Prevalence and outcome of delirium among acute general medical inpatients in Cape Town, South Africa

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Background. Delirium is a common, serious, underdiagnosed condition in medical and surgical inpatients with acute conditions. It is associated with increased risk of mortality and morbidity. Data of geriatric cohorts are largely limited to developed countries.
Objectives. To describe prevalence, risk factors and outcomes of delirium among general medical patients admitted to two hospitals in Cape Town, South Africa.
Methods. This was a prospective cohort study of patients with acute conditions admitted to a general medical inpatient service in secondary- and tertiary-level public hospitals in the Metro West area of Cape Town. Patients ≥18 years of age were recruited daily from all acute medical admissions. Patients were excluded if they were aphasic or their Glasgow coma scale was <8/15. Delirium was diagnosed using the validated confusion assessment method (CAM) tool and performed by trained neuropsychologists. Demographic data were collected by a clinical team and short- and long-term mortality data were obtained using linkage analysis of hospitalised patients and routinely collected provincial death certification records.
Results. The median age of inpatients was 51 (interquartile range 36 - 65) years, 29% were HIV-infected and the overall prevalence of delirium was 12.3%. Multivariate predictors of delirium included the presence of an indwelling urinary catheter (odds ratio (OR) 4.47; confidence interval (CI) 2.43 - 8.23), admission with a central nervous system disease (OR 4.34; CI 2.79 - 7.90), pre-existing cognitive impairment (OR 3.02; CI 1.22 - 7.43) and immobility (OR 1.88; CI 1.01 - 3.51). HIV infection was not associated with increased risk of delirium. Delirium was associated with an increased risk of inhospital (delirium v. no delirium: 29% v. 12%; $p<0.01$) and 12-month (30% v. 20%; $p<0.01$) mortality, as well as increased length of hospital stay (7 days v. 5 days; $p<0.01$).
Conclusions. In this cohort of medical inpatients (relatively young and with a high HIV prevalence) 1 of 8 (12.3%) patients was delirious. Delirium was associated with adverse outcomes. Delirium risk factors in this young cohort were similar to those in geriatric cohorts in developed countries, and neither HIV nor opportunistic infections increased risk.

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Delirium is a disorder of cerebral dysfunction, frequently encountered in acutely ill patients, and especially among elderly patients. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) considers the following features diagnostic of delirium: 'disturbance in attention and awareness; disturbance in cognition and higher functioning; a short onset and fluctuating course; a clear precipitant must be identified, whether an acute illness, drug intoxication or withdrawal; with no other neurocognitive disorder identified to account for presentation'.[1,2] Many precipitating factors for delirium have been described, including neurological conditions, local and systemic sepsis, metabolic derangements, pain and iatrogenic interventions (e.g. surgical procedures and catheterisation). Premorbid cognitive dysfunction is an important risk factor.[3-7]

Delirium is common among medical inpatients, with rates of 11 - 42%.[3,7-9] A higher prevalence is found among geriatric populations[10,11] and in intensive care units.[12] There are very few studies of delirium in unselected patients, particularly in low- and middle-income countries (LMICs) undergoing epidemiological transitions, where there may be a greater burden of infectious disease, including HIV, and relatively younger age of onset of non-communicable diseases (NCDs). A 2015 systematic review on delirium in sub-Saharan Africa described the scarcity of literature, with reported cohorts being very small; there were also technical difficulties with regard to terminology, diagnostic criteria and reporting of these studies. In contrast to high-income countries, patients were younger and more likely to have infectious precipitants.[13]

Delirium has been associated with adverse outcomes, including longer hospital stay, higher rates of readmission, and increased short- and long-term mortality. Consequently, there are greater individual, social and monetary implications associated with delirium.[3,8,14-22] Early management of the condition has been associated with shorter delirium duration and hospital length of stay, as well as improved functional outcomes.[23,24] Recognition of risk factors is an important aid in the prevention of incident delirium. Measures to improve assessment and management may have benefits in terms of improving healthcare for inpatients,[25,26] and incident delirium is used as part of quality assurance in many hospitals. Nevertheless, delirium is often undiagnosed in busy clinical settings.[27]

We therefore aimed to describe the prevalence, risk factors and short- and long-term outcomes for patients admitted with delirium to

the acute medical service of two public hospitals in Cape Town, South Africa (SA). Such knowledge would provide much-needed data from an LMIC with a high background prevalence of HIV and NCDs.

