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Diverting Stoma for Refractory Ano-perineal Crohn's Disease: Is It Really Useful in the Anti-TNF Era? A Multivariate Analysis in 74 Consecutive Patients

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Abstract

Background and Aims: Faecal diversion [FD] can be proposed in patients with refractory anoperineal Crohn's disease [APCD]. This study aimed to assess long-term results of this strategy, following the advent of the anti-tumour necrosis factor [TNF] era.

Methods: All patients who underwent FD for refractory APCD between 2005 and 2017 were included, excluding patients with a history of ileal pouch-anal anastomosis. A multivariate analysis regarding absence of stoma reversal [SR] was performed.

Results: A total of 65 consecutive patients who underwent FD for APCD (comprising anoperineal fistula [*n* = 40, 62%], rectovaginal fistula [*n* = 21, 32%], fissures and/or ulceration [*n* = 9, 14%], and/or anal stricture [*n* = 5, 8%]) were included. At the time of FD, 34 patients [52%] presented with small bowel Crohn's disease [CD] involvement, 29 [45%] with colonic involvement, and 19 [29%] with rectal involvement. Following FD, 54 patients [83%] were treated with anti-TNF therapy, prescribed for isolated APCD [*n* = 10, 15%] or luminal CD with APCD [n = 44, 68%]. After a mean follow-up of 49 ± 29 [7–120] months, SR was not possible in 32 patients [49%], including 17 patients [26%] requiring a subsequent proctectomy with abdominoperineal excision. In multivariate analysis, rectal CD involvement was the only independent factor associated with a reduced rate of SR (odds ratio: 4.0 [1.153–14.000]; *p* = 0.029), and anti-TNF therapy had no impact on SR rate.

Conclusions: FD can be performed in selected patients with refractory APCD, to avoid abdominoperineal resection. However, this strategy should be proposed with caution in patients presenting with rectal CD involvement. Anti-TNF therapy has no impact on SR rate.

Key Words: Anoperineal Crohn's disease; faecal diversion; anti-TNF therapy; surgery

1. Introduction

Anoperineal Crohn's disease [APCD] is a common CD localisation, as has been reported in 13% to 43% of patients during the course of their disease.[1–3] APCD manifestations are largely heterogeneous and vary from asymptomatic skin tags to severe and recurrent abscesses and fistulas[4] which might be responsible for anal sphincter damage,

thus jeopardising patients' long-term functional outcome and quality of life.[5]

The exact physiopathology of APCD development is still unknown and therefore optimal medical and surgical management has yet to be defined. Several surgical techniques, mainly aimed to achieve abscess drainage and fistula closure, have been proposed, such as seton placement, fibrin glue, stem cell injection, or mucosal advancement. However to date, no clear APCD management algorithm has been described[6,7] and APCD postoperative recurrence remains high.[7] Such refractory APCD might require major surgery, including anoperineal excision with definitive stoma, in 53% of the patients.[8]

Temporary faecal diversion [FD] has been proposed as an option in order to facilitate refractory APCD healing.[9] Indeed, faecal stream diversion has been shown to be associated with a significant decrease of both perineal inflammation and associated proctitis in several studies.[8,10–16] Unfortunately, reversal of these stomas may be problematic. We published in 2001 the results of FD for refractory APCD in 17 patients and reported a reversal rate as low as 47% after a mean follow-up of 135 months, mainly related to a high rate of recurrent APCD and associated proctitis.[8] These results were confirmed in a recent meta-analysis which included a total of 556 patients who underwent FD for refractory APCD, and highlighted that, among those patients, stoma reversal was attempted in only 35% of patients and successful in 17%.[13]

Since 2004, biological therapy such as anti-tumour necrosis factor [TNF] therapy has been proposed for CD medical management. Anti-TNF therapy has indeed been demonstrated to be associated with satisfactory healing rates of both luminal CD and APCD, in several randomised controlled trials.[17,18] The advent of the biologics era might have profoundly modified the prognosis of patients managed with such strategy, leading to a potentially increased rate of stoma reversal. However, data regarding the outcome of CD patients undergoing FD for APCD and treated with anti-TNF therapy are scarce.[19] Thus, the aim of this study was to identify possible risk factors associated with non-stoma closure after FD for refractory APCD, in a series of patients treated during the anti-TNF era.

