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✧ ORIGINAL ARTICLE ✧

Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis

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Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis

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The aim of this study is to examine the acceptability and effectiveness of a nurse-led hepatocellular carcinoma (HCC) surveillance clinic in high-risk patients with cirrhosis/advanced fibrosis. Early detection of HCC is associated with better treatment outcomes and improved survival. International guidelines recommend 6-monthly surveillance of patients at risk of developing HCC. A nurse-led HCC surveillance protocol was established to support patients in adherence to surveillance protocols. The design used was retrospective document analysis. Retrospective analysis of healthcare records of patients referred to the clinic between August 2009 and December 2015. Extracted data included attendance of clinic visits, blood testing, ultrasound or other imaging, and outcomes. Ultrasound was attended within 6 months in 30.3% of cases and within 7 months in 71.2% of cases. The median time between Nurse-Led Clinic appointments, ultrasound scans and blood testing did not exceed 9 months. First year FibroScans were attended by 82.9% (63/76) patients; endoscopy was indicated for 42 and attended by 35 (83.3%) patients. Lesions were identified in 16 patients (21.5%) and HCC diagnosed in two patients. One patient died because of HCC and one to sub-dural haematoma. Nurse-led HCC surveillance was an effective method of monitoring patients with cirrhosis at high risk of developing HCC. Well-defined protocols enable timely identification of patients with HCC or hepatic decompensation so that management strategies can be implemented without delay. The potential benefits identified by this study warrant further, rigorous evaluation.

Key words: cirrhosis, HCC screening, hepatocellular carcinoma, nurse-led programme, surveillance.

INTRODUCTION

Hepatocellular carcinoma (HCC) has long been identified as a major cause of liver-related deaths in patients with compensated cirrhosis.¹ Various aetiological factors such as persistent hepatitis B (HBV) or hepatitis C virus (HCV), infection, alcohol and cirrhosis are related to development of HCC.^{1–5} Despite successful clearance of hepatitis virus, the risk of HCC remains significant,⁶ particularly in patients with advanced fibrosis and cirrhosis.

Early detection of HCC is associated with better treatment outcomes and improved survival.^{7–9} As HCC is asymptomatic in the early stages, a surveillance programme is essential for its early detection. The American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend HCC surveillance using ultrasound, on a 6-monthly basis for high-risk patients, who have been identified as comprising:

- patients with advanced fibrosis and cirrhosis
- patients with HBV infection who meet the following criteria:
 - Asian males > 40 years of age,
 - Asian females > 50 years of age,
 - patients of African origin > 20 years of age
 - patients with a positive family history of HCC.^{2,10,11}

The Royal Perth Hospital Nurse-led HCC Surveillance Clinic (Nurse-Led Clinic) was established in 2005. The clinic was established in response to concerns raised by

clinicians that their patients were not attending scheduled surveillance, and that the Medical Hepatology Clinic did not have the capacity to follow up on non-attendance. The Nurse-Led Clinic was designed to focus on patient adherence to surveillance and to reduce the surveillance workload of medical staff.

STUDY METHODS

Study aims

The purpose of the study was to evaluate whether a Nurse-Led Clinic can provide an effective programme for the identification of patients with early HCC or impending hepatic decompensation.

The first aim was to examine whether the Nurse-Led Clinic could facilitate attendance for monitoring in line with guideline recommendations: every 6 months for clinical assessment, ultrasound and pathology; yearly for FibroScan. The second aim was to examine whether the clinic was effective at timely identification of patients with early HCC or impending hepatic decompensation.

