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Factors influencing lung cancer screening completion following participation in shared decision-making: A retrospective study in a U.S. academic health system

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ABSTRACT

Purpose: Shared decision making (SDM) between patients and designated health professionals is recommended by several professional organizations prior to lung cancer screening by low dose CT (LDCT). This study seeks to identify factors, including characteristics of patients and referring clinicians, that influence LDCT screening completion following participation in SDM.

Materials and methods: This retrospective study consisted of $n = 171$ patients eligible for LDCT screening and who participated in SDM between 2016 and 2017 in one of two sites in Prisma Health, an academic health care delivery system in South Carolina. Patient characteristics included age, sex, race, body mass index, marital status, insurance, smoking status and history, family history of lung cancer, SDM site, and distance to screening site. Characteristics of referred clinicians included age, sex, race, specialty, years of practice, education, and residency. Descriptive statistics and multivariable generalized linear mixed models were used to compare effects of patient and referring clinician characteristics on LDCT completion.

Results: A total of 152 patients (89%) completed LDCT screening after participation in SDM. SDM site ($p = 0.02$), longer distances to the screening site ($p = 0.03$), referrals from internal medicine clinicians ($p = 0.03$), and referrals from younger clinicians ($p = 0.01$) and from those with less years of experience ($p = 0.02$) were significantly associated with a lower likelihood of screening completion.

Conclusions: Several factors significantly associated with screening completion were identified. This information can assist with development of interventions to improve communication and decision-making between patients, clinicians, and SDM health professionals, and inform design of targeted decision aids embedded into SDM procedures.

1. Introduction

Lung cancer is the leading cause of cancer mortality in both men and women in the United States (US), and has led to an estimated 142,670 deaths in 2019 [1]. Because the majority of lung cancer cases are diagnosed at an advanced stage, the lung cancer 5-year survival rate of 19.4% is comparatively low to the survival rate of other cancers [2, 3]. Following the National Lung Cancer Screening Trial (NLST) report that annual screenings of low dose CT (LDCT) reduced lung cancer morality by 20% [4], the US Preventive Services Task Force (USPSTF) recommended annual LDCT to high-risk individuals [5]. High-risk individuals were defined as adults aged 55–80 who are current smokers or formers smokers who quit within the past 15 years, with a smoking history of at least 30 pack-years. In 2015, The Affordable Care Act mandated that private insurance companies cover LDCT and the Centers for Medicare and Medicaid Services (CMS) approved the use of LDCT for high-risk individuals [6].

While LDCT lowers patient mortality, there are potential harms to the patient. These harms have been categorized into four domains: physical effects, psychological effects, financial strain, and opportunity

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costs [7]. Specific harms include, but are not limited to, radiation, false positives, overdiagnosis, and overtreatment [7, 8]. Because of the complexities of the benefits and harms of LDCT, shared decision making (SDM) is necessary to ensure that each patient can understand and weigh the potential benefits and harms associated with annual LDCT screening [9–11]. SDM is a process where a health professional and a patient can have a face-to-face conversation about the options, benefits, harms, and patient preferences of LDCT screening [12, 13]. Ultimately, the patient and health professional arrive at a shared decision that leverages the patient's values and beliefs [13]. Several professional organizations promote SDM for lung cancer screening [14], and CMS coverage mandates participation in SDM prior to screening [5].

Support for LDCT screening is generally high [14]. However, screening uptake is comparatively low [15,16], and numerous studies found that clinician referral and patient participation in LDCT screening is influenced by both patient and clinician level barriers [17–24, 11]. Recent studies have shown that the LDCT screening rate is much higher for patients participating in SDM [9, 25–27]. While studies have examined factors that patients and clinicians consider important in the decision-making process [11, [17, 28], little is known about the factors influencing LDCT completion in this population of individuals who choose to participate in SDM. Understanding these factors is necessary for improving shared decision-making and screening rates [29].

In this paper, we examine the association between patient and referring clinician characteristics and LDCT completion following participation in SDM, across two sites in an academic healthcare delivery system in South Carolina. Knowledge of which factors influence LDCT screening in this population is important, as it can be used to improve communication between SDM health professionals, patients, and their referring clinicians, and potentially increase LDCT uptake for high-risk individuals.

