ORIGINAL ARTICLE

Comparison of Lung Cancer Surgery Outcomes in Queensland for Indigenous and Nonindigenous Australians

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ABSTRACT

Introduction: Indigenous Australians (Aboriginal and Torres Strait Islander) have lower overall survival from lung cancer compared with nonindigenous Australians. Indigenous Australians receive higher rates of chemotherapy and/or radiotherapy. The equity of peri-operative care and thoracic surgical outcomes in Australian indigenous populations have not been contemporarily evaluated.

Methods: We performed a retrospective registry analysis of the Queensland Cardiac Outcomes Registry Thoracic Database evaluating all adult lung cancer resections across Queensland from January 1, 2016 to April 20, 2022. Evaluating the time from diagnosis to surgery, operative data, and postoperative morbidity and mortality comparing Aboriginal and/or Torres Strait Islander people with nonindigenous Australians.

Results: There were 31 patients (2.56%) of 1208 who identified as indigenous. The mean age at surgery was 68.2 years versus 66 years in the indigenous and nonindigenous, respectively ($p = 0.23$). There was female predominance among indigenous patients (n = 28, 90.32%, $p < 0.01$) and the average body mass index was lower (22.52 versus 27.09, $p < 0.01$). There was no variation in the surgical parameters or histopathologic distribution of cancer type between groups. Multivariable logistic regression analysis suggested that indigenous patients were at elevated risk of blood transfusion (relative risk 3.9, $p = 0.014$, OR = 9.01, 95% confidence interval [CI]: 2.25–36.33, $p < 0.01$) and had greater transfusion requirements (risk ratio 4.08, $p = 0.0116$ and OR = 12.67, 95% CI: 2.25–71.49, $p < 0.01$);

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however, the influence of low absolute number of transfusions must be acknowledged here. Indigenous status was not associated with increased intensive care unit admission (OR = 1.79, 95% CI: 0.17–18.80, $p = 0.62$), return to operating theater (OR = 2.1, 95% CI: 0.24–18.15, $p = 0.50$), new atrial fibrillation (OR = 0.52, 95% CI: 0.07–4.01, $p = 0.55$), prolonged air leak (OR = 0.29, 95% CI: 0.04– 2.16, $p = 0.228$), or pneumonia postoperatively (OR = 4.77, 95% CI: 0.55–41.71, $p = 0.16$). With only three deaths, no meaningful trends were observed. Time from diagnosis to surgery was comparable in the indigenous and nonindigenous groups (88.6 d, 95% CI: 54.26–123.24 versus 86.2 d, 81.40–91.02, $p = 0.87$). Postoperative length of stay was not numerically or statistically different between groups. (indigenous 7.54 d versus nonindigenous 7.13 d, $p = 0.90$).

Conclusions: Indigenous patients are more likely to receive a blood transfusion than nonindigenous patients during lung resection. Reassuringly, the perioperative care provided to indigenous Australians undergoing lung resection in Queensland seems to be comparable to that of the nonindigenous population.

Keywords: Lung Cancer; Surgery; Lobectomy; Indigenous; Australian; Aboriginal

Introduction

Lung cancer is the leading cause of cancer death worldwide, independent of sex. The incidence and development of which is intimately associated with smoking.[1] Though only 15% of smokers develop lung cancer, it is thought to be the predominant modifiable risk factor for lung cancer. The average age of lung cancer diagnosis is approximately 70 years with an overall 5-year survival of 20%. The earlier stage of diagnosis and intervention is associated with increased survival (5-y survival for stage I–II is 59%).[2]

Registry review of epidemiologic trends in Aboriginal and Torres Strait Islander people, hereafter respectfully referred to as indigenous Australians, has revealed that indigenous Australians have a 6% incidence of lung cancer, compared with a 2% incidence in nonindigenous Australians. Smoking incidence in indigenous patients is estimated to be as high as 41.4% compared with 14.5% in nonindigenous Australians.[3] Moreover, there are considerable differences in the health-seeking behaviors of indigenous and nonindigenous Australians, which compound this trend of active cigarette use. Research suggests that indigenous Australians are more likely to engage in negative health risk behaviors than their nonindigenous counterparts. The reasons for this are complex and poorly understood.[4] These negative health risk behaviors and health-seeking behaviors undoubtedly contribute to the disparity in the health outcomes noted between indigenous and nonindigenous patients.[5] This is heightened by the interaction of the health care system sociodemography, geography, history, differences in cultural perceptions of health, and health literacy.[5]

