Cross-Sectional Study of a United Kingdom Cohort of Neonatal Vein of Galen Malformation

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Objective: Describe the course and outcomes in a UK national cohort of neonates with vein of Galen malformation identified before 28 days of life.

Methods: Neonates with angiographically confirmed vein of Galen malformation presenting to 1 of 2 UK treatment centers (2006–2016) were included; those surviving were invited to participate in neurocognitive assessment. Results in each domain were dichotomized into “good” and “poor” categories. Cross-sectional and angiographic brain imaging studies were systematically interrogated. Logistic regression was used to explore potential outcome predictors.

Results: Of 85 children with neonatal vein of Galen malformation, 51 had survived. Thirty-four participated in neurocognitive assessment. Outcomes were approximately evenly split between “good” and “poor” categories across all domains, namely, neurological status, general cognition, neuromotor skills, adaptive behavior, and emotional and behavioral development. Important predictors of poor cognitive outcome were initial Bicêtre score ≤12 and presence of brain injury, specifically white matter injury, on initial imaging; in multivariate analysis, only Bicêtre score ≤12 remained significant.

Interpretation: Despite modern supportive and endovascular treatment, more than one-third of unselected newborns with vein of Galen malformation did not survive. Outcome was good in around half of survivors. The importance of white matter injury suggests that abnormalities of venous as well as arterial circulation are important in the pathophysiology of brain injury.

Vein of Galen malformation (VGM) is a rare congenital cerebrovascular malformation characterized by abnormal high-flow arteriovenous connections (shunts) between feeding arteries and an embryonic vein (median prosencephalic vein of Markowski1). This commonly manifests with antenatal or neonatal cardiac failure, usually rapidly progressing to multigorgan failure and death if untreated. Although endovascular therapy and modern intensive care have revolutionized management, there is still high mortality and potential for long-term neurological morbidity.
from both the condition and complications of endovascular treatment.

Two recent meta-analyses\(^2,3\) indicated poor clinical outcomes or death in almost one-half of neonates with VGM. However, there was significant heterogeneity in studies included. Of the factors identified, biases in referral for assessment and treatment could be most significant; the most unwell neonates were not transferred to treating centers and therefore were not included in reported data. Furthermore, at many centers treatment may be withheld from neonates perceived to have the worst outcomes based on historical grading systems such as the Bicêtre score.\(^4,5\) The predictive value of presenting clinical parameters in relation to eventual outcome is poorly understood, and reliable information could critically inform families about prognosis and aid clinical decision making. Finally, the spectrum of impairments in those with poor outcomes is not currently well characterized.

Between 2006 and 2016, it has been mandated that all children with VGM diagnosed within the UK National Health Service (NHS) are managed through 2 centers (Great Ormond Street Hospital for Children, London and Royal Hospital for Sick Children, Glasgow). There were no non-NHS treatment providers in the United Kingdom over this period. Thus, we report complete capture of an unselected and consistently managed national cohort, providing a unique opportunity to report the cross-sectional characteristics of a population-based sample. We also aim to evaluate disease and treatment characteristics as predictors of neurocognitive outcome.

**Patients and Methods**

The study was approved by an independent UK research ethics committee (Integrated Research Application System (IRAS) reference 169446), with governance approval at both sites. Informed consent was obtained from a parent of all participants. The cohort comprises all neonates with angiographically confirmed VGM in the United Kingdom between 2006 and 2016, either diagnosed antenatally or presenting before 28 days of age. Cases with an antenatal diagnosis were delivered electively at 36 to 38 weeks of gestation or earlier if there were signs of compromise on ultrasound or fetal brain magnetic resonance imaging (MRI). All neonates were clinically assessed on admission to the treating unit. All had brain MRI at birth, with the exception of a small number who had brain computerized tomography (CT) because they were too unstable to tolerate transfer to the MRI scanner. The clinical MRI protocol at our center included standard T1-, T2-, and diffusion-weighted sequences. Urgent endovascular treatment was offered to those who showed signs of organ dysfunction requiring intensive supportive therapies (inotropic or ventilator support), provided there was no imaging evidence of widespread, irreversible brain injury (massive cerebral infarction, diffuse parenchymal volume loss, or porencephaly) as assessed by the multidisciplinary team. Treatment was delayed in those few neonates not requiring supportive therapy for organ failure. Unlike previously reported care pathways, treatment was not withheld on the basis of poor physiological status alone (eg, low Bicêtre score\(^4\)). Endovascular treatments typically involved the injection of Histoacryl glue (n-butyl-2-cyanoacrylate) opacified with lipiodol ultrafluid ± tantalum powder or very occasionally with detachable coils or a combination of the two. Treatment-related complications were defined as those that resulted in attributable change in clinical status or imaging and included any intracranial hemorrhage (ICH) within 4 weeks of embolization. All patients underwent repeat brain imaging at clinician discretion; usually, this was undertaken prior to repeat embolization or at the time of a clinical event. Patients with partially or totally closed shunts were also followed with reimagining, again at variable intervals according to clinical need.

