Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Altered mental status predicts length of stay but not death in a community-based cohort of hospitalized COVID-19 patients

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ABSTRACT

Introduction: Altered Mental Status (AMS) is a common neurological complication in patients hospitalized with the diagnosis of COVID-19 (Umapathi et al., 2020; Liotta et al., 2020). Studies show that AMS is associated with death and prolonged hospital stay. In addition to respiratory insufficiency, COVID-19 causes multi-organ failure and multiple metabolic derangements, which can cause AMS, and the multi-system involvement could account for the prolonged hospital stay and increased mortality. In this study, we built on our previous publication (Chachkhiani et al., 2020) using a new, larger cohort to investigate whether we could reproduce our previous findings while addressing some of the prior study's limitations. Most notably, we sought to determine whether AMS still predicted prolonged hospital stay and increased mortality after controlling for systemic complications such as sepsis, liver failure, kidney failure, and electrolyte abnormalities.

Objectives: The primary purpose was to document the frequency of AMS in patients with COVID-19 at the time of presentation to the emergency room. Secondary aims were to determine: 1) if AMS at presentation was associated with worse outcomes as measured by prolonged hospitalization and death; and 2) if AMS remained a predictor of worse outcome after adjusting for concomitant organ failure and metabolic derangements.

Results: Out of 367 patients, 95 (26%) had AMS as a main or one of the presenting symptoms. Our sample has a higher representation of African Americans (53%) than the US average and a high frequency of comorbidities, such as obesity (average BMI 29.1), hypertension (53%), and diabetes (30%). Similar to our previous report, AMS was the most frequent neurological chief complaint. At their admission, out of 95 patients with AMS, 83 (88%) had organ failure or one of the systemic problems that could have caused AMS. However, a similar proportion (86%) of patients without AMS had one or more of these same problems. Age, race, and ethnicity were the main demographic predictors. African Americans had shorter hospital stay [HR1.3(1.0,1.7),$p = 0.02$] than Caucasians. Hispanics also had shorter hospital stay than non-Hispanics [HR1.6(1.2,2.1), $p = 0.001$]. Hypoxia, liver failure, hypernatremia, and kidney failure were also predictors of prolonged hospital stay. In the multivariate model, hypoxia, liver failure, and acute kidney injury were the remaining predictors of longer hospital stay, as well as people with AMS at baseline [HR0.7(0.6,0.9), $p < 0.02$] after adjusting for the demographic characteristics and clinical predictors. AMS at baseline predicted death, but not after adjusting for demographics and clinical variables in the multivariate model. Hypoxia and hyperglycemia at baseline were the strongest predictors of death.

Conclusion: Altered mental status is an independent predictor of prolonged hospital stay, but not death. Further studies are needed to evaluate the causes of AMS in patients with COVID-19.

1. Introduction

Despite the availability of effective and safe vaccines [1,2], Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) remains a significant problem worldwide with the daily new positive tests of ~800,000 and daily deaths of ~14,000 at the time of writing this paper (https://www.nytimes.com). Disease caused by SARS-CoV-2 is called coronavirus disease 2019 [3] (COVID-19). There is a growing body of evidence that COVID-19 is associated with neurologic complications [4–6].

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2. Background

Altered Mental Status (AMS) is a common neurological complication in patients hospitalized with the diagnosis of COVID-19 [7,8]. Studies show that AMS is associated with death and prolonged hospital stay [9, 10].

Our understanding of the pathology of COVID-19 in the brain that could be the cause of the AMS is still limited [11]. A systematic review of the findings of 20 manuscripts with 184 neuropathology case reports found a broad range of findings, including microglial activation, lymphoid inflammation, acute hypoxic-ischemic changes, astrogliosis, acute/subacute infarcts, hemorrhages, and microthrombi [12]. The virus was detected by polymerase chain reaction (PCR) test in up to 53% of cases, although the copy numbers were low, and the virus may have only been present inside the blood vessels. On immunohistochemistry, the virus was present in 28% of the cases but with a disconnect between viral presence and inflammation. Tuma et al. (2020) studied cerebrospinal fluid (CSF) and imaging data in COVID-19 patients with encephalopathy and showed that only 1 out of 21 patients who underwent the CSF analysis had a positive CSF PCR test, and only a few had changes on neuroimaging [13]. An autopsy study from Columbia University showed minimal presence of the viral RNA and protein in the brain tissue [14].

