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'Dengue-COVID-19 overlap': Is it an 'antigenic mimicry' or coexistent two different viral genotypic diseases? Prospective, observational study in tertiary care setting in India

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ABSTRACT

Introduction: Dengue-COVID-19 overlap is mixture of both diseases sharing few similarities in pulmonary and extra pulmonary involvement.

Methods: Prospective, observational study, included 300 COVID-19 cases with dengue NS1 or dengue IgM positive, with lung involvement documented and categorized on HRCT thorax at entry point. All cases were subjected to dengue IgG antibody titers and dengue IgM/IgG antibody titer analysis after 12 weeks of discharge form hospital.

Results: Hematological evaluation, white blood cell count & platelet count were having significant association with dengue-COVID-19 overlap ($p<0.0076$) & ($p<0.00001$), respectively. Clinical parameters as hypoxia have significant association with dengue-COVID-19 overlap ($p<0.00001$). Inflammatory markers as IL-6, CRP, and LDH has significant association in dengue-COVID-19 overlap ($p<0.00001$), respectively. Dengue-COVID-19 overlap was documented in 16.33% (49/300) cases. CT severity has documented significant correlation with dengue-COVID-19 overlap cases ($p<0.00001$). In study of 49 cases of 'dengue-COVID-19', post-COVID-19 lung fibrosis ($p<0.004$), and serological assessment in dengue IgM/IgG and COVID-19 antibody titers has significant association ($p<0.00001$).

Conclusion: 'Dengue-COVID-19' is disease of concern in ongoing pandemic in critical care setting, and timely workup is crucial step in preventing delay in diagnosis and final adverse outcomes.

Keywords: dengue-COVID-19 overlap, COVID-19, antigenic mimicry, post-COVID-19 lung fibrosis

INTRODUCTION

Corona virus related global pandemic (COVID-19), declared by World Health Organization (WHO) in March 2020, caused by novel coronavirus SARS-CoV-2 resulted in significant mortality morbidity, with impact on health care systems globally resulting shortage of resources to manage rapidly growing pandemic [1]. Dengue fever is arboviral vector born disease with four antigenic variants, and as per WHO figures, dengue has shown significant increase in disease burden in all parts of world causing 100-400 million infections each year with more than 50% in tropical settings [2]. Asian countries are significantly affected by COVID-19 and dengue both, due to favorable geographical trends in tropical settings concurrent occurrence is more possible along with predicted antigenic cross reactivity and resurgence of both disease is expected in future [3-5]. COVID-19 and dengue, both are viral disease sharing clinical and laboratory similarities and increase in chances of underestimation resulting in delay in diagnosis if proper laboratory workup and specific diagnostic tests are not performed [6]. Antigenic cross-reactivity resulted in false positive results, and will manifest significantly in patient view and public health due to increased disease burden and poor outcomes due to delay in diagnosis and treatment [7, 8].

COVID-19 pandemic is a big health concern in dengue endemic areas due to overlapping of clinical and laboratory features and its challenging job for critical care physicians for correct diagnosis and management of both the diseases [9-11]. Many case reports and case series published the concurrent COVID-19 and dengue co-infections [12, 13], which has been associated more mortality than isolated single infection [14, 15]. Both viral diseases share may pathogenic and clinical features, as antibody dependent enhancement phenomenon (ADE) has documented in both dengue and COVID-19, which is the reason for overlapping nature of both the disease and behaving like 'two sides of same coin.' Both are RNA viruses and shown similar pathologic pathways as cytokines and chemokine release, altering the integrity of the vascular endothelium leading to vasculopathy, coagulopathy and capillary leak [16].

