RESEARCH ARTICLE

Supplemental oxygen in Queen Elizabeth Central Hospital Malawi: a prospective cohort study of patients admitted to medical wards [version 1; peer review: awaiting peer review]

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Abstract

Background: Oxygen is designated an essential drug by the World Health Organisation, and reduces mortality in hypoxic patients. In low-resource settings the provision of oxygen seldom meets its demand. This study describes the predictors and observed time-course of hypoxaemia in order to inform needs assessments for oxygen in hospitals in low and middle income countries.
Methods: A prospective cohort study of adults with hypoxaemia admitted to medical wards of a teaching hospital in Malawi between January and March 2020. Vital signs and oxygen therapy were recorded daily. We analysed outcomes (death, discharge from hospital or ongoing inpatient care at 14 days after admission) using Kaplan-Meier and Cox regression time-to-event analysis.
Results: 33 patients were recruited with median age 45 years (IQR 33-61), and 13 (39%) female. Median pre-treatment oxygen saturations were 84% (IQR 76-87%). Oxygen delivery devices were often shared with other patients (n=10, 33%) and the flow rate was often unknown (n=14, 47%), mostly because of broken equipment (n=8, 57%). Median duration of oxygen therapy was 3 days (IQR 1-7). Death occurred in 16 (49%). Hazard ratios for short oxygen therapy were reduced in patients who had a chest radiograph performed (HR 0.08, 95% CI 0.02–0.30), in ex-smokers (HR 0.01, 95% CI 0.00-0.22) and in never smokers (HR 0.03, 95% CI 0.00 – 0.78).
Conclusions: Delivering oxygen therapy in lower-middle income countries is challenging; broken equipment and shared delivery devices prevented titration of flow rates. Patients were relatively young and at a high risk of death. Patients with a chest radiograph received oxygen for longer than those without. Knowledge of oxygen therapy durations will allow careful assessment of the oxygen supply need at the hospital level.

Open Peer Review

Reviewer Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Oxygen, Oxygen therapy, Hypoxaemia, Chest radiograph

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Introduction

Oxygen reduces morbidity and mortality in hypoxaemic patients, and is listed as an essential drug by the World Health Organisation (WHO) (Evans *et al.*, 2016; World Health Organization, 2015c). If untreated, failure of oxygen supply to tissues precipitates organ failure and death (Duke *et al.*, 2010b; Goldhill, 2001). Supplemental oxygen can prevent hypoxia, and in paediatric studies has reduced pneumonia mortality by 35% (Duke *et al.*, 2008). However, supply in resource-limited settings is frequently restricted by availability, equipment cost and maintenance difficulties (Enarson *et al.*, 2008; Evans *et al.*, 2016; La Vincente *et al.*, 2011). Prominent causes of hypoxaemia are lower respiratory tract infections, which cause 3 million annual deaths globally and 15,000 deaths in Malawi alone, which represent 9% of the national mortality, and are the most common cause of adult hospitalization ('GBD 2015 LRI Collaborators', 2017; SanJoaquin *et al.*, 2013).

Previous studies in a regional hospital in Malawi (Queen Elizabeth Central Hospital, Blantyre; QECH) showed that less than one-third of patients that required supplemental oxygen received it, highlighting the disparity between supply and demand (Evans *et al.*, 2016). This prospective cohort study explored the observed time course of hypoxaemia and predictors of supplemental oxygen therapy requirements in medical patients in Blantyre to inform needs assessment for oxygen at the hospital level.

Methods

Setting and study design

We conducted a prospective cohort study of adults with hypoxaemia at the QECH in Blantyre, Malawi, between 18th February 2020 and 20th March 2020. The hospital has 200 medical beds, providing healthcare to approximately 1 million people in a context of high community prevalence of human immunodeficiency virus (HIV, 10.6%) and incidence of tuberculosis (159 cases per 100,000 population) ('Government of Malawi', 2015; World Health Organization, 2015a; World Health Organization, 2017).

