

Pneumomediastinum in patients with COVID-19 undergoing CT pulmonary angiography: a retrospective cohort study

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ABSTRACT

Background Various complications have been reported in patients with COVID-19 including pneumomediastinum.

Methods The primary objective of the study was to determine the incidence of pneumomediastinum in COVID-19 positive patients who underwent CT pulmonary angiography (CTPA). The secondary objectives were to analyse if the incidence of pneumomediastinum changed between March and May 2020 (peak of the first wave in the UK) and January 2021 (peak of the second wave in the UK) and to determine the mortality rate in patients with pneumomediastinum. We undertook an observational, retrospective, single-centre, cohort study of patients with COVID-19 admitted to Northwick Park Hospital.

Results 74 patients in the first wave and 220 patients in the second wave met the study criteria. Two patients during the first wave and eleven patients during the second wave developed pneumomediastinum.

Conclusions The incidence of pneumomediastinum changed from 2.7% during the first wave to 5% during the second wave and this change was not statistically significant (p value 0.4057). The difference in mortality rates of patients with pneumomediastinum in both waves of COVID-19 (69.23%) versus patients without pneumomediastinum in both waves of COVID-19 (25.62%) was statistically significant (p value 0.0005). Many patients with pneumomediastinum were ventilated, which could be a confounding factor. When controlling for ventilation, there was no statistically significant difference in the mortality rates of ventilated patients with pneumomediastinum (81.81%) versus ventilated patients without pneumomediastinum (59.30%) (p value 0.14).

INTRODUCTION

On 11 March 2020, the WHO announced that SARS-CoV-2, now referred to as COVID-19, should be characterised as pandemic.¹ Various complications have been reported in patients with COVID-19 including pneumomediastinum^{2 3} (figure 1). Pneumomediastinum is an uncommon finding in patients with pneumonia. However, it was seen relatively more commonly in patients with SARS caused by a novel coronavirus (SARS-CoV) in a study in Hong Kong, China, during a community outbreak from 24 March to 28 April 2003. The study demonstrated that 11.6% of patients with SARS-CoV developed pneumomediastinum.⁴

The occurrence of pneumomediastinum is being reported more often in patients with COVID-19 similar to SARS. This increased frequency of pneumomediastinum is occurring despite lung protective mechanical ventilation protocols being used for patients with severe pneumonia or acute respiratory distress syndrome.³

It is important to study the incidence of pneumomediastinum in patients with COVID-19 and to establish if the presence of pneumomediastinum is associated with increased mortality. If the mortality in patients with pneumomediastinum is indeed higher, it would provide further data which would be relevant for reasons of prognostication.

Chest pain, dyspnoea and subcutaneous emphysema are the most common clinical manifestations of pneumomediastinum.⁵ The causes of pneumomediastinum are varied. It is most often caused by increased airway pressure, secondary to mechanical ventilation or airway obstruction. Other causes include: a rise in intrathoracic pressure from the Valsalva manoeuvre, excessive coughing during asthma or respiratory infections, trauma to the thoracic cavity, oesophageal rupture, and alveolar injury due to underlying lung diseases such as infection and sarcoidosis.⁵

Various studies and case reports have described the occurrence of pneumomediastinum in COVID-19 pneumonitis patients who received mechanical ventilation or positive airway pressure support.^{6 7} There are also reported cases of pneumomediastinum in patients with COVID-19 unrelated to intubation or noninvasive ventilation (NIV).^{8 9} Although the precise mechanism of pneumomediastinum in COVID-19 is unknown, barotrauma secondary to mechanical ventilation may be a significant aetiological factor.⁵ The increase of alveolar pressure causes alveoli to rupture, therefore releasing air into the lung interstitium. Subsequently, this air migrates through the peribronchial and perivascular sheaths to the mediastinum along a pressure gradient between the lung periphery and the mediastinum.^{5 8}

The presence of pneumomediastinum in patients with COVID-19 may indicate extensive alveolar membrane destruction and highlight to the clinician the need for closer monitoring.

