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CASE REPORT

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Atypical presentation of *Abiotrophia defectiva* infective endocarditis in an octogenarian

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Abstract

Blood cultures should be performed in non-specifically unwell older adults following nonspecific presentations. Prompt diagnosis and commencement of targeted antimicrobial therapy are essential in older patients with *A. defectiva* IE.

KEYWORDS

Abiotrophia defectiva, atypical presentation, infective endocarditis, nutritionally variant Streptococci, older patients

1 | INTRODUCTION

Abiotrophia defectiva, is an organism which is part of the normal flora of the intestinal tract, oral cavity, and urogenital tract.[1] It accounts for up to 6% of streptococcal infective endocarditis (IE) and has also been proposed as a possible pathogen in culture-negative endocarditis.[2]

Classified as a nutritionally variant streptococcus (NVS), *A. defectiva* can have devastating implications if missed due to its high frequency of septic embolization.[3] A case of aortic valve infective endocarditis in an 87-year-old woman with a background history of severe aortic stenosis (AS) who presented atypically with bleeding per rectum (PR), and functional decline is described. The patient gave written informed consent to reporting her clinical and laboratory data as well as her radiographic images.

2 | CASE HISTORY

An 87-year-old woman self-presented to the emergency department (ED) with a 3-day history of bleeding PR associated with general malaise, subacute weight loss of 5 kg over 3 months, and functional decline over a 5-week period.

This octogenarian was frail (Clinical Frailty Scale score: 8) preadmission with known severe aortic stenosis. Past medical history was otherwise significant for ischaemic heart disease (IHD) with percutaneous coronary intervention 5 months previously, diverticular disease, anal squamous cell carcinoma (treated definitively with radiotherapy), dystonic tremor, hypertension, and an 80-pack-year smoking history.

The patient denied any significant abdominal pain and had stable exertional dyspnoea without any recent deterioration in symptoms. Initial physical examination revealed a blood

pressure of 116/50 mm Hg and heart rate of 82 beats per minute, an ejection systolic and early diastolic murmur consistent with mixed aortic valve disease and none of the stigmata of IE such as splinter hemhorrages and janeway lesions . There was no recorded pyrexia with a temperature of 36.7 °C, and the patient denied any recent history of rigors. There was pallor and mild generalized abdominal tenderness on palpation. In the ED, she had blood cultures as part of her unwell adult (without obvious clinical cause) investigations, part of the protocol within our service. Intravenous (IV) co-amoxiclav 1.2 g three times daily was commenced for suspected acute diverticulitis. This woman was anaemic on admission, with a hemoglobin of 7.7 g/dL (reference range 12-15 g/dL), necessitating transfusion of one unit of red cell concentrate (RCC).

Both anaerobic and aerobic bottles of admission blood cultures flagged positive at 14 hours with Gram-positive cocci in pairs and chains, which later cultured on chocolate agar and identified as *A. defectiva* (Figure 1). Other laboratory values on admission included: white blood cell count (WBC) of 11.6 × 10^9/L (reference range 4-10 × 10^9/L), absolute neutrophil count of 9.24 × 10^9/L (reference range 2-7 × 10^9/L), mean corpuscular volume 85.0 fl (reference range 84-96 fl), platelet count of 320 × 10^9/L (reference range 150-400 × 10^9/L), serum C-reactive protein of 62 mg/L (reference range 0-5 mg/L), blood urea nitrogen of 8.6 mmol/L (reference range 2.9-8.2 mmol/L), serum creatinine of 108 μmol/L (reference range 49-90 μmol/L), serum albumin 31 g/L (reference range 39-51 g/L), and serum ferritin 1015 ng/mL (reference range 10-200 μmol/L). The hematological and biochemical parameters of the patient are tabulated in Table 1.

FIGURE 1 Image of the isolated bacteria: Fine growth of grey/green colonies of *Abiotrophia defectiva* on chocolate agar

Thereafter, the patient had two episodes of bleeding PR with associated fall in haemoglobin and RCC transfusion. She underwent an oesophagogastroduodenoscopy on day five of admission, which did not reveal any active/recent bleeding or ulceration.