In addition to respiratory insufficiency, COVID-19 causes multi-organ failure and multiple metabolic derangements [15]. Multiple organ failure can cause AMS, and the multi-system involvement could account for the prolonged hospital stay and increased mortality.

In our current study, we built on our previous publication [9] using a new, larger cohort to investigate whether we could reproduce our previous findings while addressing some of the prior study's limitations. Most notably, we sought to determine whether AMS still predicted prolonged hospital stay and increased mortality after controlling for systemic complications such as sepsis, liver failure, kidney failure, and electrolyte abnormalities.

3. Methods

The Louisiana Health Sciences Center – New Orleans Institutional Review Board and the University Medical Center Clinical Research Review Committee approved the study protocol. The primary purpose was to document the frequency of AMS in patients with COVID-19 at the time of presentation to the emergency room. Secondary aims were to determine: 1) if AMS at presentation was associated with worse outcomes as measured by prolonged hospitalization and death; and 2) if AMS remained a predictor of worse outcome after adjusting for concomitant organ failure and metabolic derangements.

We reviewed the electronic medical records (EMR) of patients hospitalized from April 1, 2020, through July 31, 2020, at the University Medical Center New Orleans (UMCNO), who tested positive for SARS-CoV-2 during the same hospitalization. The EMR team generated a list of 368 patients admitted for COVID-19. Two neurology residents (DC, MI) reviewed the EMR in detail to capture the relevant medical history, clinical course, laboratory test results, and abstracted data into an electronic data collection spreadsheet. The residents extracted the dates of admission and the date of discharge or death from the medical record and whether the patients had SIRS, sepsis, hypoxia, hypertension, kidney injury, liver failure, hypoglycemia, hyperglycemia (glucose >200), hyponatremia, hypernatremia, hypercarbia, or postictal state at the time of admission. The Mdcalc.com calculators, which use the criteria from ACCP/SSCM, were used to determine the sepsis or SIRS (https://www.mdcalc.com). Imaging studies were not routinely gathered for admission for COVID-19. Thus, imaging results were too limited to be included in the descriptives or the analysis.

3.1. Definition of variables

Age was grouped by decade (e.g. 20–29, 30–39, etc.). Hypoxia was defined as blood oxygen level <92; hypertension was defined as systolic >130, diastolic >80; liver failure was defined as AST >45, ALT >46; hypoglycemia was defined as glucose <70; hyperglycemia was defined as glucose >200; hyponatremia was defined as <135; hypernatremia was defined as >146; and hypercarbia was defined PaCO2 above 45 mm Hg on Arterial Blood Gas readings. All laboratory measurements were captured at the time of admission so intensive care unit (ICU) stay would not affect elevation of the liver function tests (LFTs).

3.2. Statistical analysis

We used SAS and Microsoft Excel to generate summary tables. To analyze length of hospital stay or death, we fitted a competing risk proportional hazards model for time to discharge or death using the Proc Phreg [16] of the SAS® software, Version 9.4 for Windows. (Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). The competing risks model allows the analysis of hospital stay, considering that censoring due to death is not random. For each model, we determined baseline demographic and clinical variables predictive of the outcomes and generated adjusted models.

4. Results

Out of 367 patients, 95 (26%) had AMS as a main or one of the presenting symptoms. Table 1 shows the demographic characteristics and comorbidities. Our sample has a higher representation of African Americans (53%) and a lower percentage of white (27%) than the US average and a high frequency of comorbidities, such as obesity (average BMI 29.1), hypertension (53%), and diabetes (30%).