The nurse-led clinic

Clinic patients

Patients with cirrhosis or advanced fibrosis were referred by doctors in the Medical Hepatology Clinic to the Nurse-Led Clinic (Fig. 1). Eligibility criteria for the Nurse-Led Clinic aligned with published guidelines^{2,10,11} to include:

- Patients with well-compensated liver disease with no history of HCC

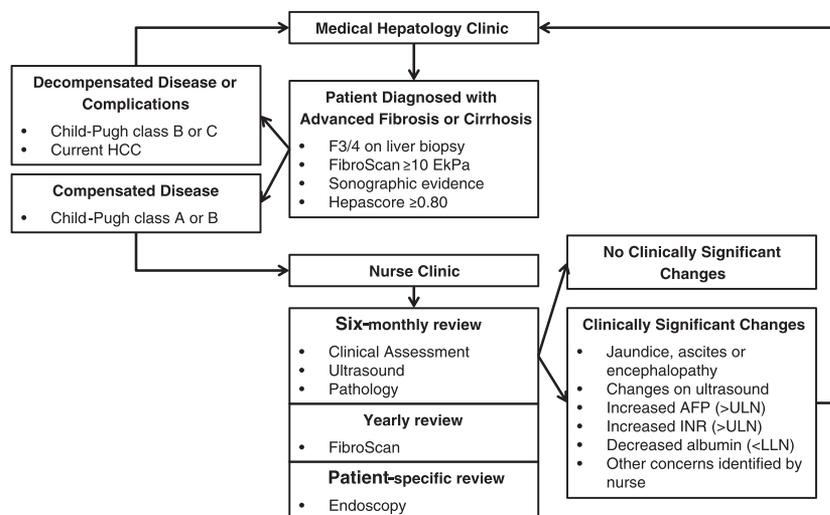


Figure 1. Flow chart of patient referrals within the surveillance system. Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; INR, international normalized ratio; LLN, lower limit of normal; ULN, upper limit of normal.

- Patients with advanced fibrosis or cirrhosis, defined as a METAVIR score of F3 or F4 on liver biopsy, liver stiffness of ≥ 10 kPa on FibroScan, a HepaScore[®] of ≥ 0.8 , ultrasound evidence of cirrhosis or portal hypertension
- Patients with hepatitis B without cirrhosis or advanced cirrhosis were also included if they were:
 - ▶ Asian males ≥ 40 years of age,
 - ▶ Asian females ≥ 50 years of age,
 - ▶ Africans ≥ 20 years of age or
 - ▶ Had a family history of HCC, in alignment with published guidelines.^{2,10,11}

The HCC surveillance protocol was established to enable identification and fast-tracking for urgent medical review of patients with either HCC or hepatic decompensation.

Clinic processes

The nurse arranged 6-monthly clinic visits, ultrasounds and laboratory tests, including for alpha-fetoprotein (AFP). Endoscopic variceal surveillance was arranged as per protocol, specific to the needs of each patient (for example, yearly, two-yearly or not required). Following the introduction of transient elastography (FibroScan[™]) at Royal Perth Hospital in 2012, patients were also referred for baseline and annual FibroScans. Clinic visits included an assessment for physical signs of progressive liver disease (e.g. ascites, jaundice, encephalopathy), review of ultrasound, pathology, FibroScan and endoscopy findings. Routine pathology tests included liver function tests, urea and electrolytes, full blood count, international normalized ratio (INR) and AFP. Patients with impaired hepatic synthetic function, including those with INR levels above the upper limit of normal or albumin below the lower limit of normal, those with

changes on ultrasound including the identified lesions or with elevated levels of AFP were discussed with medical staff and either appropriate management or referral back to the medical clinic instituted. Patients could also be referred back to the medical clinic if the nurse had any other concerns about the patient.

Management plans

All patients with clinically significant abnormalities were notified to the Hepatology Fellow or consultants, who immediately arranged appropriate follow-up testing (e.g. a computed tomography [CT] or magnetic resonance imaging [MRI] scan in patients with clinically significant changes on ultrasound). Each case of concern was presented at a fortnightly Multidisciplinary HCC Meeting, which included radiologists, hepatologists, nurses and surgeons. When HCC was identified or suspected, a management plan was established for the patient by the multidisciplinary team and the patient was discharged from the Nurse-Led Clinic and returned to the medical clinic for management. Potential treatment modalities for patients with HCC included transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation, selective internal radiation therapy (SIRT), surgery, referral for orthotopic liver transplantation (OLT) or other treatment, as appropriate.

Sample/participants

To be eligible for inclusion in this evaluation patients had to have met eligibility criteria (described previously) and been referred to the Nurse-Led Clinic.

