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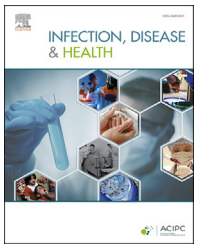

Research paper

Nosocomial SARS-CoV-2 transmission in multi-bedded hospital cubicles over successive pandemic waves: Lower mortality but wider spread with Omicron despite enhanced infection-prevention measures

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Abstract *Background:* Increased transmissibility of severe-acute-respiratory-syndrome-coronavirus-2(SARS-CoV-2) variants, such as the Omicron-variant, presents an infection-control challenge. We contrasted nosocomial transmission amongst hospitalized inpatients across successive pandemic waves attributed to the Delta- and Omicron variants, over a 9-month period in which enhanced-infection-prevention-measures were constantly maintained.
Methods: Enhanced-infection-prevention-measures in-place at a large tertiary hospital included universal N95-usage, routine-rostered-testing (RRT) for all inpatient/healthcare-workers (HCWs), rapid-antigen-testing (RAT) for visitors, and outbreak-investigation coupled with enhanced-surveillance (daily-testing) of exposed patients. The study-period lasted from 21st June 2021—21st March 2022. Chi-square test and multivariate-logistic-regression was utilized to identify factors associated with onward transmission and 28d-mortality amongst inpatient cases of hospital-onset COVID-19.
Results: During the Delta-wave, hospital-onset cases formed 2.7% (47/1727) of all COVID-19 cases requiring hospitalisation; in contrast, hospital onset-cases formed a greater proportion (17.7%, 265/1483; odds-ratio, OR = 7.78, 95%CI = 5.65—10.70) during the Omicron-wave, despite universal N95-usage and other enhanced infection-prevention measures that remained unchanged. The odds of 28d-mortality were higher during the Delta-wave compared to the Omicron-wave (27.7%, 13/47, vs. 10.6%, 28/265, adjusted-odds-ratio, aOR = 2.78, 95%

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CI = 1.02—7.69). Onward-transmission occurred in 21.2% (66/312) of hospital-onset cases; being on enhanced-surveillance (daily-testing) was independently associated with lower odds of onward-transmission (aOR = 0.18, 95%CI = 0.09—0.38). Costs amounted to $USD7141 per-hospital-onset COVID-19 case.
Conclusion: A surge of hospital-onset COVID-19 cases was encountered during the Omicron-wave, despite continuation of enhanced infection-prevention measures; mortality amongst hospital-onset cases was reduced. The Omicron variant poses an infection-control challenge in contrast to Delta; surveillance is important especially in settings where infrastructural limitations make room-sharing unavoidable, despite the high risk of transmission.

Highlights

- Hospital-onset COVID-19 (HA-COVID-19) cases were monitored over 9 months.
- HA-COVID-19 formed a larger proportion of hospitalized cases during Omicron (vs. Delta).
- Mortality in HA-COVID-19 was reduced during the Omicron wave.
- HA-COVID-19 cases identified via daily testing had lower odds of onwards transmission.

Introduction

While strict infection-prevention measures lower secondary -attack-rates of coronavirus-disease-2019 (COVID-19) in healthcare-facilities [1], increased transmissibility of severe-acute-respiratory-syndrome-coronavirus-2(SARS-CoV-2) variants, such as the Omicron-variant, presents infection-control challenges [2]. Various enhanced-infection-prevention measures have been instituted to mitigate nosocomial transmission [2]. In Singapore, emergence of the Delta-variant precipitated comprehensive enhanced-infection-prevention-measures, including universal N95-usage, routine-rostered-testing (RRT) for all inpatients/healthcare-workers (HCWs), rapid-antigen-testing (RAT) for visitors, and outbreak-investigation coupled with enhanced-surveillance (daily-testing) of exposed patients [3—6]. These measures were maintained throughout community-transmission of Delta- and Omicron-variants, allowing nosocomial inpatient transmission to be contrasted across successive waves.