Methods

Study design and setting

This was a prospective cohort study of patients admitted with acute medical conditions from 11 November 2013 to 7 April 2014 at two university-affiliated hospitals serving the Metro West area of Cape Town. Groote Schuur Hospital has ~120 acute-care medical beds and serves as a tertiary referral centre; the majority of patients with acute conditions are, however, admitted from the emergency department as 'walk-ins'– a minority are referred from other hospitals in the area for more specialised care. Victoria Hospital, a district-level hospital, has 80 acute-care medical beds. Patients with acute conditions are largely admitted to undifferentiated general medical wards under a single specialist consultant-run team.

Participants

In this prospective observational study up to 10 randomly selected patients of the daily weekday acute medical intake were reviewed for study inclusion by a team of 2 trained clinicians at each hospital during consecutive 3-month periods (November - January in the first hospital and February - April in the second hospital). All patients aged ≥18 years and admitted for the first time during this period as acute, non-elective patients to the general medical wards could be included. Patients refusing consent, those not available in the ward on the day of sampling, those who died before the day of sampling and those with aphasia or a Glasgow coma scale (GCS) <12/15 were excluded.

Delirium assessment

Within 24 hours of admission, a study physician reviewed the patients' charts and obtained data pertaining to their primary diagnosis, clinical background, admission medication, level of education and demographic characteristics. An independent study neuropsychologist then assessed the patient for delirium, using the confusion assessment method (CAM) performed during a 20 - 30-minute interview, consisting of formal cognitive testing, and also assessed delirium in conjunction with the physician according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria. For all testing tools, the language barrier was noted; a ward-based translator was engaged when possible, so that testing was performed in the patient's first language.

Demographic data, presenting complaint, primary admission diagnosis and potential associates of delirium available from routine assessment were obtained from the patient, relatives and referring physician. Data on pre-admission functional status (in the form of the Barthel index of activities of daily living), chronic medications at the time of admission, comorbidities and blood results were collected. For analysis, we dichotomised laboratory values to clinically valuable 'normal' or 'abnormal' results. For serum creatinine, a simple round number cut-off of 100 μmol/L was used, signifying renal impairment in most people. For serum urea concentration, the upper limit of normal (7 mmol/L) was used. Comorbidities were defined as any pre-existing medical or surgical condition. Data on HIV status, pre-existing cognitive impairment, depression, visual/hearing impairment and drug/alcohol abuse were also recorded, where available. The clinician recorded whether the patient was suffering from a 'terminal illness', defined as being in the last year of their life. Information on mobility was obtained; immobility was defined as a patient not being able to walk independently for >50 metres. Pre-existing cognitive impairment was defined as a patient history suggesting cognitive decline before admission. Depression was defined as a patient history suggesting depressive symptoms prior to the current admission. For analysis and reporting, diagnoses were categorised as communicable and non-communicable and classified into major and common groups, using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code grouping.

Outcomes

Length of hospital stay, inpatient mortality and 12-month mortality data were obtained from patient folders, the hospital electronic patient management system and the Western Cape Government death registry, which links a unique patient identification number with national death certificate records and system-wide electronic records. Patients for whom no death record was available, were deemed 'alive'.

Statistical methods

All data were analysed using Stata 14 (StataCorp., USA). Categorical variables were summarised as frequencies and percentages and continuous variables as medians with interquartile ranges (IQRs) if non-parametric. Sociodemographic and clinical characteristics and outcomes were assessed for differences between those with delirium and those without. Associations between categorical variables were analysed using the χ^2 test and Fisher's exact test, as appropriate. The Wilcoxon rank-sum or Kruskal-Wallis test was used to compare continuous variables between two and three groups, respectively. Significance was reported as $p<0.01$, with no correction for multiple comparisons.