Data on demographics, clinical presentation, and procedures were collected retrospectively from clinical records. Patients were allocated into 2 groups according to Bicêtre score at admission, >12 or ≤12. These categories were chosen on the basis of historical clinical practice, where children with scores <8 were traditionally not offered treatment, those with scores of 8 to 12 were treated urgently, and those with scores >12 were offered delayed treatment. Brain MRI, CT scans, and cerebral angiograms obtained for clinical care were reviewed by 2 experienced pediatric neuroradiologists (F.R., A.R.). The first and the most recent brain MRI studies were scored according to a structured schema, recording presence or absence of brain injury in (1) cortical tissue, (2) white matter, (3) deep gray structures, and (4) brainstem and cerebellum, with each hemisphere considered separately. The ventricular index was also measured (the maximal width of the frontal horns/ maximal internal diameter of the skull taken on a coronal MRI image at the level of the foramina of Monro). The initial and most recent cerebral angiograms were also systematically analyzed using a structured schema modified from that described by Geibprasert et al.\(^6\) VGM morphology was categorized as mural or choroidal. Brain perfusion was evaluated by calculating the time taken in seconds for contrast to travel from the internal carotid artery to an M3 branch of the middle cerebral artery that was not supplying the shunt, in seconds.\(^7\) Finally, VGM arteriovenous shunt patency on the most recent angiogram was evaluated.

Clinical and imaging data for those patients who did not survive the neonatal period was obtained from case

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**ANNALS of Neurology**

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Volume 84, No. 4
notes and will be described. Survivors aged > 1 year at the
time of this study were invited to attend at a single time
point for a structured neurological examination and neu-
ropsychological assessments using age-appropriate stan-
dardized measures; participants underwent assessments by
F.L. and V.G. purely for the purposes of the study. Results from these
evaluations were dichotomized into “good” and “poor” categories using recognized criteria to
allow clinically meaningful analysis within the small and heterogenous group. The measures used and interpretation
are summarized in Supplementary Table 1. Those patients
who were too severely impaired to undergo standardized
assessments were allocated to the poor outcome group.

Comparison of important clinical characteristics
between all survivors and those participating in neurocog-
nitive testing was undertaken using \( t \) tests to evaluate for
bias. Analyses were primarily descriptive. As the decision
not to treat was based on imaging appearances of severe
irreversible brain injury and inevitably resulted in death
from the effects of the disease, we decided a \textit{priori} to
examine predictors of overall cognitive outcome. This was
selected because it could be evaluated in all children using
standardized measures, whereas assessment of other
domains was affected by heterogeneity in age and ability
to comply with assessment. Within the clinical context
of a need for prognostic information at the time of
initial presentation, we focused analysis on the relation-
ship between variables that could be ascertained at pre-
sentation and overall cognition using univariate logistic
regression. Those predictors that showed significance
(\( p < 0.1 \)) on univariate analyses were then entered into
multivariate analysis. Significance was set at \( p < 0.05. \)
Analysis was undertaken using SPSS version 25 (IBM,
Armonk, NY).

