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Real World Efficacy and Safety of Sofosbuvir + Velpatasvir + Voxilaprevir in Romanian Patients with Genotype 1b HCV Infection Non-reponders to DAAs Therapy

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ABSTRACT

Background & Aims: The sofosbuvir (SOF) / velpatasvir (VEL) / voxilaprevir (VOX) combination has been evaluated in more than 800 patients enrolled in phase II and phase III studies, where it demonstrated excellent safety and efficacy, achieving overall sustained viral response (SVR) rates of more than 95%. We aimed to assess the efficacy and safety of SOF/VEL/VOX in a real-world study, including patients previously treated for genotype 1b hepatitis C virus (HCV) infection that did not obtain a sustained viral response with previous direct-acting antivirals (DAAs) therapy.

Methods: In Romania, through a nationwide government-funded program in 2019-2020, 213 patients with chronic hepatitis C non-responders to previous DAAs therapy, received treatment with SOF/VEL/VOX 400/100/100 mg/day for 12 weeks. We performed a retrospective longitudinal study that included 143 individuals who were treated in Bucharest, Iași, Craiova and Constanța clinics, all with genotype 1b HCV infection. Efficacy was assessed by the percentage of patients achieving SVR 12 weeks post-treatment (SVR12). Serious adverse events (SAE) were registered.

Results: Our cohort comprised 53% males with a median age of 60 years (27÷77); 47% were pre-treated with ombitasvir/paritaprevir/ritonavir+dasabuvir ± ribavirin, 40% with ledipasvir/SOF, 13% with elbasvir/grazoprevir. 42% of patients associated co-morbidities, 45% had compensated liver cirrhosis, 2% had treated hepatocellular carcinoma (HCC) and 1% had hepatitis B virus co-infection. SVR by intention to treat was reported in 139/143 (97.2%) and per protocol in 141/143 (98.6%). No predictive factors for SVR were identified. Rate of liver decompensation in patients with cirrhosis was 6% and was statistically associated in multivariate analysis with Child-Pugh score ($p<0.01$) and with severe steatosis ($p=0.004$). Occurrence of new HCC was reported in 3.6% of all patients with cirrhosis and was associated with poor liver function [higher Child-Pugh score ($p=0.001$) and low albumin levels ($p=0.02$)]. Serious adverse events related to therapy were reported in 1/143(0.7%).

Conclusions: SOF/VEL/VOX was highly efficient in our population of patients with a 97.2% SVR. Liver decompensation occurred in 6% of cirrhotic patients at SVR, related to hepatic dysfunction.

Key words: Sofosbuvir + Velpatasvir + Voxilaprevir – genotype 1b HCV Infection – efficacy – safety.

Abbreviations: AFP: alpha fetoprotein; BMI: body mass index; DAA: direct-acting antiviral; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; OPrD: ombitasvir/paritaprevir/ritonavir+dasabuvir; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained viral response; VEL: velpatasvir; VOX: voxilaprevir.

INTRODUCTION

Hepatitis C virus (HCV) is a flavivirus with 7 major genotypes and the major routes of contamination are unsafe drug injections and unsafe medical procedures [1, 2]. Viral hepatitis C remains a public health problem worldwide. Latest assessment of World Health Organization in 2015 reports that 71 million people are chronically infected by HCV [3].

Globally, HCV genotypes 1 and 3 are the most common, comprising 46.2% and 30.1% of cases, whereas genotypes 2, 4, 5 and 6 are each responsible for <10% of cases (9.1%, 8.3%, 5.4%, and <1%) [4, 5]. In Romania, the overall prevalence of HCV infection is lower than previously reported (1.39%) and genotype 1b is predominant (99.6%) [6-8].

The therapy goal for treating HCV infection is to obtain a sustained viral response (SVR), and all quasi-species have to be eliminated [9]. In Romania more than 39,000 received direct-acting antivirals (DAAs) therapy, with more than 96% achieving SVR [10-14]. We previously reported a 2.7-3.6% 2.7-3.6% failure rate for ombitasvir/paritaprevir/ritonavir and dasabuvir (OPrD), 3.1% for ledipasvir/sofosbuvir (SOF) and 2.9 % forelbasvir/grazoprevir, which are similar overall failure rates, independent of the initial NS5A regimen [10, 13, 14].