Adults, aged 18 years and above, were included if they were hypoxaemic, were treated with supplemental oxygen and were admitted under the medical teams. Hypoxaemia was defined as peripheral oxygen saturations of less than 90% by finger pulse oximetry. Participants were recruited either from the emergency department, or from the medical wards if they were within 48 hours of admission. Written, informed consent was gained before any data collection was commenced. Those unwilling to consent to participation and those not receiving supplemental oxygen were excluded.

Data collection

Baseline demographics, admission details including vital signs and oxygen delivery method, diagnoses and co-morbidities were recorded on admission. Diagnoses made by the attending physician were extracted from medical notes. Haemoglobin and chest radiograph results were collected only if these were conducted as part of usual clinical care. Vital signs and details of supplemental oxygen delivery were recorded daily for participants until outcomes were determined (i.e. death, discharge, or ongoing inpatient care after 14 days). Oxygen saturations were measured with oxygen therapy present and then with temporary removal of supplemental oxygen, providing it was clinically safe to do so. Data were collected using an Open Data Kit platform on tablet devices (www.kobotoolbox.org).

Statistical analysis

A sample size of 62 participants was calculated to power the study to estimate the duration of oxygen therapy with a precision 6 hours with a 95% confidence level, and a standard deviation of 24 hours. The primary outcome was the duration of oxygen therapy in days. Secondary outcomes were the availability and delivery of supplemental oxygen, length of hospital stay, factors associated with the duration of supplemental oxygen provision and clinical outcome.

Data were presented as means, standard deviations, medians, ranges or percentages, based on the type and distribution of data. Those experiencing other events (death, discharge) before the end of the study contributed to the proportional hazard until that event. The Kaplan-Meier method was used to assess time to event data and probabilities. Time to event in univariable analysis was estimated by log-rank test. Cox regression models were used for uni- and multi-variable analysis and to calculate hazard ratios. Competing risk of events were calculated using estimated cumulative incidence (Putter *et al.*, 2007). Conditional survival analysis was used to predict chances of requiring oxygen therapy on given days (Zabor *et al.*, 2013). Statistical significance was defined as $p<0.05$, and 95% confidence intervals given where appropriate. Data were analysed using R (R Core Team, 2020).

Ethical considerations

Ethical approval was gained from the College of Medicine Research Ethics Committee, Blantyre, Malawi, (reference number P.05/19/2693) and the Liverpool School of Tropical Medicine Research Ethics Committee, United Kingdom (reference number 19–088). All participants provided written informed consent prior to participating in the study.

Results

Baseline results

33 participants were recruited between 18th February 2020 and 11th March 2020. Recruitment was stopped early due to coronavirus-19, and follow up discontinued on the 20th March 2020. During this time 525 patients were admitted under the medical team at QECH.

Thirteen study participants were women (39.4%). The median age was 45 years (interquartile range (IQR) 33–61 years, Table 1). One third of participants were HIV positive, two were currently receiving treatment for tuberculosis (TB) and six had previously been treated for it. The most common presenting symptoms were dyspnoea and cough (n=18, 55% each). The

Table 1. Demographics and admission parameters of the 33 included participants. Abbreviations as per main text. Results are number (%) unless otherwise indicated.

