

Chronic Obstructive Pulmonary Disease (COPD) management in the community: how could primary care team contribute?

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Abstract

Background:

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease commonly encountered in the primary care. This study aimed to audit COPD care at 13 public primary care clinics of Hong Kong and to work out improvement strategies.

Method:

All COPD patients who were aged 40 or above and had been followed up at 13 public primary care clinics of Kowloon Central Cluster (KCC), Hong Kong were included in this clinic audit. Evidence-based audit criteria and performance standards were established after thorough literature review. Phase 1 was from 01/04/2016 to 31/03/2017, with deficiencies identified, followed by one-year implementation phase with improvement strategies being executed. Phase 2 was from 01/04/2018 to 31/03/2019 with outcome of enhancement reviewed. Chi-square test and student's t test were used to compare the significance of relevant changes noted.

Results:

2,358 COPD cases were identified in phase 1. Among the 658 smokers, 332 (50.5%) had been referred to Smoking Counselling and Cessation and Service (SCCS) and 289 (43.9%) actually attended it. 991 cases (42%) received Seasonal Influenza Vaccine (SIV) and 938 (39.8%) received Pneumococcal Vaccine (PCV). 698 (29.6%) patients had spirometry done before and 423 cases (17.9%) had been admitted to hospital due to acute exacerbation of COPD (AECOPD). With the concerted effort taken during the implementation phase, phase 2 data showed significance improvement in almost all criteria. There was a marked improvement in SIV and PCV coverage, spirometry performance rate and most important of all, a reduction in the AECOPD (n=294, 13.5%, P=0.000043). However, the SCCS referral rate and attendance rate among smokers remained stagnant (both P>0.05).

Conclusion:

COPD care at primary care clinics of KCC has been tremendously improved in most of the audit criteria via a systematic team approach, therefore reducing the burden to specialist and hospital.

Background

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease commonly encountered in the primary care. According to The Global Burden of Disease Study, there were 251 million COPD cases in 2016 around the world and around 3.2 million people died from COPD in 2015. (1) Locally, 0.5% of all non-institutionalized persons aged 15 and above had doctor-diagnosed COPD (2) and 9% of the elderly above the age of 70 are its victim too. (3) Furthermore, COPD accounted for almost 30,000 hospital

admissions in the Hospital Authority (HA) and resulted in 2.7% of all registered death in 2016. (4) Therefore, COPD represents a substantial economic and social burden to the health care system.

The chronic disease nature of COPD warrants regular follow up and multi-disciplinary team assessment to optimize its control. Proper diagnosis by spirometry, removal its risk factors such as smoking and vaccination against influenza and pneumococcal infections have all been shown to reduce the disease burden and improve patients' quality of life. (5–7) Despite all these evidence, the management of COPD is still far from satisfactory. For example, Kesten et al. found that only 5% of Canadian general practitioners requested a pulmonary function test when consulted by an individual with clear signs of COPD. (8) In addition, COPD patients who are active smokers have a particularly low referral rate and attendance rate for smoking cessation counselling service (9). It is also not surprising that the actual take-up rate of seasonal influenza vaccine (SIV) has consistently been dismally low at 20–60%. (10–13)

Locally, a large proportion of COPD cases are managed in the public primary care clinics HA. Primary care professionals have an important role in improving the quality of care to COPD patients. Starting from 1 April, 2017, COPD audit has been conducted across all primary care clinics of Kowloon Central Cluster (KCC) to review the performance of COPD care so as to improve its clinical outcome. This study tried to audit the management of COPD cases from primary care clinics of KCC and to work out improvement strategies. We believe that by improving the standard of care to COPD patients managed in the community, the disease morbidities including the number of admissions due to COPD acute exacerbations would be greatly reduced.

Method

Study design

Clinic audit conducted at 13 primary care clinics of KCC, HA of Hong Kong.

Setting Audit Criteria And Justification Of Audit Standards

After thorough literature review, members of Quality Assurance Subcommittee of Coordination Committee of Family Medicine, HA had recommended to adopt the following evidence-based audit criteria and performance standards for the COPD audit across all GOPCs in HA.