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{All Survivors, n = 51} & \textbf{Neurocognitive Testing Group, n = 34} & \textbf{Nonsurvivors, n = 34} \\
\hline
Antenatal diagnosis & 23 (45\%) & 16 (47\%) & 14 (41\%) \\
\hline
Age at postnatal diagnosis, days, median (range) & 2 (1–28) & 2.5 (1–27) & 2 (1–5) \\
\hline
Gestation & & & \\
\hline
Term & 39 (77\%) & 26 (76\%) & 30 \\
Preterm & 23 (23\%) & 8 (24\%) & 4 \\
\hline
Mode of delivery & & & \\
\hline
Caesarean section & 30 (59\%) & 20 (59\%) & 12 (35\%) \\
Vaginal & 21 (41\%) & 14 (41\%) & 22 (65\%) \\
\hline
Presentation & & & \\
\hline
Antenatal & 23 (45\%) & 16 (47\%) & 14 (41\%) \\
Organ dysfunction & 28 (55\%) & 18 (53\%) & 20 (59\%) \\
\hline
Bicêtre score at presentation & & & \\
\hline
\(< 12\) & 11/42 & 10/29 & 28/30 \\
\>12 & 31/42 & 19/29 & 3/30 \\
\hline
Embolizations, n, median (range) & 3 (1–6) & 3 (1–4) & 1 (0–3) \\
\hline
Age at first embolization, days, median (range) & 5 (0–814) & 5 (0–814) & 2 (1–7) \\
\hline
Treatment complications, n & 20 (39\%) & 11 (32\%) & 14/19 (74\%) \\
\hline
Age at testing, yr, median (range) & & 5.2 (1–11) & \\
\hline
Head circumference percentile at testing, median (range) & & 56 (1–99) & \\
\hline
\end{tabular}
\caption{Clinical and Demographic Characteristics}
\end{table}
Results

Survival and Recruitment
Of 85 newborns with a diagnosis of VGM before 28 days of age, 51 (60%) survived the neonatal period. The families of 11 surviving children could not be traced due to relocation or lack of response to approach. Forty children were eligible for and invited to participate in neurocognitive assessment; 34 were ultimately enrolled (21 males). See Figure 1 for details of recruitment.

Clinical and Demographic Features of Whole Group
Table 1 summarizes the demographic features of all patients, separated into survivors and nonsurvivors, and separately describes those recruited for neurocognitive testing (“neurocognitive testing group”).

Nonsurvivors
Fourteen of 34 (41%) nonsurvivors had VGM identified prior to birth on antenatal ultrasound. This was usually detected on a third trimester scan undertaken for a variety of indications, usually unrelated to the ultimate diagnosis. The 20 nonsurviving patients diagnosed after birth presented with cardiac failure at a median age of 2 days (range = 1–5 days). The median Bicêtre score at presentation was 7 (range = 4–21).

Fifteen neonates were not treated because the first brain scan showed extensive and irreversible brain injury. Nineteen neonates underwent endovascular treatment (median number of treatments = 1, range = 1–3) at a median age of 2 days (range = 1–7). Of these, 14 neonates had ICH either periprocedurally or in the early postoperative period, although in many, death was considered multifactorial. The remaining 5 neonates died of refractory multiorgan failure (without ICH) despite embolization and maximal intensive care support. Median age at death was 4 days (range = 1–87; see Table 1).

Surviving Patients
All survivors had undergone endovascular treatment (median number of treatments = 3, range = 1–3). Non-participant survivors who were uncontactable or declined neurocognitive testing did not significantly differ from participants in terms of age at postnatal diagnosis (p = 0.83), clinical presentation (heart failure or antenatal diagnosis; p = 0.61), number of treatments (p = 0.43), and number of procedural complications (p = 0.11) as confirmed by t tests. Most events categorized as postprocedural complications occurred almost immediately after the embolization; exceptions to this were a case of spontaneous intraventricular hemorrhage 3 weeks after embolization and another of spontaneous vermian hemorrhage identified on a routine scan 1 week after treatment.

Neurocognitive Testing Group
Thirty-four children participated in neurocognitive assessment. Median age at first embolization was 5 days (range = 0–814); all but 6 had their first embolization within the first 28 days of life. Procedural and/or technical complications occurred in 11 children, with attributable clinical sequelae in 9. These included ICH, glue escape into the venous sinuses, intracranial microcatheter adherence, and the late spontaneous vermian hemorrhage previously described. The final cerebral angiograms (after latest treatment) showed that 21 (64%) patients had complete angiographic closure of the VGM. The remaining patients were clinically stable with minor, nonprogressive shunt and with no further treatments currently planned.