Data evaluating cancer trends in indigenous Australians suggest that, as a group, they are more likely to present with more advanced disease. Furthermore, indigenous Australians generally wait longer for treatment, are less likely to receive treatment (surgical or otherwise), and have lower survival (hazard ratio 1.3, 95% confidence interval [CI]: 1.1–1.5).[6] Indigenous Australians are also more likely to receive chemotherapy and/or radiotherapy than nonindigenous Australians.[7] Contemporary studies in parts of Australia suggest that the average time to surgery from diagnosis is 14 days; the time to surgery, specifically for the indigenous population of Queensland, is unknown.[8] Indigenous Australians have lower overall survival from lung cancer, compared with nonindigenous Australians.

Evaluating lung cancer surgery for indigenous and nonindigenous Australians is essential to identify any differences in the delivery of care and outcomes, to help improve the care provided to indigenous Australians.

Materials and Methods

We performed a retrospective multicenter review of Queensland's Cardiac Outcomes Registry's (QCOR) thoracic database from January 1, 2016 to April 20, 2022. This included all patients undergoing lung resection for lung cancer or metastasis within the Queensland Health hospital network and catchment area. Patients undergoing resection for noncancerous lesions (i.e., infective or inflammatory disease) were excluded. Patients with no recorded race/ethnicity were excluded. A waiver of consent was approved by the Gold Coast Hospital and Health Service's Human Research and Ethics Committee in accordance with the National Health and Medical Research Council of Australia's regulations.

The primary outcomes evaluated were operative mortality (defined as death within 30 d postoperatively), mortality at 90 days, and major morbidity. Major morbidity included composite and individual analysis of the following within 30 days of the primary operation: (1) reoperation/return to the operating theater; (2) prolonged air leak (>72 h); (3) postoperative length of stay; (4) pneumonia; (5) pulmonary embolism; (6) wound infection; (7) new atrial fibrillation; (8) intensive

care unit (ICU) admission (planned and unplanned); (9) duration of ventilation in ICU; (10) transfusion requirement and quantity of red blood cells; (11) lung herniation; (12) lung torsion; (13) bronchial stump leak; (14) perioperative myocardial infarction; and (15) cerebrovascular accident.

The time from diagnosis to surgery was considered in three ways, namely: (1) the number of days from the earliest recorded date of Imaging to surgery, (2) the number of days from the earliest recorded date of tissue sampling to surgery, and (3) the time from the earliest recorded date of diagnosis (tissue or imaging) to surgery, represented in days.

Statistical Methodology

All statistical analyses were conducted using Stata 17 statistical software (StataCorp, College Station, TX). For this study, patients were grouped into two groups: (1) those who identified as Aboriginal and/or Torres Strait Islander were collectively termed as "indigenous"; and (2) patients who did not identify as Aboriginal or Torres Strait Islander were assigned as "nonindigenous" group. Simple descriptive statistics were used to assess the baseline characteristics of the participants. Mean and SD or median and interquartile range were used to describe continuous variables. Categorical variables were analyzed and displayed as proportions/frequencies. Continuous variables were compared with the Student's t test or Mann-Whitney U test depending on their distribution. For categorical and binary variables, univariate analysis was performed using chi-square or Fisher's exact test. Those identified to have a p value less than 0.1, were included in multivariable logistic regression modeling. Variables found to have a p value less than 0.05 in the multivariable logistic regression analysis were considered statistically significant.

Results

We evaluated 1202 patients in total, 31 of whom identified as Aboriginal or Torres Strait Islander, 1043 who identified as nonindigenous, and 128 patients without a race/ethnicity specified, which were not analyzed further. There was a female sex predominance in the indigenous group, with 90.32% (n = 29, $p < 0.01$) women. Indigenous patients were also more often active smokers, with 51% versus 25% of nonindigenous patients actively smoking ($p < 0.01$). Indigenous patients also had a lower mean body mass index (22.52 versus 27.09, $p < 0.01$), and lower preoperative creatinine levels (59 μmol/liter versus 73 μmol/liter, $p < 0.01$). Indigenous patients had low rates of preoperative adjuvant therapy, with only one patient receiving radiation. However, the overall use of preoperative adjuvant therapy was low. Otherwise, the indigenous and nonindigenous patients had reasonably well-matched premorbid status (Table 1).