1. **Global Initiative for Obstructive Lung Disease:** Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (GOLD guideline) (2018 report). (14)
2. NICE guideline [NG115] Chronic obstructive pulmonary disease in over 16s: diagnosis and management, 2018. (15)

Table 1
list of audit criteria and performance standards of the study

Item no.	Recommendations and audit criteria	Standard
1	<p>Recommendations: All COPD patients should be regularly reviewed with a pre-scheduled appointment in GOPC;</p> <p>Criteria 1: % of COPD patients with pre-scheduled appointments in GOPC</p>	85%
2	<p>Recommendations: All smoker COPD patients should be advised on smoking cessation and be referred to receive Smoking Counselling and Cessation Services (SCCS);</p> <p>Criteria 2: COPD patients who are smokers and have ever been</p> <p>a. % of COPD patients referred to SCCS before or</p> <p>b. % of COPD patients ever attended SCCS before</p>	50% 50%
3	<p>Recommendations: All COPD patients should receive seasonal influenza vaccine (SIV) annually unless contraindicated;</p> <p>Criteria 3: % of COPD patients who have received SIV in the preceding year</p>	45%
4	<p>Recommendations: All COPD patients should receive pneumococcal vaccine (PCV) unless contraindicated;</p> <p>Criteria 4: % of COPD patients who have received PCV before;</p>	45%
5	<p>Recommendations: Spirometry is recommended for all COPD cases at diagnosis, or when the alternative diagnosis needs to be ruled out, and to monitor the disease progression.</p> <p>Criteria 5: % of COPD patients with spirometry test done before.</p>	50%
6	<p>Recommendations: All efforts should be made to reduce the acute exacerbation of COPD (AECOPD).</p> <p>Criteria 6: % of COPD patients admitted to hospitals due to AECOPD.</p>	< 15%

Data Collection And Analysis

Audit objects

All COPD patients who were aged 40 or above and have attended any of the 13 GOPCs of KCC for regular FU during the study period were included. KCC is one of the biggest hospital clusters in HA, with a catchment of 1.2 million populations in year 2017. Around 15% of the population were aged over 65 years old in year 2017. The diagnosis of COPD is identified via the GOPC attendance(s) coded with International Classification of Primary Care, Second edition (ICPC-2) of 'R79-Chronic bronchitis' or 'R95-Chronic obstructive pulmonary disease' over the 12-month reporting period. COPD patients who were

managed in the Specialist Outpatient Clinics (SOPCs) or who were certified dead during the study period were excluded.

The Audit Cycle

Phase 1 was from 1st April 2016 to 31st March 2017, with deficiencies identified. It was followed by one-year implementation phase from 1st April 2017 to 31st March 2018 with all improvement strategies being executed. Phase 2 was from 1st April 2018 to 31st March 2019 with the outcome of enhancement being reviewed.

First-phase data collection and analysis:

Totally 2,496 COPD patients were found to have regular FU in 13 GOPCs of KCC during phase 1. Among them, 125 cases were certified dead and 13 cases were found to have FU at SOPDs and therefore were excluded. The remaining 2,358 cases (94.5%) fulfilled the inclusion criteria were included into data analysis.

Implementing changes and intervention:

At department level, the COPD audit working group (WG) led by the authors was formed in 1 April, 2017, with doctor and nurse subject officers assigned. A structured team approach was adopted with strategies at policy, practice, staff and patient level being worked out. COPD case registry had been retrieved from the Clinical Data Analysis and Reporting System (CDARS) of HA at least annually and the information was shared with clinic doctor and nurse in-charge for follow up action. Regular service review meeting had been conducted quarterly to half yearly. At the practice level, the management of COPD cases across all 13 GOPCs were aligned. All COPD cases would be referred to attend a nursing led program called Nurse and Allied Health Clinic - Respiratory Team (NAHC-Respi) upon their routine FU, where a comprehensive bunch of service would be provided including nursing assessment and counselling, spirometry assessment, smoking cessation service referral if smoker and a course of pulmonary rehabilitation by allied health workers including physiotherapist and occupational therapist. For those COPD cases in the registry but do not have a FU appoint, a FU with doctor's consultation within 6 months had been offered. 5 more Spirobank machines were purchased to meet the increasing service demand on spirometry assessment. All COPD cases would receive standard assessment including the Modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) score evaluation, therefore were graded according to the GOLD guideline. At the clinic level, a policy on COPD risk factor screening was advocated and a continuous monitoring and feedback system with ongoing problem solving was reinforced. At the doctor level, promulgation on diagnosis and management of COPD and prevention of acute exacerbation based on GOLD guideline had been conducted to all frontline doctors to sharpen their skill set. All doctors were advised to manage the COPD cases according to its severity as suggested in the grading and make appropriate referrals if deemed necessary. Regular quarterly review on the progress of the audit was carried out and feedback regarding deficiencies was tackled promptly. At