Univariable and multivariable logistic regression analyses were performed to identify risk factors for delirium. Risk factors that were strongly associated with delirium in the univariable analysis ($p<0.05$) were retained in a multivariable logistic regression model. Terminal illness was removed owing to the low number of cases and its negative impact on model fit. Model diagnostics were performed and the Hosmer-Lemeshow test was used to determine goodness of fit. Kaplan-Meier survival curves for delirious v. non-delirious patients were compared using the log-rank test. A p-value of <0.05 was regarded as statistically significant.

Ethical approval

No patient consent was required. Ethical approval was obtained from the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town (ref. no. HREC 532/2017).

Results

A total of 1 027 patients from all admissions were screened for inclusion in the study, of whom 138 were excluded for the following reasons: 43 had a depressed level of consciousness with a GCS <12/15; 35 were not admitted directly into a general medical ward or were transferred to another discipline; 47 were aphasic; 2 were deaf and could not be tested effectively; and 8 died before testing. A further 84 patients were not included in the final analysis: in the case of 49, their data were missing, and 35 refused consent. A total of 808 participants were included in the analysis. The number of patients enrolled per day varied as a percentage of the total admissions owing to the carrying size of admissions; the total also varied because of exclusions.

Patient demographics

The median (IQR) age was 51 (36 - 65) years; only 17.7% of participants were >70 years of age. The gender distribution was equal, with 52% females. The most frequent admission diagnoses

were NCDs of the cardiovascular (*n*=170), central nervous (*n*=86) and respiratory (*n*=76) systems, followed by pulmonary tuberculosis (*n*=60) and non-tuberculous respiratory infections (*n*=58). The majority of patients received chronic medication before admission (*n*=581; 72%), and 29% were using >6 chronic medications.

Delirium prevalence, using either the DSM-IV or CAM reference method, was only discrepant in 11 cases; therefore, the results are presented using CAM. The overall prevalence of delirium was 12.3%. Patients with delirium were older (median age 55 years v. 51 years; *p*=0.03), were more likely to be frail (19% had a pre-admission Barthel score of <50) and were more likely to have pre-existing predisposing factors, such as cognitive impairment (14%), terminal illness (9%) or a urinary catheter at home (30%). The prevalence of infection as a primary admission diagnosis was similar in the delirium and non-delirium cohorts. Patients with delirium were more likely to have been admitted primarily because of a neurological disease (Table 1).

Twenty-nine percent of our cohort were confirmed as being HIV-infected, with a median (IQR) CD4+ count of 150 (66 - 132) cells/μL. The median (IQR) age of HIV-infected patients was lower than that of HIV-uninfected patients (36 (30 - 44) v. 52 (38 - 65) years), there was a greater female predominance (*n*=110; 60%) and a different profile of primary admission diagnoses, with a predominance of communicable diseases. In the HIV-infected cohort, the median (IQR) CD4+ count was not significantly lower in patients with delirium than in those without (113 (60 - 282) v. 155 (66 - 313) cells/μL; *p*=0.73). In HIV-infected patients the prevalence of delirium was 13% and did not differ significantly from that in HIV-uninfected patients (13% v. 11%; *p*=0.8). Supplementary Table 1 (http://www.samj.org.za/public/sup/14363.doc) reports on patients by HIV status.

Predictors of delirium

Table 2 shows univariate and multivariate logistic regression analysis of factors associated with delirium. After adjustment for covariates, the multivariate predictors of delirium were the presence of an indwelling urinary catheter (OR 4.47; CI 2.43 - 8.23), admission with a central nervous system disease (OR 4.34; CI 2.79 - 7.90), pre-existing cognitive impairment (OR 3.02; CI 1.22 - 7.43) and immobility (OR 1.88; CI 1.01 - 3.51). Neither of the following were statistically significant in predicting delirium in this cohort: HIV status, infection as the admission diagnosis, age, number of comorbidities, number of chronic medications or other laboratory abnormalities. The goodness-of-fit test of the logistic regression equation showed a high significance of the model, with χ^2 80.41.