In present study, we have documented COVID-19 pneumonia cases with concurrent dengue like manifestations and dengue serology positivity i.e., either NS1 or IgM antibody

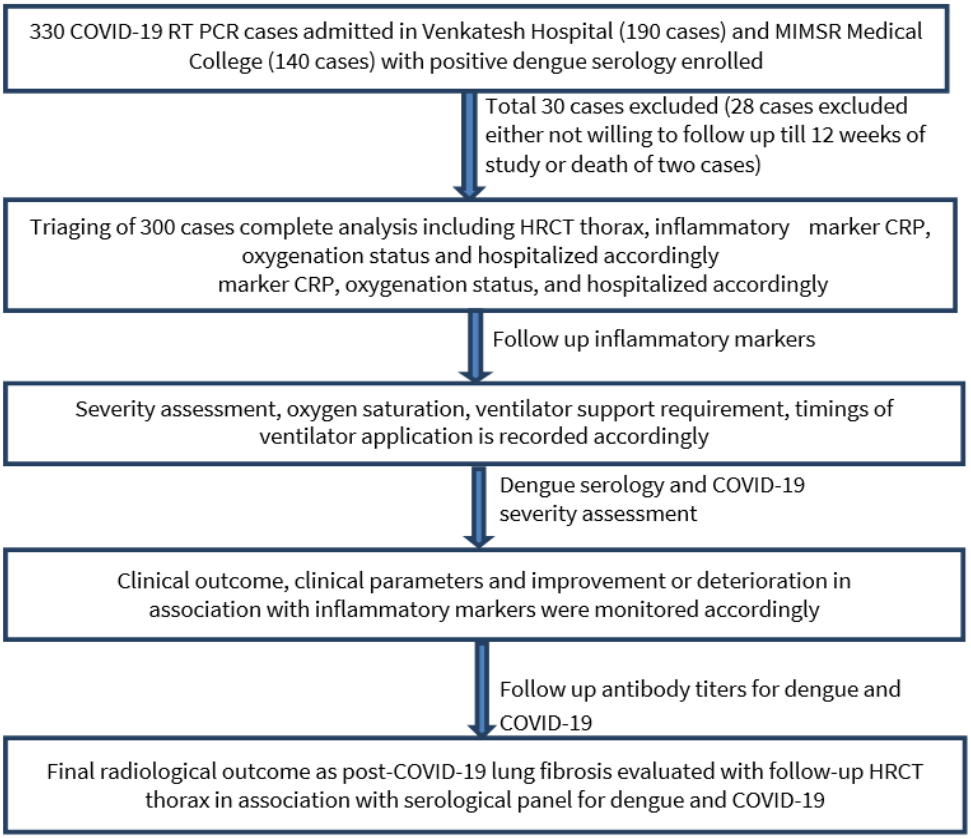

Figure 1. Flow of the study

positive, and we have followed these cases for 12 weeks to exactly confirm dengue-COVID-19 overlap.

METHODS

Data Source

Prospective, observational study conducted in Venkatesh Chest Hospital, and Pulmonary Medicine, MIMSR Medical College Latur during May 2021 to October 2021, to find out 'COVID-19-dengue overlap' in diagnosed COVID-19 pneumonia cases admitted in critical care unit. Total 300 cases were enrolled in study after IRB approval and written informed consent of patient.

Inclusion criteria

COVID-19 patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation were included in the study.

Exclusion criteria

Those not willing to give consent, not able to perform follow-up dengue and COVID-19 antibody titers and patients less than 18 years of age were excluded.

Ethical Approval

This study was approved by the Institutional Review Board/Ethics Committee at Venkatesh Hospital and Critical Care Center Latur India and MIMSR Medical college Latur India, (Approval # VCC/141-2020-2021; Approval date 20/06/2021).

Study Design

COVID-19 RT PCR test performed in all cases, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive COVID-19 RT-PCR test. HRCT thorax to assess severity of lung involvement, and categorized as mild if score <7, moderated if score 8-15, and severe if score >15 or 15-25. Clinical parameters with oxygen saturation and respiratory system examination laboratory parameters-hemoglobin, renal functions, blood sugar level, liver functions, ECG. Viral inflammatory markers like CRP, LDH, IL-6 assessed at entry point and repeated whenever required during course of illness as for monitoring the COVID-19-dengue overlap cases for necessary interventions. Normal and abnormal parameter readings were considered as per pathological laboratory standard. COVID-19 antibody titers and dengue IgM and IgG titers and follow-up HRCT thorax done at 12 weeks or three months of discharge from hospital.

Methodology

Figure 1 shows the flow of the study.