Certain virological factors may predict DAAs failure such as HCV genotypes 1a and 3 that have proven to be more difficult to cure than others, especially in patients with liver cirrhosis and patients infected with viruses harboring drug resistance associated substitutions, present either as natural polymorphisms at baseline or following selection due to DAAs failure [15-16].

The approval of the protease inhibitor voxilaprevir (VOX) combined with the NS5A inhibitor SOF and the NS5A inhibitor velpatasvir (VEL) offers the clinician a potent retreatment option targeting all steps of HCV replication. The SOF/VEL/VOX combination has been evaluated in more than 800 patients enrolled in phase II and phase III studies, where it demonstrated excellent safety and efficacy, achieving overall SVR rates of more than 95% [16-21].

The aim of this study is to assess the efficacy and safety of SOF/VEL/VOX in a real-world study, including patients previously treated for genotype 1b HCV infection that did not obtain a sustained viral response with previous DAAs therapy.

METHODS

We included 213 patients treated with SOF/VEL/VOX 400/100/100 mg/day for 12 weeks between June 2020 and June 2021 in Romania. We performed a retrospective longitudinal study, collecting complete data for 143 individuals who were treated in centers from Bucharest, Iași, Craiova and Constanța. All patients signed an informed consent that their clinical and demographic data could be used for scientific purposes and the study was approved by the Ethics Committee of Fundeni Clinic Institute.

The inclusion criteria were previous treatment with DAAs, the presence of detectable HCV- RNA viral load, lack of significant ethanol consumption in the last 3 months.

We excluded all patients with decompensated cirrhosis. All patients had genotype 1b HCV infection. Demographic and clinical parameters were recorded at baseline and included: age, gender, body mass index (BMI), diagnosis of cirrhosis, history of hepatocellular carcinoma (HCC), prior HCV DAAs experience. A standardized blood panel was determined at baseline and 3 months after the end of treatment: alanine aminotransferase, albumin, aspartate aminotransferase, platelets and baseline HCV RNA, INR, creatinine, alpha fetoprotein (AFP). Results for treatment-emergent resistance-associated substitutions (RAS) were available only for 18 patients, therefore they were omitted from the statistical analysis.

Liver fibrosis was estimated mostly by FibroMax™ (Biopredictive, Paris, France) (80%) and secondly by transient elastography (TE) (FibroScan, EchoSens, Paris, France) (20%). 20% of patients had both measurements. FibroMax™ is a non-invasive method for estimation of the liver injury through of the association of three tests: FibroTest™, SteatoTest™ and NashTest™, respectively. It is well validated for HCV, especially for detecting cirrhosis (AUROC 0.87) [22]. FibroScan is an ultrasound based elastography technique that was developed for the non-invasive assessment of liver fibrosis. In HCV, FibroScan can identify patients with ≥ F2 fibrosis with AUROC value of 0.89 and patients with F4 fibrosis with AUROC value of 0.92. The presence of cirrhosis was determined by a FibroScan score of more than 12.5 kPa or a FibroTest score of more than 0.75 [23].

Screening for HCC before starting the DAAs therapy was done in all subjects according to AASLD guidelines liver ultrasound with AFP [24], and in 9 cases a computed tomography scan because of limited ultrasound reliability (they have truncal obesity or marked parenchymal heterogeneity). In the 3 patients with treated HCC, absence of recurrence of HCC was defined according to imaging criteria (via contrast-enhanced computed tomography in 1 patient and contrast-enhanced magnetic resonance imaging in 2 patients) 3 months after the last therapeutic procedure.

All existing co-morbidities were recorded before initiating treatment with SOF/VEL/VOX. Only severe adverse events leading to discontinuation of therapy were reported.

All patients that finished the antiviral therapy performed HCV-RNA viral load 12 weeks after the completion of therapy. HCV RNA levels were assessed by quantitative PCR assays: COBAS TaqMan HCV v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA).

All patients underwent follow-up visits at post-treatment week 12.

The primary efficacy outcome was achievement of SVR at post-treatment week 12 (SVR12), defined as HCV-RNA concentration below the LLOQ 12 weeks after the end of treatment. The secondary outcome measure was the evolution of liver function tests at post-treatment week 12, and the appearance of HCC.