Data collection

The healthcare records of all patients referred to the Nurse-Led Clinic between August 2009 and December 2015 were reviewed and relevant data extracted. Data for complete years 2010–2015 were analysed. Relevant data for the analysis included the number of referrals, patient demographic data, baseline clinical characteristics and medical history, current treatment, patient attendance for clinic visits, blood testing, ultrasound, FibroScan and endoscopy results, outcome of additional imaging (HCC diagnosis), HCC treatment received and outcome.

Data analysis

Data were analysed using univariate analysis and summarized using descriptive statistics (e.g. range, mean, median, standard deviation [SD]).

Aim one: To examine whether attendance for monitoring occurred in line with guideline recommendations, percentages of patients attending for monitoring in line with guidelines every 6 months with one month tolerance/one year with one month tolerance (see Fig. 1) from referral were calculated. Because of the complexities of appointments and patient availability, a tolerance of one month was added to the maximum of six months between monitoring appointments recommended by international guidelines.

Aim two: To examine whether the clinic was effective at timely identification of patients with early HCC or impending hepatic decompensation, numbers and percentages were calculated of those for whom these diagnoses were identified.

Ethical considerations

The project was approved by the Nursing Safety and Quality Committee at Royal Perth Hospital.

RESULTS

Patients

A total of 86 patients were referred to the Nurse-Led Clinic between August 2009 and November 2015. Of these,

medical records were not available for four patients, and six patients did not attend any Nurse-Led Clinic visits; therefore, data were extracted from the records of 76 patients. The numbers of patients referred to the clinic were generally steady, with an average of approximately 12 patients (range 7–16) referred annually (Table 1).

Patient demographics and clinical characteristics of the 76 patients with at least one Nurse-Led Clinic attendance are shown in Table 2. The majority of patients were male (73.7%). Patients ranged 28–75 years of age, with a mean (SD) age 57 (8.5) years. Mean body weight was 76 (17.5) kg (range 49–131 kg). Underlying liver diseases included hepatitis C, hepatitis B, alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH) or autoimmune hepatitis. A total of 57.9% of patients were assessed as cirrhotic and 32.9% had advanced fibrosis. Most patients (92%) reported current or past HCV infection. Four patients received HCV treatment during surveillance, which included pegylated interferon/ribavirin/boceprevir in three patients and pegylated interferon/ribavirin in one patient. All four patients achieved sustained virologic response (SVR).

Aim 1: adherence to the monitoring schedule

Follow-up is ongoing for most patients, with the longest follow-up duration to date being 64 months. Seventy-five patients attended an initial ultrasound; one patient who was discharged because of relocation interstate did not attend ultrasound. Sixty two patients attended at least one follow-up ultrasound. Only 26% of patients (16/62) had a mean duration between ultrasounds of within 6 months, but 65% of patients (40/62) attended ultrasounds before 7 months on average, which was deemed compliant with international recommendations. No patients had a mean ultrasound interval of greater than 12 months.

The total number of ultrasound scans attended was 339, of which 264 were follow-up ultrasounds. Overall, 80 follow-up ultrasounds (30.3%) were completed within 6 months of the previous ultrasound. With a tolerance of one month accepted, 188 follow-up ultrasounds (71.2%)

Table 1 Number of patient referrals to the clinic each year

Year of referral	2010	2011	2012	2013	2014	2015
Number of patients	11	16	7	10	13	16

Table 2 Baseline demographics and clinical characteristics of patients who attended at least one Nurse-Led Clinic visit