patient level, to improve patient's awareness and knowledge on COPD, regular health talk had been conducted by various ranks of staff. All COPD smoker patients would be advised to receive the smoking cessation counselling service (SCCS) unless with strong objection. Possible deficiencies and corresponding implementation strategies are summarized in Table 2.

Second-phase data collection and analysis

Totally 2,282 COPD patients were found to have regular FU in GOPCs of KCC during phase 2. Among them, 103 cases were certified dead and 2 cases were found to have been FU at SOPDs and therefore were excluded. The remaining 2,177 cases (95.4%) fulfilled the inclusion criteria were included into data analysis.

Determination Of Variables

The recruited patients' age, gender, smoking status, body mass index (BMI) were retrieved

from the Clinical Management System (CMS) of the HA. The BMI was calculated as body weight/body height² (kg/m²). The severity of COPD symptoms was graded into Group A, B, C and D according to the GOLD guideline (14). All data of the 6 audit criteria were retrieved by the CDARS via HA head office statistical team.

Statistical Methods

All data were entered and analyzed using computer software (Windows version 16.0; SPSS Inc, Chicago [IL], US). The results of the first phase and second phase were compared for statistically significant differences. The Chi squared test was used for categorical variables and student's t test for continuous variables. A P value of < 0.05 was regarded as statistically significant.

Table 2
Deficiencies identified and strategies implemented

Areas of deficiencies	Strategies implemented*
<p>Policy</p> <p>Lack of a responsible team</p> <p>Lack of regular review to monitor the COPD management performance</p> <p>Lack of collaboration with SOPDs</p>	<p>Set up of COPD audit Working Group (WG) with members from both doctors and nurse. Appointment of one doctor and one nurse from the WG as the audit coordinator.</p> <p>Quarterly review policy to monitor the process</p> <p>Collaborate with Respiratory Medicine Team, Kowloon Hospital on handling severe COPD cases and download mechanism for stable COPD cases.</p>
<p>Practice</p> <p>Lack of COPD registry</p> <p>Lack of guideline or protocol</p> <p>Lack of aligned workflow</p> <p>Lack of spirometry machine</p> <p>Lack of drugs for COPD care, such as LAMA.</p>	<p>COPD case registry has been retrieved from CDARS and updated by the WG quarterly</p> <p>Adopt standard guidelines, development of protocol and structural COPD assessment form</p> <p>The workflow of managing COPD cases were streamlined across all 13 GOPCs in KCC.</p> <p>Purchased 5 more Spirobank machine to cater for the service demand in local GOPCs.</p> <p>Newly introduced LAMA to FM Specialist Clinic in 2018.</p>
<p>Staff</p> <p>Lack of continuous education and training</p> <p>Lack of team work</p> <p>Standardized COPD management workflow</p> <p>Lack of feedback</p>	<p>Improvement in education and training via workshop, clinical meeting and journal club.</p> <p>Sharing of workload among staffs of all ranks, including doctors, nurses, Shroff colleagues, allied health workers such as physiotherapist, occupational therapist and dietitian.</p> <p>All COPD patients are groups according to the latest GOLD guideline and managed according to its severity.</p> <p>Quarterly to biannually review on the progress of the audit was carried out and deficiencies was tackled promptly.</p>
<p>Patient</p> <p>Lack of awareness and knowledge and not motivated about smoking cessation</p>	<p>Improve patient's awareness and knowledge by regular health talk and nurse counselling.</p>

Results

Table 3 summarizes the demographic characteristics of COPD patients recruited into the two phases. Among the 2,177 patients recruited in phase 2, 1,578 were follow-up cases from phase 1, the overlapping case rate being 72.5%. The demographic profiles of patients in the two phases of this audit were comparable.