Statistical Analysis

All analysis was done in intention-to-treat. Results were summarized as median and range for nonnormally distributed scales or ordinal variables or as numbers and percents for categorical variables. We looked for differences concerning the independent variables by outcome in bivariate analysis (Mann-Whitney U test or Fisher's exact test, depending on variables). A Kruskall-Wallis test was used for finding a correlation between nominal and ordinal data. A logistic regression model was computed, and all independent variables associated with $p<0.10$ with the dependent variable in bivariate analysis were introduced in a stepwise manner. The model with the independent variables retained by both the forward and the backward stepwise method was kept. A two-sided p value of < 0.05 was noted as statistically significant. Data analysis was performed with statistical software (SPSS version 20.0 from IBM Corporation, Armonk, NY, USA).

RESULTS

We initially included 143 patients from which we report 2 dropouts: one due to intolerance (severe nausea and vomiting), and one death (severe coronavirus disease 19 after completion of therapy).

In this cohort the proportion of male patients was 53%, the median age was 60 years (27÷77) and 42% had co-morbidities. The most frequent comorbidities were hypertension (29.5%) and type 2 diabetes (13.7%). 1% were co-infected with hepatitis B virus and 2% had a history of previously treated hepatocellular carcinoma. Most of the patients were overweight or obese, with a median BMI of 27.32. Regarding previous exposure to DAA, 47% were pre-treated with OPrD ± RBV, 40% with ledipasvir/SOF, 13% with elbasvir/grazoprevir. Most patients had significant liver fibrosis (45% F4, 23% F3) estimated by Fibromax and/or Fibroscan, while 25% were F2, 5% F1 and 2% F0. The majority of cirrhotic patients (69%) had a Child Pugh score of 5. As previously mentioned, patients with decompensated cirrhosis were excluded from study.

Sustained viral response by intention to treat was reported in 139/143 (97.2%), and per protocol in 141/143 (98.6%).

The patient that stopped the therapy because of severe nausea and vomiting was a female, 80 years old, with compensated cirrhosis. The other 2 patients who did not obtain SVR (relapsers), one male aged 68 and one female aged 67, were one with compensated cirrhosis one with F2 estimated fibrosis. No predictive factors for SVR were identified (Fig. 1). Treatment effectiveness was not affected by other baseline features: BMI>25 kg/m^2 (p=0.97), baseline HCV-RNA (<600000 IU/ml vs ≥600000 IU/ml) (p=0.5).

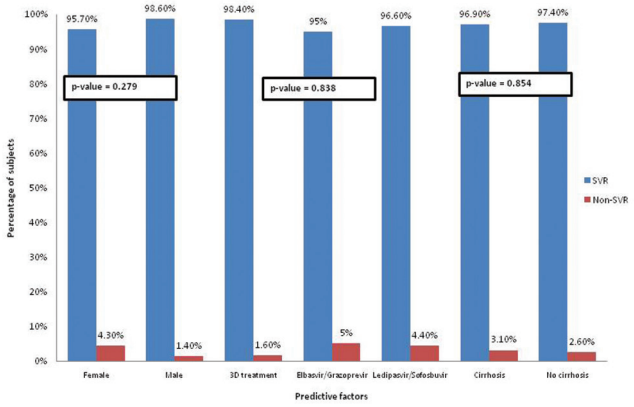

Fig. 1. Possible predictive factors to SOF/VEL/VOX

Regarding necro-inflammatory activity estimated by FibroMax, most of our patients showed severe inflammatory activity (38%), 33% had moderate inflammation and 29% mild or absent.

FibroMax testing also allowed assessment of coexisting non-alcoholic steatohepatitis (NASH) changes: 65% with moderate-severe coexisting NASH. The distribution of steatosis severity is similar to that of NASH: approximately 71% of patients showing moderate to severe steatosis.

All patients were followed-up during their treatment period and 12 weeks after they finished the therapy with SOF/VEL/VOX. Rate of liver decompensation during these 24 weeks follow-up period was low in patients with cirrhosis: 6%.

The dynamics of the biological parameters from the start of SOF/VEL/VOX therapy and 12 weeks after the end of antiviral therapy is described in Table I. A significant improvement of aminotransferases level, platelets number and liver function were noticed; also a significant decrease of blood glucose after DAA treatment was registered.