The *primary objective* of this study was to determine the incidence of pneumomediastinum in COVID-19 positive patients who underwent CT pulmonary angiography (CTPA). The *secondary*



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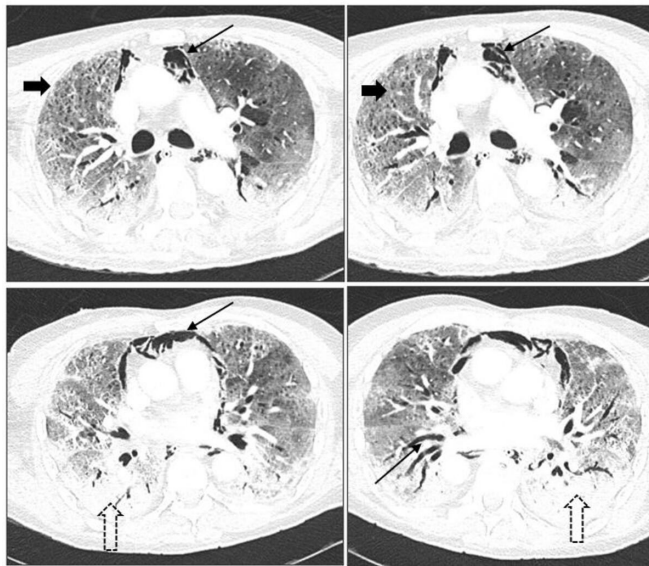


Figure 1 CT PA of a patient with COVID-19 infection showing a large volume of free gas within the mediastinum in keeping with pneumomediastinum (black arrow), extensive bilateral ground-glass opacities (thick black arrow) in keeping with COVID-19 pneumonitis, and large areas of consolidation in the dependent portions of both lower lobes suggesting bacterial infection (thick square dotted arrow).

objectives were to analyse whether the incidence of pneumomediastinum changed between March and May 2020 (peak of the first wave in the UK) and January 2021 (peak of the second wave in the UK) and to determine the mortality rate in patients with COVID-19 with pneumomediastinum who underwent CTPA.

MATERIALS AND METHODS

We conducted an observational, retrospective, single-centre, cohort study of patients who have tested positive for COVID-19 and were admitted to Northwick Park Hospital, part of London North West University Healthcare NHS Trust, during the periods of March to May 2020 (peak of the first wave in the UK) and January 2021 (peak of the second wave in the UK).

Inclusion criteria

Patients admitted to Northwick Park Hospital with symptoms of COVID-19 pneumonitis requiring CTPA between March to May 2020 and January 2021.

Patients with positive reverse transcriptase PCR (RT-PCR) test for SARS-CoV-2 and/or radiological patterns of COVID-19 on CT imaging.¹⁰

Patient's age ≥ 18 years.

Exclusion criteria

Patients transferred to other hospitals (due to space constraints at Northwick Park Hospital or requirement of extra-corporeal membrane oxygenation).

We evaluated data from electronic patient records of patients meeting the inclusion and exclusion criteria. Patients were not contacted for the study. The data collected included age, gender, C reactive protein (CRP), COVID-19 RT-PCR, CTPA, complications such as pneumomediastinum, interventions received such as NIV, invasive ventilation (IV) and use of dexamethasone. Data about outcome (alive at discharge, dead or transferred to other hospitals for further treatment) and length of stay was also

collected. The presence or absence of pneumomediastinum was based on reporting of CTPA by the radiology department.

During March to May 2020, the first wave of COVID-19 pandemic in the UK, 74 patients admitted to the Northwick Park Hospital met the inclusion criteria. Two hundred and twenty patients admitted to the Northwick Park Hospital in January 2021 met the inclusion criteria. A total of 27 patients were transferred to other hospitals during both waves and hence excluded from the study.

One of the differences in the treatment approach of COVID-19 pneumonitis during these two waves was that dexamethasone became standard care for all patients with COVID-19 requiring oxygen from June 2020 at Northwick Park Hospital after the publication of the RECOVERY trial (Randomised Evaluation of COVID-19 Therapy).¹¹ Hence, all patients in the January 2021 cohort received intravenous or oral dexamethasone, but patients during March to May 2020 did not receive steroids.

Statistical analysis

Descriptive analysis was done using R software V.4.0.5. Pearson χ^2 test and Pearson χ^2 test with Yates's continuity correction were used in the analysis to calculate statistical significance. Yates's continuity correction was also used to prevent overestimation of small data. P value of <0.05 was used to consider any statistical significance.