The patient stabilized over the next 48 hours with clinical improvement but then had further bleeding PR, although remaining hemodynamically stable. She was unfit for bowel preparation and/or colonoscopy. Computed tomography (CT) scans of the abdomen and pelvis were performed to investigate ongoing gastrointestinal (GI) blood loss against a background of subacute weight loss. This revealed appearances consistent with multiple splenic infarcts (Figure 2) and diverticular disease. Concurrently with the identification of splenic infarcts, the patient had further bleeding PR with requirement for 2 further units of RCC transfusion and developed clinical sepsis, evidenced by fluctuating consciousness, mild hypoactive delirium, tachycardia, and low-grade pyrexia.

The combination of *A. defectiva* bacteraemia with ongoing pyrexia, known aortic murmur and apparent splenic infarcts on CT scan prompted the decision to treat as infective endocarditis (IE), as advised by Clinical Microbiology. Ceftriaxone Two g once daily was started empirically while sensitivity tests were pending. Transthoracic echocardiogram revealed a large mobile echodensity suggestive of a vegetation on a stenotic (maximum gradient 74 mm Hg) aortic valve with evidence of aortic regurgitation (Figure 3A). A diagnosis of *A. defectiva* IE was made. The infection diseases' team was consulted, and intravenous antimicrobial therapy was switched to amoxicillin 1 g every 4 hours and gentamicin 50 mg three times daily, with monitoring of gentamicin serum levels as per protocol. A CT scan of the brain revealed no radiographic evidence of septic emboli in the brain parenchyma, a complication frequently associated with *A. defectiva* endocarditis.[4]

The patient was deemed not to be a candidate for valve replacement given her frailty and significant premorbid comorbidities. However, an initial clinical and biochemical response to antimicrobial therapy was noted.

Unfortunately, on day 15, the patient had further bleeding PR with a drop in Hb necessitating further RCC transfusion. Later that day, she was found pulseless and unresponsive, and being declared not for active resuscitation, she died peacefully on the ward. She had a postmortem which confirmed severe aortic stenosis with calcification and vegetation of the valve leaflets grossly and microscopically (Figure 3B-D) and severe widespread critical coronary atherosclerosis adjacent to coronary stents associated with 90% occlusion involving the three coronary vessels (Figure 4). There was no evidence of acute ischemic changes within the heart. The entire aorta showed severe calcified atheroma. There was no bleeding focus found in the upper gastrointestinal (GI) tract, small bowel, or large bowel, which demonstrated mild diverticular

TABLE 1 Routine hematological and biochemical investigations from admission to day 15 of hospitalization

Laboratory parameter (Unitage)	Reference interval	Day 1 Admission Low Hb: 1 unit of RCC	Day 2 [a]IV Co-amoxiclav 1.2 g tds for 5 d	Day 5 OGD No active/ recent bleeding/ ulceration	Day 7 CTAP Revealed multiple splenic infarcts & diverticula disease During the afternoon the patient suffered an additional bleeding PR: 1 unit of RCC given overnight	Day 8 1 unit of RCC	Day 10 @08:00 h Oral Co-amoxiclav switched to IV Ceftriaxone 2 g/d @ 14:00 h TTE Revealed a large echo density suggestive for vegetation @ 16:30 h [a]Amoxicillin 1 g every 4 h & Gentamicin 50 mg tds	Day 15 Further bleeding PR 1 unit RCC Pulse-les, unresponsive, declared dead (Rest in peace)
White cell count (10^9/L)	4-10	**11.6**	9.8	8.6	**10.6**	**9.9**	9.2	8.9
Neutrophil count (10^9/L)	2-7	**9.2**	**7.6**	6.9	**8.8**	**8.2**	**7.6**	6.9
Hemoglobin (g/dL)	12-15	**7.7**	**8.5**	**9.7**	**9.0**	**8.2**	**8.6**	**9.2**
Mean corpuscular volume (fL)	84-96	85	84	86	85	84	84	83
Platelet count (10^9/L)	150-400	320	263	327	338	312	292	231
C-reactive protein (mg/L)	<5	**62**	n/r	**52**	**37.8**	**33.3**	**25.7**	**19.6**
Serum urea (mmol/L)	2.9-8.2	**8.6**	n/r	4.3	5.2	4.1	3.8	2.7
Serum creatinine (μmol/L)	49-90	**108**	n/r	60	59	61	58	58
Serum albumin (g/L)	39-51	**31**	n/r	**32**	**32**	**30**	**27**	**23**
Serum ferritin (ng/mL)	10-200	**1015**	n/r	n/r	n/r	n/r	n/r	n/r
Plasma lactate (mmol/L)	0.6-1.4	n/r	n/r	nr	nr	0.8	0.8	n/r