Diagnosis of dengue infection [4]:

1. *Dengue NS1 antigen:* Rapid detection, qualitative screening test, and analyzing presence of nonstructural protein NS1 antigen (SD Dengue Duo, Standard Diagnostics, Germany)
2. *Dengue IgG and IgM:* Qualitative IgM and IgG antibody assays were performed by immune-chromatography strip method (SD Dengue Duo, Standard Diagnostics, Germany), with sensitivity and specificity of 94.2% and 96.4%, respectively.

Table 1. Other variables in 'COVID-19-dengue overlap' cases

COVID-19 RT PCR positive (n=300)	Dengue NS1/IgM positive (n=49)	Dengue NS1/IgM negative (n=251)	Analysis
Normal platelets level (n=110)	3	107	$\chi2=23.52$
Abnormal platelets level (n=190)	46	144	$p< 0.00001$
Normal white blood counts (n=105)	9	96	$\chi2=7.12$
Abnormal white blood counts (n=195)	40	155	$p< 0.0076$
Normal CRP level (n=28)	22	6	$\chi2=87.53$
Abnormal CRP level (n=272)	27	245	$p< 0.00001$
Normal LDH level (n=58)	12	46	$\chi2=66.98$
Abnormal LDH level (n=242)	37	205	$p< 0.00001$
Normal IL-6 level (n=58)	46	12	$\chi2=208.67$
Abnormal IL-6 level (n=242)	3	239	$p< 0.00001$
Required BIPAP/NIV (n=96)	6	90	$\chi2=10.50$
Not required BIPAP/NIV (n=204)	43	161	$p< 0.0011$
Cases with hypoxia (n=239)	12	227	$\chi2=110.07$
Cases without hypoxia (n=61)	37	24	$p< 0.00001$

3. *Diagnosis of SARS-CoV-2 infection by RT-PCR:* Qualitative screening of the SARS-CoV-2 virus, performed on nasopharyngeal swab samples as fully automated RT PCR on Cobas 6800 instrument (Roche Molecular Diagnostics, USA).

Case definition used in this study:

1. *Dengue-COVID-19 overlap:* COVID-19 RT PCR positive cases with serology detected dengue NS1 with or without IgM antibody with clinical and laboratory parameters corelated with concurrent possibility of both illnesses.
2. *False dengue or antigenic mimicry*: Initially presented with dengue-COVID-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM or dengue IgG antibody negative
3. *Concurrent COVID-19-dengue illness:* Initially presented with dengue-COVID-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM or dengue IgG antibody positive.
4. *COVID-19-dengue immune senescence:* Initially presented with dengue-COVID-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM and dengue IgG antibody negative and COVID-19 antibody test negative or weakly positive.

Statistical analysis

The statistical analysis was done using Chi test in R-3.4 software. Significant values of χ^2 were seen from probability table for different degree of freedom required. p-value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

RESULTS

Covariates

In this study, total 300 COVID-19 pneumonia cases, dengue-COVID-19 overlap was documented in 16.33% (49/300) cases, cases enrolled between age group 18-95 years of age; age above 50 years were 60% (180/300) and age below 50 were 40% (120/300). In gender distribution in study group, male population was 70.33 % (211/300) and females were 29.66% (89/300). Main symptoms in study group were shortness of breath in 79% cases, fever in 71%, cough especially dry in 48% cases, and fatigability in 79% cases, tachycardia in 72% cases, tachypnea in 24% cases and oxygen desaturation on six minutes walk in 29% cases. Hematological parameters were having significant association in COVID-19 cases with and without dengue overlap as like abnormal white blood cell count ($p<0.0076$) and abnormal platelet count ($p<0.00001$) (**Table 1**).

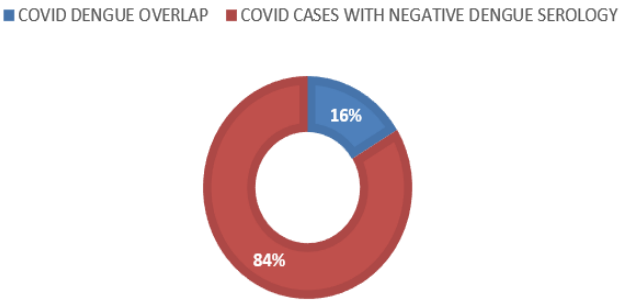

Figure 2. 'COVID-19-dengue overlap' in study cases

Clinical parameters like hypoxia have significant association in COVID-19 cases with and without dengue overlap ($p<0.00001$) (**Table 1**). Inflammatory markers analysis CRP, IL-6, and LDH has documented significant association in COVID-19 cases with and without dengue overlap (**Table 1**).