2. Materials and methods

2.1. Setting, participants, and procedures

Prisma Health, formerly known as Greenville Health System (GHS) prior to 2019, is a not-for-profit academic healthcare delivery system geographically located in the Upstate of South Carolina. Prisma Health compromises of seven medical campuses, six acute care hospitals, two specialty hospitals, nine outpatient facilities and 155 affiliated practice sites. In 2015, Prisma Health launched a multidisciplinary lung cancer screening program, which was accredited with American College of Radiology (ACR).

There are two sites for SDM of lung cancer screening in Prisma Health: The Center for Integrative Oncology and Survivorship (CIOS) and the Pulmonology Clinic (Pulm). Every appointment was conducted by a designated nurse practitioner to ensure patient understanding of the LDCT screening, discuss the benefits and risks, and address any concerns the patient may have about the process. Both SDM sites used a lung cancer screening pamphlet as a decision aid. This pamphlet was developed by Prisma Health based on several national guidelines [30]. It included a basic introduction of LDCT, eligibility criteria of screening, potential benefits and risks of screening, advice on smoking cessation, and contact information for a lung cancer screening program. In addition to the pamphlet, CIOS used a Lung Nodule Information Sheet to educate the patients on how to interpret the margin, size, and density of lung nodules.

In this retrospective study, we identified LDCT eligible individuals who were referred for LDCT and participated in SDM at one of the two SDM sites in Prisma Health between February 1, 2016 and January 31, 2017. Consistent with CMS requirements, LDCT eligible individuals were defined as 55–77 years of age who are either current smokers or former smokers who have quit within the past 15 years, and have a tobacco history of 30 or more pack-years [6]. Exclusion criteria included any patients with a history of lung cancer (n = 1), patients who were self-referred (n = 2), or patients with continuous referrals (n = 4). These patients did not represent the target population of interest. The final sample consists of 171 patients who participated in SDM for lung cancer screening but have not been previously screened. The characteristics of patients and referring clinicians, as well as LDCT completion status, were extracted from the Prisma electronic health record (EHR). The study was approved by the Prisma Institutional Review Board (IRB); informed consent was waived, and a partial Health Insurance Portability and Accountability Act waiver was granted to support data extraction.

2.2. Study measures

The primary outcome measure was a binary indicator of whether the patient completed LDCT screening (yes or no). Patient characteristics included age (55–59, 60–69, or 70–77), sex, race (Caucasian or non-Caucasian), body mass index (<25, 25–29.9, or ≥30), marital status (married or not married), insurance provider (Medicare, Medicaid, Private, or uninsured), smoking status (current smoker or former smoker), smoking history (30–39, 40–59, or 60+ pack-years), family history of lung cancer (yes or no), the site where SDM took place (CIOS or Pulm), and distance from patient's home to LDCT site (miles). Characteristics of referring clinicians included age (30–39, 40–49, 50–59, or 60–69), sex, race (Caucasian or non-Caucasian), specialty (internal medicine, family medicine, or oncology/hematology), years of practice (<5, 5–9, 10–19, or 20+), education level (medical doctor or osteopathic doctor (MD/DO), physician assistant, or nurse practitioner), and the status of current residency training (yes or no). The inclusion of these variables was based on existing literature, and is summarized in Supplementary Table 1.

2.3. Statistical methods

We first used descriptive statistics to compare patient-level and clinician-level characteristics by LDCT completion (yes/no). Categorical variables are reported as number (%) and compared with a chi-squared test. Exact tests were used for variables with small cell counts. Continuous variables are reported as the mean ± standard deviation and differences between the groups were testing using the Kruskal-Wallis rank test. To examine whether the effects of these variables differ by SDM site, data were stratified by SDM site and descriptive statistics are reported by site.

Multivariable generalized linear mixed effects models (GLMM) were used to analyze the joint effects of these characteristics on LDCT screening to account for dependent observations [31]. Random intercepts were used to account for correlation between patients referred by the same clinician. Given the limited sample size, the model only adjusted for variables with a p-value < 0.20 in the univariate analyses. Current smoking status was also included in the model, as this is a well-known predictor of LDCT completion [18, 29]. All categorical variables with > 2 categories were dichotomized for the regression models in order to account for small cell counts. Clinician years of practice, age, and residency were included in separate models to avoid collinearity. Multiple imputation was performed to replace missing values in some of the variables. Inference is based on the parameter estimates from the GLMM corresponding to 20 imputed data sets. An interaction between each variable in the GLMM and SDM site was included to test whether the odds ratios of screening completion differed by SDM site.. All analyses were conducted using the MI, GLIMMIX, and MIANANALYZE procedures in SAS.