Methodology

Institutional setting, study-period, outcome measures

Our healthcare-campus hosts a 1785-bedded tertiary-hospital and a 545-bed community-hospital. Patients are housed on general-wards containing a mixture of normal-pressure single rooms and 5—6 bedded cohorted-cubicles (beds six-feet apart). Toilet facilities are en-suite in some wards and located outside the cohorted-cubicle/room in others. Each cohorted-cubicle/single room has its own ventilation system, with ≥six air-exchanges/hour, and air is not recirculated between cubicles/rooms. Toilets have their own ventilation system, with all air exhausted to outdoors. Ward areas are air-conditioned, given heat and humidity in tropical Singapore. Air in transplant wards is HEPA-filtered. Almost 13,000 HCWs work on-campus. 89.6% of HCWs and 65.0% of inpatients received2 doses of mRNA-vaccines by end-June 2021. The study-period lasted from 21st June 2021—21st March 2022. Chi-square test and multivariate-logistic-regression was utilized to identify factors associated with onward transmission and 28d-mortality amongst inpatient cases of hospital-onset COVID-19 using SPSS (version 20.0). Costs arising from hospital-onset COVID-19 cases were also collated.

Definitions

Hospital-onset COVID-19-infection was defined as-follows [7].

- Indeterminate-hospital-onset: PCR-positive 3—7d post-admission
- Probable-hospital-onset: PCR-positive 8—14d post-admission
- Definite-hospital-onset: PCR-positive ≥15d post-admission

As inpatient PCR-testing was conducted weekly, prior negative PCR-results up-to 14d prior were utilised to evaluate potential nosocomial-transmission. Incubation-periods were defined as 1—14d prior to positive-PCR. Infectious-period was defined as 2d prior to symptom-onset if symptomatic or 7d prior to positive-PCR if asymptomatic. Significant patient-close-contact was defined as contact within six-feet for ≥15 min [6], during the index-patient's infectious-period. Onward-transmission was defined as >1 hospital-onset COVID-19 cases in the same cohorted-cubicle, or if the index was in a single-room, in the same ward; with overlap during the index-patient's infectious-period; ending when no cases were diagnosed for 14d. Whenever hospital-onset inpatient cases were identified, exposed inpatient close-contacts who had originally shared the cohorted-cubicle were placed on an enhanced-surveillance regimen (d1/4/7 PCR, daily-RAT post-exposure for 7-days) which

Table 1 Univariate analysis of risk factors for 28-day mortality amongst hospital-onset COVID-19 cases (N = 312).

Covariates (index cases)	28-day mortality amongst hospital-onset cases (N%)	Odds ratio, 95% CI[a]	P-value
Clinical characteristics			
Aged<70 years	12/141 (8.5)	**1.00**	
Aged≥70 years	29/171 (17.0)	**2.22 (1.07–4.55)**	**0.030***
Female	17/122 (13.9)	1.00	
Male	24/190 (12.6)	0.89 (0.46–1.74)	0.735
ISARIC score<7[b]	3/83 (3.6)	**1.00**	
ISARIC score≥7	38/229 (16.6)	**5.31 (1.59–17.69)**	**0.002***
Not on hemodialysis	34/257 (13.2)	1.00	
On hemodialysis	7/55 (12.7)	0.96 (0.40–2.29)	1.00
Not immunocompromised	22/200 (11.0)	1.00	
Immunocompromised	19/112 (17.0)	1.65 (0.85–3.21)	0.162
Not mobile	33/118 (28.0)	**1.00**	
Mobile	8/194 (4.1)	**0.11 (0.05–0.25)**	**<0.001***
Not fully vaccinated	14/66 (21.2)	**1.00**	
Fully vaccinated	27/246 (11.0)	**0.46 (0.22–0.93)**	**0.039***
Admission characteristics			
Admitted for ≤7 days prior to diagnosis	11/124 (8.9)	1.00	
Admitted for >7 days prior to diagnosis	30/188 (16.0)	1.95 (0.94–4.01)	0.087
Upper-respiratory-tract-infection	15/227 (6.6)	**1.00**	
Pneumonia	26/85 (30.6)	**6.23 (3.10–12.52)**	**<0.001***
Did not require high-dependency/intensive care	36/298 (12.1)	**1.00**	
Required high-dependency/intensive care	5/14 (35.7)	**4.04 (1.28–12.74)**	**0.025***
Did not receive therapeutics	13/126 (10.3)	1.00	
Received therapeutics	28/186 (15.1)	1.54 (0.76–3.10)	0.238
Cycle-threshold value ≥ 20 at onset	19/151 (12.6)	1.00	
Cycle-threshold value < 20 at onset	22/161 (13.7)	1.10 (0.57–2.12)	0.867
Delta variant	13/47 (27.7)	**1.00**	
Omicron variant	28/265 (10.6)	**0.31 (0.15–0.65)**	**0.004***