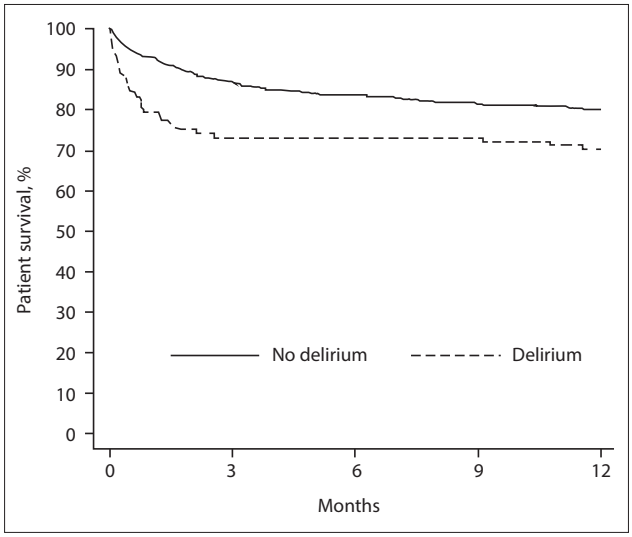

Fig. 1. Kaplan-Meier survival curves for delirious compared with non-delirious patients (p=0.008).

Outcomes

Patients with delirium showed a greater risk for adverse outcomes than those without delirium (Table 3). The median length of hospital stay was longer (7 days v. 5 days; *p*<0.01), and inpatient mortality (29% v. 12%; *p*<0.01) and 12-month mortality (30% v. 20%; *p*<0.01) were greater. Fig. 1 shows Kaplan-Meier survival curves for patients with and without delirium. Survival was significantly better without delirium (χ^2 7.492; *p*=0.0062), with the majority of differences associated with greater early mortality in patients with delirium.

Discussion

Delirium was common in this young cohort, diagnosed in 1 of 8 patients admitted with acute conditions to general medical wards in two public-sector hospitals in Cape Town. The predisposing factors for delirium were similar to those reported for geriatric cohorts, and included premorbid cognitive impairment, a central nervous system disease, presence of an indwelling urinary catheter and immobility. Despite the high prevalence of HIV, HIV status and HIV-associated opportunistic infections were not associated with an increased risk of delirium. Delirium at admission was associated with increased mortality, predominantly early mortality, although the difference was evident up to 12 months after discharge.

In this study, the overall rate of delirium was 12.3%, i.e. within the range reported in the international literature.[3,7-9] Importantly though, the composition of this cohort was distinct from that in the majority of published reports, and more generalisable to other LMICs. A 2006 systematic review by Siddiqi *et al.*[8] reported on the occurrence and outcome of delirium in medical inpatients. In this review, the mean age was >70 years in 31 of 33 cohorts, and HIV infection rates were not reported in any of the included cohorts. In contrast, our median age was 50 years, and our study population was unique by virtue of the higher incidence of HIV and HIV-related illnesses.[28,29] Nonetheless, in our cohort, HIV status was not associated with increased risk for delirium. This is in contrast to a systematic review by Paddick *et al.*,[30] who consistently found HIV positivity to have a higher association with delirium.

Study strengths and limitations

The study has several strengths. It was a large prospective study among acute general medical admissions in an LMIC. SA's dual burden of communicable disease and NCD makes it an important setting in which to consider delirium prevalence, risk factors and outcomes.[31] Reference testing was robust – using well-validated tools and performed by experienced neuropsychologists. Limitations included that only a selection of patients were sampled, with the number enrolled per day of the week varying as a total and as a percentage of all admissions, which may have led to unanticipated confounding. The national death certification records were not accessed – patients who moved province and died would therefore not have been identified as such. We lacked a very detailed assessment of comorbidities, such as the Charlson index or comorbidity-polypharmacy score. This may have allowed a better understanding of the interplay between premorbid functioning, predisposing factors, precipitants and development of delirium. We also did not capture data on readmission rates and functional status after discharge. Such information might have further demonstrated the range of long-term sequelae in patients with delirium. Furthermore,

Table 1. Characteristics for the overall cohort, stratified by absence/presence of delirium