Table 3
Demographic characteristics of COPD patients in the two phases

	Phase 1	Phase 2	P value
COPD cases fulfilled the inclusion criteria (n)	2,358	2,177	/
Gender	1,981 (84.0%)	1,835 (84.3%)	0.80
Male	377 (16.0%)	342 (15.7%)	
Female			
Age (years)	75.9 ± 10.6	75.8 ± 10.7	0.82
<65 yrs old	368 (15.6%)	339 (15.6%)	0.97
≥65 yrs old	1,990 (84.4%)	1,838(84.4%)	
Smoker	658 (27.9%)	661 (30.4%)	0.07
Body Mass Index (BMI, kg/m ²)	23.1 ± 4.0	23.4 ± 4.1	0.76
Underweight (BMI < 18.5)	314 (13.3%)	263 (12.1%)	0.06
Normal (BMI 18.5–22.9)	915 (38.8%)	797(36.6%)	
Overweight (BMI 23.0-24.9)	405 (17.2%)	433 (19.9%)	
Obesity (BMI > 25)	724 (30.7%)	684 (31.4%)	
Data are shown as No. (%) of cases or mean ± standard deviation.			

Table 4

Number and percentage of patients with criteria fulfilled in phase 1 and phase 2 and comparison of the results in the two phases

Item no.	Audit criteria	Phase 1 (n = 2,358)	Phase 2 (n = 2,177)	P value
1	COPD patients with pre-scheduled appointments in GOPC	1,886 (80.0%)	1997 (87.6%)	< 0.00001
2	COPD patients who are smokers	658 (27.9%)	n = 661 (30.4%)	0.069
	a. have ever been referred to Smoking Counselling and Cessation Services (SCCS) before or	332 (50.5%)	367 (55.5%)	0.065
	b. have ever attended SCCS before	289 (43.9%)	317 (48.0%)	0.141
3	COPD patients who have received seasonal influenza vaccine (SIV) in the preceding year;	991 (42.0%)	1,072 (49.2%)	< 0.00001
	< 65 years old	28/368 (7.6%)	78/339 (23.0%)	< 0.00001
	> 65 years old	963/1990 (48.4%)	994/1838 (54.1%)	< 0.00001
4	COPD patients with have received pneumococcal vaccine (PCV) before;	938 (39.8%)	1,244 (57.1%)	< 0.00001
5	COPD patients with spirometry test done before	698 (29.6%)	1,582 (72.7%)	< 0.00001
6	COPD patients admitted to hospitals due to acute exacerbation (AECOPD).	423 (17.9%)	294 (13.5%)	0.000043
Data are shown as No. (%).				

A comparison of the standards achieved in the two phases is summarized in Table 4. In the first phase, there were marked deficiencies in almost all criteria. Among the 658 smokers in the first phase, 332 cases (50.5%) were referred to receive the SCCS but only 289 cases (43.9%) actually attended. Furthermore, only 42% and 39.8% of COPD cases had received SIV and PCV in the audit year. Fewer than one third of COPD patients (29.6%) had clearly documented spirometry findings in the consultation note and 423 cases (17.9%) had at least one episode of hospital admission due to COPD acute exacerbation (AECOPD).

After proactive execution of the enhancement strategies during the implementation phase, significant improvement was observed with respect to most of these criteria in phase 2. The improvement was impressive for regular pre-scheduled appointment arrangement, SIV and PCV vaccination rate (all $P < 0.00001$). The most prominent advance was observed in the spirometry performance rate, increased from 29.6% in phase 1 to 72.7% in phase 2. With the above enhancement in preventive measures, as expected, the AECOPD rate was significantly reduced from 17.9% in phase 1 to 13.5% in phase 2 ($P = 0.000043$).

Regretfully, despite the concerted effort on promotion of SCCS to all smoker COPD patients, the referral rate and attendance rate at SCCS was not significantly improved, although the trend was positive.

Discussion

This study was the largest clinical audit on COPD management ever conducted in Hong Kong and describes the current practice on COPD care in public primary care settings.