Table I. Biological parameters and Child-Pugh score at baseline and at 12 weeks after the end of antiviral therapy

Parameter	Baseline	12 weeks after the end of treatment	p
Platelets	168, 000/mm^3 (30÷362)	183,000/mm^3 (31÷362)	<0.001
AST, IU/ml	57 (15÷181)	27 (9÷119)	<0.001
ALT, IU/ml	57 (13÷240)	24 (10÷91)	<0.001
INR	1.14 (0.85÷2.33)	1.19 (0.76÷5)	0.001
Creatinine, mg/dl	0.81 (0.59÷1.47)	0.83 (0.32÷8)	0.001
Alpha fetoprotein, ng/ml	5.69 (0.3÷52.60)	4.56 (0.80÷43)	<0.001
Child-Pugh score	5 (5÷6)	5 (5÷8)	0.153
Blood glucose in diabetics, mg/dl	141 (95÷179)	116 (89.5÷200)	0.034

AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalised ratio.

Sixty-five subjects (45.3%) had compensated liver cirrhosis at the beginning. From those, 29 patients (46%) had comorbidities, the most frequent being arterial hypertension (30.2%), followed by diabetes mellitus type 2 (17.5%). 73.3% of cirrhotic patients had severe necro-inflammatory activity (73.3%), followed by a moderate activity (26.7%). More than half of them had severe NASH (57.8%) and 68.9% had moderate to severe steatosis.

Predictive factors for hepatic decompensation are shown in Table II. However, in multivariate analysis (Table III), only the Child-Pugh score was confirmed as a predictive factor for

Table II. Predictive factors of hepatic decompensation at 12 weeks after the end-of-therapy in patients with liver cirrhosis (bivariate analysis)

Variable	Hepatic decompensation N=6	Preserving liver function N=59	p
Gender M (%)*	66.7%	64.4%	0.938
Age **	44 (39, 69)	60 (40, 74)	0.123
Platelets (x10^3)**	42 (36, 52)	102 (30, 298)	<0.001
Child-Pugh score**	6 (6, 6)	5 (5, 6)	<0.001
Child-Pugh score***			
5 points	0 (0%)	45 (76.3%)	<0.001***
6 points	6 (100%)	14 (23.7%)	
INR**	1.43 (1.15, 1.57)	1.12 (0.91, 1.90)	0.028
Total bilirubin**	2.1 (1.32, 2.3)	1.27 (0.45, 2.70)	0.007
Albumin**	3.6 (3.2, 3.72)	4.18 (2.7, 5.09)	0.054
Moderate-severe steatosis***	100%	64.5%	0.004

* percent, compared by Fisher exact test; ** median (minimum, maximum), compared by Mann-Whitney U; *** percent, compared by Kruskall-Wallis test; INR: international normalised ratio.

Table III. Predictive factors of hepatic decompensation at 12 weeks after the end-of-therapy in cirrhotic patients (multiple regression analysis)

Variable	B	SE	p	95% CI
Gender M	-0.017	0.041	0.674	-0.099-0.064
Median Age	0.001	0.002	0.757	-0.003-0.005
Platelets	0.000	0.000	0.612	-0.001-0.000
AST	0.000	0.001	0.941	-0.002-0.002
ALT	0.000	0.000	0.300	-0.001-0.000
INR	-0.153	0.102	0.133	-0.354-0.048
Total bilirubin	0.047	0.044	0.290	-0.041-0.135
Child-Pugh score	0.268	0.051	<0.001	0.167-0.370
Albumin	0.023	0.045	0.510	-0.066-0.112
Constant	-1.324	0.265	<0.001	

CI: confidence interval. For other of abbreviations see Table I.