The relative risk (RR) of unplanned ICU admission (Table 2), in the indigenous group was 1.25 (95% CI: 0.22–7.24, $p = 0.8$), multivariable analysis of the relationship between indigenous status and unplanned ICU admission revealed an OR of 1.79 (95% CI: 0.17–18.80, $p = 0.63$) (Table 3). In those who were admitted to ICU and consequently ventilated, the mean duration of ventilation was 34 versus 13.76 hours in the nonindigenous ($p = 0.62$) (Table 4).

Indigenous status was associated with an increased risk of blood transfusion (RR = 3.9, 95% CI: 1.24–12.23, $p = 0.01$, OR = 9.01, 95% CI: 2.24–36.33, $p < 0.01$). Multivariable analysis revealed male sex and higher preoperative staging were associated with a higher risk of transfusion, whereas lower preoperative creatinine levels were protective for transfusion. The mean transfusion requirement for indigenous patients was 3 versus 2.39 (95% CI: 1.56–3.23, $p = 0.65$).

The preoperative timing for indigenous patients to reach surgery from diagnosis was similar to the nonindigenous group. From radiological diagnosis, the mean time to surgery was 88.75 versus 89.21 days ($p = 0.87$) between the indigenous and nonindigenous groups, and 82.78 versus 90.32 days ($p = 0.64$) from the earliest diagnosis to surgery. From biopsy to surgery, however, there was an approximate 12-day difference between the indigenous and nonindigenous groups (74.37 versus 62.62 d, $p = 0.48$) but these differences were not statistically significant (Table 5).

The postoperative length of stay between the two groups was similar, with a mean day-to-discharge of 7.54 days in the indigenous group and 7.13 in the nonindigenous group ($p = 0.90$), without statistically significant difference.

With respect to other major morbidities, postprocedurally, the incidence of new atrial fibrillation, pulmonary embolism, pneumonia, prolonged air leak, lung torsion/herniation, myocardial infarction, cerebrovascular accident, wound infection, and mortality were so low that no true meaningful analysis on their incidence or risk could be performed.

Discussion

From this study of the Queensland state-wide surgical database, there does not seem to be a significant discrepancy in the delivery of care to indigenous patients undergoing lung resection compared with nonindigenous patients. The time from imaging diagnosis and tissue diagnosis to surgery was generally slightly longer in the indigenous group but without statistical

Table 1. Baseline Characteristics

Characteristics	Subgroups	Nonindigenous n = 1,043	Indigenous n = 31	*p* Value
Age, mean (SD)		66.01 (9.97)	68.16 (9.18)	0.23
Sex				
	Female	560 (53.69)	28 (90.32)	<0.01
	Male	483 (46.31)	3 (9.68)	
Smoking Status				<0.01
	Never	125 (11.98)	4 (12.90)	0.88
	Former	633 (60.77)	9 (29.03)	<0.01
	Current	265 (25.29)	16 (51.61)	<0.01
BMI, mean (SD)		27.09 (5.38)	22.52 (3.65)	<0.01
Coronary artery disease		169 (19.07)	0 (0)	0.40
Last preoperative creatinine (μmol/liter)		73 (63–87)	59 (56–70)	<0.01
Diabetes mellitus		172 (16.59)	2 (6.45)	0.13
Cerebrovascular disease		59 (5.68)	3 (9.68)	0.35
Peripheral vascular disease		56 (5.39)	2 (6.45)	0.80
Respiratory disease		418 (40.58)	13 (41.94)	0.88
FEV1 (L)		2.52	1.96	0.40
Preoperative adjuvant therapy		34 (3.28)	1 (3.23)	0.99
Preoperative adjuvant therapy type				0.08
	Radiation	5 (14.71)	1 (100)	
	Chemotherapy	13 (38.24)	0	
	Combined	16 (47.06)	0	
Immunosuppressive		49 (4.73)	2 (6.45)	0.22
Anticoagulant therapy (within 7 d)		73 (7.05)	4 (12.9)	0.22
Antiplatelet therapy (within 7 d)		179 (17.31)	2 (6.45)	0.11
Previous surgery				
	Cardiac	73 (7.18%)	1 (3.23%)	0.40
	Thoracic	42 (4.05%)	1 (3.23%)	0.82
Incision Type				0.89
	VATS	256 (24.59)	7 (22.58)	0.80
	Thoracotomy	780 (74.93)	24 (77.42)	0.76
	Sternotomy	5 (0.48)	0	0.70
Resection type				0.53
	Lobectomy	959 (91.95)	29 (93.55)	0.75
	Bilobectomy	36 (3.45)	2 (6.45)	0.37
	Pneumonectomy	44 (4.22)	0 (0)	0.24
Lymph node sampling technique				0.91
	Sampling	787 (91.94)	21 (93.55)	
	Dissection	69 (8.06)	2 (8.70)	
ICU admission		80 (7.71)	11 (3.45)	0.39
Cancer histopathology				0.90
	Adenocarcinoma	676 (66.08)	20 (64.52)	
	Squamous Cell Carcinoma	217 (21.21)	7 (22.58)	
	Small Cell Carcinoma	5 (0.49)	0 (0)	
	Neuroendocrine	65 (6.35)	3 (9.68)	
	Metastasis	6 (0.59)	0	
	Other	26 (2.54)	0	
	Large Cell Carcinoma	14 (1.37)	0	
	Mixed Types	14 (1.37)	1 (3.23)	
Preoperative TNM stage				0.93
	I	489 (68.887)	13 (68.42)	
	II	157 (22.11)	4 (21.05)	
	III	55 (7.75)	2 (10.53)	
	IV	9 (1.27)	0 (0)	