Neurocognitive Testing Group: Imaging Findings
Imaging data for 1 child could not be traced. Brain MRI performed at presentation was available for review in 27 patients, with preprocedural CT study available in the remaining 6 (Fig 2). The interval between the most recent brain imaging and neurocognitive assessment was a median of 1 year and 5 months before follow-up (range = 1 day to 7.9 years). Imaging findings in the neurocognitive testing group are summarized in Table 2. It is apparent that more than one-third of children already had brain injury at presentation, most commonly in white matter. The more complex choroidal VGM angiographic morphology was observed more commonly in this group. By the time of the most recent imaging, most patients had had some degree of brain injury, which again most often affected white matter. There was no significant difference in age at the most recent scan between those with and without brain injury on the latest scan (t test, p = 0.18). Treatment-related complications were not significantly associated with worsening of the scan over time (chi-squared...
Neurocognitive Outcomes

The specific assessment measures administered for each assessed domain and interpretation are summarized in Supplementary Table 1 and the results in Table 3. Of the 34 children assessed, 17 (50%) had a Pediatric Stroke Outcome Measure score indicating good outcome, that is, normal or mild neurological impairment not impacting on daily life. Of the remaining 17, 8 presented with moderate to severe signs of bilateral motor abnormality and global developmental delay, 7 with moderate to severe cognitive and language delay but normal motor development and 2 with a lateralized motor abnormality only. Of the 19 school-aged children, 11 (58%) children are in mainstream schooling, 1 requiring special classroom support for learning. Eight (42%) attend a school for children with significant neurodevelopmental impairment. Six (18%) children have epilepsy, and 4 (12%) have received a diagnosis of autism spectrum disorder.

As summarized in Table 3, the children were roughly equally split into good and poor outcomes across all cognitive domains assessed. From Supplementary Table 2, it is apparent that patients tended to be allocated to the same outcome group across all domains, that is, that neurocognitive impairments were global rather than selective.

Clinical and Demographic Associations with Overall Cognitive Outcome: Descriptive Analyses

Fourteen of the 34 children were categorized as having good overall cognition. This was not related to age at testing \( (t\text{-test, } p = 0.7) \). Children with good outcome had a significantly higher head circumference percentile than those with poor outcome (mean percentile = 80th vs 35th; \( t\text{-test, } p < 0.001 \)). Considering the most recent brain scan, the presence of brain injury and specifically cortical injury was not significantly associated with poor cognitive outcome (Fisher exact test, \( p = 0.14 \) and \( p = 0.16 \), respectively). However, white matter injury on
the most recent scan was significantly associated with poor cognitive outcome (Fisher exact test, \( p = 0.03 \)). The importance of white matter injury is also reflected in the significantly larger ventricular index (likely reflecting white matter volume loss) in the poor cognitive outcome group (mean = 0.4 vs 0.3 in good outcome group; \( t \) test, \( p = 0.02 \)). Patients in the good outcome category were significantly more likely to have a closed VGM at the time of testing (Fisher exact test, \( p = 0.03 \)). Procedural complications were more common in the poor outcome group (9/20 [45%] vs 2/14 [14%] of good outcome group), but not significantly so (Fisher exact test, \( p = 0.07 \)).

**Predictors of Overall Cognitive Outcome**

Logistic regression analysis was undertaken to explore the relationship between clinical and radiological variables apparent at initial presentation and overall cognitive outcome; these included antenatal versus postnatal diagnosis, initial Bicêtre score category (categorized as \( \leq 12 \) or \( > 12 \)), brain injury, cortical injury and white matter injury at presentation, angioarchitecture (choroidal vs mural), and cortical steal. Results of univariate analysis are summarized in Table 4. These indicated a significant association of Bicêtre score \( \leq 12 \), presence of brain injury and specifically white matter injury, and poor outcome. In multivariate analysis including these variables, only Bicêtre score \( \leq 12 \) remained significantly associated with poor outcome (odds ratio = 22, 95% confidence interval = 1.6–295, \( p = 0.019 \)).