Note: Data in bold = abnormal values.

Abbreviations: CTAP, Computed tomography of the abdomen and pelvis; d, day; h, hour; Hb, Haemoglobin; IV: intravenous; n/r: not requested; OGD, Oesophago-Gastro-Duodenoscopy; RCC, red cell concentrate; tds: three times daily; TTE, transthoracic echocardiogram.

[a]Commencement of antibiotic treatment.

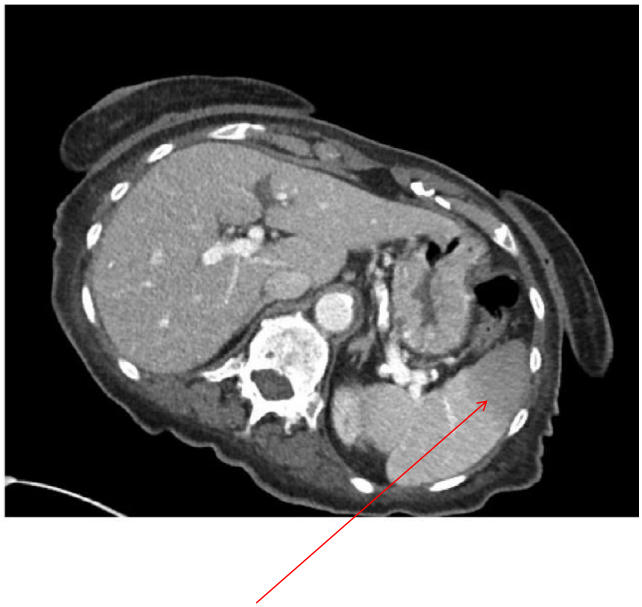

FIGURE 2 Axial view of CT Abdomen with appearances consistent with splenic infarcts

disease. There was no evidence of recurrent tumor within the anal area, examination of which revealed evidence of internal hemorrhoids (Figure 5).

Unexpectedly, the spleen showed no evidence of infarction on detailed examination grossly and microscopically. Kidneys showed granular cortical surfaces with evidence of hypertensive changes represented by thickened blood vessels. Lethal cardiac arrhythmia secondary to severe triple coronary atheroma was the most likely cause of death.

3 | DISCUSSION

This frail octogenarian presented non-specifically, with relatively limited hematological and biochemical derangement of acute phase reactants associated with symptoms of bleeding PR, functional decline, and anemia. The initial working diagnosis was acute diverticulitis with associated sepsis. While the patient had initial clinical improvement on IV co-amoxiclav, she had further bleeding PR and evidence of sepsis following a switch to oral antibiotics prompting further imaging of the abdomen and subsequently the heart. The confirmation of *A. defectiva* bacteraemia with known AS and evidence of potential embolization prompted the investigations which lead to a diagnosis of aortic valve IE. Following the initiation of penicillin-based antimicrobial therapy, repeat blood cultures were sterile. Postmortem examination confirmed evidence of aortic valve IE with the likely cause of intermittent major PR bleeding being hemorrhoids. It is possible that the source of bacteraemia was secondary to bowel translocation in the context of recurrent hemorrhagic episodes.