Figure 2 shows a pie diagram illustrating 'COVID-19-dengue overlap' in study cases.

Core Observations

'Dengue-COVID-19 overlap' as per CT severity scoring was documented as 26/42 in mild CT severity cases, 16/92 in moderate CT severity cases and 7/166 in severe CT severity cases ($p<0.00001$) (**Table 2**).

In study of 49 cases of 'dengue-COVID-19 overlap', post-COVID-19 lung fibrosis was documented in one case while in 251 COVID-19 patients with negative dengue serology documented post-COVID-19 lung fibrosis in 45 cases ($p<0.004$) (**Table 3**).

In study of 49 cases of 'COVID-19-dengue overlap', serological assessment in dengue IgM/IgG and COVID-19 antibody titers was documented in significant association ($p<0.00001$) (**Table 4**).

Table 2. Pattern of COVID-19 disease in study cases (n=300)

CT severity and COVID-19 RT PCR positive (n=300)	Dengue NS1/IgM positive (n=49)	Dengue NS1/IgM negative (n=251)	Analysis
Mild (n=42) (score <8)	26	16	χ^2=81.71 p< 0.00001
Moderate (n=92) (score 9-15)	16	76	
Severe (n=166) (score 16-25)	07	159	

Table 3. Radiological outcome in 'COVID-19-dengue overlap' cases

COVID-19 RT PCR (n=300)	Lung fibrosis present (n=46)	Lung fibrosis absent (n=254)	Analysis
Dengue NS1/IgM positive (n=49)	1	48	χ^2=7.97
Dengue NS1/IgM negative (n=251)	45	206	p< 0.004

Table 4. Actual serological assessment in COVID-19-dengue overlap and COVID-19 with dengue coexistent pathology (n=490) follow up at 12 weeks

COVID-19-dengue overlap cases (n=49)	COVID-19 antibody titers raised (n=29)	COVID-19 antibody titers negative (n=20)	Analysis
Dengue IgM/IgG positive (n=33)	27	6	χ^2=21.43
Dengue IgM/IgG negative (n=16)	2	14	p< 0.00001

DISCUSSION

Prevalence of 'Dengue-COVID-19 Overlap' in Present Study

In this study, 'COVID-19-dengue overlap' was documented in 16.33% and this will be first study enrolling and analyzing a greater number of cases having COVID-19-dengue overlap. Dengue became endemic in Asian countries due to trading industry and transportation services in last century due to movement of people [17, 18]. Presently, majority of the Asian countries are badly affected with COVID-19 pandemic and resulted in socioeconomic crisis due significant disease burden in compromised health sector [19-23]. India is one of the most affected country due to COVID-19 with ranked second and third in number of affected cumulative cases and deaths, respectively [24]. Now, most of the South East Asia region has documented full blown COVID-19 pandemic with more cases and deaths in comparison to rest of world [25-27].

In present study, we have observed many cases were initiated treatment in consideration of dengue fever due to overlap of common symptom of fever and later on during course of illness when these patients started cough and or shortness of breath, were evaluated for COVID-19 and documented positive serology with lung parenchymal involvement on HRCT thorax. The researchers in [9, 14, 28] documented similar findings. We have also observed that clinical worsening or requirement of oxygen supplementation due to fall in oxygen saturation was reason to investigate for underlying COVID-19 in primary dengue hospitalizations, and vice versa. The researchers in [15, 28-33] documented similar observation. As both diseases share same pathophysiologic mechanism, hematological manifestations as thrombocytopenia resulted from decreased production due to bone marrow suppression or increase immune mediated consumption [34, 35] or immune complex mediated and autoantibody dependent platelet destruction which has been documented in COVID-19 and dengue both [35, 36].