Table 2 shows the most common neurological chief complaints. Similar to our previous report [9], AMS was the most frequent neurological chief complaint. At their admission, out of 95 patients with AMS, 83 (88%) had organ failure or one of the systemic problems that could have caused AMS. However, a similar proportion (86%) of patients without AMS had one or more of these same problems. Sepsis was more common in patients with AMS (44%) compared to patients with no AMS (36%). Hypernatremia was more common in the AMS group than in the group without AMS (18% vs. 5%), while hyponatremia occurred less frequently (2% vs. 18%). Hypercarbia was rare, but occurred more frequently in those with AMS (5% vs. 1%), while hypoxia was common and occurred less frequently in those with AMS (33% AMS vs. 38%).

4.1. Predictors of hospital stay

Table 3 shows the results for the competing risks model for length of hospital stay. In this part of the analysis, discharge is the event of interest, and thus higher hazard ratios indicate a shorter hospital stay. There were very few Asians and Hawaiians, so we combined these race categories under the "other" category with those who had no race reported. Too few patients had a glucose< 70, SIRS, hypercarbia, or a postictal state to analyze these variables.

Age, race, and ethnicity were the main demographic predictors. African Americans had shorter hospital stay [HR1.3(1.0,1.7),p = 0.02] than Caucasians. Hispanics also had shorter hospital stay than non-hispanics [HR1.6(1.2,2.1), p = 0.001]. Former and current smokers had similar times to discharge than nonsmokers, but the group with unknown smoking status had significantly longer hospital stays [HR0.6 (0.4,0.8), p < 0.001]. Hypoxia, liver failure, hypernatremia, and kidney failure were also predictors of prolonged hospital stay.

Table 4 shows the results of the final multivariate model built after sequential stepwise selection. In this multivariate model, people with AMS at baseline had a more extended hospital stay [HR0.7(0.6,0.9),p <

Table 1
Baseline demographics.

	Total Sample	Without AMS or lethargy	AMS or Lethargy	AMS only	Lethargy only	AMS and Lethargy
N	367	247	120	95	25	32
	Mean±SD					
Age	59 ± 18	56 ± 17	65 ± 19	66 ± 20	61 ± 17	67 ± 13
BMI	26 ± 7	26 ± 8	24 ± 6	28 ± 7	24 ± 6	24 ± 6
	N (%)					
Sex - Male	205 (56%)	138 (56%)	67 (56%)	52 (55%)	15 (60%)	16 (50%)
Race						
Asian	3 (1%)	3 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hawaiian	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AA	193 (53%)	127 (51%)	66 (55%)	53 (56%)	13 (52%)	20 (63%)
White	98 (27%)	55 (22%)	43 (36%)	33 (35%)	10 (40%)	9 (28%)
Not Reported	72 (20%)	61 (25%)	11 (9%)	9 (9%)	2 (8%)	3 (9%)
Ethnicity - Hispanic	73 (20%)	62 (25%)	11 (9%)	7 (7%)	4 (16%)	3 (9%)
Smoking						
Never	178 (49%)	125 (51%)	5 (44%)	40 (42%)	13 (52%)	10 (31%)
Former	45 (12%)	28 (11%)	17 (14%)	12 (13%)	5 (20%)	5 (16%)
Current	79 (22%)	60 (24%)	19 (16%)	16 (17%)	3 (12%)	4 (13%)
Unknown	65 (18%)	34 (14%)	31 (26%)	27 (28%)	4 (16%)	13 (41%)
Comorbid medical conditions						
Asthma/COPD	47 (13%)	32 (13%)	15 (13%)	12 (13%)	3 (12%)	3 (9%)
Hypertension	204 (56%)	140 (57%)	64 (53%)	50 (53%)	14 (56%)	20 (63%)
Diabetes	110 (30%)	70 (28%)	40 (33%)	31 (33%)	9 (36%)	16 (50%)
Epilepsy	11 (3%)	3 (1%)	8 (7%)	8 (8%)	2 (8%)	4 (13%)
CVA	33 (9%)	20 (8%)	13 (11%)	11 (12%)	0 (0%)	4 (13%)
Complications at presentation						21 (66%)
Sepsis	139 (38%)	84 (34%)	55 (46%)	42 (44%)	13 (52%)	0 (0%)
SIRS	4 (1%)	4 (2%)	0 (0%)	0 (0%)	0 (0%)	13 (41%)
Hypoxia	133 (36%)	89 (36%)	44 (37%)	31 (33%)	13 (52%)	7 (22%)
Hypertension	115 (31%)	84 (34%)	31 (26%)	27 (28%)	4 (16%)	6 (19%)
Liver Failure	110 (30%)	68 (28%)	42 (35%)	28 (29%)	14 (56%)	9 (28%)
Hyperglycemia	63 (17%)	42 (17%)	21 (18%)	17 (18%)	4 (16%)	1 (3%)
Hypoglycemia	3 (1%)	1 (0%)	2 (2%)	2 (2%)	0 (0%)	2 (6%)
Hyponatremia	55 (15%)	43 (17%)	12 (10%)	5 (5%)	7 (28%)	8 (25%)
Hypernatremia	22 (6%)	3 (1%)	19 (16%)	17 (18%)	2 (8%)	28 (88%)
Hypercarbia	8 (2%)	2 (1%)	6 (5%)	5 (5%)	1 (4%)	4 (13%)
Post Ictal	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AKI	130 (35%)	77 (31%)	53 (44%)	43 (45%)	10 (40%)	20 (63%)
Transfer	54 (15%)	34(14%)	20 (17%)	12 (13%)	8 (32%)	3 (9%)