<i>n</i> (%)	<i>N</i> = 76
Gender	
Male	56 (73.7)
Female	20 (26.3)
Current/past substance use [†]	
None	35 (46.1)
Alcohol	29 (38.2)
Tobacco	20 (26.3)
Marijuana	11 (14.5)
IVDU	10 (13.2)
Unknown	4 (5.3)
Liver disease	
HBV	2 (2.6)
HCV past	50 (65.8)
HCV current	20 (26.3)
NASH	2 (2.6)
ALD	2 (2.6)
Fibrosis stage	
Early fibrosis	4 (5.3)
Advanced fibrosis	25 (32.9)
Cirrhosis	44 (57.9)
Unknown	1 (1.3)
Initial assessment of fibrosis	
Liver biopsy	30 (39.5)
Ultrasound	8 (10.5)
HepaScore	24 (31.6)
FibroScan	13 (17.1)
Clinical	1 (1.3)
History of decompensation	5 (6.6)
Signs of chronic liver disease	2 (2.6)
Comorbidities	
Any	49 (64.47)
Psychiatric	10 (13.2)
T2DM	9 (11.8)
HIV	4 (5.3)
Child-Pugh score	
5	73 (96.1)
6	1 (1.3)
7	1 (1.3)
Unknown	1 (1.3)

[†]Some patients had multiple substance use. ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus infection; IVDU, intravenous drug use; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

were completed within less than 7 months of the previous ultrasound. Only 12 (4.5%) were > 1 year apart (Fig. 2). The mean (SD) duration between ultrasounds ranged 4.98 (2.19) months at the 12th ultrasound to 7.27 (2.66) months at the 8th ultrasound (Fig. 3). The mean (SD) duration between Nurse-Led Clinic appointments ranged 4.41 (2.59) months for Visit 10 to 7.48 (5.27) months for Visit 12. The mean (SD) duration between blood samples ranged 4.74 (3.76) months for Visit 10 to 8.89 (3.59) months for Visit 9. The overall median time between Nurse-Led Clinic appointments, ultrasound scans and blood testing did not exceed 9 months.

FibroScan was a relatively new modality for assessing fibrosis. First and second year FibroScans were attended by 82.9% (63/76) and 2.6% (2/76) of patients, respectively.

Endoscopic variceal surveillance was arranged specifically to meet the needs of each patient and ranged from no endoscopy (as not required), to a single endoscopy or repeat endoscopy every 12 or 24 months. Overall 55.0% (42/76) of patients met the criteria for endoscopy (cirrhosis with the absence of a prior endoscopy confirming no further endoscopy required) and 35 of these 42 patients (83.3%) attended an initial endoscopy. Of the seven who did not attend, three relocated, one was discharged from the Nurse-Led Clinic, one refused the procedure and two patients did not attend. Second, third and fourth endoscopies were attended by 10, 7 and 4 patients respectively.

In total 15 patients were discharged from the Nurse-Led Clinic. Reasons for discharge included HCC surveillance no longer required ($n = 6$), referral to the Gastroenterology Medical Clinic for follow-up of a pancreatic lesion ($n = 1$), HCC ablation ($n = 1$), deceased ($n = 2$), lost to follow up ($n = 1$), patient decision ($n = 1$) and referral to a treatment programme ($n = 1$). Two patients with HBV were referred to the Nurse-Led Clinic but returned to the Medical Clinic for concurrent HBV treatment. To date 51 patients (62%) continue to be monitored regularly in the Nurse-Led Clinic.

Aim 2: timely detection of deterioration and complications

Referrals for additional imaging were made for 13 patients (17.1%) for CT and 5 patients (6.6%) for MRI. The reasons for referral were predominantly derived from the regular ultrasound investigations, and, for CT, included hepatic lesions ($n = 6$); hyperechoic hepatic nodules/foci ($n = 3$); hypoechoic foci in the spleen ($n = 1$); acute

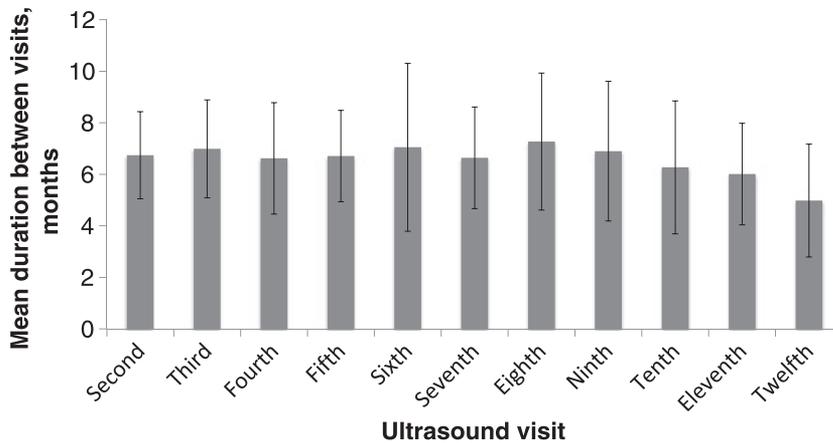


Figure 2. Episodes of care for ultrasound meeting guideline recommendations.