* p-value <0.05.
[a] Chi-square test.
[b] ISARIC score: risk stratification score that predicts in-hospital mortality for hospitalised COVID-19 patients, derived from the following variables: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein (score range 0–21 points).

remained unchanged throughout the study-period; however new admissions were still continuously accepted to the cubicle. Patients who subsequently tested positive (RAT/PCR) were transferred immediately to isolation so as not to cohort COVID-19 patients together with patients who tested negative. Onward-transmission was classified as occurring between or beyond adjacent-beds (six-feet-apart). Fully-vaccinated status was defined according to our Ministry of

Table 2 Multivariate analysis of risk factors for 28-day mortality amongst hospital-onset COVID-19 cases (N = 312).

Covariates (index cases)	Adjusted odds ratio, 95% CI[b]	P-value
Clinical characteristics		
ISARIC score≥7[c] (vs. ISARIC <7)	**3.97 (1.05–14.99)**	**0.042**[a]
Immunocompromised (vs. not immunocompromised)	2.00 (0.89–4.53)	0.093
Mobile (vs. immobile)	**0.11 (0.04–0.28)**	**<0.001**[a]
Admission characteristics		
Pneumonia (vs. upper-respiratory-tract-infection)	**4.63 (2.07–10.33)**	**<0.001**[a]
Required high-dependency/intensive care (vs. general ward care)	**3.97 (1.03–15.34)**	**0.045**[a]
Omicron variant (vs. Delta variant)	**0.36 (0.13–0.98)**	**0.047**[a]

[a] p-value <0.05.
[b] Multivariate logistic regression.
[c] ISARIC score: risk stratification score that predicts in-hospital mortality for hospitalised COVID-19 patients, derived from the following variables: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein (score range 0–21 points).

Table 3 Analysis of risk factors for onward transmission of SARS-CoV-2 from hospital-onset COVID-19 cases (N = 312).