AA: African American; CVA: cerebrovascular accident; SIRS: Systemic inflammatory response syndrome; AKI: acute kidney injury.

Table 2
Neurological chief complaint.

Neurological Chief Complaint	
Headache	34 (9%)
Seizure	7 (2%)
Syncope	21 (6%)
Lethargy	57 (16%)
Altered Mental Status	95 (26%)

0.02] after adjusting for the demographic characteristics and clinical predictors. Hypoxia, liver failure, and acute kidney injury were also predictors of hospital stay.

4.2. Predictors of death

Tables 5 and 6 show the univariate and the final multivariate model for death. AMS at baseline predicted death in the univariate test, but not after adjusting for demographics and clinical variables. Hypoxia and hyperglycemia at baseline were the strongest predictors of death.

5. Discussion

The aim of this follow up study was to replicate the analyses we used in a previous study using an expanded number of subjects. To address a serious limitation in our first sample analysis, we also controlled for potential confounders which were unavailable during our previous analysis. In this sample, we still had a high number of African Americans (53%) however, it was a significantly lower portion as compared to our first study (80%). Interestingly, AMS remained the most common neurological chief complaint at presentation. In our first study, we found that AMS was a predictor of prolonged hospital stay and death, however, after controlling for covariables in this second study, AMS no longer predicted death. AMS did remain predictive of prolonged hospital stay. Lethargy did not predict death after accounting for the metabolic and systemic confounders. Although there is significant overlap in what clinicians consider AMS and lethargy, only AMS predicted prolonged hospital stay after accounting for the metabolic disarrangements and organ system failure. A possible explanation is that the patients that are altered but not lethargic may have direct brain dysfunction due to the virus instead of indirect brain dysfunction due to the systemic complications of the virus. This may also explain why AMS predicts length of stay, but not death. If AMS indicates a direct relationship between the virus and the brain, it may complicate recovery but not be associated with the systemic issues found among deaths from the COVID-19 virus.

We noted that persons with “no documented smoking status” had a significantly longer hospital stay than those with known smoking status, including current or previous smokers and nonsmokers. While there could be a more complex reason for this finding, we hypothesize that patients who had no documented smoking status could have presented with more severe disease state, preventing the capture of smoking status.

6. Limitations

This retrospective analysis only included people who presented to the emergency room, had to be admitted, and tested positive for COVID-

Table 3
Univariate hazard ratios for prediction of length of stay.