Abiotrophia defectiva is an NVS considered part of the normal flora of the oral cavity, GI, and urogenital tract in humans. In 1961, Fenkel and Hirsch first isolated a series of satellite streptococci growing adjacent to larger bacteria on agar media. The larger colonies were noted to be supplementing the growth of the satellite bacteria, later termed NVS.[1] NVS was further speciated in 1991 by Bouvet et al[5] to *Streptococcus defectivus* and *Streptococcus adjacens*. In 1995, a new genus of NVS was identified through 16S rRNA sequencing, named *Abiotrophia*.[6] Further sequencing carried out by Collins et al brought about the reclassification of a number of *Abiotrophia* strains in 2000, and the *Granulicatella* genus was named.[7]

Fastidious in nature, NVS characteristically requires the addition of L-cysteine or pyridoxal to grow on blood agar.[1,7] Due to the variation in Gram stains, colony morphology, and difficulty culturing by routine laboratory methods, NVS must be considered a potential pathogen in all culture-negative endocarditis.[1] However, the introduction of molecular methods of identification such as matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry has made it increasingly possible to identify these pathogens in the clinical laboratory by providing a rapid, accurate, and cost-effective means of bacterial identification.[9-11] Following ionization of samples, isolates are separated according to mass and analyzed by their "time of flight" to the detector where sample analysis is cross-referenced to a data base and the bacteria is matched and identified.[8]

Nutritionally variant streptococcus accounts for 5%-6% of all streptococcal endocarditis.[1] *Abiotrophia defectiva* is rarely cultured successfully and has been attributed to <1% of all bacterial endocarditis.[9] The organism has a number of virulence factors such as the production of exopolysaccharide and the ability to bind with fibronectin, which may account for its propensity to adhere to heart valves and produce the associated embolic phenomenon, which have been previously described.[13,15,16]

Evidence suggests that resistance of *A. defectiva* to penicillin is increasing.[10] Alberti et al carried out an extensive investigation of susceptibility patterns of a number of NVS. One third of the isolates examined in the study were susceptible to penicillin, 14% were resistant, and the remaining 53% were of intermediate sensitivity. In general, *A. defectiva* was found to be more resistant than *G. adiacens* with 18.9% of *A. defectiva* resistant to penicillin. No resistance of *A. defectiva* to third generation cephalosporins was observed whereas 50% of *G adiacens* isolates were resistant to cefotaxime. All isolates were fully susceptible to meropenem and vancomycin.[11] Choice of antimicrobial treatment in the setting of NVS IE is often not straightforward, as guidelines on treatment vary and results of susceptibility testing can often be delayed if isolates are sent to reference laboratories for workup. The European Society of Cardiology (ESC)