In phase 1, marked deficiencies were identified in various aspects of COPD care. According to NICE guideline, COPD cases should be assessed at least twice per year (15), depending on its severity. Despite the recommendation, 20% COPD patients were found not to have a prescheduled FU for regular assessment in phase 1. To overcome this, we went through their CMS record to see whether they had been FU by other health care workers such as private doctors or respiratory specialists. All of them were called up by nursing staff enquiring about their symptom control. For those without being assessed by any doctor in the recent one year, an appointment for doctor's consultation within 6 months had been offered. With such effort, many lost-to-FU COPD cases came back to GOPCs for spirometry and clinical assessment, with 87.6% of all COPD cases having regular FU in GOPCs in phase 2 ($P < 0.0001$).

Cigarette smoking is a major cause of COPD and smoking cessation is the most effective intervention to slow down its disease progression. Therefore, all professionals should, at every opportunity, advise and encourage the smokers to stop the smoking. Having said so, smoking cessation can be very difficult for patients with COPD, and there is no single factor that predict the long-term success. (16) A combination of behavioral and pharmaceutical interventions has been provided at the SCCS in our department since 2010. Although we encouraged all smoker COPD patients to attend the SCCS during their routine consultation, only about half of them were referred and even fewer (43.9%) actually attended in phase 1. More disappointing is that, despite our proactive promulgation, the condition in phase 2 was not significantly improved although the trend was positive. These findings were consistent with literature that COPD smokers are poorly motivated to quit smoking (9). Another possibility is the physicians related factor. For example, literature shows that some physicians do not routinely deal with smoking cessation during their consultations with smokers, partly due to the lack of cessation specific knowledge and skills and partly due to insufficient consultation time. (8) This is particularly true in the GOPCs of HA where averagely 6 minutes is allocated for each consultation. Definitely a more proactive approach is needed to promote the smoking cessation among all health care workers and COPD patients.

For **criteria 3 and 4** on SIV and PCV vaccination rate, although our performance was significantly improved during the audit cycle, only about half of COPD patients were vaccinated against SIV (49.2%) and PCV (57.1%) in phase 2. Indeed, influenza vaccination coverage rates among COPD patients remain low in many countries (10–11). In HK, all elderly patients aged 65 years or older are entitled to receive the SIV and PCV for free under Government Vaccination Program (GVP). However, the breakdown figure of SIV coverage among those under 65 yrs were still far from satisfactory (7.6% in phase 1 and 23.0% in phase 2). Given the widely established evidence on the long-term benefits of SIV on COPD care, such as

reduced number of exacerbations, hospitalizations and decreased all-cause mortalities (6), we would like to propose that government should launch out free SIV to COPD patients of all ages to reduce the mortality.

It is disappointing to find that only **29.6%** COPD patients were found to have conducted spirometry test before in phase 1. The reasons accounting for this poor performance is multifactorial. At doctors' level, some doctors often make the diagnosis of COPD based on clinical features only. At clinic level, spirometry service was previously only available at hospital setting. Therefore, all suspected patients had to be referred to Respiratory Specialist Clinic to do the lung function test with a waiting time ranging from months to 2 years in HA. To plug this loophole, a series of education talks on the proper diagnosis and management of COPD were delivered, with importance of spirometry test emphasized. Furthermore, almost all GOPCs were equipped with spirometry machine during the implementation phase so that the spirometry test could be conveniently performed locally within 2–4 weeks. In addition, at least 1–2 designated nurses from each GOPC have been trained on how to perform the spirometry correctly and the standard of practice was aligned and audited. With such facilitations both on the skill set and tool set, it is not surprising that a tremendous improvement was observed for this criteria in phase 2 (72.7%, $P < 0.00001$).

The **last criteria 6**, the rate of AECOPD leading to hospital admission, is the only outcome criteria of this audit as well as the most important one. In phase 1, we found it quite alarming that almost 1 in 5 of COPD patient had been admitted to hospital due to AECOPD in the preceding year (**17.9%**). This data was similar with Canada studies which showed that approximately 20% of COPD patients had experienced severe acute exacerbations annually. (17) Indeed, acute exacerbations lead to accelerated decline in lung function, worse health status and increased health care utilization, and are the main cause of COPD-related hospitalizations and mortality.(18) In order to decrease the burden of exacerbations, prevention and prompt treatment of exacerbations are important goals in COPD care. In view of this, a series of service enhancement strategies were executed. Firstly, early identification of COPD patients with spirometry and proper staging according to the GOLD guideline was done as mentioned above. Secondly, all COPD cases were managed according to their severity, putting right patients at the right level of care. Stable group A patient would continue regular FU at GOPCs where only short acting bronchodilators are available. Group B patients would be managed at Family Medicine Specialist Clinic (FMSC), where Long Acting Antimuscarinic Antagonist (LAMA) was newly introduced in 2018 to improve the symptom control. For more severe group C/D patients that warrant advanced care, a timely referral to the specialist care would be initiated. Lastly, relatively stable AECOPD patients were advised to FU at GOPC more closely instead of being admitted to hospital. With all these proactive interventions and efforts, the AECOPD rate was significantly reduced to **13.5%** in phase 2.