(continued)

Table 1. Continued

Characteristics	Subgroups	Nonindigenous n = 1,043	Indigenous n = 31	*p* Value
Postoperative TNM stage				0.58
	I	582 (60.31)	20 (66.67)	
	II	225 (23.32)	5 (16.67)	
	III	127 (13.16)	5 (16.67)	
	IV	31 (3.21)	0 (0.00)	

Notes: All values are n (%) unless otherwise specified.
BMI, body mass index; FEV1, forced expiratory volume in 1 second; ICU, intensive care unit; VATS, video-assisted thoracoscopic surgery.

significance. Furthermore, the longest delay to surgery between groups noted in the study was from tissue diagnosis to surgery, which was 12 days longer in the indigenous group—this is not likely a clinically significant finding. However, this trend toward slightly longer wait times may reflect the geographic distribution of the indigenous Australians in Queensland. Although not captured within this review, it is known that the greatest representation of indigenous patients in this cohort comes from far North Queensland. Therefore, whereas the overall proportion of indigenous patients in this review is approximately 2.58% (comparable with the national population), we postulate that if geography was considered in this analysis, one would expect to find significant regional variation. Although indigenous patients represent a small proportion of the work in metropolitan areas, as a group, they constitute close to 20% of the surgical cohort in North Queensland.[9] Therefore, the delay in surgery may reflect the logistic challenges to health care in North Queensland.

The incidence of lung cancer in indigenous Australians is estimated to be at least two times that of nonindigenous Australians. In this analysis, the indigenous group represents only 2.56% of the study, which is similar to the total representation of indigenous people in the Australian population.[7] With twice the incidence of the nonindigenous group, one would expect a higher representation. This may be a result of the selection bias of the registry, using only surgical patients. There may be a proportion of indigenous patients not captured in this data set with advanced-stage lung cancers that are receiving chemotherapy or radiation therapy.

This study makes some interesting observations in the demographics of indigenous Australians undergoing lung cancer surgery. There was an overwhelming female predominance among the indigenous people undergoing surgery. The data provided here does not explain these findings and the reasons for this are likely complex and multifactorial. Furthermore, the small absolute number of indigenous Australians in this study must be considered in the interpretation (n = 31) and the selection bias that accompanies the use of a surgical registry. First, the female sex carries a threefold risk for the development of lung cancer compared with the male sex, which may contribute to the sex distribution presented here.[10] Second, acknowledging that the average life expectancy of indigenous Australians is 61 years, compared with the contemporary average age of diagnosis of 70 years in the literature and 68 years in our data, suggest that a group of indigenous patients may have passed away before

