amorsolo St., Legaspi Village, Makati City 1229
Tel. No.:+632-84207460
E-mail: marionsarigumba@gmail.com
ORCiD: https://orcid.org/0000-0002-7913-6941

The coexistence of these two global pandemics, COVID-19 and type 2 diabetes mellitus, has been implicated with worse prognosis. The association of diabetes and worse outcome in viral infections stems from the detrimental effect of hyperglycemia to the control of viremia and different components of the host response, including the function of immune cells and regulation of cytokines. The aim of this analysis is to describe the epidemiological and clinical characteristics of patients confirmed to have COVID-19 and to establish the association between baseline glycemic status and outcomes of persons with diabetes with COVID-19 infections.

METHODOLOGY

This single-center observational study was approved by the Institutional Review Board of Makati Medical Center (protocol number: MMCIRB 2020-082; date of approval: July 28, 2020).

A list of patients was generated from the Infection Prevention Control Unit (IPCU) of Makati Medical Center by identifying persons with diabetes who were laboratory-confirmed (RT-PCR) to have COVID-19. Medical records of the study population from March 1 to August 31, 2020 were reviewed. Retrospective data review was done on an electronic medical record system.

The subjects were classified according to severity using the WHO COVID-19 Disease Severity Classification (27 May 2020). For each subject, the following data will be gathered: duration of diabetes, Hba1c on admission, presence of diabetes complications (ketosis, ketoacidosis, hyperosmolar hyperglycemic state), oral hypoglycemic and insulin use prior to admission and other comorbidities. The following complications were likewise recorded for each patient: ARDS, Septic Shock, ECMO, Gastro-intestinal Bleeding, Myocarditis or Heart Failure as well as their outcome.

Descriptive statistics was used to summarize the general and clinical characteristics of the subjects. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution while Levene's test was used to determine the homogeneity of variance of continuous variables. Continuous quantitative data that met the normality assumption was summarized using mean and standard deviation (SD), while those that did not was described using median and range.

Continuous variables which are normally distributed were compared using the Independent t-test. Otherwise, the non-parametric Mann-Whitney U test was used. For categorical variables, Chi-square test was used to compare the outcomes. If the expected percentages in the cells are less than 5%, Fisher's Exact test was used instead.

Both Cox proportional hazards models and logistic regression models were fitted. To assess the factors associated with mortality as a dichotomous endpoint (died/survived), binary logistic regression was performed. On the other hand, a time-to-mortality analysis was performed using Cox regression. For the effect estimate, we refer to hazard ratios in the Cox proportional hazards model and

odds ratios in the logistic regression models. All analyses were adjusted for age and sex and two models were additionally adjusted for any presence of comorbidity.

All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

We analyzed a total of 156 patients with diabetes (26%) out of 584 COVID confirmed cases. One subject was excluded due to history of solid organ transplantation. Of these, 25 (16%) expired. Most were male (63%), the mean (±SD) age was 60±13 years, and median BMI was 27 (range 18-52) kg/m2. About 1 in 5 patients were admitted to ICU (17%). The most common comorbidities besides diabetes were hypertension (76%) and chronic kidney disease (17%).

Upon admission, 13% were in diabetic ketosis, 4% were in a state of DKA, and 2% had hypoglycemia. The median baseline diabetes duration, HbA1c, and CBG of patients were 5 (range 0-51) years, 7.52 (range 4.79-18.42) %, and 196 (range 61-568) mg/dl, respectively. About 66% were on oral hypoglycemic agents (OHA), while 14% were using injectables. Comparing the non-survivors with the survivors, they differed in terms of age and need for ICU admission. About 5%, 33%, 26%, and 36% of patients had mild, moderate, severe, and critical COVID-19, respectively.

Between non-survivors and survivors, the latter group were significantly younger in age ($p < .003$) and had less ICU admissions ($p < .001$) (Table 1).

Patient complications in decreasing order were pneumonia (92%), renal failure (47%), and ARDS (26%), and shock (10%). There were significantly higher proportions of renal failure (68% vs 44%), ARDS (84% vs 15%), and shock (32% vs 5%) among those who did not survive. The median durations of hospital for survivors and non-survivors were 13 (range 0-30) and 9 (range 1-26) days ($p=.064$), respectively (Table 2).

Although DKA status upon admission seemed to result in increased odds of non-survival (cOR 5.8 [95% CI 1.1-30.7]), no feature in the glycemic history was significantly associated with mortality outcome after having adjusted for age, sex and any comorbidity (Table 3).

Among patients with severe or critical COVID-19, all except 2 developed pneumonia, more than 7 in 10 were intubated, just over 6 in 10 suffered renal failure, and about 4 in 10 were complicated by ARDS. These incidences were significantly greater compared to their counterparts in the mildly to moderately ill (respectively 83%, 3%, 25%, and 3%). Death in this study was limited to patients with severe or critical disease.