**Discussion**

We present a unique, contemporary 11-year national experience of outcomes in VGM neonates presenting

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**TABLE 2. Brain Imaging Angiographic Features in Neurocognitive Testing Participants**

| Feature                        | First Brain Imaging/Angiography | Most Recent Brain Imaging |
|-------------------------------|---------------------------------|---------------------------|
| Any brain injury              | 13 (39%)                        | 28 (85%)                  |
| Cortical injury               | 7 (21%)                         | 15 (45%)                  |
| White matter injury           | 12 (36%)                        | 26 (79%)                  |
| Ventricular index mean (SD)   | 0.36 (0.11)                     |                           |
| Angioarchitecture              |                                 |                           |
| Mural                         | 9 (27%)                         |                           |
| Choroidal                      | 24 (73%)                        |                           |
| Normal MCA branch flow rate, s, mean (SD) | 1.01 (0.43)            |                           |
| Malformation closed at follow-up | 21/33 (64%)                  |                           |

MCA = middle cerebral artery; SD = standard deviation.

**TABLE 3. Results of Neurocognitive Testing**

| Domain                  | Good | Poor | Not Assessable |
|-------------------------|------|------|----------------|
| Neurological outcome    | 17 (50%) | 17 | 9 |
| Cognitive development   | 14 (41%) | 11 | 9 |
| Language development    | 16 (47%) | 9 | 9 |
| Neuromotor function     | 17 (50%) | 9 | 8 |
| Adaptive skills         | 15 (44%) | 9 | 19 |
| Emotional development   | 21/31 | 10/31 | 3 |
| Executive functions     | 7/15 | 8/15 | 19 |

Please refer to Supplementary Table 1 for definitions of “good” and “poor” for each category.
before 28 days of life. All cases were managed between 2 high-volume pediatric neuroscience centers, both with dedicated multidisciplinary teams. The key findings are mortality in 40% of the whole group and roughly equal proportions of globally good and poor outcomes in survivors. Unsurprisingly, those with significantly deranged physiology at presentation were most likely to have a poor outcome. Interestingly, white matter rather than cortical injury appeared to be prognostically important.

In the United Kingdom, there is no national program of third trimester antenatal screening, so “incidental” diagnosis of subclinical VGM is uncommon and we are likely to have identified a more severe group than in countries where late pregnancy ultrasound is routine. Termination of pregnancy for antenatally diagnosed VGM is uncommon in the United Kingdom. Our universal health-care system captures all VGM patients and delivers them early to an experienced treatment center. Thus, although patient numbers are small, these data provide a unique, population-based insight into the longitudinal impact of this rare disease. Despite aggressive highly specialized neonatal intensive care, relatively few of our patients could be stabilized with medical therapy treatment alone and we did not find that delayed embolization was generally feasible in our cohort. The cause for this divergence from other published experience is not clear, but seems likely to reflect our unbiased capture of the national patient cohort.

Historically, endovascular treatment was not offered to babies in a poor clinical state on the basis of futility. The Bicêtre score was developed to guide transfer to specialist centers; conventionally, patients with scores < 8 were not transferred (or treated), those with scores of 8 to 12 were offered urgent embolization, and those scoring >12 were typically stabilized with medical therapy and embolized later. Published series from centers following this paradigm will, therefore, show further significant selection bias, with potential for underrepresenting poor outcomes. Unsurprisingly, we found Bicêtre score ≤ 12 predicted poor outcome; however, it is important to note that we have previously published good outcomes in patients presenting with Bicêtre scores < 8.16 We were not able to examine the prognostic value of the Bicêtre at additional cutoff points due to small numbers but believe the groups selected reflect established clinical practice.

The added value of our study is in examining the importance of several clinical and radiological factors. Although limited by relatively small numbers and the retrospective study design (where imaging protocols were clinically driven), we make the novel observation of the predictive importance of early white matter injury. We postulate that this relates to venous hypertension rather than arterial steal and ischemia. Venous hypertension is thought to be the major precipitant of “melting brain” syndrome well recognized in older patients with VGM.