Table 2. RR and Descriptive Statistics

Morbidity/Mortality Outcome	Nonindigenous n = 1043	Indigenous n = 31	RR	95% CI	*p* Value
Unplanned ICU admission	3 (0.29)	1 (3.23)	1.25	0.22-7.24	0.8
Blood transfusion	28 (2.68)	3 (9.68)	3.90	1.24-12.23	0.01
Return to theatre	30 (2.88)	1 (3.23)	0.75	0.12-5.30	0.77
New AF	30 (2.88)	1 (3.23)	0.52	0.07-3.61	0.49
Wound infection	31 (2.97)	0			
Pneumonia	30 (2.88)	1 (3.23)	2.80	0.38-20.89	0.30
PE	31 (2.97)	0			
Prolonged air leak	31 (2.97)	1 (3.23)	0.31	0.05-2.18	0.20
MI	31 (2.97)	0			
30 d mortality	3 (0.29)	1 (3.23)			
90-d mortality	10 (0.96)	1 (3.23)			

Notes: All values are n (%) unless otherwise specified.
CI, confidence interval; ICU, intensive care unit; MI, myocardial infarction; PE, pulmonary embolism; RR, risk ratio.

Table 3. Multivariable Morbidity and Mortality Analysis

	Nonindigenous	Indigenous			
Morbidity/Mortality Outcome	n = 1043	n = 31	OR	95% CI	*p* Value
Return to theater	30 (2.88)	1 (3.23)	2.1	0.24-18.15	0.5
ICU admission					
Unplanned	3 (0.29)	1 (3.23)	1.79	0.17-18.80	0.63
Transfusion					
Red blood products	28 (2.68)	3 (9.68)	9.01	2.24-36.33	<0.01
Units transfused	2.39	3	12.67	2.25-71.49	<0.01
New AF	30 (2.88)	1 (3.23)	0.52	0.07-4.01	0.53
Pneumonia	30 (2.88)	1 (3.23)	4.77	0.55-41.71	0.16
Prolonged air leak	31 (2.97)	1 (3.23)			
30-d mortality	3 (0.29)	1 (3.23)			
90-d to mortality	10 (0.96)	1 (3.23)	–	–	–

Notes: All values are n (%) unless otherwise specified.
AF, atrial fibrillation; CI, confidence interval; ICU, intensive care unit.

developing or being diagnosed with lung cancer.[2] The leading causes of death in indigenous Australians are ischemic heart disease, diabetes, chronic obstructive pulmonary disease, lung cancer, and self-harm. Earlier mortality aside, the cumulation of these diseases in indigenous Australians may render them unfit for surgery; as such, they will not be recorded in the QCOR database. More importantly, lung cancer itself is one of the top five causes of death in this population, and indigenous Australians are more often diagnosed with more advanced diseases.[6,11] Early mortality and/or advanced-stage diagnosis both would exclude patients from being recorded in the QCOR database; as such, the full burden of disease is not captured by this analysis. Finally, the health-seeking behavior of indigenous Australians with respect to lung cancer surgery has not been specifically evaluated. Indigenous Australian men have been identified to have unique deleterious patterns of health-seeking behaviors compared with indigenous women and nonindigenous Australians.[12] These behavioral differences have been correlated with adverse health outcomes and may be influencing the demographic trends presented here; however, the complexities of this interaction are not captured within this review.[4]

Reassuringly, the overall rates of morbidity and mortality in this study were low, and indigenous patients were not at an overtly higher risk of morbidity or mortality, except for transfusion. The knowledge of this elevated risk in indigenous patients, particularly male patients, is important. First, it allows a greater understanding of the risks of surgery that indigenous patients face and serves to improve the quality of culturally-specific informed consent. Second, although these data suggest an elevated risk of transfusion in the indigenous patients, the absolute number of transfusions given in both groups was low. Consequently, this association may or may not be maintained in larger sample sizes. Whereas the reason for the trend toward higher transfusion requirement is not clear in this study, acknowledging its presence can help guide further research. The equal length of stay and overall low rates of ICU admission in both groups are also suggestive that postoperative morbidity in this population is not statistically or clinically different from nonindigenous patients. This useful analysis provides information that can help inform patients regarding their expected care trajectory.

Limitations

As a retrospective registry study, this data set does not capture, explain, or explore the differences in culture, health-seeking behavior, health literacy, sociodemographic factors, and geographic distribution between the indigenous and nonindigenous participants. All of these are important to fully understand the disease

Table 4. Mean Testing for Continuous Variables

	Nonindigenous		Indigenous		
Morbidity/Mortality Outcome	Mean	95% CI	Mean	95% CI	*p* Value
Postoperative length of stay	7.13 ± 17.56	6.04-8.22	7.54 ± 11.01	3.51-11.59	0.89
Hours ventilated	13.76 ± 69.28	−99.59 to 167.59	34 ± 53.78	−7.82 to 35.35	0.62
RBC units transfused	2.39	1.56-3.23	3	−3.57 to 9.57	0.65

CI, confidence interval; RBC, red blood cell.