Results

The final sample consisted of 171 patients, 152 (88.8%) which proceeded to complete LDCT screening. Patient characteristics are described in Table 1. Patients referred to CIOS were more likely to

Table 1
Patient Characteristics.

Variable	Total N (%[a])	LDCT Completion Yes (N = 152) N (%[b])	No (N = 19) N (%[b])	P-value
Age Group	.	.	.	0.71
55–59	39 (22.9)	36 (92.3)	3 (7.69)	.
60–69	97 (57.1)	84 (86.6)	13 (13.4)	.
70–77	34 (20.0)	31 (91.2)	3 (8.82)	.
Race Group	.	.	.	0.72
Non-Caucasian	23 (13.5)	20 (87.0)	3 (13.0)	.
Caucasian	148 (86.5)	132 (89.2)	16 (10.8)	.
Gender	.	.	.	1.00
Male	89 (52.0)	79 (88.8)	10 (11.2)	.
Female	82 (48.0)	73 (89.0)	9 (11.0)	.
Body Mass Index	.	.	.	0.83
<25	50 (29.6)	44 (88.0)	6 (12.0)	.
25–30	64 (37.9)	58 (90.6)	6 (9.38)	.
>30	55 (32.5)	48 (87.3)	7 (12.7)	.
Marital Status	.	.	.	1.00
Not married	72 (43.6)	64 (88.9)	8 (11.1)	.
Married	93 (56.4)	82 (88.2)	11 (11.8)	.
Insurance Provider Group	.	.		0.61
Medicare	124 (72.9)	110 (88.7)	14 (11.3)	.
Medicaid	15 (8.82)	12 (80.0)	3 (20.0)	.
Private	29 (17.1)	27 (93.1)	2 (6.90)	.
Uninsured	2 (1.18)	2 (100)	0.0 (0.0)	.
Smoking History, pack-years	.	.	.	0.33
30–39	42 (24.9)	40 (95.2)	2 (4.76)	.
40–59	82 (48.5)	71 (86.6)	11 (13.4)	.
60+ packs	45 (26.6)	39 (86.7)	6 (13.3)	.
Smoking Status	.	.	.	0.30
Former smoker	58 (33.9)	54 (93.1)	4 (6.90)	.
Current Smoker	113 (66.1)	98 (86.7)	15 (13.3)	.
Family History of Lung Cancer	.	.	.	0.15
No	124 (77.0)	112 (90.3)	12 (9.68)	.
Yes	37 (23.0)	30 (81.1)	7 (18.9)	.
SDM site patient referred to	.	.	.	**<0.01**
CIOS	115 (67.3)	110 (95.7)	5 (4.35)	.
Pulm	56 (32.7)	42 (75.0)	14 (25.0)	.
Distance from patient home to screening [c]	15.8 (12.0)	14.9 (11.0)	22.7 (17.0)	**0.03**

Note: **Boldface** indicates statistical significance ($p < 0.05$). Variables may not add to N due to missing data.

[a] % represents proportion of patients included in each category of socio-demographic characteristics.

[b] % represents proportion of patients within a variable category who received, or did not receive, LDCT screening.

[c] Variables reported as mean (SD); otherwise as N (%).

proceed with LDCT screening compared to those referred to PULM (95.7% vs 75.0%, $p < 0.01$). Compared to patients who completed LDCT screening, patients who did not complete LDCT screening lived further (on average) from the imaging center where LDCT screening was performed (14.9 miles vs 22.7 miles, $p = 0.03$). No other variables, including current smoking status and smoking history, were deemed statistically significant at the 0.05 level.

Characteristics of the referring clinicians are described in Table 2. There were 81 Prisma clinicians identified in the study that referred patients for LDCT screening. Each clinician referred a median of 2 patients for LDCT screening (IQR = 1 to 2, range = 1 to 19). A total of 70 clinicians (86.4%) referred four patients or less, 9 clinicians (11.1%) referred four to seven patients, and 2 clinicians (2.5%) referred at least 10. The highest number of patients referred by a clinician was 19,

Table 2
Referring Clinician Characteristics.