### Table 4. Univariate Logistic Regression Analyses

| Predictor                        | Good Cognitive Outcome, n = 14 | Poor Cognitive Outcome, n = 20 | OR Predicting Poor Outcome (95% CI) | p    |
|----------------------------------|-------------------------------|-------------------------------|-----------------------------------|------|
| Bicêtre score                    |                               |                               |                                   |      |
| ≤12                              | 1/12                          | 9/17                          | 12.3 (1.3–118)                    | 0.03 |
| >12                              | 11/12                         | 8/17                          |                                    |      |
| Antenatal diagnosis              |                               |                               |                                   |      |
|                                 | 7 (50%)                       | 11 (55%)                      | 1.2 (0.31–0.38)                   | 0.77 |
| Brain injury at presentation     |                               |                               |                                   |      |
|                                 | 1 (7%)                        | 12 (53%)                      | 22.3 (2.4–208)                    | 0.007|
| Cortical injury at presentation  |                               |                               |                                   |      |
|                                 | 1 (7%)                        | 6 (31%)                       | 6.0 (0.63–57)                     | 0.12 |
| White matter injury at presentation | 1 (7%)                   | 11 (58%)                      | 17.9 (1.9–166)                    | 0.01 |
| Choroidal angioarchitecture c/w mural | 9 (%)                     | 15 (79%)                      | 2.1 (0.44–9.8)                    | 0.35 |
| Cortical steal, s, mean (SD)     | 0.99 (0.37)                   | 1.04 (0.41)                   | 1.29 (0.25–6.7)                   | 0.77 |

Cortical steal was defined as the time taken in seconds from contrast first appearing in the arterial phase to it reaching the M3 branch of the middle cerebral artery.

*Score ≤ 12 compared with score ≥ 12.

c/w = compared with; CI = confidence interval; OR = odds ratio; SD = standard deviation.
Our new observation might support an early treatment strategy over a more expectant policy of medical management and delayed treatment, in reducing exposure of the developing brain to the harmful effects of venous hypertension.

Transarterial cerebral embolization is challenging and hazardous in neonates, and all approaches carry risk of vascular injury, extravasation, and nontarget embolization, potentially contributing to poor outcomes. No comparable data are available to evaluate one treatment modality with respect to another. In our series, almost exclusively treated with Histoacryl glue (n-butyl-2-cyanoacrylate) embolization, we noted cases of early posttreatment ICH in both survivors and nonsurvivors. This probably relates to vascular injury and changes in vascular pressure and/or flow dynamics following embolization, although contribution from coexisting coagulopathy, acidosis, and profound circulatory failure is likely. ICH has been described both after treatment and also occasionally as part of the natural history of untreated neonatal VGM. Inevitably, it is likely that early intervention increases risk of early ICH, but this must be balanced against the risk of cerebral and systemic damage due to ongoing high-flow arteriovenous shunting. Alternative endovascular strategies, in particular, transvenous partial occlusion of the sac with detachable coils, have been successful in controlling heart failure in a few published cases, although there are few long-term outcome data. This technique is technically feasible, particularly with enhanced coil technology, but takes time and has also been associated with venous hemorrhagic complications. Additionally, coil obscuration will hamper visualization in subsequent treatment attempts, and this is not currently favored in our neonatal practice. Clearly, there is scope to improve therapeutic technologies and approaches in this condition.

Our relatively crude dichotomization of outcomes into “good” and “poor” is open to criticism, but more complex analysis of structure–function relationships was limited by small sample size and multiplicity of variables. Even with the limitations, these data are uniquely informative for counseling families of newborns presenting with VGM both antenatally and postnatally. Poor neurocognitive outcomes tended to occur across all measured categories, reflecting the frequent and often very widespread patterns of brain injury seen. Our findings suggest that future research should focus on understanding the causes and consequences of white matter injury in particular and relating this prospectively to systemic and shunt characteristics. As with many rare diseases, single center studies are likely to be underpowered and, although we are continuing nationwide UK collaboration, an international effort is likely to be ultimately more fruitful and allow more meaningful insights.

Acknowledgment
This article presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit program (grant reference number PB-PG-0214-33090). This project was supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Author Contributions
V.G., F.R., P.L., M.J.P., F.V.-K. contributed to conception and design of the study; all authors contributed to acquisition and analysis of data; all authors contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest
Nothing to report.

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