Table 5. Time to Surgery

	Nonindigenous		Indigenous		
Time to Surgery	Mean	95% CI	Mean	95% CI	*p* Value
Imaging Diagnosis to Surgery (d)	89.21 ± 75.51	81.40-91.02	88.75 ± 81.67	54.26-123.24	0.87
Tissue Diagnosis to Surgery (d)	62.62 ± 70.59	57.60-67.64	74.37 ± 85.99	32.92-115.81	0.48
Earliest Diagnosis to Surgery (d)	90.32 ± 81.16	85.16-95.47	82.78 ± 78.98	32.92-115.81	0.64

CI, confidence interval

burden in this population and help improve outcomes for all Australians.

The use of a surgical database and retrospective study has limitations. More importantly, patients who declined surgery were too high risk for surgery but may have had anatomically and oncologically resectable disease, and patients who presented with nonsurgical disease (advanced-stage lung cancer) will not be captured by this database and review. Consequently, this analysis is subject to an innate selection bias and cannot comment on the care provided or outcomes in those not captured within the surgical database.

Although the cohort size for this study was large, there were only 31 patients who identified as indigenous Australians. Weighted analysis was considered; however, given the existing limitations of the data set and innate selection bias, the ability of weighted analysis to correct for class imbalances without the introduction of additional analytical bias was unclear. Consequently, unweighted modeling was performed as it reflects the real-life data set without manipulation. This limits the generalizability and extrapolation of this information in practice; however, given the paucity of data surrounding lung cancer in indigenous populations, it is important to explore this data set.

The data was analyzed as it was presented from the QCOR database. No imputation methods were performed for missing data and variables with greater than 10% of the cohort missing data were not analyzed in the review.

This review was conducted during the coronavirus disease 2019 pandemic and includes patients diagnosed and operated on during the pandemic. The influence of the coronavirus disease 2019 pandemic on access to care, operative capacity or performance, and health-seeking behaviors is unclear.

Future Directions

This study has identified that there are very few indigenous men undergoing lung resection for lung cancer. The reasons for this are likely multifactorial and not explained by this analysis. The Australian government's report on the lung cancer screening inquiry has recommended indigenous Australians between 50 and 74 years and nonindigenous Australians between 55 and 74 years with a current or former smoking history be screened.[13] It is hoped that the inclusion of younger indigenous Australians will reduce the mortality burden of lung cancer and identify people at earlier stages of the disease. Acknowledging the limitations of this study, it serves to explore the gap in the literature around the complex relationship between indigenous Australians and lung cancer with respect to incidence, treatment, and outcome. Further research is required to fully understand these trends outside of the Queensland surgical cohort.

Recommendations

Cross-linkage with the Queensland oncology database to evaluate the outcomes and staging of indigenous patients with lung cancer may help explain the trends observed here. Further investigation into why indigenous patients require greater rates and volumes of transfusion is required. A review of the efficacy of screening in the indigenous population should be performed after the introduction of the national screening program. Consultation with key indigenous stakeholders and elders, moving forward, might help improve the equity of care and guide further research into the findings detailed here.

In conclusion, there is a clear sex disparity in the indigenous people requiring lung surgery, the lack of male patients in this cohort needs further research. Indigenous patients with lung cancer may be at elevated risk of requiring blood transfusion during lung resection. Postoperative morbidity, mortality, and time to surgery within the limitations of this analysis are comparable between indigenous and nonindigenous Australians.

CRediT Authorship Contribution Statement

Frazer Kirk: Conceptualization, Data analysis, Investigation, methodology, writing, drafting.

Syed Danial Syed Ahmad: Writing- review & editing.

Clayton Lam: Data analysis, investigation.

Matthew S. Yong: Supervision, Writing- review & editing.

Cheng He: Supervision, Writing- review & editing, Conceptualization.

Sumit Yadav: Writing- review & editing.

Wing Lo: Writing- review & editing.

Christopher Cole: Writing- review & editing.

Morgan Windsor: Writing- review & editing.
Rishendran Naidoo: Writing- review & editing.
Andrie Stroebel: Supervision, Writing- review & editing.

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