'Dengue-COVID-19 Overlap': Is It an 'Antigenic Mimicry'?

In present study of these 49 cases with COVID-19-dengue overlap antigenic cross reactivity has been documented initially in 16 cases i.e., false positive dengue NS1 without dengue antibody titer documentation at three weeks follow up. Few studies have documented similar observation [49, 50]. 'Dengue-COVID-19 overlap' documentation needs high index of suspicion due to overlapping clinical and laboratory markers and concurrent double infection complicates either disease clinical outcome. All cases with dengue NS1 and or IgM positive needs COVID-19 to be ruled out as many cases are having underlying OCVID-19, we specially recommend in scenario with abnormal chest radiograph or cases with adventitious sounds on auscultation clinically. Few studies [38, 39] have similar observations collaborating with our study.

'Dengue-COVID-19 Overlap': Is It a Coexistent Two Different Viral Genotypic Disease?

In study of 49 cases of 'dengue-COVID-19 overlap', actual serological assessment in dengue IgM/IgG antibody and COVID-19 IgG antibody titers at three weeks was documented in significant association (p<0.00001). Initially, dengue-COVID-19 overlap was considered important health issue in ongoing COVID-19 pandemic in high dengue burden setting in tropical countries in South East Asia region and as pandemic grown across globe irrespective of dengue trends, now it is considered as global health issue. Various studies [41, 42] and the studies [13, 40] documented similar observation.

'COVID-19-Dengue Immune Senescence'–Is It a Natural Trend or Worrisome Pattern in Ongoing Pandemic?

In study of 49 cases of 'dengue-COVID-19 overlap', actual serological assessment in dengue IgM/IgG antibody and COVID-19 IgG antibody titers at 12 weeks of illness were negative 16 and 20 cases, respectively (p<0.00001). In study of these cases in follow up, 14 cases were showing negative both COVID-19 and dengue antibody titers. Negative antibody titer is really a concern and it would suggest 'weak antigen-antibody memory link' and issue of great research being all such cases again become virgin to catch reinfection due to COVID-19.

In [51], it was observed that acute COVID-19 illness usually last for four weeks and beyond this time virus isolation from respiratory samples is rare, as viral load is highest among first two weeks of illness, which will decrease till four weeks, with exemption in few cases where viral load can be documented as till six weeks to 60 days [51], and factors associated with persistence of virus for longer duration is area of research [45]. In COVID-19 serology, IgM antibody increase during first week with peak at around two week of illness and then disappear over two to four weeks, while IgG antibody start rising by the end of first week and remains elevated and detectable level till

90 days of infection. Still, exactly protective value of these antibodies in preventing reinfections is not clearly known [46].

In [47], it was observed that in primary acute dengue infection, NS1 and viral RNA has been documented in first week of illness till first five days of infection, serology as IgM antibody documented at three to five days and remains detectable for several weeks to months, and at the end of acute phase, IgG antibody start rising, which last for 10 days which establishes immunological memory for several years. While in secondary dengue infection, IgG antibody rises earlier than IgM [47]. Recent studies [52-54] have documented role of neutralizing antibodies in these infections which will disappear after three months. In [52], it was observed that short lasting serological stage and early waning of humoral immunity with 40% percent asymptomatic individuals became seronegative and 12.9% of the symptomatic cases became negative for IgG in the early convalescent phase. In [54], it was mentioned that the doubtful role of these neutralizing antibodies in protection from future infections due to various variants, and really how much they protect us from reinfection is not known at present.

We have further analyzed these 14 cases, and documented that all these 14 cases were having mild lung involvement on CT thorax imaging, which means that more immunopathological nature of corona virus disease leading to short lasting humoral immunity and ultimately 'short lasting immune memory' or 'viral escape from immune restoration phenomenon' by altering and targeting 'immune escape pathway' which will hide the COVID-19 antigen presentation and sensing to memory T cells of host and developing protective antibodies for same.