Variable	Number (percentage)
Female sex, n (%)	13 (39.4 %)
Age, median (range)	45 (22 – 91)
Co-morbidities	
HIV, n (%)	11 (33 %)
Receiving anti-retroviral therapy	9
Previous TB treatment, n (%)	6 (18 %)
Current TB treatment, n (%)	2 (6 %)
Hypertension, n (%)	7 (21 %)
Malignancy, n (%)	4 (12 %)
Smoking status	
Current, n (%)	2 (6 %)
Ex, n (%)	9 (27 %)
Never, n (%)	22 (67 %)
Presenting symptoms	
Dyspnoea, n (%)	18 (55 %)
Cough, n (%)	18 (55 %)
Fever, n (%)	15 (45 %)
Productive cough, n (%)	12 (36 %)
Orthopnoea, n (%)	11 (33 %)
Headache, n (%)	10 (30 %)
Chest pain, n (%)	10 (30 %)
Vital signs on admission	
Heart rate, beats / min, median (IQR)	109 (89 – 123)
Respiratory rate, breaths / min, median (IQR)	28 (23 – 32)
Temperature, °C, median (IQR)	36.7 (36.1 – 37.8)
SpO2 on air, %, median (IQR)	84 (76 - 87)
SpO2 with oxygen, %, median (IQR)	98 (95 – 99)
Method of supplemental oxygen on admission	
Oxygen concentrator, n (%)	11 (33.4 %)
Oxygen cylinder, n (%)	22 (66.6 %)
Sharing device on admission, n (%)	10 (30.3 %)
Interface of oxygen delivery on admission	
Reservoir mask, n (%)	4 (12 %)
Simple mask, n (%)	6 (18 %)
Nasal cannula, n (%)	23 (70 %)
Oxygen flow on admission, L/min, median (range)	6 (4-6)
Oxygen flow on admission unknown, n (%)	14 (42 %)
Chest radiograph performed, n (%)	14 (42 %)
Haemoglobin test performed, n (%)	20 (61 %)
Haemoglobin level, mg/dL, mean ± SD	11.8 ± 2.6
Length of stay, days, median (IQR)	6 (2 – 9.5)
Length of oxygen therapy, days, median (IQR)	3 (1 – 7)
Final diagnosis (can have multiple)	
Pneumonia, n (%)	14 (42 %)
TB, n (%)	5 (15 %)
Heart failure, n (%)	5 (15 %)
Meningitis, n (%)	4 (12 %)
Sepsis, n (%)	3 (9 %)
Outcome at end of study	
Death, n (%)	16 (48 %)
Discharge before 14 days, n (%)	9 (27 %)
Inpatient, n (%)	5 (15 %)
Lost to follow up, n (%)	3 (9 %)

commonest admission diagnosis was pneumonia (n=14, 42%). 14 participants had a chest radiograph (CXR) performed (42%), and haemoglobin level was measured in 20 participants, mean 11.8g/dL (SD 2.6).

At initiation of oxygen therapy, median oxygen saturation was 84% (IQR 76–87%), and median respiratory rate 28 breaths per minute (IQR 23–32). Most patients received oxygen therapy via nasal cannulae (n=23, 77%) supplied by a cylinder (n=22, 73%). One oxygen source was shared with at least one other patient in 10 participants (33%). Median oxygen saturations after initiation of oxygen therapy were 98% (IQR 95–99%). Hypoxaemia resolved in 30 participants (91%). Oxygen flow rate at time of initiation of therapy was often unknown due to broken equipment (n=14, 42%).

The median period of oxygen therapy was 3 days (IQR 1–7). The most frequent outcome was death (n=16, 48%), followed by discharged from hospital (n=9, 27%) and continued inpatient at 14 days (n=5, 15%). 75% of deaths occurred by day 3 of follow up (75%, Figure 1). Three participants were lost to follow-up (9%).