Covariates (index cases)	Onward transmission amongst hospital-onset cases (N%)	95% CI[a]	P-value	Transmission beyond immediately-adjacent beds (N%)	95% CI[a]	P-value
Clinical characteristics						
Aged<60 years	15/75 (20.0)	1.00	0.872	11/15 (73.3)	1.00	0.543
Aged≥60 years	51/237 (21.5)	1.10 (0.56–2.10)		31/51 (60.8)	0.56 (0.16–2.02)	
Female	22/122 (18.0)	1.00	0.321	14/22 (63.6)	1.00	1.00
Male	44/190 (23.2)	1.37 (0.77–2.43)		28/44 (63.6)	1.00 (0.34–2.90)	
ISARIC score<7[b]	15/83 (18.1)	1.00	0.530	8/15 (53.3)	1.00	0.374
ISARIC score≥7	51/229 (22.3)	1.28 (0.69–2.46)		34/51 (66.7)	1.75 (0.54–5.64)	
Not on hemodialysis	57/257 (22.2)	1.00	0.467	34/57 (59.6)	1.00	0.139
On hemodialysis	9/55 (16.4)	0.68 (0.32–1.50)		8/9 (88.9)	5.41 (0.63–46.23)	
Not immunocompromised	40/200 (20.0)	1.00	0.564	26/40 (65.0)	1.00	0.799
Immunocompromised	26/112 (23.2)	1.21 (0.69–2.12)		16/26 (61.5)	0.86 (0.31–2.40)	
Not mobile	30/118 (25.4)	1.00	0.156	16/30 (53.3)	1.00	0.131
Mobile	36/194 (18.6)	0.67 (0.39–1.16)		26/36 (72.2)	2.28 (0.82–6.33)	
Not fully vaccinated	15/66 (22.7)	1.00	0.736	10/15 (66.7)	1.00	1.00
Fully vaccinated	51/246 (20.7)	0.89 (0.46–1.71)		32/51 (62.7)	0.84 (0.25–2.84)	
Ward characteristics						
In single room	1/20 (5.0)	1.00	0.088	1/1 (100.0)	1.00	1.00
In cohorted cubicle	65/292 (22.3)	5.43 (0.71–41.7)		41/65 (63.1)	0.63 (0.52–0.76)	
Dedicated toilet within cohorted cubicle or room	23/145 (15.9)	**1.00**	**0.037***	14/23 (60.9)	1.00	0.792
Shared toilet (outside cohorted cubicle or room)	43/167 (25.7)	**1.84 (1.05–3.24)**		28/43 (65.1)	1.20 (0.42–4.32)	
General ward	45/224 (20.1)	1.00	0.538	26/45 (57.8)	1.00	0.178
Haematology/oncology/ renal ward	21/88 (23.9)	1.25 (0.69–2.25)		16/21 (76.2)	2.34 (0.73–7.50)	
General ward	62/294 (21.1)	1.00	1.00	40/62 (64.5)	1.00	0.618
High-dependency/ intensive-care-unit	4/18 (22.2)	1.07 (0.34–3.36)		2/4 (50.0)	0.55 (0.07–4.18)	
Admission events						
Admitted for ≤7 days prior to diagnosis	26/124 (21.0)	1.00	1.00	17/26 (65.4)	1.00	1.00
Admitted for >7 days prior to diagnosis	40/188 (21.3)	1.02 (0.58–1.79)		25/40 (62.5)	0.88 (0.32–2.47)	
Not on enhanced-surveillance (daily testing) prior to diagnosis	55/183 (30.1)	**1.00**	**<0.001***	35/55 (63.6)	1.00	1.00
On enhanced-surveillance (daily testing) prior to diagnosis	11/129 (8.5)	**0.22 (0.11–0.43)**		7/11 (63.6)	1.00 (0.26–3.84)	
Did not use common toilet	27/116 (23.3)	1.00	0.478	12/27 (44.4)	**1.00**	**0.010***
Used common toilet	39/196 (19.9)	0.82 (0.47–1.43)		30/39 (76.9)	**4.12 (1.44–12.07)**	

No aerosol-generating procedure[↑]	46/263 (17.5)	**1.00**	**< 0.001***	28/46 (60.9)	1.00	0.583
Aerosol-generating procedure	20/49 (40.8)	**3.25 (1.69–6.25)**		14/20 (70.0)	1.50 (0.49–4.62)	
No diarrhea	62/294 (21.2)	1.00	1.00	40/62 (64.5)	1.00	0.618
Ongoing diarrhea	4/18 (22.2)	1.07 (0.34–3.36)		2/4 (50.0)	0.55 (0.07–4.18)	
SARS-CoV-2 testing results						
Cycle-threshold value ≥ 20	24/151 (15.9)	**1.00**	**0.037***	18/24 (75.0)	1.00	0.188
Cycle-threshold value < 20	42/161 (26.1)	**1.89 (1.01–3.27)**		24/42 (57.1)	0.44 (0.15–1.35)	
Delta variant	8/47 (17.0)	1.00	0.562	7/8 (87.5)	1.00	0.241
Omicron variant	58/265 (21.5)	1.37 (0.61–3.08)		35/58 (60.3)	0.22 (0.03–1.89)	

* p-value <0.05.
↑ Aerosol-generating procedures defined as: nebulizers, high flow nasal cannula, noninvasive positive pressure ventilation, intubation.
[a] Chi-square test.
[b] ISARIC score: risk stratification score that predicts in-hospital mortality for hospitalised COVID-19 patients, derived from the following variables: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein (score range 0–21 points).

Health's guidelines [8]; prior to February 2022, receipt of 2 doses of mRNA vaccines was required to maintain fully-vaccinated status, while after February 2022, receipt of a 3rd booster dose was required to maintain fully-vaccinated status for all adults aged ≥18 years.