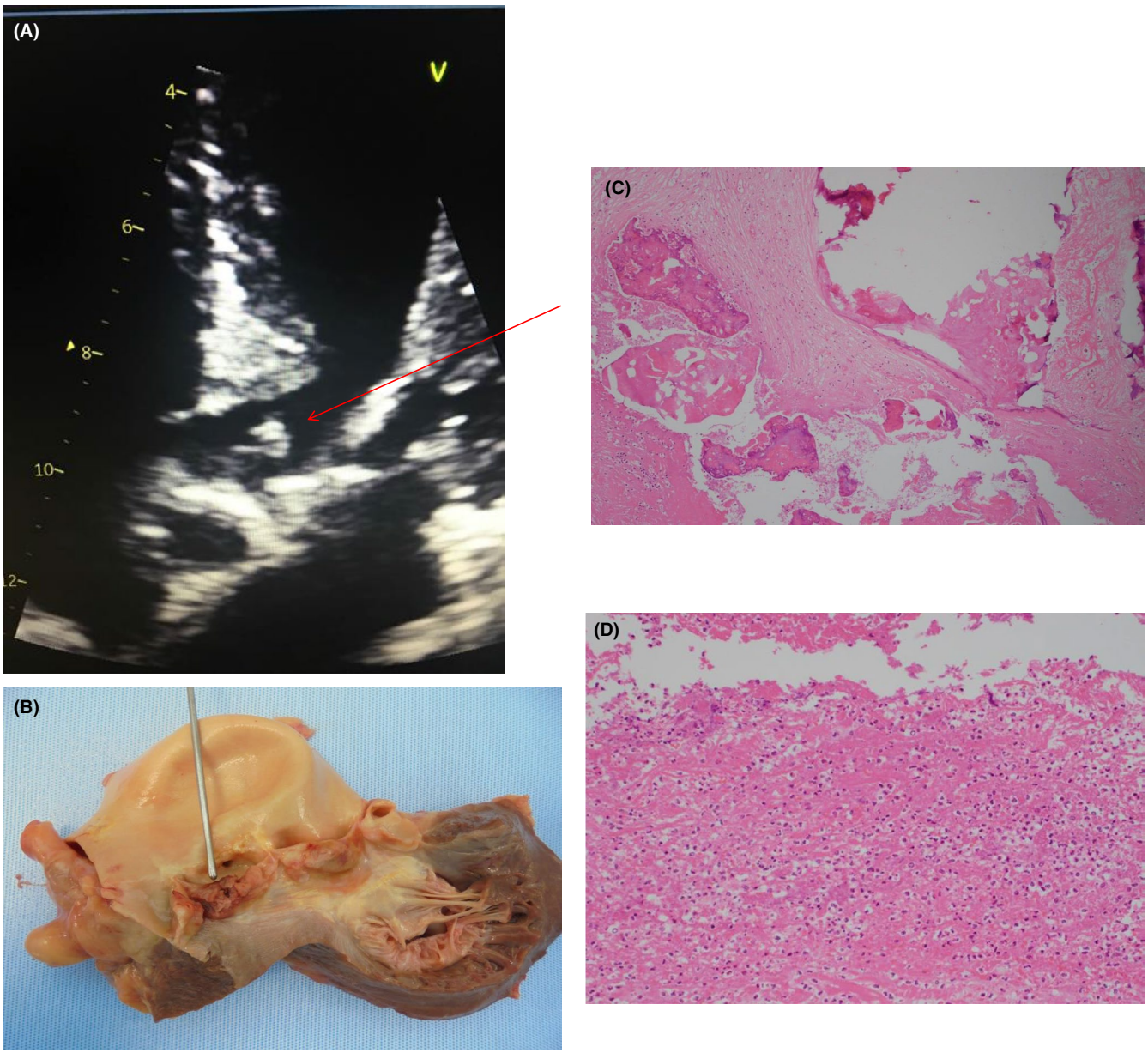

FIGURE 3 A, Echocardiographic evidence of aortic valve vegetation (Five-chamber view). B, Calcification and vegetation of the aortic valve. C, Calcified valve leaflets. D, Vegetation represented by fibrin, acute inflammation, and some bacterial colonies

recommends a number of antimicrobial treatment options including benzylpenicillin, ceftriaxone, and vancomycin combined with an aminoglycoside for the first 2 weeks of treatment.[12] However, the British Society of Antimicrobial Chemotherapy does not advise the use of ceftriaxone with gentamicin in the setting of prosthetic valve endocarditis or if there is an extracardiac focus of infection or if the person is deemed a candidate for surgery. This is due the risk of nephrotoxicity and *Clostridium difficile* infection.[12] The isolate in this case report was sensitive to both penicillin and ceftriaxone with minimum inhibitory concentrations of 0.125 mg/L and 0.5 mg/L, respectively. Despite the sensitivity of this organism, the clinical outcome was poor, reflecting the frequent presence of life threatening comorbidities in older patients, such as severe IHD in this case as well as the high pathogenicity and virulence of NVS, which is independent to its antimicrobial sensitivity.

There are over one hundred-case reports of *A. defectiva* deep-seated infection in the literature. These range from quadruple-valve endocarditis, vertebral osteomyelitis to endophthalmitis and peritonitis.[152123] This pathogen affects all age groups from young children to very old patients.[13] However, outcomes in children are much better as surgical intervention is generally successful despite the presence of embolic complications.[14] The sudden mortality of this case is consistent with other case reports of this age-group and is often a reflection of the high rates of valvular endothelial damage observed in patients over the age of 60, or severe comorbidities as in this case.