2. Methods

2.1. Study population

All patients who had FD for refractory APCD between March 2005 and August 2017 were identified from our institutional review board-approved prospective database. All patients who underwent FD for CD in the absence of active APCD, and all patients with a surgical history of restorative proctocolectomy with ileal pouch-anal anastomosis, were excluded. Patients with a follow-up of less than 6 months following FD were also excluded from the present study.

The diagnosis of CD was performed using a combination of clinical symptoms and radiological, endoscopic, and histological criteria. Refractory APCD was defined as persistent active or symptomatic lesion [abscess, fissures or ulceration, complex fistula, rectovaginal fistula associated or not with anal strictures] in which optimal medical treatment associated with optimal surgical drainage had failed. Fistulas with multiple tracts and/or external opening, and/or rectovaginal fistulas, were considered as complex fistulas according to the classification proposed by the American Gastroenterological Association.[4]

Data collection included: patient characteristicss [gender, age, smoking habit], previous surgical procedures, type of the APCD, number of drainages before FD, type of FD, CD localisation, and previous anti-TNF treatment. CD luminal localisation was divided into three types: small bowel CD involvement, colonic CD involvement, and/or rectal CD involvement.

2.2. Management of patients with refractory APCD

Patients with refractory APCD, who were planned for an FD, were discussed in a multidisciplinary team [MDT] meeting including surgeons, gastroenterologists, pathologists, and radiologists, after preoperative work-up including magnetic resonance enterography [MRE], elvic magnetic resonance imaging [MRI], and colonoscopy to assess both perineal and luminal CD involvement.

Patients did not receive any bowel preparation before the surgery. All patients had a pelvic examination under anaesthesia before beginning the FD. All identified perianal abscesses and fistula tract were drained using a loose seton placement. Stoma creation was performed laparoscopically when feasible. The stoma could be an ileostomy or a colostomy, depending on the associated luminal CD localisation. Postoperative medical treatment was then discussed during multidisciplinary team meetings. Finally, stoma reversal was discussed on a case-by-case basis during MDT meetings, and was usually planned as soon as the APCD was quiescent, in the absence of luminal active CD.

2.3. Outcome measure

All included patients were followed-up in outpatient clinics every 6 months following FD. Success was defined as the absence of FD at the end of follow-up, defined as the last patient's visit. Failure included both patients still with a 'temporary' FD at the end of follow-up and patients who underwent a definitive end-stoma with proctectomy and abdominoperineal resection.

2.4. Statistical analysis

Quantitative data were reported as mean ± standard deviation [range]. Normally distributed quantitative data were analysed with Student's *t* test, and the Mann-Whitney test was used otherwise. Qualitative data were reported as number of patients [percentage of patients] and were compared with either the Pearson χ^2 test or Fiscer's exact test, depending on the sample size. Multivariate analysis regarding assessment of the risk factors for failure was performed using a logistic regression model including all variables with a *p*-value <0.1 in univariate analysis. Results of this multivariate analysis are shown as odds ratio [OR] [95% confidence interval]. All tests were two-sided with a level of significance set at $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences [SPSS] [version 22.0, Chicago, IL, USA].

This study was conducted according to the ethical standards of our institutional committee on human experimentation, and was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] guidelines.[20]

3. Results

3.1. Patient characteristics

A total of 65 patients undergoing FD for refractory APCD at our institution during the study period were included. Patients' demographics are detailed in Table 1. Mean age at CD diagnosis was 25 ± 11 [range, 11–59] years. Mean age at the time of FD was 36 ± 12 [range, 16–69] years. Mean CD duration was 16 ± 10 [2–57] years. At the time of FD, mean age of patients was 36 ± 12 [range, 16–69] years. CD behaviour, according to the Montreal classification,[21] included

Table 1. Characteristics of 65 consecutive patients who underwent faecal diversion for refractory anoperineal Crohn's disease.