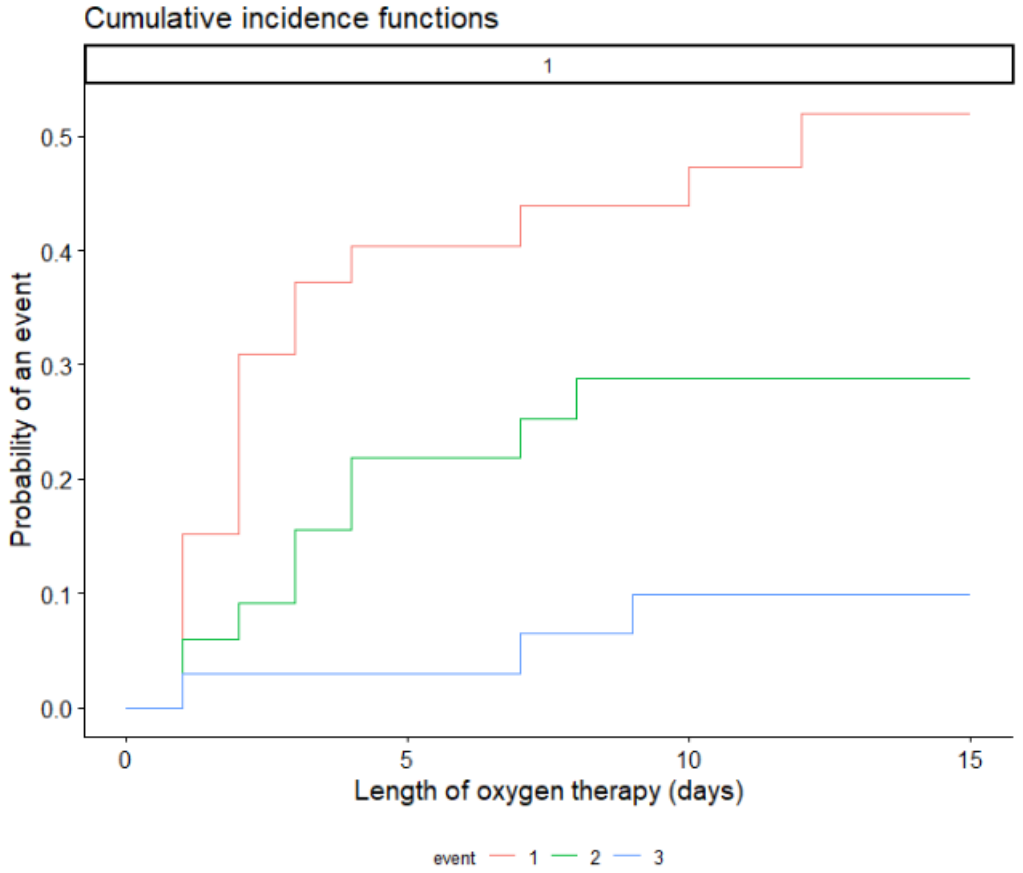

Figure 1. Competing interest graph of the probability of death (red), discharge (green) or inpatient without supplemental oxygen at study end (blue) by length of oxygen therapy (days). Calculated using cumulative incidence functions. Baseline comparison: inpatient on day 15 requiring supplemental oxygen therapy.

Of a total of 167 cumulative follow up days, oxygen was given for 107 days (64%, Table 2). During this time, oxygen was usually supplied from cylinders (83%) and through nasal cannulae (83%). For most days one oxygen source was shared between at least two patients (71% of days). The median of peripheral saturations whilst receiving supplemental oxygen was 93% (IQR 88–97%) compared to 91% (IQR 85–96%) without supplemental oxygen. The median of oxygen saturations was 99% when supplemental oxygen was no longer required.

Duration of oxygen therapy

The use of oxygen declined by two-thirds between study commencement and day five of follow up, and then approximately halved from days 5 to 10 and from days 10 to 15 (Figure 2). Two participants continued to receive supplemental oxygen up to day 15. The duration of therapy was associated with smoking status (p=0.03), the availability of a CXR (p<0.01), and the initial delivery device (p<0.01, Figure 3). In the univariable Cox regression analysis (Table 3), obtaining a chest radiograph had a reduced hazard ratio of still requiring oxygen on day 15 (HR 0.04, 95% CI 0.01–0.33, p< 0.01), i.e. an increased hazard of prolonged therapy. Requiring a reservoir mask on admission had an increased hazard of requiring supplemental oxygen at the end of the study (HR 14.5, 95% CI 2.28–92.7, p <0.01). CXR, being an ex-smoker, or a never smoker remained significantly associated in multivariable analysis (respective HR 0.08, 95%CI 0.02–0.30, p<0.01, HR 0.01, 95%CI 0.00–0.22, p<0.01, and HR 0.03, 95%CI 0.00–0.78, p=0.03). There was a statistically non-significant trend to an association with age (HR 0.95,95% CI 0.89–1.00, p=0.05). The likelihood of receiving supplemental oxygen at the end of the study increased with prolonged oxygen therapy (Table 4).

Discussion

Despite oxygen therapy resolving hypoxaemia in most participants, mortality was almost 50% and three quarters of these deaths occurred in the first three days of admission, indicating that hypoxaemia was a marker of severe and significant pathology. This recapitulates previous observations that hypoxaemia is associated with increased 30-day mortality in adult patients with pneumonia (Aston *et al.*, 2019).

In the absence of piped oxygen, it is recommended that oxygen concentrators are used when power supply is reliable (such as

Table 2. Description of oxygen delivery whilst on the medical wards by days of study. Results are total number (%), unless otherwise specified.