RESULTS

During the first wave of COVID-19 in the UK, from March 2020 to May 2020, 74 patients were suitable to be included in the study. A total of 28 patients received ventilatory support in the form of NIV (4) or IV (24). None of the patients developed pneumothorax among the study cohort during the first wave. Eighteen patients developed pulmonary embolism (table 1).

During the second wave of COVID-19 in the UK, in January 2021, 220 patients met the study criteria. All these patients received dexamethasone of 6 mg (intravenously or orally) up to 10 days as per the protocol which was established after the first wave of COVID-19 from June 2020 onwards. A total of 69 patients received ventilatory support in the form of NIV (24) or IV (45). Four patients developed pneumothorax in the cohort of patients during the second wave (table 1). Three of these patients were on IV before the development of the pneumothorax and two of these patients also had pneumomediastinum. All these four patients received a chest drain. All four patients died due to COVID-19 pneumonitis. Sixty-one patients developed pulmonary embolism (table 1).

From March to May 2020, during the first wave of COVID-19, 2 patients out of 74 developed pneumomediastinum. Both patients were intubated and ventilated before the development of pneumomediastinum and both patients died. In January 2021, during second COVID-19 wave, 11 patients developed pneumomediastinum. Nine patients were ventilated before the occurrence of pneumomediastinum and two did not require any ventilatory support (table 2).

The incidence of pneumomediastinum for the entire study period was found to be 4.42%. The incidence changed from 2.7% in the first wave in March–May 2020 to 5% in January 2021 in patients meeting the study inclusion criteria (table 2). This change was not statistically significant as p value was >0.05 . The result of Pearson's χ^2 test was: $\chi^2=0.69149$, $df=1$, p value= 0.4057 . The results of the Pearson's χ^2 test with Yates' continuity correction was: $\chi^2=0.25474$, $df=1$, p value= 0.6138 .

Table 1 Demographics and clinical details

	March–May 2020	Percentage	January 2021	Percentage
Total patients with COVID-19 symptoms, oxygen requirement and CTPA showing features of COVID-19	74		220	
Positive RT-PCR*	72		213	
Males	46	62.16	126	57.27
Females	28	37.84	94	42.73
Median age (years)	61		62	
Age range (years)	32–94		23–91	
Average CRP (mg/L)†	125		65	
Pneumothorax	0		4	
Pulmonary embolism	18		61	
Average length of hospitalisation for discharged patients (days)	26		11	
Ventilated (IV or NIV) patients	28	37.84	69	31.36
Non-ventilated patients	46	62.16	151	68.64
Patients with pneumomediastinum	2	2.70	11	5.00
Patients with pneumomediastinum on ventilation	2	7.14	9	13.04
Patients with pneumomediastinum but not ventilated	0	0.00	2	1.32
Patients ventilated but without pneumomediastinum	26		60	

*Two and seven patients had negative RT-PCR in the cohort during the first and the second wave, respectively. These patients had clinical and radiological symptoms/signs of COVID-19 pneumonitis.

†CRP values were recorded from the day of the CTPA. There was a wide variation in CRP during admission (0.4–404 mg/L).

CRP, C reactive protein; CTPA, CT pulmonary angiography; IV, invasive ventilation; NIV, non-invasive ventilation; RT-PCR, reverse transcriptase PCR.

Mortality in ventilated patients, in both waves, was higher than in non-ventilated patients. Furthermore, mortality in patients with pneumomediastinum was higher compared with patients without pneumomediastinum (table 2).

The difference in the mortality of patients with pneumomediastinum in both waves combined during the period of the study versus the cohort of patients without pneumomediastinum was statistically significant with a p value of 0.0005805 (table 3). The result of Pearson's χ^2 test was: $\chi^2=11.838$, $df=1$, p value=0.0005805. Using Pearson's χ^2 test with Yates' correction also showed that the results were statistically significant with p value of 0.00179. $\chi^2=9.7537$, $df=1$, p-value=0.00179.

There is a greater probability of developing pneumomediastinum in patients receiving ventilation.¹² This could result in ventilation being a confounding factor in the mortality difference in patients with and without pneumomediastinum, given that patients requiring mechanical ventilation will be a more unwell cohort. As a result, it was important to ascertain whether there was a statistical difference in mortality in ventilated patients without pneumomediastinum versus mortality in ventilated patients with pneumomediastinum (table 4).