	Study population *n* = 65
Age at diagnosis	25 ± 11 [11–59] [a]
CD duration	16 ± 10 [2–57]
Montreal classification of disease	
B1	18 [28] [b]
B2	37 [57]
B3	10 [15]
Age at FD	36 ± 12 [16–69]
Gender	
Male	25 [39]
Female	40 [61]
Active smoking at the time of FD	
Yes	31 [48]
No	34 [52]
Previous surgical procedures	
Ileocaecal resection	25 [39]
Small bowel resection	6 [9]
Colorectal segmental resection	4 [6]
Total/subtotal colectomy	11 [17]
Patients with history of digestive resection	40 [62]
Patient without history of digestive resection	25 [38]
Type of APCD	
Anoperinal fistula	40 [62]
Rectovaginal fistula	21 [32]
Fissures and ulceration	9 [14]
Anal strictures	5 [8]
Complex fistula	58 [89]
Duration of APCD before FD [months]	74 ± 78 [1–336]
Number of previous APCD procedures before FD	2.5 ± 1.9 [0–9]
Type of FD	
Ileostomy	52 [80]
Colostomy	13 [20]
Associated active luminal CD at the time of FD	
Small bowel	34 [52]
Colon	29 [45]
Rectum	19 [29]
Patients with active luminal CD at the time of FD	55 [85]
Pre-FD anti-TNF treatment	
Yes	43 [66]
No	22 [34]
Post-FD anti-TNF treatment	
Yes	54 [83]
No	11 [17]
Post-FD ustekinumab treatment	
Yes	13 [20]
No	52 [80]
Post-FD vedoluzimab treatment	
Yes	6 [9]
No	59 [91]

CD, Crohn's disease; FD, faecal diversion; APCD, anoperineal Crohn's disease; TNF, tumour necrosis factor.

[a]Mean ± standard deviation [range].

[b]Number of patients [percentage of patients].

B1 behaviour in 18 patients [28%], B2 in 37 patients [57%], and B3 in 10 patients [15%]. A total of 40 patients [62%] had previous surgical resection for CD, including ileocaecal resection [*n* = 25, 39%], small bowel resection [*n* = 6, 9%], colorectal segmental resection [*n* = 4, 6%], and/or total or subtotal colectomy [*n* = 11, 17%].

Patients presented with anoperineal fistula [*n* = 40, 62%], rectovaginal fistula [*n* = 21, 32%], fissures and/or ulceration [*n* = 9, 14%], and/or anal stricture [*n* = 5, 8%]. A total of 58 patients [89%] had complex fistula. The mean delay between the occurrence of the first APCD and the FD was 74 ± 78 months [1–336], and patients had a mean number of surgical procedures for APCD management of 2.5 ± 1.9 [0–9] before FD. Before FD, a total of 43 patients [66%] were treated with anti-TNF therapy, comprising infliximab in 22 patients [34%] and adalimumab in 21 patients [32%], during a mean length of treatment of 24 [2–72] months.

FD was performed using ileostomy in 52 patients [80%] or a colostomy in 13 patients [20%]. A loop stoma was performed in all patients. At the time of FD, 55 patients [85%] had active luminal CD, including small bowel [*n* = 34, 52%], colonic [*n* = 29, 45%], and/or rectal involvement [*n* = 19, 29%]. Postoperatively, the large majority of patients [*n* = 54, 83%] received anti-TNF therapy, after a mean delay of 9 [1–43] weeks following surgery, comprising infliximab in 28 patients [43%], adalimumab in 22 patients [34%], certolizumab in three patients [5%], and golimumab in one patient [1%]. Anti-TNF therapy was prescribed for isolated APCD [*n* = 10, 15%] or luminal CD associated with APCD [*n* = 44, 68%]. Anti-TNF therapy was continued after FD in all patients who received anti-TNF therapy before FD.

Additionally during the postoperative period, 13 patients received ustekinumab [20%], six patients received vedolizumab [9%], and two patients received azathioprine [3%]. No patients received postoperative systematic steroids.

3.2. Long-term outcomes

Mean follow-up after FD was 49 ± 29 [7–120] months. As shown in Figure 1, 43 patients [66%] presented with APCD primary healing, leading to stoma reversal with a mean delay of 16 ± 17 [2–87] months. On the other hand, 22 patients [34%] presented with persistent active APCD despite FD, which did not allow stoma reversal. Additionally, among the 43 patients who underwent stoma reversal following a primary FD, 15/43 patients presented with APCD recurrence that required a re-do FD with a mean delay of 30 ± 29 [3–104] months. Following this second FD, 5/15 patients presented with APCD healing, therefore allowing stoma reversal with a mean delay of 12 ± 11 [4–33] months. However, in 10/15 patients, this second FD did not allow satisfactory APCD healing, leading to a failure of management strategy.