Table V. Predictive factors of HCC occurrence at 12 weeks after the end-of-therapy in cirrhotic patients (multiple regression analysis)

Variable	B	SE	p-value	95% CI
Gender M	0.103	0.062	0.102	-0.021-0.227
Median age	0.000	0.003	0.897	-0.007-0.006
Platelets	-0.001	0.001	0.160	-0.002-0.000
AST	-0.001	0.001	0.252	-0.002-0.001
ALT	-0.001	0.001	0.946	-0.001-0.001
INR	-0.222	0.139	0.116	-0.500-0.056
Total bilirubin	-0.039	0.058	0.500	-0.155-0.077
Child-Pugh score	0.227	0.062	0.001	0.103-0.350
Albumin	0.109	0.046	0.022	0.017-0.202
Alpha fetoprotein	0.003	0.003	0.263	-0.002-0.009

CI: confidence interval. For other of abbreviations see Table I.

hepatic decompensation (p<0.01). There was a statistically significant correlation between the level of steatosis and hepatic decompensation (p=0.004), but not for NASH (p=0.082) or the level of BMI (p=0.545).

Occurrence of a new case of HCC was reported in 3.6% of all patients with cirrhosis (3 cases), 2 men and one woman. These de novo HCC were diagnosed at 3 months after the end of antiviral therapy: one patient developed decompensation concomitantly to HCC diagnosis, while in the other 2 patients cirrhosis remained compensated. Patients were treated through transarterial chemoembolisation. We found the following risk factors for HCC occurrence in multivariate analysis: higher Child-Pugh score (p=0.001) and low albumin levels (p=0.02). There was no statistically significant correlation between HCC and NASH (p=0.133) or steatosis (p=0.282) or the level of BMI (p=0.062).

Table IV. Predictive factors of HCC occurrence at 12 weeks after the end-of-therapy in cirrhotic patients (bivariate analysis)

Variable	HCC occurrence N=3	NO HCC occurrence N=62	p
Gender M (%)*	66.7%	64.4%	0.195
Age **	48 (46, 71)	60 (40, 74)	0.084
Platelets (x10^3)**	46 (38, 52)	94 (30-268)	0.063
Child-Pugh score**	6 (6, 6)	5 (5, 6)	0.007
INR**	1.32 (1.12-1.47)	1.14 (0.91-1.90)	0.5
Total bilirubin**	1.4 (1.32-1.52)	1.30 (0.45-2.70)	0.64
Albumin**	4.24 (3.8-4.72)	4 (2.70-5.09)	0.514
Alpha fetoprotein**	5.50 (4.2-12)	7.70 (2.11-52.60)	0.362

* percent, compared by Fisher exact test; ** median (minimum, maximum), compared by Mann-Whitney U; HCC: hepatocellular carcinoma; INR: international normalised ratio.

DISCUSSION

Our real-life study showed that VOX combined with the NS5B inhibitor SOF and the NS5A inhibitor VEL was a highly efficient and safe therapy in patients with genotype 1b HCV infection and previous DAAs failure, with a SVR in intention to treat analysis of 97.2%. These findings are similar to the high eradication rates obtained in clinical trials (Polaris-1 and Polaris-4) and also on a limited number of cohort studies [2, 5, 15, 20, 21, 25-29]. Belperio et al. [16] in their large real-world cohort of 573 patients with genotype 1-4 chronic HCV infection reported lower SVR in intention to treat analysis (90% in genotype 1). However, their subjects were older, had multiple comorbidities and predominantly genotype 1a infection (80%), with 46 patients having discontinued treatment before week 12 [16].

The rate of severe adverse events leading to the discontinuation of therapy was very low in our cohort, with only one patient reporting severe nausea and vomiting, similar with other reports. Authors of clinical trials Polaris-1 and Polaris-4 described the following adverse events: fatigue (21%), headache (20%), diarrhea (19%), and nausea (14%), but no severe adverse events leading to discontinuation of therapy [27].

We did not identify any features associated with treatment failure. Degasperi et al. [29] in a large Italian cohort of 179 patients identified cirrhosis and hepatocellular carcinoma onset, mostly in patients with HCV genotypes 1a and 3 [29]. The Spanish real-life cohort reported by Llaneras et al. [30] including 135 patients, 30 of them with genotype 3 HCV infection found that genotype 3 and presence of cirrhosis in association with genotype 3 were the only predictive factors of viral non-response to SOF/VEL/VOX therapy [30].

The main strength of our study was that it included the highest number of patients reported this far in a very homogenous population: our subjects are only genotype 1b, 45% with compensated liver cirrhosis. Another important aspect of our study was the monitoring of hepatic, renal function and the rate of hepatocellular carcinoma during SOF/VEL/VOX therapy.