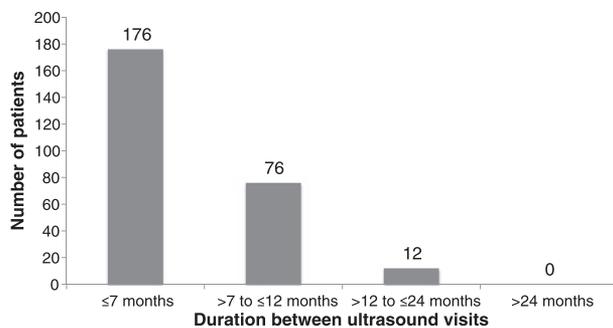


Figure 3. Mean (standard deviation) duration since previous ultrasound scan.

(right-sided) abdominal pain, nausea, vomiting and diarrhea ($n=1$); previous possible evidence of HCC ($n=1$) and suprahepatic inferior vena cava narrowing ($n=1$). The reasons for MRI included hepatic lesions suspicious of HCC (4), only one of whom had raised AFP and possible pancreatic lesion (1).

Of the 35 patients who attended the first endoscopy visit, six patients were found to have oesophageal varices.

Among 16 patients with suspicious lesions, follow-up revealed cyst(s) in eight patients, haemangioma in three patients, other benign lesions in three patients and HCC in two patients. The first patient (Patient A) diagnosed with HCC was a 66-year-old African male with HCV Child-Pugh class A cirrhosis, METAVIR score of F3/4 (Box A).

Box A: Patient A with HCC

Patient A had received prior treatment with pegylated interferon/ribavirin, and achieved an SVR in 2011. As he had advanced liver disease, he was referred to the Nurse-Led Clinic in February 2011. The patient underwent regular HCC surveillance with ultrasound and/or CT scans

during follow-up in nurse-led HCC surveillance clinics and scans were discussed regularly at Multidisciplinary HCC Meetings.

- ▶ An initial hypervascular lesion (< 1 cm) identified in 2009 in segment 6 on CT scan was followed-up regularly. CT scan was performed because of rise in alpha-fetoprotein to 140 KIU/L ($N < 11$ KIU/L).
- ▶ There were no changes in the lesion on serial imaging until 2013. In May 2013 a CT scan revealed that the lesion in segment 6 was suspicious, with classical arterial enhancement and wash-out in the portal venous phase.
- ▶ An ultrasound in June 2013 showed increase in size of the lesion to $14 \times 16 \times 17$ mm, confirming the lesion in segment 6 as HCC. The patient's case was discussed at the Multidisciplinary HCC meeting and the patient was initially successfully treated with microwave ablation. However, a CT scan conducted 5 months after ablation showed recurrence at the same site and the patient underwent resection. The patient died in July 2014 following admission to hospital with ascites and widespread metastases, 13 months after confirmed diagnosis of HCC.

The second patient (Patient B) was a 56-year-old male with HCV Child-Pugh class A cirrhosis. He had been previously treated with pegylated interferon/ribavirin with SVR in 2008 (Box B).

DISCUSSION

This evaluation shows that the Nurse-Led Clinic was generally acceptable to patients and met its primary aim of retaining patients in a monitoring programme in line with guideline recommendations. This allowed timely detection of abnormalities and use of a well-defined pathway of management of abnormal results which expedited patient management. Ultrasound was attended within 6 months in

Box B: Patient B with HCC

Patient B experienced oesophageal variceal bleeding in 2009. The varices were successfully eradicated, and the patient was referred to the Nurse-Led Clinic in August 2010. In March 2013, a $21 \times 25 \times 23$ mm lesion was detected in segment 6 by ultrasound and the patient underwent CT and MRI scans. He was successfully treated with TACE. At his latest follow-up in September 2015, MRI showed no recurrence of the lesion.