Univariate Hazard Ratios Time to Discharge			
Parameter	Parameter Description	Pr > ChiSq	HR (95%CI)
Age (10 years)		<.0001	0.8 (0.8,0.9)
Sex	Female	0.8	1.0 (0.8,1.3)
Race[a]	AA	0.02	1.3 (1.0,1.7)
	Other[b]	<.0001	2.1 (1.6,2.9)
Ethnicity	Hispanic	0.001	1.6 (1.2,2.1)
Smoking	Current	0.5	0.9 (0.7,1.2)
	Former	1.0	1.0 (0.7,1.4)
	Unknown	0.0001	0.6 (0.4,0.8)
CVA	Yes	0.9	1.0 (0.7,1.4)
HTN	Yes	0.4	0.9 (0.7,1.1)
DM	Yes	0.4	0.9 (0.7,1.1)
Epilepsy	Yes	0.05	0.6 (0.3,1.0)
Asthma_COPD	Yes	0.7	0.9 (0.6,1.3)
BMI		0.8	1.0 (1.0,1.0)
CC AMS	Yes	<.0001	0.6 (0.5,0.7)
CC Headache	Yes	0.2	1.3 (0.9,1.8)
CC Syncope	Yes	0.7	0.9 (0.6,1.5)
CC Lethargy	Yes	0.001	0.6 (0.4,0.8)
Baseline Sepsis Criteria	Yes	0.02	0.8 (0.6,1.0)
Baseline Hypoxia	Yes	<.0001	0.6 (0.5,0.7)
Baseline HTN	Yes	0.4	1.1 (0.9,1.4)
Baseline Liver Failure	Yes	0.02	0.8 (0.6,1.0)
Baseline Hyperglycemia	Yes	0.06	0.7 (0.5,1.0)
Baseline Hyponatremia	Yes	0.3	0.8 (0.6,1.2)
Baseline Hypernatremia	Yes	<.0001	0.4 (0.2,0.6)
Baseline AKI	Yes	<.0001	0.6 (0.5,0.8)

CVA: cerebrovascular accident; HTN: hypertension, DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; BMI: body mass index: CC: chief complaint, AMS: altered mental status; B: baseline; AKI: acute kidney injury.
[a] To calculate race HR AA and "Other" were compared to Caucasians.
[b] Other refers to individuals where race was not reported, Asians, and Hawaians.

Table 4
Multivariate hazard ratios for prediction of length of stay.

Multivariate Hazard Ratios Discharge			
Parameter		Pr > ChiSq	HR (95%CI)
Age 10y		<.0001	0.9(0.8,0.9)
Sex	Female	0.4	0.9(0.7,1.1)
Race[a]	AA	0.01	1.5(1.1,2.0)
	Other[b]	<.0001	2.2(1.5,3.1)
Ethnicity	Hispanic	0.8	1.0(0.7,1.5)
Smoking	Current	0.5	0.9(0.6,1.2)
	Former	0.7	1.1(0.8,1.5)
	Unknown	0.03	0.7(0.5,1.0)
CC AMS		0.005	0.7(0.6,1.0)
B_Hypoxia		<.0001	0.9(0.7,1.1)
B_LiverFailure		0.03	0.6(0.5,0.7)
B_AKI		0.01	0.8(0.6,1.0)

CC: chief complaint; AKI: acute kidney injury.
[a] To calculate race HR AA and "Other" were compared to Caucasians.
[b] Other refers to individuals Asians, Hawaians and individualse whose race was not reported.

19. The patients were already "worse" than other people who tested positive but had mild symptoms or were asymptomatic. Thus, results cannot extend to patients discharged from the emergency room or seen as outpatients. Our sample had a high proportion of African Americans, persons with hypertension, and persons with diabetes. The results of our study may not generalize to populations with more diverse racial or ethnic backgrounds or with fewer comorbidities.

Our analysis focused on the findings at admission because capturing AMS and comorbidities during every day of the hospital stay is challenging. It would be attractive to complete a day-to-day analysis of the

Table 5
Univariate hazard ratios for prediction of death.