We found no statistically significant difference as shown by Pearson χ^2 test or Pearson's χ^2 test with Yates' correction as the p values were 0.14 (p value >0.05) and 0.26, respectively. The result of Pearson's χ^2 test was: $\chi^2=2.0955$, $df=1$, p value=0.1477. The result of Pearson's χ^2 test with Yates' continuity correction was: $\chi^2=1.2499$, $df=1$, p value=0.2636.

Seventy-four patients without pneumomediastinum (combined first and second wave) developed pulmonary embolism (26.33%). Five patients in the pneumomediastinum group (combined first and second wave) developed pulmonary embolism (38.46%).

The average length of stay for the study cohort during first and second wave was 26 days (median 17.5) and 11 days (median 9.5). Average length of stay for study cohort with pneumomediastinum was 25.92 days (median 20) and without pneumomediastinum was 15.15 (median 10) days.

The average CRP of the study cohort on the day of CTPA during the first wave was 126 mg/L (median 110) and during the second wave was 65 mg/L (median 37.5). In the pneumomediastinum cohort, average CRP was 119 mg/L (median 90) and in the non-pneumomediastinum cohort, CRP was 75 mg/L (median 47).

Table 2 Incidence of pneumomediastinum and mortality by gender, ventilation support and presence or absence of pneumomediastinum

	March–May 2020	Percentage	January 2021	Percentage
Case with pneumomediastinum	2		11	
Cases without pneumomediastinum	72		209	
Incidence of pneumomediastinum	2.7%		5%	
Mortality in ventilated patients	14	50.00	46	66.67
Mortality in non-ventilated patients without pneumomediastinum	3	6.52	18	12.08
Mortality in non-ventilated patients with pneumomediastinum	N/a*		0†	
Mortality in ventilated patients without pneumomediastinum	12	46.15	39	65.00
Mortality in ventilated patients with pneumomediastinum	2	100.00	7	63.64
Mortality in males	10	21.74	31	24.60
Mortality in females	7	25.00	26	27.66

*In the non-ventilated cohort during the first wave, there were no pneumomediastinum cases.

†In the non-ventilated cohort, during the second wave, two patients developed pneumomediastinum. Both of them improved and were subsequently discharged.

Table 3 Outcomes of the study patients with and without pneumomediastinum (both waves combined)

Outcome	Patients without pneumomediastinum	Patients with pneumomediastinum
Survived	209	4
Died	72	9
Total number	281	13
Mortality	25.62%	69.23%

DISCUSSION

This study is an important addition to the growing literature describing pulmonary complications of COVID-19. Majority of 250 plus literature (based on PUBMED search on 4 February 2022) on pneumomediastinum in COVID-19 are cases or case series and only a few were retrospective, observational studies looking to establish incidence of pneumomediastinum in COVID-19.

The peak of COVID-19 cases admitted to Northwick Park Hospital occurred from March to May 2020 during the first wave and then in January 2021 during the second wave in the UK. Majority of these patients had a positive RT-PCR test for SARS-CoV-2, although some patients had negative RT-PCR test but were included in the study as symptoms and CTPA patterns were strongly suggestive of COVID-19 and were treated as COVID-19 pneumonitis. The limitation in the sensitivity of RT-PCR for COVID-19 is well reported.¹³

The incidence of pulmonary embolism has been reported to be much higher in patients with COVID-19 than in patients without COVID-19.¹⁴ Clinical deterioration in patients with COVID-19 is due to worsening of COVID-19 pneumonitis, added bacterial infection, pulmonary embolism, pneumomediastinum/pneumothorax or non-respiratory complications. In our hospital, if chest X-ray could not explain worsening of clinical symptoms or pulmonary embolism was suspected based on high d-dimer, CTPA was the imaging of choice as it can reliably identify all above pathologies, including PE. Unenhanced CT scans and high resolution CT scan (HRCT) of the lungs would not be sensitive enough to identify pulmonary embolism. This was the reason CTPA was CT imaging of choice in our hospital, like many others in the UK. HRCT scans of the lung were still being done in patients who were suspected to have fibrosis after prolonged COVID-19 pneumonitis and failed to improve.

The incidence of pneumomediastinum for the entire study period was found to be 4.42%. An incidence of 3.3% (9/271) was found in a study by Rodriguez-Arciniega *et al* looking at unenhanced CT scans.¹⁵ Kangas-Dick *et al* looked at incidence of pneumomediastinum in a cohort of 346 intubated patients with COVID-19 and found the incidence of 10%.¹⁶ This is comparable to the incidence of 11.34% (11/97) of pneumomediastinum in our cohort of ventilated (intubated and CPAP/NIV together) patients with COVID-19.