FIGURE 4 Cross sections through coronary artery show patent lumen (left) with narrow lumen and stent (right)

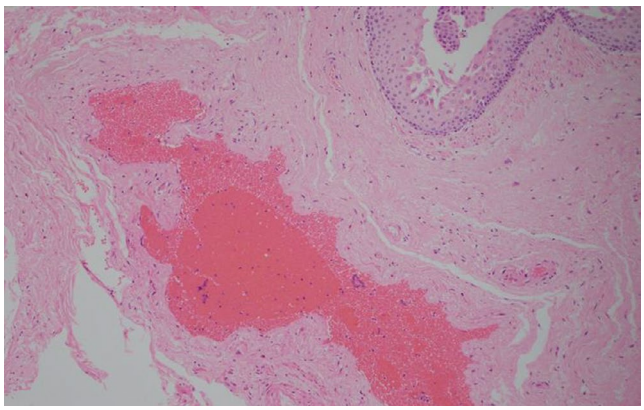

FIGURE 5 Anal biopsy (haemorrhoid) showed benign squamous lining (top right) with dilated congested vascular spaces (centre)

The vast majority of NVS endocarditis cases evaluated in the literature refer to presentations with pyrexia associated with features of septic shock and heart failure.[15] Cases of *A. defectiva* IE reported often involve immunocompromised patients and/or the presence of non-native or structurally defective valves. ?need reference.

The atypical presentation of this older patient with non-specific symptoms represents an unusual manifestation of infection with a rare organism which classically presents with more florid signs of sepsis often with devastating consequences. Given the difficulty with culture and identification of this organism, it is likely that *A. defectiva* may be associated with a higher proportion of culture-negative IE than previously reported.[16] Moreover, it is conceivable that the prevalence of *A. defectiva* infection in older patients is higher than reported in the literature.

In this case, an intra-abdominal source of sepsis was thought to be likely. Persistent bleeding PR during the patient's admission against a background of apparent septic splenic emboli, raised the possibility of colonic septic embolization with associated bowel ischemia. However, the patient's serum lactate level was always within normal parameters and her clinical status was not consistent with extensive bowel ischemia. Unfortunately, she was unfit for proctoscopy, sigmoidoscopy, or colonoscopy but acute diverticulitis and/or colonic carcinoma were the most plausible clinical causes for bleeding PR. However, at postmortem, hemorrhoids were the likely actual source, with no pathological evidence of bowel ischemia, tumor or diverticulitis. This suggests that bacterial translocation from the lower GI tract was the most likely source of bacteraemia.

This pathogen is rarely identified clinically and can have devastating complications often associated with septic embolization in up to one third of cases.[17] This case highlights the importance of performing blood cultures in non-specifically unwell older adults and cardiac imaging, especially with known or suspected valvular disease. The patient, albeit frail and unfit for invasive tests, responded to IV antibiotics and was returning toward her baseline functional status, emphasizing the importance of accurate diagnosis and definitive treatment in this frequently encountered population. Her pre-existing established severe IHD was the likely attributable cause of death, probably resulting in fatal arrythmia.

Prompt diagnosis, pathogen isolation, and commencement of targeted antimicrobial therapy are essential in older patients with *A. defectiva* IE. This is particularly important in order to prevent potentially fatal complications, since presenting symptoms are highly variable and non-specific especially in older patients.

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Not applicable. Published with written consent of the patient.

CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

AUTHOR CONTRIBUTION

GF: involved in conceptualization (lead); writing—original draft (lead); writing—review and editing (equal). ML: involved in conceptualization (secondary); writing—original draft (secondary). PMOS: involved in data curation (lead); formal analysis (lead). RS: involved in writing—original draft (secondary); resources (lead). JO: involved in conceptualization (secondary); writing—review and editing (equal). ECM: involved in Supervision (lead); conceptualization (secondary); writing—review and editing (equal).

ETHICAL APPROVAL

All procedures were under the ethical standards of the local ethics committee.

DATA AVAILABILITY STATEMENT

The data produced in this manuscript are available from the corresponding author via reasonable request.

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