Similar to the clinical trials Polaris-1 and Polaris-4, we showed a significant improvement of laboratory features 12 weeks after the end of antiviral therapy: value of platelets increased, transaminases returned to normal value in most of the patients, serum AFP normalized. The rate of deterioration in renal function was negligible during the 24-week follow-up period, the rate of hepatic decompensation was low among patients with cirrhosis (6%), and the number of new cases of HCC was 3 out of 65 cirrhotic patients. Degasperi et al. [29] found 6 cases of new onset HCC in their cohort of 179 patients prospectively followed-up, only in those with cirrhosis,

2 with viral non-response. All our patients with new onset of hepatocellular carcinoma were recorded with SVR. The novo occurrence of hepatocarcinoma in patients with chronic HCV hepatitis treated with DAAs is widely debated in the literature, with reported incidence rates varying between 1-7%, depending on the proportion of patients with advanced fibrosis (F3/F4) and the follow-up interval [31-35].

Regarding special populations, our real-life cohort included only one patient with HBV coinfection, who received Entecavir during antiviral treatment with SOF/VEL/VOX and 6 months after HCV treatment; this patient was recorded with SVR. Three patients with treated HCC (one with liver transplant and two with transarterial chemoembolisation) received SOF/VEL/VOX and achieved SVR; no HCC relapse was recorded 12 weeks after the end of therapy. By multivariate analysis we showed that the most important predictive factor for liver decompensation and for HCC occurrence was the poor liver function at the beginning of therapy (Child-Pugh score). According to the literature data, presence of cirrhosis, stage of liver disease (high Child-Pugh score), low platelet count, HBV coinfection, presence of diabetes and virological failure may predict HCC occurrence in patients with chronic hepatitis C treated with DAA [31-35]. Other authors found a lower rate of hepatic decompensation compared to our data in patients with compensated liver cirrhosis treated with DAAs therapy (1-2% depending on the follow-up interval), and this was associated with severe portal hypertension and increased Child-Pugh score and MELD score [10, 36-39]. Our data suggest that liver decompensation in cirrhotic patients treated with SOF/VEL/VOX is associated with severe hepatic steatosis, an association previously not reported in literature.

Incidence of type 2 diabetes in people with chronic HCV infection is increased compared to the general population, because HCV induces insulin resistance and promotes β-cell dysfunction [40]. Our study showed a significant drop in fasting glucose level in treated patients with diabetes, which is concordant with others authors findings (interestingly, this metabolic change was BMI-independent) [41, 42].

The major drawback of our study is that only a minority of our subjects performed baseline NS3 or NS5a/5b RAS and therefore we did not include these data in our analysis. However, these RAS had no impact on the primary efficacy outcome in other studies. Bourliere et al. [27] reported data coming from Polaris-1, that included 248 patients with chronic hepatitis C with previous DAAs failure: the SVR 12 rate for those with baseline RAS was 97% (199/205) and 98% (42/43) for those without RASs. Our data showed that SVR 12 rates were similar, regardless of the previous treatment regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir, or ledipasvir/SOF or elbasvir/grazoprevir), suggesting that pretreatment RAS testing might not be necessary. Another limitation of our study is that it did not include any patient previously treated with velpatasvir/SOF or glecaprevir/pibrentasvir since these antiviral combinations were just recently available in Romania (starting from February 2022). Finally, the treating physicians reported only the SAE leading to discontinuation of the antiviral therapy, so there was not a systematic reporting of adverse events, and we could not assess adherence to treatment.

CONCLUSIONS

Our efficacy and safety results support SOF/VEL/VOX treatment for 12 weeks in patients with chronic HCV hepatitis. It is a safe, well tolerated and effective treatment for patients who have initial DAA treatment failure, irrespective of the previous regimen, the presence of compensated cirrhosis and other comorbidities.

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Authors' contribution: L.G. and L.I. designed the study. C.M.P. drafted the manuscript. A.T., C.P.P., C.S.P., C.G.T., T.M., T.S., S.I. and M.M. collected the data. D.I. performed the statistical analyses. L.G., L.I., A.T., M.M., C.S., M.M.D., C.S.P. critically revised the manuscript. All authors read and approved the final manuscript.

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