Table 4 Outcomes of ventilated patients with and without pneumomediastinum (both waves combined)

Outcome	Ventilated with no pneumomediastinum	Ventilated with pneumomediastinum
Survived	35	2
Dead	51	9
Total number	86	11
Mortality	59.30%	81.81%

A study done by Udawadia *et al* included 4906 patients admitted to three tertiary hospitals in India for COVID-19 infection. Twenty-four patients developed pneumomediastinum giving an incidence of 0.24%.¹⁷ These pneumomediastinum were identified on chest X-ray as a part of routine care or when patients clinically worsened. The paper reports the incidence of pneumomediastinum for critically ill patients as 1.81% (24/1324), where critically ill patients are defined as mean NEWS-2 (National Early Warning Score) score of 8 (4–16), mean CT CORAD (The coronavirus disease 2019 Reporting and Data System) score of 5 (4–6), mean CT severity score of 15 (9–20) and receiving oxygenation. The paper does not elaborate on the number of patients who received mechanical ventilation, NIV or oxygen only. The case mix may explain lower incidence of pneumomediastinum. Different studies have used different radiological exams to identify the incidence of pneumomediastinum. This has also resulted in difference in incidence of the pneumomediastinum in patients with COVID-19.

The limitation of our study is that we examined only those patients who underwent CTPA and therefore selected a patient group with more profound hypoxaemia or other physiological derangements which might lead to an overestimation of the incidence of pneumomediastinum in a general population of patients with COVID-19 not requiring CT imaging.

In our study, the mortality in patients with pneumomediastinum was 69.23% and mortality in patients without pneumomediastinum was 25.62% (table 3). This difference is statistically significant. There is a greater probability of developing pneumomediastinum in patients receiving ventilation.¹² This could result in ventilation being a confounding factor in the mortality difference in patients with and without pneumomediastinum, given that patients requiring mechanical ventilation will be a more unwell cohort. As a result, it was important to ascertain whether there was a statistical difference in mortality in ventilated patients without pneumomediastinum versus mortality in ventilated patients with pneumomediastinum (table 4).

The mortality was 59.30% (51/86) in ventilated patients without pneumomediastinum. The mortality in ventilated patients with pneumomediastinum was 81.81% (9/11). We found no statistically significant difference as shown by Pearson χ^2 test or Pearson's χ^2 test with Yates' correction as the p values were 0.14 (p value >0.05) and 0.26 respectively.

Lemmers *et al* included 169 ventilated patients with COVID-19 admitted to intensive care unit (ICU) with and without pneumomediastinum and mortality was 56.5% in patients with COVID-19 with pneumomediastinum/subcutaneous emphysema (23 patients) and 50% in patients without pneumomediastinum (146 patients).³ This difference in mortality was not significant with a p value of 0.46. They also found that the only significant difference between patients with and without pneumomediastinum/subcutaneous emphysema was a lower minute ventilation on the day of ICU admission in patients with pneumomediastinum/subcutaneous emphysema. There was no statistically significant difference in PEEP, plateau pressure, tidal volume/ideal body weight and compliance.

Interestingly, Özdemir *et al* compared mortality in COVID-19 ventilated patients with and without pneumomediastinum and found the difference in mortality to be statistically significant, unlike our study. Özdemir *et al* analysed 427 patients with RT PCR-confirmed COVID-19 admitted to the ICU.¹⁸ Seventy-three patients received NIV and 354 were mechanically ventilated. Twenty-four (2 in NIV and 22 in mechanically ventilated) patients developed pneumomediastinum. The mortality was 56.3% in patients without pneumomediastinum and 83.3% in

patients with pneumomediastinum. They used multivariate analyses to assess pneumomediastinum affecting mortality in ventilated cohort with an OR of 5.234, 95% CI 1.379 to 19.857 and *p* value of 0.01 (statistically significant <0.05).

It is likely that although our percentage mortality was very similar to Özdemir *et al*, but our results were not significant due to low numbers. Further studies are needed to confirm whether there is a statistically significant difference in the mortality of ventilated patients with or without pneumomediastinum given conflicting results from different studies.