Enhanced infection-prevention measures

Universal-admission-testing for SARS-CoV-2 via PCR and RAT was practiced for all inpatients [4,5], with weekly-PCR/mid-week RAT thereafter for all asymptomatic patients [4]. This testing regimen remained unchanged through the whole study period. Patients who developed new respiratory symptoms/undifferentiated fever were tested at symptom-onset for SARS-CoV-2 via PCR. Inpatients testing positive were managed in designated COVID-19 wards (isolation-areas comprising negative-pressure rooms) separate from patients who tested negative. HCWs in isolation-areas designated for the management of confirmed/suspected COVID-19 cases donned N95-respirators/disposable gloves/gowns/faceshields as personal-protective-equipment (PPE), with disposal after each use. All HCWs donned N95 respirators in all clinical-areas as a mandatory minimum. Aerosol-generating-procedures (AGPs) outside of the isolation-ward were performed with HCWs using N95-respirators/disposable gloves/gowns/faceshields and in single rooms where feasible. Surgical-mask-usage was mandated for all inpatients and visitors. Two asymptomatic, fully-vaccinated-visitors/inpatient/day were allowed; visitors underwent RAT if visiting ≥30 min [6]. Symptomatic HCWs could access free PCR-testing at Staff Clinic [4].

Results

Over the study-period, 312 hospital-onset cases were identified, of which the majority (53.8%, 168/312) were probable/definite; the remainder were indeterminate. Up to December 2021, whole-genome-sequencing (WGS) revealed that all hospital-onset-cases were attributable to the Delta-variant (N = 47) [9]. The first Omicron case was identified in a returned traveler on 24th December 2021. By January 2022, all hospital-onset cases demonstrated S-gene dropout on PCR-testing, indicative of the Omicron-variant. During the Delta-wave, hospital-onset cases formed 2.7% (47/1727) of all COVID-19 cases requiring hospitalisation; in contrast, hospital onset-cases formed a greater proportion (17.7%, 265/1483; odds-ratio, OR = 7.78, 95%CI = 5.65–10.70) during the Omicron-wave. The majority of hospital-onset cases (78.8%, 246/312) were fully-vaccinated. Three-fifths (59.6%, 186/312) received therapeutics; 4.5% (14/312) required intensive-care-unit/high-dependency admission; and 13.1% (41/312) demised within 28d of infection. Stratifying by variant (Delta vs. Omicron), 55.3% (26/47) received therapeutics during the Delta-wave, while 60.4% (160/265) received therapeutics during the Omicron-wave (odds ratio, OR = 0.81, 95%CI = 0.44–1.52, p = 0.310). Only 6.4% (3/47) required intensive-care-unit/high-dependency admission during the Delta-wave, while 4.2% (11/265) required intensive-care-unit/high-dependency admission during the Omicron-wave (OR = 1.54, 95%CI = 0.45–5.31, p = 0.701). The majority (76.5%, 36/47) were fully-vaccinated during the

Delta-wave, while 79.2% (210/265) were fully vaccinated during the Omicron-wave (OR = 0.86, 95%CI = 0.41−1.79, p = 0.700). On univariate analysis, older age (age≥70 years), higher ISARIC-score (≥7), being immobile, partial/unvaccinated status, pneumonia, high-dependency/intensive-care-unit admission, and infection with the Delta-variant were associated with 28d-mortality (Table 1). On multivariate-logistic-regression, higher ISARIC-score (≥7), immobility, pneumonia, and intensive-care-unit/high-dependency admission were all independently associated with 28-day mortality amongst hospital-onset COVID-19 cases (Table 2). The odds of 28d-mortality were higher during the Delta-wave compared to Omicron (27.7%, 13/47, vs. 10.6%, 28/265, adjusted-odds-ratio, aOR = 2.78, 95%CI = 1.02−7.69).