Thus, at the end of follow-up, success of FD strategy was observed in 33/65 patients [51%]. On the other hand, failure of FD strategy was observed in 32/65 [49%] patients, including patients who were still either diverted [*n* = 15/65, 23%] or who underwent a subsequent proctectomy with abdominoperineal excision [*n* = 17/65, 26%] at the end of follow-up [Figure 1].

3.3. Risk factors of FD failure

As detailed in Table 2, three variables were associated with a failure of FD, with a *p*-value <0.1 in univariate analysis: B2 CD behaviour according to the Montreal classification [patients with stoma: *n* = 22/32, 69% versus patients without stoma: *n* = 15/33, 45%; *p* = 0.058]; at least three previous episodes of APCD drainage before FD [patients with stoma: *n* = 12/32, 38% versus patients without stoma: *n* = 20/33, 61%; *p* = 0.062]; and an associated rectal CD involvement at the time of FD [patients with stoma: *n* = 14/32, 44% versus patients without stoma: *n* = 5/33, 15%; *p* = 0.015]. These three variables were therefore entered in the subsequent multivariate logistic regression model.

After multivariate analysis, the only independent factor significantly associated with failure of FD, and therefore a stoma at the

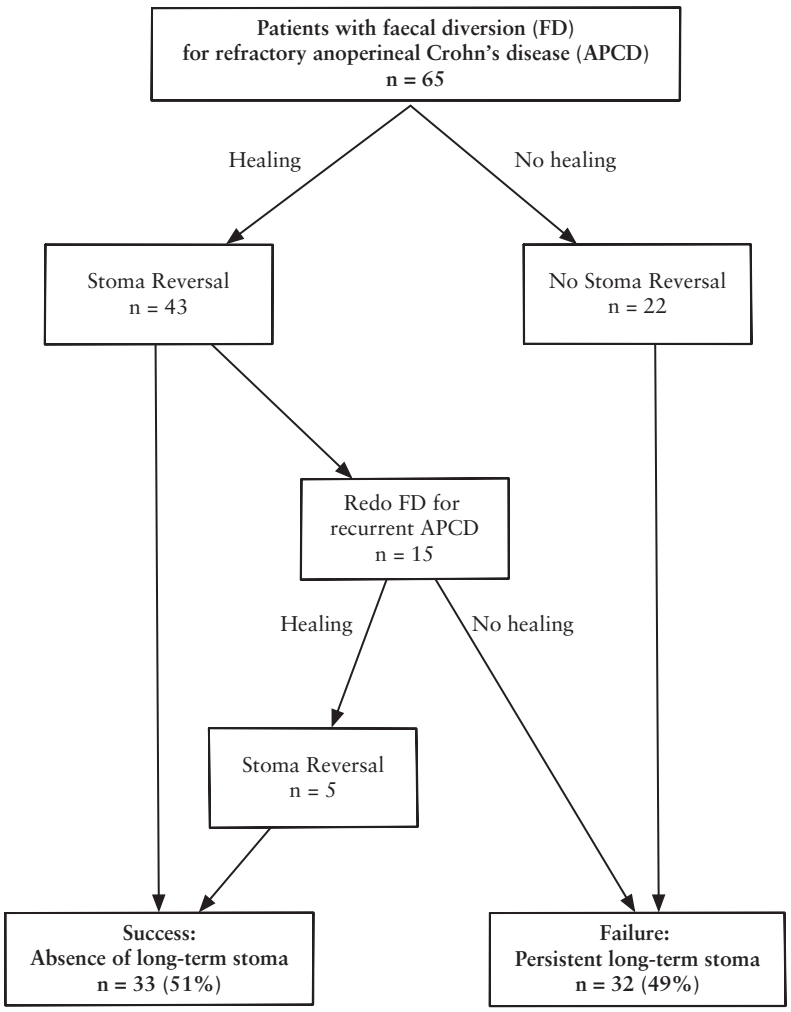

Figure 1. Flowchart of the study population.

end of follow-up, was rectal involvement with CD at the time of FD (odds ratio: 4.0 [1.153–14.000]; $p = 0.029$).