Variable	Clinician [a] (N = 81)	Patient [a] (N = 171)	LDCT Completion Yes (N = 152) [b]	No (N = 19) [b]	P-value
Age Group			.		**<0.01**
30–39	26 (37.68)	46 (30.3)	35 (76.1)	11 (23.9)	.
40–49	17 (24.64)	38 (25.0)	37 (97.4)	1 (2.63)	.
50–59	19 (27.54)	58 (38.2)	55 (94.8)	3 (5.17)	.
60–69	7 (10.14)	10 (6.58)	8 (80.0)	2 (20.0)	.
Race Group	.	.	.	.	0.22
Non-Caucasian	9 (12.16)	16 (9.82)	13 (81.3)	3 (18.8)	.
Caucasian	65 (87.84)	147 (90.2)	133 (90.5)	14 (9.52)	.
Gender	.	.	.	.	0.22
Male	41 (50.62)	81 (47.4)	75 (92.6)	6 (7.41)	.
Female	40 (49.38)	90 (52.6)	77 (85.6)	13 (14.4)	.
Physician Specialty	.	.	.		**0.04**
Internal Medicine	40 (52.63)	98 (59.4)	83 (84.7)	15 (15.3)	.
Family Medicine	23 (30.26)	47 (28.5)	45 (95.7)	2 (4.26)	.
Oncology/ Hematology	13 (17.11)	20 (12.1)	20 (100)	0.0 (0.0)	.
Years of Practice	.	.	.	.	**0.03**
< 5	11 (15.28)	14 (8.75)	12 (85.7)	2 (14.3)	.
5–9	17 (23.61)	33 (20.6)	25 (75.8)	8 (24.2)	.
10–20	21 (29.17)	64 (40.0)	61 (95.3)	3 (4.69)	.
> 20	23 (31.94)	49 (30.6)	44 (89.8)	5 (10.2)	.
Education Level	.	.	.	.	1.00
Nurse practitioner	7 (8.64)	11 (6.43)	10 (90.9)	1 (9.09)	.
Physician Assistant	1 (1.23)	1 (0.58)	1 (100)	0.0 (0.0)	.
MD/DO	73 (90.12)	159 (93.0)	141 (88.7)	18 (11.3)	.
Resident	.	.	.	.	0.27
No	67 (82.72)	149 (87.1)	134 (89.9)	15 (10.1)	.
Yes	14 (17.28)	22 (12.9)	18 (81.8)	4 (18.2)	.

Note: **Boldface** indicates statistical significance ($p < 0.05$). Variables may not add to N due to missing data.

[a] Variables reported as N (%), where% represents proportion of patients included in each category of the variable.

[b] Variables reported as N (%), where% represents proportion of patients within a variable category who received, or did not receive, LDCT screening.

accounting for 11.1% of the patient sample. Patients of clinicians who were younger (30–39 years of age) were less likely to complete screening ($p < 0.01$). Patients of clinicians in internal medicine were less likely to complete screening (15.3%) compared to clinicians in family medicine (4.3%) or oncology/hematology (0%). Patients of clinicians with less years of practice were less likely to complete screening compared to clinicians with more years of practice ($p = 0.03$).

Table 3 contains the results from the multivariable regression analysis of LDCT completion on patient-level and (referring) clinician-level variables. Patients who lived further away from the screening center were less likely to proceed with LDCT screening (OR = 0.94, 95% CI = 0.89 to 0.99, $p = 0.03$). Patients participating in SDM at Pulm were less likely to proceed with LDCT screening compared to CIOS (OR = 0.22, 95% CI = 0.06 to 0.80, $p = 0.02$). Patients referred by clinicians in internal medicine were less likely to proceed with LDCT screening (OR = 0.09, 95% CI = 0.01 to 0.77, $p = 0.03$). Patients of referring clinicians with less years of experience (< 10 years) were less likely to proceed with LDCT screening (OR = 0.21, 95% CI = 0.05 to 0.80, $p = 0.02$). While current smokers were nearly twice as likely to not proceed with LDCT screening compared to former smokers, this difference was not statistically significant (OR = 0.53, 95% CI = 0.13 to 2.14, $p = 0.38$). A separate model replacing clinician years of practice with clinician age concluded that patients with younger

Table 3
Adjusted regression analysis.