Other Important Observations in Present Study

Hematological parameters were having significant association in COVID-19 cases with and without dengue overlap, and rational for similar observations were more immunological nature of dengue-COVID-19 overlap' syndrome. Clinical parameters like oxygen saturation at entry point has significant association in COVID-19 cases with and without dengue overlap, and rational for similar observation in dengue-COVID-19 overlap as compared to isolated COVID-19 illness, where lung involvement was predominant pathological nature of COVID-19 and hypoxia was predominantly documented in these cases due to more pulmonary involvement [48]. Inflammatory markers analysis as IL-6, CRP, and LDH has significant association in COVID-19 cases with and without dengue overlap and rational for same findings were more immune nature of overlap cases as compared to isolated COVID-19 cases, and predominant pattern of involvement is pulmonary, leading to direct pulmonary alveolar and vasculature involvement and correlated with raised inflammatory markers IL-6, CRP, and LDH. We used LDH as marker of assessment of oxygen status and hypoxia, and observed grossly raised it with predominant lung involvement as documented in previous study [48].

HRCT severity has significant association with and without dengue-COVID-19 overlap, rational for these observations may be antigenic cross-reactivity or mimicry is feature of early course of COVID-19 illness and as disease evolves over period of time and enters in second to third week of illness this cross-reactivity decreases, CT radiological features progresses and presented with advanced stage or more CT severity. CT documented mild lung involvement in cases with prolonged fever and these cases were initially documented as dengue and later on diagnosed as concurrent COVID-19 coinfection in many cases and few cases were shown antigenic cross reactivity. While in majority of moderate to severe COVID-19 cases on HRCT thorax, proportionately high number of cases were having antigenic cross reactivity and only small proportion of cases were having concurrent COVID-19-dengue coinfection.

In study of 49 cases of 'COVID-dengue overlap', post-COVID-19 lung fibrosis was documented in one case while 251 COVID-19 patients with negative dengue serology documented post-COVID-19 lung fibrosis in 45 cases ($p<0.004$). Rational for same findings may be immunological nature of disease which has resolved over period of 12 weeks and usually these cases may have lesser lung parenchymal necrosis and more extrapulmonary features or manifestations. As disease progressed to 12 weeks of illness and chances of antigenic cross-reactivity decreased and isolated COVID-19 cases were predominant category showing lung fibrosis and we have confirmed these cases with antibody titer analysis.

Issues Needs to Analyze Further

1. Dengue-COVID-19 overlap' and antigenic mimicry scenario was documented in second wave i.e., delta variant of corona virus and less frequently documented with Wuhan variant coronavirus of first wave. Is there any antigenic cross-reactivity with genetic makeup of corona virus is behaving selectively, really, we don't know, and further workup is required?
2. Is immunological phenomenon documented in dengue-COVID-19 overlap reversible? or is it persists longer? and or pre-requisite for certain autoimmune rheumatological syndromes in post-COVID-19 illness cases which has been documented in all clinical settings, needs further work up.
3. How much dengue will impact in ongoing COVID-19 pandemic in spite of increase in cost of care of both the illnesses with fatigued manpower and health system? or we should prepare for both the disease as top priority in incoming few years with rising trends of various variants of corona virus? Time will decide, but as of now it is also warranted COVID-19-dengue as a hot topic of medical research and disease of concern for medical experts across the globe due to shared common pathophysiological and biological pathways [39].

CONCLUSIONS

Dengue-COVID-19 overlap is clinical syndrome with overlapping clinical and laboratory workup of both the illnesses. High index of suspicion is must in all COVID-19 cases in tropical setting where dengue is endemic; and all cases with leucopenia and thrombocytopenia with fever should be screened for dengue serology. False positive dengue serology or dengue antigen cross-reactivity is known to occur in underlying COVID-19 illness, and have impact on clinical outcome as it will result in delay in COVID-19 appropriate treatment initiation and many cases require intensive care unit treatment due to progressed COVID-19 pneumonia.

COVID-19-dengue antigenic cross-reactivity has significant association with lung fibrosis as resultant pathophysiological effect of immune activation pathway; and these cases were required longer oxygen supplementation and anti-fibrotics in

follow up. 'Dengue-COVID-19 overlap' is very frequently documented in tropical setting and disease of concern in critical care setting; as natural trend of this entity is different and having impact on clinical outcome if diagnosis is delayed. Both diseases may behave like 'two sides of same coin', and rational for coexistent pathology were still undetermined.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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