Strength and Limitations of this study

To our knowledge, this study was the first clinical audit on COPD management ever conducted locally and has provided important information on current COPD care in public primary care settings. The sample size was quite large with more than 2000 cases included in both phase 1 and 2. In addition, all audit criteria are based on objective assessment parameters with data being retrieved from the computer system from HA, therefore recall bias or data entry error had been minimized.

That said, this study has several limitations. First, the study was carried out in one single cluster of HA and therefore selection bias might exist. These results from the public primary health care sector might not be applicable to the private sector or secondary care. Never the less, since COPD cases from all 13 GOPCs of KCC have participated in the clinic audit, these data are well representative of COPD care in the public primary care settings and have provided important background information for future improvement strategies. Second, this clinical audit mainly focused on some short-term outcome aspects of COPD management. Long-term outcomes such as lung function improvement, smoking cessation rate or COPD mortality rate were not compared. In addition, some process indicators such as assessment on bronchodilator use had not been included. Subsequent studies focusing on the long-term outcome criteria may provide a better guide for the evaluation of COPD care. lastly, the one-year intervention phase might not be long enough for some criteria to achieve the targeted standard, although marked improvements were shown. Therefore, continuous effort in more audit cycles would be needed to further improve the clinic outcome in COPD care.

Conclusion

COPD management at primary care clinics of KCC have been tremendously improved during the past two years. Via a team approach with a streamlined governance and structure, regular staff promulgation and proactive staff engagement, significant improvement had been achieved in most of the audit criteria for COPD management, therefore reducing the burden to specialist care and hospital.

Abbreviations

Abbreviations	Full name
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Decease
BMI	Body Mass Index
CAT	COPD Assessment Test
CDARS	Clinical Data Analysis and Reporting System
CMS	Clinical Management System
COPD	Chronic Obstructive Pulmonary Disease
FMSC	Family Medicine Specialist Clinic
FU	Follow Up
GOLD guideline	Global Initiative for Obstructive Lung Disease guideline
GOPCs	General Outpatient Clinics
GVP	Government Vaccination Program
HA	Hospital Authority
HK	Hong Kong
ICPC-2	International Classification of Primary Care-2
KCC	Kowloon Central Cluster
LAMA	Long Acting Anti-muscarinic Antagonist
mMRC	Modified Medical Research Council)
NAHC-Respi	Nurse and Allied Health Clinic - Respiratory Team
PCV	Pneumococcal Vaccine
SCCS	Smoking Counselling and Cessation Service
SIV	Seasonal Influenza Vaccine
SOPCs	Specialist Outpatient Clinics

Declarations

Ethics

No ethics approval is needed in view of audit nature of the study. This complies with local ethics committee from Hospital Authority of Hong Kong that no formal ethics approval was required for clinic audit.

Consent to participate

Since this is a clinical audit, only the medical records of the recruited cases within the Clinical Management System (CMS) of the Hospital Authority (HA) will be reviewed, that their clinical management will not be affected, neither verbal nor written consent to participate in the study will be required, according to regulations of Research Ethics Committee of Kowloon Central Cluster (KCC) of HA.

Competing interest

All authors have declared no conflicts of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Authors contributions

This study has not been presented, published or posted online before. All authors had full access to the data, contributed to the study, approved the final version for publication, and taken responsibility for its accuracy and integrity. All authors contributed to the concept and design of the study. Dr. Catherine CHEN contributed to the acquisition of data, analysis or interpretation of the data, drafting the manuscript and critical revision for important intellectual content.

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