Variable	Odds Ratio	95% CI	P-value
Current Smoker	0.42	(0.10, 1.74)	0.23
Family History of Lung Cancer	0.60	(0.17, 2.12)	0.42
Distance from patient home to screening	0.94	(0.89, 0.99)	**0.03**
SDM site (ref: CIOS)	.	.	.
PULM	0.22	(0.06, 0.80)	**0.02**
Clinician specialty (ref: Other)	.	.	.
Internal Medicine	0.09	(0.01,0.77)	**0.03**
Clinician years of practice (ref : ≥ 10 years)	.	.	.
0–10 years	0.21	(0.05, 0.80)	**0.02**
Clinician age (ref: ≥ 40 years) [a]	.	.	.
30–39 years	0.19	(0.05, 0.72)	**0.01**
Resident [a]	0.28	(0.05, 1.69)	0.17

Table displays the odds ratio of LDCT completion, corresponding 95% confidence intervals (CI), and p-values. Note: Boldface indicates statistical significance ($p < 0.05$).
a Variable replaced clinician years of practice in separate model to avoid collinearity.

referring clinicians (30–39 years) were less likely to proceed with LDCT screening (OR = 0.19, 95% CI = 0.05 to 0.72, $p = 0.01$). Patients referred by residents were also less likely to complete screening, but this effect did not reach statistical significance ($p = 0.17$).

Patient and referring clinician characteristics stratified by SDM site are presented in Supplementary Tables 2 through 5. Patient characteristics were not significant predictors of screening completion when univariable analysis stratified by site (CIOS: Supplementary Table 2; Pulm: Supplementary Table 3). Effects of clinician characteristics who referred patients to CIOS and Pulm are presented in Supplementary Tables 4 and 5, respectively. In both sites, patients of younger clinicians were less likely to complete screening; however, the effect of clinician age only reached statistical significance at Pulm ($p = 0.02$). Similarly, patients of clinicians with less years of experience, and residents, were less likely to complete screening at both sites. However, these effects only reached statistical significance at CIOS (years of practice: $p = 0.05$; residency: $p = 0.03$). Multivariable regression analyses revealed no significant differences between the two sites in the odds ratios of patient and referring clinician characteristics on screening completion (Supplementary Table 6).

4. Discussion

Using data from an academic health system, information was collected on patients who participated in the SDM process for lung cancer screening, and their referring clinicians, in an attempt to determine factors that influence screening completion. SDM meetings conducted at the Pulmonology Clinic, longer distances from the patient's home to the LDCT screening site, referrals from internal medicine clinicians, referrals from clinicians with less years of experience, and referrals from younger clinicians were associated with a lower likelihood of screening completion.

In this study population, 89% of patients who participated in the SDM process proceeded with LDCT screening. Previous studies have also reported a high rate of LDCT completion after SDM that is close to 90% or higher [9, 25, 26]. However, this study found that LDCT completion rates were significantly different between the two SDM sites: 95.7% in CIOS vs. 75% in Pulm. Potential reasons could be different patient populations or different procedures across the two sites. After adjusting for patient and referring clinician characteristics in our multivariable analysis, SDM site still remained a significant predictor of LDCT completion. Thus, the different SDM processes between the two sites could be a potential explanation. Variation in the SDM process has been previously reported. A recent study rated the SDM process as poor in quality due to poor communication of potential harms of screening and lack of decision aids for the patients [32], while other studies have reported the SDM process to be of high quality [9, 25].

Although our study did not evaluate the quality of the SDM process, we were able to collect some information about the SDM processes through discussions with the nurse practitioners at CIOS and PULM. The SDM meetings at CIOS were conducted by one of two nurse practitioners, while the SDM meeting at Pulm was conducted by one nurse practitioner. In both sites, each in-person meeting took an average of 25–30 min, and covered smoking cessation, lung cancer screening benefits and risks, interpretation of screening results, and the follow-up procedure for positive screening results. Both sites used a Prisma Health Lung Cancer Screening pamphlet as a decision aid. CIOS additionally provided a Lung Nodule Information Sheet to educate patients on how to interpret the margin, size, and density of lung nodules.

A major difference in procedures between the two sites is same day screening. Very few patients receive same day screening at Pulm. Due to insurance authorization issues, most patients schedule their LDCT screening one to two weeks after participation in SDM. At CIOS, a dedicated nurse navigator works with a financial counselor to obtain prior insurance authorization as needed. As a result, most of the patients who agree to screening receive their LDCT scan on the same day of SDM. Future research should investigate the role of waiting time after participation in SDM, as it may be an important predictor of screening completion.