Cox regression
Cox proportional hazard model was estimated to determine the association of glycemic control to time to mortality. Hazard ratios and the corresponding 95% confidence intervals were reported (Figure 1).

Table 1. Characteristics of COVID-19 patients with diabetes mellitus (n=156)

	Overall (n=156)	Non-survivors (n=25)	Survivors (n=131)	p
	Mean ± SD; Frequency (%); Median (Range)			
Age (years)	59.83 ± 13.26	66.96 ± 14.99	58.47 ± 12.60	<.003*
Sex				.501†
Male	98 (62.82)	14 (56)	84 (64.12)	
Female	58 (37.18)	11 (44)	47 (35.88)	
BMI (kg/m²)	27.02 (18.14–52.22); [n=116]	28.34 (18.79–40.9); [n=17]	27 (18.14–52.22); [n=99]	.325‡
Need for ICU admission				<.002§
ICU	26 (16.67)	10 (40)	16 (12.21)	
Non-ICU	130 (83.33)	15 (60)	115 (87.79)	
Comorbidities				
Hypertension	119 (76.28)	21 (84)	98 (74.81)	.322†
CKD	26 (16.67)	6 (24)	20 (15.27)	.377§
CVD	11 (7.05)	3 (12)	8 (6.11)	.385§
Cancer	5 (3.21)	1 (4)	4 (3.05)	.588§
Others	19 (12.18)	4 (16)	15 (11.45)	.511§
Baseline glycemic status				
Duration of diabetes (years)	5 (0–51); [n=134]	5 (0–51); [n=19]	5 (0–30); [n=115]	.614‡
<5	58 (43.28)	6 (31.58)	53 (45.22)	.286§
5 – 10	54 (40.30)	11 (57.89)	43 (37.39)	
>10	22 (16.42)	2 (10.53)	20 (17.39)	
HbA1c (%)	7.52 (4.79–18.42); [n=153]	6.84 (5.35–12.19); [n=24]	7.59 (4.79–18.42); [n=129]	.192‡
<9	98 (64.05)	16 (66.67)	82 (63.57)	.771†
≥9	55 (35.95)	8 (33.33)	47 (36.43)	
Initial CBG (mg/dl)	196 (61–568)	188 (61–401)	196 (71–568)	.643‡
<180	59 (37.82)	10 (40)	49 (37.40)	.806†
≥180	97 (62.18)	15 (60)	82 (62.60)	
Admission status				
DKA	6 (3.85)	3 (12)	3 (2.29)	.053§
Diabetic ketosis	20 (12.82)	3 (12)	17 (12.88)	1.000†
Hypoglycemia	3 (1.92)	1 (4)	2 (1.53)	.410§
Medications				.019‡
None	47 (30.13)	5 (20)	42 (32.06)	
OHA only	87 (55.77)	14 (56)	73 (55.73)	
Injectables only	6 (3.85)	4 (16)	2 (1.53)	
Both	16 (10.26)	2 (8)	14 (10.69)	
COVID-19 severity				<.001§
Mild	7 (4.49)	0	7 (5.34)	
Moderate	52 (33.33)	0	52 (39.69)	
Severe	41 (26.28)	0	41 (31.30)	
Critical	56 (35.90)	25 (100)	31 (23.66)	

Statistical Tests Used: *–Independent t-test; †–Chi-square test; ‡–Mann Whitney U test; §–Fisher's Exact test.

Table 2. Complications and duration of hospital stay among patients (n=156)

	Overall (n=156)	Non-survivors (n=25)	Survivors (n=131)	p
	Frequency (%); Median (Range)			
Pneumonia	144 (92.31)	25 (100)	119 (90.84)	.216§
Renal failure	74 (47.44)	17 (68)	57 (43.51)	.025†
ARDS	41 (26.28)	21 (84)	20 (15.27)	<.001†
Shock	15 (9.62)	8 (32)	7 (5.34)	<.001§
Gastrointestinal	2 (1.28)	1 (4)	1 (0.76)	.296§
Heart failure or myocarditis	1 (0.64)	0	1 (0.76)	1.000§
Seizure	0	0	0	-
Hospital days	13 (0–30)	9 (1–26)	13 (0–30)	.064‡

Statistical Tests Used: †–Chi-square test; ‡–Mann Whitney U test; §–Fisher's Exact test.

The risk of mortality is five times higher among patients admitted with diabetic ketoacidosis. No other feature in the glycemic history was significantly associated with hazard of mortality on crude analysis.

The median survival time across all patients was estimated at no later than 26 days from admission, based on the 95% confidence intervals of survival probabilities, which should contain 50% survivorship.