Characteristics	Overall, *N*=808	Without delirium, *n*=709	With delirium, *n*=99
Age (years), median (IQR)	51 (36 - 65)	50.52 (35 - 65)	54.93 (40 - 70)
Females, *n* (%)	418 (52)	372 (52)	46 (46)
Education, years (*n*=765)			
Education, median (IQR)	9 (7 - 11)	9 (7 - 11)	9 (7 - 11)
<7, *n* (%)	167 (22)	150 (22)	17 (23)
Communication barriers, *n* (%)			
Deafness	12 (1)	8 (1)	4 (4)
Dysphonia	6 (1)	6 (1)	0 (0)
Language barrier	51 (6)	41 (6)	10 (10)
Visual impairment	18 (2)	12 (2)	6 (6)
Dysarthria	36 (4)	27 (4)	9 (9)
Risk factors for delirium, *n* (%)†			
Age >70 years	143 (18)	118 (17)	25 (25)
Cognitive impairment	39 (5)	26 (4)	13 (14)*
Terminal illness	23 (3)	14 (2)	9 (9)*
Depression	60 (7)	53 (7)	7 (7)
Indwelling urinary catheter	79 (10)	50 (7)	29 (30)*
Immobility	108 (14)	83 (12)	25 (27)*
Comorbidities, median (IQR)	2 (1 - 3)	2 (1 - 3)	3 (2 - 4)*
>3 comorbidities	355 (44)	300 (42)	55 (56)
Barthel index <50	36 (5)	18 (3)	18 (19)*
Diagnostic category – 4 most frequent categories, *n* (%)			
Communicable diseases			
Pulmonary TB	60 (7)	53 (8)	7 (7)
Respiratory infections	58 (7)	48 (7)	10 (10)
HIV-related infections	24 (3)	20 (3)	4 (4)
GIT infections	23 (3)	20 (3)	3 (3)
Non-communicable diseases			
Cardiovascular	170 (21)	160 (23)	10 (10)*
CNS	86 (11)	63 (9)	23 (23)*
Respiratory	76 (9)	75 (11)	1 (1)*
Renal	48 (6)	41 (6)	7 (7)
HIV status			
HIV-positive, *n* (%)	183 (29)	159 (29)	24 (32)
CD4+ (cells/μL), median (IQR)	150 (66 - 312)	155 (66 - 313)	113 (60 - 282)
Chronic medications, *n* (%)			
None	227 (28)	198 (28)	29 (29)
1 - 5 drugs	349 (43)	307 (43)	42 (42)
≥6 drugs	232 (29)	204 (29)	28 (28)
Admission investigations, median (IQR)			
Sodium, mmol/L	139 (136 - 142)	139 (136 - 142)	140 (136 - 144)
Potassium, mmol/L	4.63 (4.16 - 5.20)	4.63 (4.20 - 5.18)	4.59 (4.03 - 5.21)
Urea, mmol/L	7.3 (4.9 - 9.3)	7.2 (4.8 - 9.1)	8.3 (6.0 - 15.5)*
Creatinine, μmol/L	85.5 (68.0 - 99.0)	85.0 (67.0 - 98.0)	91.0 (74.0 - 195.0)*
Haemoglobin, g/dL	11.90 (9.70 - 14.10)	11.90 (9.60 - 14.20)	11.20 (9.70 - 13.70)
White cell count, /μL	9.13 (7.40 - 10.07)	9.18 (7.44 - 9.98)	9.03 (7.15 - 11.70)

IQR = interquartile range; TB = tuberculosis; GIT = gastrointestinal; CNS = central nervous system.
*$p<0.01$; *p*-values for differences between those with and without delirium were calculated with Fisher's exact test, χ^2 test or Wilcoxon test, as appropriate. No correction for multiple comparisons was made.
†Unless otherwise indicated.

Western Cape Province has a lower HIV prevalence than most other provinces, limiting the total proportion of HIV-infected patients in this cohort.

Conclusions

Our study informs acute general medical practice in LMICs, although repeating similar work across the country and in other countries would strengthen its findings. Delirium is common in this setting, an important predictor of morbidity and mortality. 'Brain failure' should be awarded similar status as heart failure, respiratory failure and renal failure. Delirium is under-recognised. There should be greater emphasis on the clinical training of doctors, nurses, carers and members of allied health services to effectively screen for delirium and ameliorate risk factors. As an important quality indicator, efforts