30.3% of cases, and within 7 months in 71.2% of cases. This appears better than in published studies where adherence to surveillance is reported as low as 12%, less than 20%, 22% and 17.4% with a longer acceptable interval of 12 months.^{12–16} An overall median time between monitoring appointments of less than 9 months showed clinically significant improvement following establishment of the Nurse-Led Clinic.

Increased patient knowledge and involvement in treatment decisions have been associated with better adherence to medical recommendations.¹⁷ The provision of patient education through the Nurse-Led Clinic might have contributed to the better patient adherence noted in this study.

NASH and ALD have been associated with poor compliance with surveillance.^{12,15,18} Because very few patients in this study had NASH or ALD (two patients each; Table 2), this might have contributed to the better adherence achieved compared to these published studies.

Some patients develop widespread disease despite close surveillance and two cases of HCC were identified through the Nurse-Led Clinic. Despite the lesion in Patient A being relatively small when initially confirmed ($14 \times 17 \times 16$ mm) and successfully treated with microwave ablation at that site, the patient developed widespread metastases and died less than 12 months later. This might be because of the presence of other lesions in the liver not detected by imaging techniques, especially in the diffuse form of HCC. Alternatively the initial lesion, despite its small size, might have already resulted in metastatic disease. Patient A also had type 2 diabetes mellitus, which has been associated with a greater risk of developing HCC¹⁹, although it is unknown whether this contributed to the rapid progression of his disease. These two cases (Patients A and B) highlighted the importance of HCC surveillance in patients who have been successfully treated for hepatitis C. Superimposed factors such as NASH can also contribute to development of HCC^{20,21} even in those patients who had not developed significant fibrosis after SVR.

Poor outcome despite surveillance and early detection has been observed in another study. A Belgian study of 141 patients with cirrhosis undergoing surveillance detected a total of 6 HCC lesions, all single nodules < 4 cm in size, yet four patients died 3–15 months later (median 8 months) despite treatment with percutaneous acetic acid injection.¹⁸ Two of the patients who died had extensive HCC. Despite these observations, studies have confirmed the usefulness of surveillance programmes,^{22,23} for example demonstrating mean survival duration of 27 months for patients diagnosed in surveillance programmes (95% Confidence Interval (CI) 16.6, 37.4) compared with only 6 months (95% CI 2.6, 9.4) among those diagnosed outside of a surveillance programme ($p = 0.001$).²³ This is reflected in the current study where the mean duration of follow-up in the Nurse-Led Clinic is currently 23.6 months. Only two deaths have occurred in the Nurse-Led Clinic from its inception in 2005 until the present day and 62% of the patients enrolled in this clinic remain in follow-up.

This study is limited by its retrospective nature and reliance upon routinely collected health service data, but this is a cost-effective approach for an initial evaluation. The positive results demonstrated to date indicate that a nurse-led HCC surveillance programme has the potential to ensure that HCC is detected earlier with better outcomes for patients. An additional benefit accrued from reduced surveillance workload of medical staff, enabling them to focus on treatment of patients with more severe and complex problems.

CONCLUSIONS

This retrospective analysis provided an evaluation demonstrating that a nurse-led HCC surveillance clinic is an acceptable and effective method of monitoring patients with cirrhosis who are at high risk of developing HCC, and of reducing the surveillance workload of medical staff. Well-defined protocols enable timely identification of patients with HCC or hepatic decompensation so that management strategies can be implemented without delay.

The potential benefits identified by this study warrant further, rigorous evaluation: a formal randomized trial of the two models of surveillance with cost-effectiveness analysis to detail the economic effects of nurse-led versus medical surveillance models. Detailed exploration of the patients' perspectives is also needed, to fully understand what elements of the Nurse-Led Clinic attract and retain these patients within this programme.

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AUTHORSHIP STATEMENT

All listed authors meet the authorship criteria and are in agreement with the content of the manuscript.

CONFLICTS OF INTEREST

None

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