DISCUSSION

This present study demonstrates that the risk of mortality is five times higher among patients admitted with diabetic ketoacidosis. No other features in the glycemic history was significantly associated with mortality outcome after having adjusted for age, sex and any comorbidity. The incidence of complications were significantly greater and mortality was limited to patients with severe or critical disease. The non-survivors and survivors differed in terms of age and need for ICU admission.

**Table 3.** Association between glycemic history and mortality (n=156)

	Crude OR (95% CI)	p	Adjusted[a] OR (95% CI)	p	Adjusted OR[c] (95% CI)	p
DM history						
Duration of diabetes (years)						
<5	Reference	-	Reference	-	Reference	-
5–10	2.217 (0.76–6.49)	.146	1.401 (0.44–4.43)	.566	1.376 (0.43-4.36)	.588
>10	0.867 (0.16–4.66)	.868	0.425 (0.07–2.64)	.359	.409 (0.07-2.56)	.340
HbA1c, ≥9%	0.872 (0.45–2.19)	.771	1.295 (0.48–3.48)	.609	1.308 (0.48-3.53)	.596
Initial CBG, ≥180 mg/dl	0.896 (0.37–2.15)	.806	1.207 (0.48–3.03)	.689	1.224 (0.48-3.09)	.669
Admission status						
Any complication	1.926 (0.72–5.16)	.192	2.070 (0.73–5.83)	.169	2.015 (0.71-5.71)	.187
DKA	**5.818 (1.10–30.69)**	**.038**	5.186 (1.01–1.09)	.063	4.650 (0.82-26.46)	.083
Diabetic ketosis	0.914 (0.25–3.39)	.894	1.148 (0.29–4.56)	.845	1.168 (0.29-4.68)	.827
Hypoglycemia	2.688 (0.23–30.82)	.427	1.658 (0.13–21.14)	.697	1.562 (0.12-19.82)	.731

[a] Model adjusted for age and sex; [b] Model adjusted for age, sex and any comorbidity

Table 4. Comparison of clinical outcomes by COVID-19 severity (n=156)

	Overall (n=156)	Mild/Moderate (n=59)	Severe/Critical (n=97)	p
	Frequency (%)			
Pneumonia	144 (92.31)	49 (83.05)	95 (97.94)	**<.001**
Renal failure	74 (47.44)	15 (25.42)	59 (60.82)	**<.001**
ARDS	41 (26.28)	2 (3.39)	39 (40.21)	**<.001**
Shock	15 (9.62)	0	15 (15.46)	**<.001**
Gastrointestinal	2 (1.28)	0	2 (2.06)	.527
Heart failure or myocarditis	1 (0.64)	0	1 (1.03)	1.000
Death	25 (16.03)	0	25 (25.77)	**<.001**

Statistical Tests Used: Chi-square test/Fisher's Exact test.
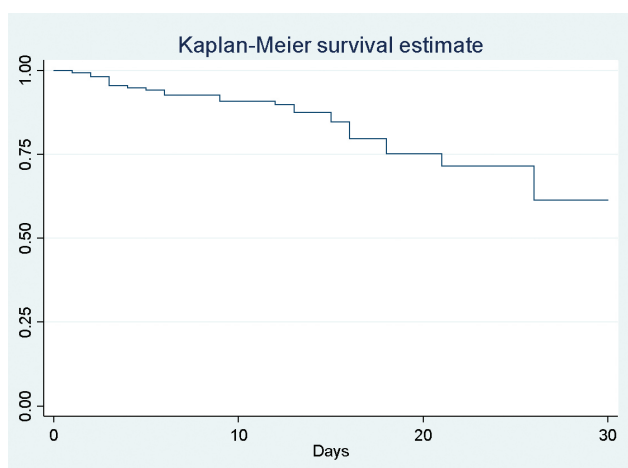
Figure 1. Kaplan-Meier curve of survival probability.

The findings are consistent with the study done by Pal et al., that DKA in COVID-19 patients portend a poor prognosis with a mortality rate approaching 50%.[7] An investigation in the United States by Bode et al., showed that those with uncontrolled hyperglycemia had a longer length of hospital stay than cohorts with good glycemic control.[8] NHS England suggested that patients with both controlled and uncontrolled diabetes with COVID-19, have a significant increase in death in comparison to cohorts without diabetes even after adjusting possible confounders.[9] Zhu et al., analyzed the largest diabetic COVID-19 cohort so far involving 9,663 patients in China, and found unequivocal results to implicate diabetes mellitus in higher risk of death and other detrimental outcomes of COVID-19.[10] Nevertheless, the Chinese Centre for Disease Control and Prevention reported a case fatality rate (CFR) of 7.3% in patients with diabetes, compared to a CFR of 2.3% of overall population of 44,672 patients with COVID-19.[11]

There are limited studies to date which analyzed the outcomes of COVID-19 based on severity, stratified on the baseline glycemic control in patients with diabetes. To the best of our knowledge, this is the first study conducted in the Philippine setting to determine the association of baseline glycemic status and outcome of persons with type 2 diabetes with COVID-19 infections.