Table 2. Univariate and multivariate analysis of predictors of delirium

Variable	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value*
Male gender	1.27 (0.83 - 1.94)	0.264	-	-
Risk factors				
Age >70 years	1.69 (1.03 - 2.77)	0.037	1.16 (0.62 - 2.28)	0.635
HIV-infected	1.19 (0.71 - 2.00)	0.514	-	-
Visual impairment	2.3 (0.73 - 7.21)	0.18	-	-
Depression	0.97 (0.42 - 2.2)	0.94	-	-
Pre-existing cognitive impairment	4.16 (2.06 - 8.41)	<0.01**	3.02 (1.22 - 7.43)	0.016
Immobility	2.80 (1.67 - 2.68)	<0.01**	1.88 (1.01 - 3.51)	0.047
Terminal illness	5.07 (2.13 - 12.06)	<0.01**	-	-
Indwelling catheter	4.54 (2.61 - 7.93)	<0.01**	4.47 (2.43 - 8.23)	<0.001
Admission diagnosis – 4 most frequent categories				
Communicable diseases				
Pulmonary TB	0.94 (0.42 - 2.13)	0.886	-	-
Respiratory infections	1.55 (0.76 - 3.17)	0.232	-	-
HIV-related infections	1.45 (0.49 - 4.33)	0.505	-	-
GIT infections	1.08 (0.31 - 3.69)	0.907	-	-
Non-communicable diseases				
Cardiovascular	0.39 (0.20 - 0.76)	<0.01	-	-
Central nervous system	3.10 (1.82 - 5.29)	<0.01**	4.34 (2.38 - 7.90)	<0.001
Respiratory	0.09 (0.12 - 0.63)	0.016	-	-
Renal	1.24 (0.54 - 2.84)	0.612	-	-
Admission investigations				
Serum sodium <135 mmol/L	1.05 (0.60 - 1.86)	0.863	-	-
Serum sodium >145 mmol/L	2.54 (1.29 - 5.00)	<0.01**	1.72 (0.77 - 3.83)	0.187
Serum potassium <3.5 mmol/L	0.86 (0.33 - 2.26)	0.765	-	-
Serum potassium >5.3 mmol/L	0.79 (0.44 - 1.43)	0.441	-	-
Serum creatinine >100 µmol/L	2.10 (1.33 - 3.32)	<0.01**	1.67 (0.98 - 2.89)	0.062
Serum urea >7 mmol/L	1.45 (0.94 - 2.25)	0.095	-	-
Haemoglobin <12.5 g/dL	1.44 (0.93 - 2.23)	0.103	-	-
White cell count >12 000/µL	1.28 (0.77 - 0.12)	0.336	-	-
White cell count <4 000/µL	0.66 (0.08 - 5.17)	0.691	-	-
>6 admission drugs	0.98 (0.61 - 1.56)	0.92	-	-

OR = odds ratio; CI = confidence interval; TB = tuberculosis; GIT = gastrointestinal.
*p-values were calculated with Fisher's exact or χ^2 test, as appropriate.
**Covariates were selected on an *a priori* basis and retained in the multivariate model if they were significantly associated with outcome ($p<0.05$).

Table 3. Outcomes of patients without/with delirium

Variable	Total	Without delirium	With delirium	*p*-value*
Length of stay (days), median (IQR)	5 (3 - 9)	5 (3 - 9)	7 (4 - 12)	<0.01
Inpatient mortality, *n* (%)	41 (5)	29 (4)	12 (12)	<0.01
3-month mortality, *n* (%)	135 (17)	105 (15)	30 (30)	<0.01
12-month mortality, *n* (%)	169 (21)	139 (20)	30 (30)	0.014

IQR = interquartile range.
*p-values for no delirium v. delirium at each time point were calculated with the use of the χ^2 test.

should be made to ensure early detection and management. Research into why patients who develop delirium have worse outcomes should be explored.

Declaration. The research for this study was done in partial fulfilment of the requirements for NdP's MMed degree at the University of Cape Town.

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Author contributions. JP and PJR designed and led the study. FA, KJ, LG and CD enrolled patients and collected data for the validation study. CD, FA, NV and CA entered and collated the initial data. NdP and PJR designed and wrote the study protocol. NdP, KM and PJR analysed and interpreted the data. NdP wrote the first draft and all authors reviewed and approved the final version of the manuscript.

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Conflicts of interest. None.

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