Onward-transmission occurred in 21.2% (66/312) of hospital-onset cases, with a median of 1.00 (inter-quartile-ratio, IQR = 1.00−2.00) cases arising from exposure to each index-case. During the Delta-wave, epidemiologically-linked cases (N = 26) previously exposed to an index inpatient case were identified on average at 5.65 days (S.D = 2.45) post-exposure. In comparison, during the Omicron-wave, epidemiologically-linked cases (N = 102) were identified at 3.90 days (S.D = 2.09) post-exposure (mean-difference = 1.75, 95%CI = 0.69−2.91). On univariate analysis (Table 3) and multivariate-logistic-regression, being on enhanced-surveillance (d1/4/7 PCR, daily-RAT post-exposure for 7-days) was independently associated with lower odds of onward-transmission (aOR = 0.18, 95%CI = 0.09−0.38), whereas AGPs occurring during the index's infectious period, prior to positive SARS-CoV-2 testing and subsequent isolation (aOR = 4.07, 95%CI = 1.88−8.78, p < 0.001), cycle-threshold-value of <20 on PCR-testing (aOR = 1.85, 95% CI = 1.01−3.48), admission to a cubicle/room with a shared toilet (outside cohorted cubicle or room) (aOR = 1.90, 95% CI = 1.01−3.54), and being in a cohorted-cubicle instead of a single-room (aOR = 13.32, 95%CI = 1.63−109.10) were all independently associated with higher odds of onward-transmission. Onward-transmission beyond immediately-adjacent beds occurred in the majority (63.6%, 42/66) and was independently associated with common-toilet usage by the index-case (OR = 4.12, 95%CI = 1.44−12.07) (Table 3). Costs of COVID-19 therapeutics, isolation, COVID-19-related testing and surveillance of exposed inpatients attributable to all hospital-onset inpatient cases (N = 312) amounted to USD$2,228,055, or USD$7141 per-case (Table 4).

Discussion

During the Delta-wave, inpatient clusters remained small and sporadic in the setting of comprehensive enhanced infection-prevention measures [10]. However, a surge in nosocomial transmission occurred with the Omicron-variant, despite continuation of all infection-prevention measures. Mortality was reduced during the Omicron-wave, and was comparable to estimates of mortality attributed to hospital-associated influenza [11]. Daily inpatient-testing for COVID-19 cluster-control was associated with reduced onward-transmission in cohorted-cubicles. Additionally, COVID-19 index cases identified in rooms with shared bathroom

Table 4 Cost of COVID-19 therapeutics, isolation-ward stay, COVID-19-related laboratory testing and surveillance for exposed inpatients for hospital-onset COVID-19 cases amongst hospitalised inpatients (N = 312).

Cost of COVID-19 therapeutics, isolation-ward stay, COVID-19-related laboratory testing and surveillance for exposed inpatients	Number of patient-days (d)/number of tests/number of patients	Total cost (USD$)
COVID-19 therapeutics		
Antivirals		
Remdesivir	690d	362,500
Nirmatrelvir-ritonavir	5d	800
Monoclonal antibodies		
Casirivimab-imdevimab	2d	2500
Sotrovimab	21d	52,000
Tixagevimab-cilgavimab	2d	7000
Anti-IL6/JAK1-2		
Baricitinib	6d	75
Tocilizumab	3d	2300
COVID-19 in-hospital isolation		
Isolation in hospital's isolation general ward	3269d	1,242,700
Isolation in hospital's isolation intensive-care-unit	126d	98,280
COVID-19 related-testing		
SARS-CoV-2 PCR	624 tests	54,000
SARS-CoV-2 IgG (RBD)	165 tests	6000
Costs of surveillance for exposed inpatients to index hospital-onset COVID-19 cases		
SARS-CoV-2 PCR on d1/4/7, as well as daily-RAT for 7 days post-exposure	1045 patients	399,900
Total costs	—	2,228,055
Total cost per patient (N = 312)	—	7141

facilities had higher odds of onward transmission; likely due to the possibility of fomite transmission [12] and increased human traffic in shared facilities. Generalisability is limited by our study's single-site nature; however, continuity of infection-prevention measures allowed contrast between pandemic waves. In conclusion, we highlight the challenge of the Omicron variant when contrasted against Delta and reinforce the importance of reducing onward transmission, especially given infrastructural limitations posed by cohorted rooms [13].

Ethics

This study was conducted as part of outbreak-investigation; ethics approval was waived under our institutional-review-board guidelines.

Authorship statement

WLE: Conceptualization; data curation; formal analysis; investigation; methodology; writing- original draft; writing-review and editing. EPC, MKA, AMO, YY, SA: Data curation; formal analysis; investigation; methodology; writing-review and editing. KKK: Investigation; methodology; writing-review and editing. IV: Conceptualization; investigation; methodology; supervision; writing-review and editing.

Conflict of interest

The authors report no conflicts of interest

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Provenance and peer review

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