The mortality in the second wave was higher (table 2), in all subgroup of patients, compared with the first wave in our study cohort. We are not sure why mortality was higher during the second wave in our cohort. This is contrary to the reported mortality benefit from steroids in the RECOVERY trial.¹¹

One possibility is that our study cohort included sickest subset among all patients who received steroids. This is based on the fact that our study cohort patients during the second wave deteriorated despite being on steroids, requiring CTPA to establish the cause of clinical worsening. This could have led to higher mortality in our cohort during the second wave and diluted the mortality benefit of steroids. It is important that researchers should design future studies to look into this aspect in greater detail.

The incidence of pneumothorax in patients with COVID-19 have been reported as 0.66%–1% of admitted patients, but incidence in invasive ventilated patients have been reported to be 12%–28%.^{19–21} In our cohort of invasive ventilated patients, incidence was 5.08% or incidence of 1.36% among all patients included in the study. This incidence could be an underestimation as only patients undergoing CTPA were included in the study.

Another limitation of our study is that we didn't look into ventilation parameters such as positive end expiratory pressure, inspiratory pressures, PaO₂/FiO₂ ratio, etc. Further studies are needed to understand the interplay of barotrauma and pathophysiological effect of COVID-19 infection.^{22 23}

The average length of stay was longer in the first wave than in the second wave. The RECOVERY trial data did not report shorter duration of length of stay for patients who received dexamethasone.¹¹ Further studies are needed to establish if similar trends were observed in other places and potential reasons. The average and median length of stay were longer in the pneumomediastinum cohort than in non-pneumomediastinum cohort. Pneumomediastinum cohort was sicker and this probably led to increased length of stay.

The average and median CRP were much higher in pneumomediastinum (119, 90) cohort versus non-pneumomediastinum (75, 47) cohort. Other studies have widely reported similar findings. It is also known that CRP is associated with disease severity and prognosis.²⁴

The average CRP during the first wave was higher than in the second wave in our study cohort. There was a wide variation in CRP for most patients during the admission and CRP on day of the CTPA did not often represent peak CRP. As a result, this difference in average CRP during these two waves may not reflect any patterns and making any conclusion about it would be factually and statistically incorrect. The role of dexamethasone administration in reducing CRP response also needs to be explored.^{25–27}

CONCLUSION

The study found the incidence of pneumomediastinum in patients with COVID-19 undergoing CTPA to be 4.42%: 2.7% in the first wave of COVID-19 in the UK during March to May

Main messages

- ▶ The incidence of pneumomediastinum during first and second wave in the UK remained same.
- ▶ The mortality is higher in patients with COVID-19 with pneumomediastinum than without it.

Current research questions

- ▶ Impact of invasive and noninvasive ventilation as a confounding factor in increased mortality in patients with COVID-19 with pneumomediastinum.
- ▶ Mortality before and after use of steroids-data from a large cohort of patients during different COVID-19 waves is needed.
- ▶ Establishing pathophysiology of pneumomediastinum in patients with COVID-19 given higher incidence compared with other viral or bacterial pneumonitis.
- ▶ Establishing whether increased acuity of COVID-19 illness or ventilation parameters or both contributed to higher incidence of pneumomediastinum and mortality is important for prognosticating and developing better lung protection ventilation strategies.

What is already known on the subject

- ▶ Patients with COVID-19 have higher occurrence of pneumomediastinum than patients without COVID-19 and patients with COVID-19 with pneumomediastinum have higher mortality compared with patients with COVID-19 without pneumomediastinum.

2020 and 5% during the second wave of COVID-19 in January 2021. There was no statistically significant difference in the incidence of pneumomediastinum in the first and second wave of COVID-19. The study also found that there was a statistically significant difference in mortality in patients with pneumomediastinum versus patients without it. Given high mortality in patients with pneumomediastinum, clinicians should look for it, if patients fail to improve or deteriorate clinically.

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Contributors RB conceptualised the study. RB and DGC designed data collection tools, monitored data collection for the whole research, cleaned and analysed the data, and drafted and revised the paper. RB and AJ wrote the statistical analysis plan and AJ led the statistical analysis. JFdW supervised the study process, reviewed and edited the final manuscript. MC provided revision of the manuscript. All authors read and approved the final manuscript. RB is the guarantor of the paper.

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Competing interests None declared.

Patient consent for publication Not applicable.

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