4. Discussion

This study aimed to identify, since the routine use of anti-TNF in clinical practice, the possible risk factors associated with the impossibility of long-term stoma reversal following an FD performed for refractory APCD. We included 65 consecutive patients who underwent FD for refractory APCD, including 83% who were treated with anti-TNF therapy. After a mean follow-up of more than 4 years after FD, 51% of the patients were free of stoma. Active rectal CD involvement at the time of FD was the only independent risk factor for long-term failure of FD, whereas anti-TNF therapy showed no significant impact on the potential success of FD.

Refractory APCD remains a therapeutic challenge for both medical and surgical practitioners, as it is associated with frequent recurrence and leads to definitive stoma in up to 40% of the patients with severe APCD. When a surgical treatment is indicated, it is recommended to perform a surgical procedure as conservative as possible, in order to preserve the integrity of the anal sphincter[22–24] and therefore avoid anal incontinence that is associated with aggressive and repeated surgeries.[25] In this setting, FD has been therefore proposed in an attempt to reduce local inflammation and improve APCD healing rate.[9] This strategy has been evaluated in few studies.[8,10–16,26,27] The majority of those studies were included in a recent meta-analysis[13] which effectively reported a high rate [64%] of early clinical response of APCD following FD. The results of the present study are in line with those numbers, as 43/65 [66%] patients presented with initial APCD healing, allowing primary stoma reversal.

However, despite the use of new drugs such as anti-TNF agents, stoma reversal following FD for refractory APCD may expose the patient to APCD recurrence, potentially leading to the necessity for re-do FD to allow appropriate control of APCD symptoms. This explains the potential risk of long-term stoma maintenance in some patients with refractory APCD. The few studies focusing on the possible benefit of FD in APCD reported high rate of long-term stoma persistence, above 50%,[13] suggesting that temporary FD becomes in fact permanent in a significant number of patients with refractory APCD.[8]

The risk factors associated with long-term persistence of stoma following FD for refractory APCD has been previously studied.[8–10,14,26,27] Those studies, including a previous study from our group before the use of anti-TNF agents, suggested that associated rectal CD involvement was the main risk factor for persistent long-term stoma. In our first experience published in 2001, 89% of the patients with rectal CD involvement at the time of FD presented with persistent stoma at the end of follow-up, versus only 13% in

Table 2. Predictive factors of long-term persistent stoma among 65 patients who underwent a faecal diversion for refractory anoperineal Crohn's disease.

	Stoma at latest follow-up *n* = 32	No stoma at latest follow-up *n* = 33	Univariate analysis *p*-value	Multivariate analysis	
				p-value	Odds ratio
Age at CD diagnosis [years]			0.337	-	-
Age >25	9 [28][a]	13 [39]			
Age ≤25	23 [72]	20 [61]			
Age at FD			0.531	-	-
Age ≥35	14 [44]	17 [52]			
Age <35	18 [56]	16 [49]			
CD duration	16 ± 10 [2–57][b]	16 ± 8 [7–35]	0.880	-	-
Montreal classification of CD					
B1	6 [19]	12 [36]	0.190		
B2	22 [69]	15 [45]	0.058	0.078	2.612 [0.898–7.597][c]
B3	4 [12]	6 [19]	0.475		
Female gender	18 [56]	22 [68]	0.388	-	-
Active smoking at the time FD	15 [47]	16 [49]	0.897	-	-
Previous resection for CD					
Previous ileocaecal resection	12 [38]	13 [39]	0.875	-	-
Previous small bowel resection	3 [9]	3 [9]	1.000	-	-
Previous colorectal segmental resection	3 [9]	1 [3]	0.355	-	-
Previous subtotal colectomy	6 [19]	5 [15]	0.751	-	-
No previous resection for CD	11 [34]	14 [42]	0.505	-	
Type of APCD					
Fistula	20 [62]	20 [61]	0.875	-	-
Rectovaginal fistula	9 [28]	12 [36]	0.478	-	-
Fissures and ulceration	6 [19]	3 [9]	0.303	-	-
Anal strictures	4 [13]	1 [3]	0.197	-	-
Complex fistula	28 [88]	30 [91]	0.708	-	-
Duration of APCD before FD [months]	76 ± 75 [1–306]	72 ± 82 [1–336]	0.619	-	-
More than three procedures before FD	12 [38]	20 [61]	0.062	0.111	0.42 [0.141–1.222]
FD with ileostomy	25 [78]	27 [82]	0.710		
Associated active luminal CD at the time of FD					
Small bowel	16 [50]	18 [54]	0.714	-	-
Colon	17 [53]	12 [36]	0.174	-	-
Rectum	14 [44]	5 [15]	**0.015**	**0.029**	4.0 [1.153–14.000][d]
Pre-FD anti-TNF therapy	22 [69]	21 [64]	0.663		
Post-FD anti-TNF therapy	27 [84]	27 [82]	1.000	-	-
Post-FD ustekinumab treatment	6 [19]	7 [21]	0.804	-	-
Post-FD vedolizumab treatment	4 [13]	2 [6]	0.427	-	-