Due to the current Coronavirus (COVID-19) pandemic, remote SDM could be used to replace in-person SDM for patients requiring LDCT screening. This may also help address issues associated with longer waiting times. However, it is unknown whether remote SDM has the equal effect and quality as in-person SDM.

To our knowledge, our study is the first to investigate factors associated with LDCT completion in a population that has participated in SDM. In addition to SDM site, several factors associated with LDCT completion were identified. Further investigation of these factors is needed to improve the process of LDCT screening to ultimately reduce lung cancer mortality. Distance is an established barrier to diagnosis and treatment of lung cancer [33]. Yet the fact that distance remains a barrier after participation in SDM indicates a need to address this issue during or before the SDM appointment. It is unclear why patients referred by internal medicine clinicians, younger clinicians, or those with less years of experience were less likely to complete screening. While these findings warrant further investigation, they do suggest that interventions aimed at improving LDCT screening may need to target clinicians earlier in their careers and be tailored to accommodate the various clinician specialties.

While the LDCT completion rate was lower for current smokers, there was not enough evidence to conclude that current smokers were less likely to complete LDCT screening compared to former smokers. Previous research has shown that current smokers tend to have different beliefs about the risk of cancer, less understanding of screening test characteristics and benefits of early detection of cancer, and are over 3 times less likely to consider lung cancer screening [12]. One possible explanation for our findings is that patients in our study obtained a clinician referral and chose to participate in SDM, and thus represent a different population than all high-risk smokers who are simply eligible for LDCT.

Our study has several limitations. First, the high rate of LDCT completion in this population reduces the power to detect factors associated with screening completion (only 5 of 115 patients failed to complete screening at CIOS). This may explain why some of the results in the study did not reach statistical significance despite a large effect size. Furthermore, adjustments for multiple comparisons were not performed in this exploratory study. While strict adjustment for multiple comparisons is not as critical in exploratory studies, subsequent studies with pre-planned hypothesis must be conducted to confirm the observed associations found here [34].

A second limitation is an inability to identify the causes for SDM site

differences. We are not able to determine whether the difference in screening rates between the two sites are due to differing protocols, personnel, or a combination of the two. Therefore, quality of the SDM process across the two sites needs to be measured and evaluated.

Because patients likely discussed LDCT screening with their referring clinician, the decision to proceed with screening may have been made prior to the SDM appointment. Previous research has shown that referring clinicians' perspective and beliefs about LDCT influence the patient decision to complete LDCT [11, 35, 36]. This makes it difficult to disentangle the impact of referring clinicians from tertiary SDM clinics on a patient's decision to proceed with screening, and may explain the high completion rates seen in this study and others. Future research should examine the relative impact of these processes.

5. Conclusions

This study fills an important gap in the literature regarding the factors that influence LDCT screening following participation in SDM. The factors associated with screening completion included the site of the SDM appointment, distance from the patient's home to the LDCT screening site, referring clinician specialty, and referring clinician age and years of practice. SDM is a critical part of the lung cancer screening process, and is necessary to help patients understand the benefits and risks of LDCT and guide the decision on whether to proceed with screening. Findings from this real-world population of screening eligible patients who participated in SDM can be used to improve the lung cancer screening process by aiding the formulation of consistent procedures across SDM sites, informing the design of targeted decision aids, and developing interventions to facilitate communication and decision-making between patients, clinicians, and SDM health professionals.

Author contributions

LR and RWG wrote the initial draft of the manuscript. Revisions and final manuscript written by LR, LZ, and RWG. JWH and RWG initially conceptualized the study. The biostatistics and data analysis strategy were developed by LR and LZ. The outcome measures component was conceptualized and authored by RWG, JWH, MA, LT, and KH. Descriptions and interpretations of SDM process provided by JWH. Data collection was performed by LT, KH, and MA. formating of data for analysis was conducted by KH, LT, MA, and BL. Literature review was conducted by LR, KH, LT, and MA. Statistical analyses were conducted by LR and BL. Interpretation of the data was performed by LR and LZ. All authors read, contributed to, critically reviewed, and approved the final manuscript.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2020.100198.

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