Univariate Hazard Ratios Death			
Parameter	Parameter Description	Pr > ChiSq	HR (95%CI)
Age (10years)		<.0001	1.4(1.2,1.6)
Sex	Female	0.8	0.9(0.6,1.6)
Race[a]	AA	0.8	0.9(0.5,1.6)
	Other[b]	0.02	0.3(0.1,0.9)
Ethnicity	Hispanic	0.1	0.5(0.2,1.1)
Smoking	Current	0.4	1.4(0.7,2.7)
	Former	0.5	0.7(0.2,2.0)
	Unknown	0.01	2.3(1.2,4.4)
CVA	Yes	0.6	0.8(0.3,2.1)
HTN	Yes	0.6	1.2(0.7,2.0)
DM	Yes	0.3	1.3(0.8,2.3)
Epilepsy	Yes	0.2	2.1(0.6,6.8)
Asthma_COPD	Yes	0.2	1.5(0.8,3.1)
BMI		1.0	1.0(1.0,1.0)
CC AMS	Yes	0.002	2.4(1.4,4.0)
CC Headache	Yes	0.3	0.5(0.2,1.7)
CC Syncope	Yes	0.7	1.2(0.5,3.3)
CC Lethargy	Yes	0.001	2.7(1.5,4.7)
Baseline Sepsis Criteria	Yes	0.1	1.6(0.9,2.7)
Baseline Hypoxia	Yes	<.0001	2.9(1.7,5.0)
Baseline HTN	Yes	0.1	0.6(0.3,1.2)
Baseline Liver Failure	Yes	0.1	1.6(0.9,2.7)
Baseline Hyperglycemia	Yes	0.001	2.6(1.5,4.5)
Baseline Hyponatremia	Yes	0.3	1.4(0.7,2.8)
Baseline Hypernatremia	Yes	<.0001	4.0(2.1,7.6)
Baseline AKI	Yes	0.0007	2.5(1.5,4.2)

CVA: cerebrovascular accident; HTN: hypertension, DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; BMI: body mass index: CC: chief complaint, AMS: altered mental status; B: baseline; AKI: acute kidney injury.
[a] To calculate race HR AA and "Other" were compared to Caucasians.
[b] Other refers to individuals Asians, Hawaians and individualse whose race was not reported.

Table 6
Multivariate hazard ratios for prediction of death.

Multivariate Hazard Ratios Death			
Parameter	Parameter Description	Pr > ChiSq	HR (95%CI)
Age (10 years)		0.01	1.3(1.1,1.6)
Sex	Female	0.5	0.8(0.5,1.4)
Race[a]	AA	0.8	1.0(0.6,1.9)
	Other[b]	0.01	0.3(0.1,0.8)
Ethnicity	Hispanic	0.5	0.3(0.1,0.8)
Smoking	Current	0.6	1.2(0.6,2.4)
	Former	0.3	0.6(0.2,1.6)
	Unknown	0.3	1.4(0.7,2.8)
CC AMS		0.1	1.6(0.8,3.0)
Baseline Hypoxia		0.0008	2.7(1.5,4.7)
Baseline Hyperglycemia		0.0003	3.0(1.6,5.3)

CC: chief complaint.
[a] To calculate race HR AA and "Other" were compared to Caucasians.
[b] Other refers to individuals where race was not reported, Asians, and Hawaians.

mental status and the metabolic complications and use these as time-dependent covariates to more accurately predict the time to discharge or death, but compiling these data was beyond our manpower resources. We did not analyze other important outcomes, such as disability at discharge because, unfortunately it is not systematically recorded.

Altered Mental Status is a nonspecific term. Ideally, we should use more specific terms, e.g delirium, or agitation. Given the nature of the study, we depended on the documentation available and this limitation was unavoidable. It is also debatable whether lethargy is AMS or not, which prompted us to report this complication in combination with AMS and separately.

7. Conclusion

Altered mental status is an independent predictor of prolonged hospital stay, but not death. Further studies are needed to evaluate the causes of AMS in patients with COVID-19.

CRediT authorship contribution statement

David Chachkhiani MD* Conceptualization, Methodology, Investigation, Writing - original draft visualization. Marine Isakadze MD Conceptualization, Methodology, Investigation. Nicole R. Villemarette-Pittman PhD Methodology, Writing - review & editing, Visualization, Supervision, Project administration. Deidre J. Devier PhD Methodology, Data curation, Writing - review & editing, Supervision. Jesus F. Lovera MD, MsPH* Methodology, Formal analysis, Data curation, Supervision.

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