Variable	Number (%)
Total days of follow up	167
Total days that supplemental oxygen was given	107 (64 %)
Total days that oxygen was not given	62 (36 %)
Peripheral oxygen saturations receiving supplemental oxygen, % (mode)	93
Peripheral oxygen saturations without supplemental oxygen (normally receiving supplemental oxygen), % (mode)	91
Oxygen saturations without supplemental oxygen (not normally receiving supplemental oxygen), % (mode)	99
Oxygen source used on the ward	
Cylinder, n (%)	89 (83 %)
Concentrator, n (%)	18 (17 %)
Method of facial interface on the ward	
Nasal cannulae, n (%)	89 (83 %)
Reservoir mask, n (%)	5 (5 %)
Simple face mask, n (%)	13 (12 %)
Oxygen source and facial interface on the ward	
Oxygen cylinder with	
Nasal cannulae, n (%)	72 (81 %)
Simple face mask, n (%)	13 (15 %)
Reservoir mask, n (%)	4 (4 %)
Oxygen concentrator with	
Nasal cannulae, n (%)	17 (94 %)
Reservoir mask, n (%)	1 (6 %)
Number of people connected to single oxygen source on the ward	
Only one person connected	31 (29 %)
2 persons in total connected to same device	60 (56 %)
3 persons in total connected to same device	16 (15 %)
Unable to record oxygen flow	91 (85 %)
Reason why oxygen flow could not be reported	
Dial broken	80 (88 %)
Unknown	11 (12 %)

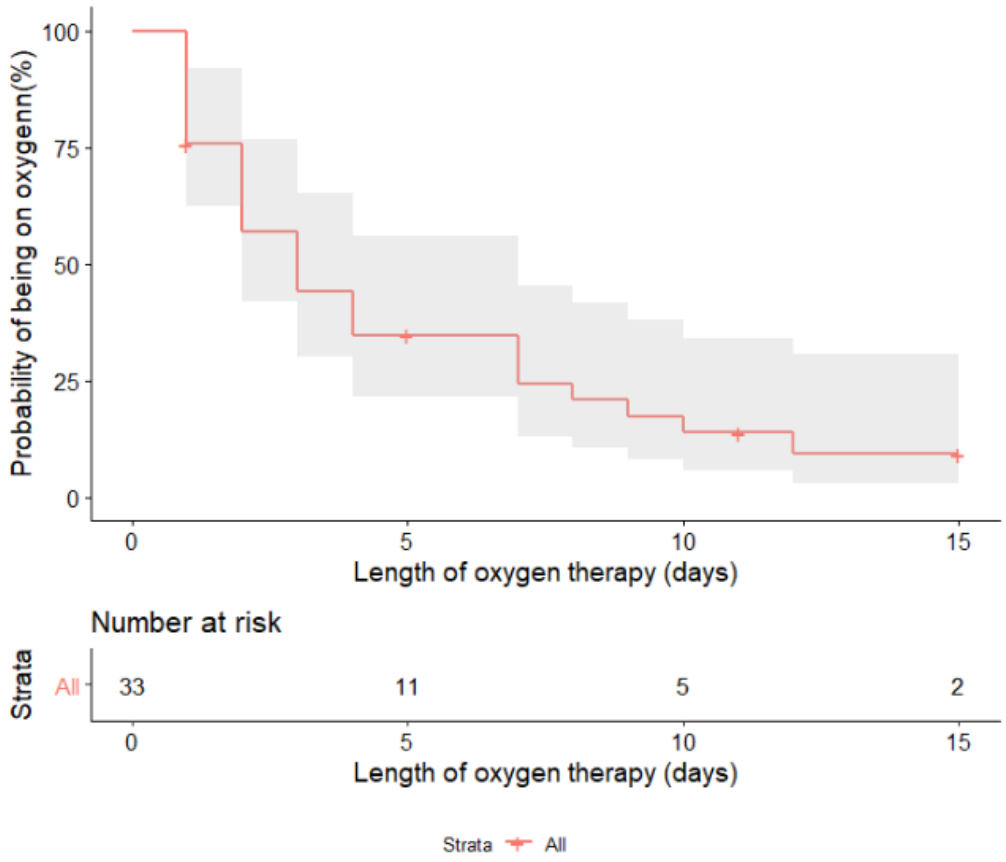

Figure 2. Kaplan-Meier curve of overall probability of receiving supplemental oxygen (%) and length of oxygen therapy (days). Censored data appear as crosses, grey area: 95 % confidence interval.