CD, Crohn's disease; FD, faecal diversion; APCD, anoperineal Crohn's disease; TNF, tumour necrosis factor.

[a]Number of patients [percentage of patients].

[b]Mean ± standard deviation [range].

[c]Odds ratio [95% confidence interval].

[d]Significant *p*-values after multivariate analysis are in bold text.

patients without rectal CD involvement [p <0.01].[8] This was later confirmed in a series from the Cleveland Clinic, published in 2015.[26] Unsurprisingly, the present study confirmed our first study, as CD rectal involvement was also associated with a 4-fold risk of persistent stoma at the end of follow-up in multivariate analysis.

Anti-TNF therapy has been shown to be associated with satisfactory healing results regarding both luminal and perineal CD in randomised controlled trials.[17,18,28–30] These results might lead to the hypothesis that the advent of the anti-TNF therapy era might have modified the outcomes of the FD strategy for refractory APCD. However, the majority of the studies reporting the results of this strategy did not include patients treated with anti-TNF therapy.[8,10,14–16] To our knowledge, only three studies assessed the outcomes of patients treated with anti-TNF therapy undergoing FD for APCD.[10,26,27] However, these studies are impaired by important biases. Two studies reported small populations of 21[10] and 49[27] patients, respectively, thus not allowing satisfactory multivariate analysis. In the largest study to date, published by the Cleveland Clinic Group and including 138 patients, the authors did not highlight any impact of anti-TNF therapy on the rate of stoma reversal following FD for APCD.[26] Furthermore, this latest study is impaired by the very low rate [37/138, 27%] of patients in which stoma reversal was attempted. Conversely, in the present study, 43/65 patients [66%] underwent initial stoma reversal, suggesting a more aggressive reversal strategy, allowing better assessment of FD failure rate in a larger number of patients.

As expected, the large majority [83%] of the patients included in the present study received anti-TNF therapy after FD. Despite these high numbers, we did not reveal any impact of such anti-TNF therapy on FD success rate at the end of follow-up. This

result is in line with those suggested by the previously published studies,[10,26,27] and might be explained by two principal reasons. First, anti-TNF therapy is known to be less effective in inducing APCD healing than luminal CD remission,[13,31] as a meta-analysis of randomised controlled trials suggested that only 33% of patients treated with anti-TNF therapy will present with APCD healing.[31] Second, this absence of statistical impact of anti-TNF therapy on stoma reversal rate might be explained by a selection bias, as patients in which an FD is proposed for refractory APCD are more likely to represent a subgroup of patients with more severe and anti-TNF refractory disease.

The present study is limited by its retrospective nature and by the relatively low number of included patients. However, it represents the largest study to date to focus on the risk of persistent stoma following FD for APCD since the advent of anti-TNF therapy.

In conclusion, our study suggests that FD for APCD might be proposed in patients with refractory APCD, to avoid or delay abdominoperineal resection and definitive stoma, but that this strategy should be proposed with caution in patients presenting with associated rectal CD involvement, as the probability of stoma reversal in those patients remains low. Finally, our results suggest that anti-TNF therapy does not have any impact on stoma reversal rate in those patients.

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Conflict of Interest

No conflicts of interest.

Author Contributions

EH: data acquisition, data analysis and interpretation, manuscript drafting. LM: study design and concept, data analysis and interpretation, manuscript drafting. MO: data acquisition, data analysis and interpretation. XT: data acquisition, data analysis and interpretation. YB: data acquisition, data analysis and interpretation. YP: study design and concept, data analysis and interpretation, manuscript drafting, final approval of the manuscript.

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