SARS-CoV binds to ACE2 in the pancreatic islets leading to islet damage, and acute diabetes. This interaction leads to insulinopenia and increased risk of diabetic ketoacidosis (DKA), especially in patients with pre-existing diabetes. Interleukin-6 is an important cytokine of the hyper-inflammatory state in COVID-19 which has been found to be elevated in DKA and serves as a driver of ketogenesis. Co-existence of DKA in COVID-19 may pose an increased risk over other infectious diseases of equivalent severity.[12] Furthermore, diabetes is associated with the activation of the renin-angiotensin system in different tissues. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) to bind and gain entry to infected cells and reduces the expression of ACE2. Beta cell injury has been implicated in its pathogenesis, leading to viral 'sepsis' which could induce resistance to action of insulin posing additional challenges to management.[13]

An effort to efficiently manage uncontrolled glycemia is strongly advocated with an aim to lower morbidity and mortality. Economic problems exacerbated by the lockdown and COVID-19 has potentially led to non-compliance to pre-admission treatment regimens. Other factors which could affect glycemic control among patients during this pandemic include disorderly lifestyles with consequent weight gain, the lack of readily available access to contact their physicians, and fear of contracting the infection by clinic visits. The increased risk of mortality as found in this study in patients with hyperglycemic

crisis at presentation should encourage us all to achieve aggressive glycemic control.

As with any retrospective review, there are limitations in the data available. The single-center study design with a relatively small sample size is inherently prone to bias. There is also an unprecedented scale of the COVID-19 pandemic, thus, full pre-hospital status of diabetes mellitus from the current cohort were not retrieved due to urgent circumstances. Interestingly, Bode et al., reported a significantly higher percentage of in-patients with COVID-19 who had uncontrolled hyperglycemia but were not diagnosed as diabetes. This suggests that stress hyperglycemia may have a worse outcome in ICU, compared to a known patient with diabetes.[13] It was also noteworthy in some studies that history of microvascular and macrovascular complications was independently associated with risk of death. However, these are factors which were not included in the present study and should be looked into as a future research direction.

CONCLUSION

In conclusion, the risk of mortality is five times higher among patients admitted with diabetic ketoacidosis. The incidence of complications were significantly greater and mortality was limited to patients with severe or critical disease. Although DKA status upon admission seemed to result in increased odds of non-survival, no other feature in the glycemic history was significantly associated with mortality outcome after having adjusted for age and sex in this study.

Statement of Authorship
All authors certified fulfillment of ICE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References
1. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress, Diabetes Res Clin Pract. 2020;162:108-42. PMID: 32278764. PMCID: PMC7144611. https://doi.org/10.1016/j.diabres.2020.108142.
2. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report – 93. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200422-sitrep-93-covid-19.pdf.
3. Department of Heath. COVID 19 tracker Philippines. https://www.doh.gov.ph/2019-nCoV.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. PMID: 32109013. PMCID: PMC7092819. https://doi.org/10.1056/NEJMoa2002032.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. PMID: 32031570. PMCID: PMC7042881. https://doi.org10.1001/jama.2020.1585.
6. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020. PMID: 32077115. https://doi.org/10.1111/all.14238.
7. Pal R., Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature. Diabetes Metab Syndr. 2020;14(6):1563-69. PMID: 32853901. PMCID: PMC7434433. https://doi.org/10.1016/j.dsx.2020.08.015.
8. Bode B, Garrett V, Messler J, McFarland, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol. 2020;14(4):813-21. PMID: 32389027. PMCID: PMC7673150 (available on 2021-05-09). https://doi.org/10.1177/1932296820924469.
9. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: A population-based cohort study. Lancet Diabetes Endocrinol. 2020;8(10):823-33. PMID: 32798471. PMCID: PMC7426091. https://doi.org/10.1016/S2213-8587(20)30271-0.
10. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-77.e3. PMID: 32369736. PMCID: PMC7252168. https://doi.org/10.1016/j.cmet.2020.04.021.
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42. PMID: 32091533. https://doi.org/10.1001/jama.2020.2648.
12. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020;162:108142. PMID: 32278764. PMCID: PMC7144611. https://doi.org/10.1016/j.diabres.2020.108142.
13. Cristelo C, Azevedo C, Marques JM, Nunes R, Sarmento B. SARS-CoV-2 and diabetes: New challenges for the disease. Diabetes Research Clin Pract. 2020;164:108228. PMID: 32446801. PMCID: PMC7242186. https://doi.org/10.1016/j.diabres.2020.108228.