in QECH) as they are comparatively cheap and provide consistent oxygen (Duke *et al.*, 2010a; World Health Organization, 2015b). In our study, which immediately predates the introduction of an on-site oxygen plant, oxygen cylinders were preferentially used. This may be due to the unavailability of concentrators or broken equipment, as has been described in paediatric wards e.g. in Malawi and Mongolia (Evans *et al.*, 2016; La Vincente *et al.*, 2011). Equipment difficulties were evident in our study, notably broken flow meters, which meant titration was not possible for 91 of 107 follow up days. Sharing the oxygen source was also usual practice, making it difficult to titrate flow rates to the individual's needs, and possibly resulting in wasting of oxygen resource. Moreover, over-oxygenation is associated with excess mortality, highlighting the need for good monitoring and the ability to control oxygen flow (Chu *et al.*, 2018; Kane *et al.*, 2013).

The median duration of supplemental oxygen therapy was three days, which was influenced by the large number of early deaths. Two participants required continuous, supplemental oxygen for more than two weeks. These observations could be used in planning oxygen services, and prioritizing the use of this finite resource. Previous research from QECH has highlighted that hypoxaemic patients often do not receive supplemental oxygen, and similar findings have been recorded in other LMICs (Duke *et al.*, 2010b; Evans *et al.*, 2016).

Patients who were investigated with a CXR received oxygen for longer than those who had no radiography performed. A CXR may have allowed the identification of reversible pathology and thus justified the medical decision to continue oxygen therapy. However, sicker patients with a higher oxygen requirement and poorer prognosis may have been less likely to have had a CXR initially, creating confounding bias.

Oxygen therapy duration was also statistically significantly associated with the initial delivery interface that was used. However, three out of the four participants who were using a reservoir mask died, two within two days of admission, indicating sicker patients may have needed a reservoir mask. HIV status was not associated with oxygen therapy duration.

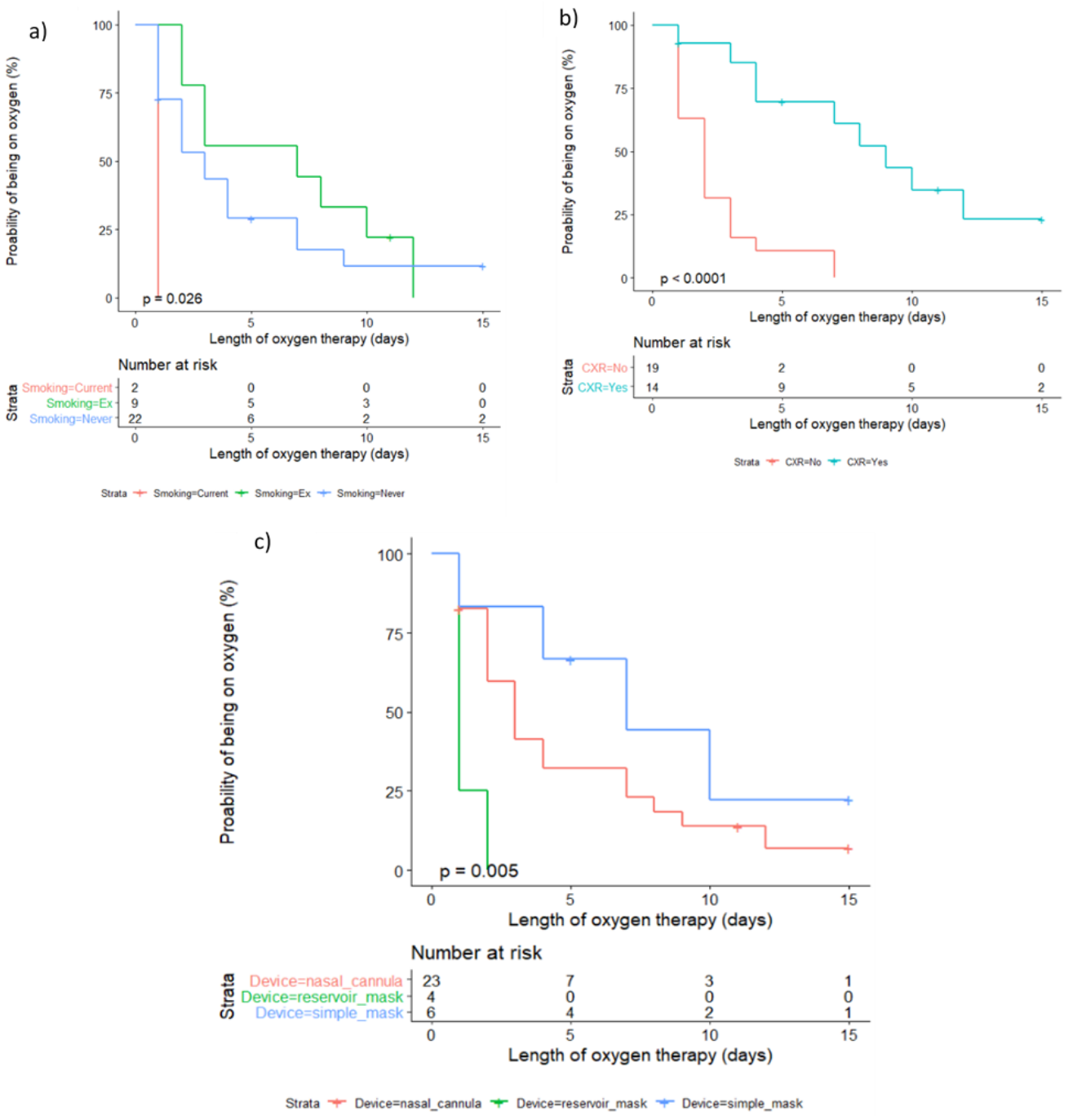

Figure 3. Kaplan-Meier curves of probability of receiving supplemental oxygen and length of oxygen therapy (days) by **a**) smoking status, **b**) having a chest radiograph and **c**) initial device used to deliver oxygen. Censored data appears as crosses, grey area: 95% confidence interval.

Table 3. Single and multi-variable hazard ratios (HR) by Cox regression analysis for not requiring supplemental oxygen at end of study. CI: confidence interval. * p < 0.05.

Variable	Univariable HR 95 % CI	p value	Multivariable HR 95 % CI	p value
Male sex	1.47 0.68 – 3.16	0.32	3.16 0.42 - 24.1	0.3
Age	0.99 0.97 – 1.01	0.33	0.95 0.89 – 1.00	0.05*
Co-morbidities				
Hypertension	2.15 0.85 – 5.46	0.11	4.07 0.55 – 30.2	0.2
HIV status				
Negative	1.00			
Positive	1.48 0.63 – 3.49	0.37	0.67 0.16 – 2.83	0.6
Unknown	1.08 0.40 – 2.89	0.88	0.50 0.10 – 2.50	0.4
Previously treated for TB	0.45 0.14 – 1.53	0.20	0.26 0.05 – 1.47	0.13
Smoking status				
Current	1.00			
Ex	0.08 0.01 – 0.47	< 0.01*	0.01 0.00 – 0.22	< 0.01*
Never	0.12 0.02 – 0.64	0.01*	0.03 0.00 – 0.78	< 0.01*
Presenting symptoms				
Fever	0.83 0.39 – 1.75	0.63	1.21 0.19 – 7.77	0.8
Fatigue	0.74 0.34 – 1.60	0.45	1.07 0.24 – 4.65	> 0.9
Cough	0.79 0.37 – 1.68	0.55	2.31 0.36 – 14.6	0.4
Breathlessness	0.66 0.31 – 1.40	0.28	0.97 0.23 – 4.12	> 0.9
Peripheral oxygen saturations without oxygen on admission	1.02 0.98 – 1.06	0.34	1.01 0.94 – 1.07	0.9
Respiratory rate on admission	0.93 0.88 – 0.99	0.03*	1.03 0.91 – 1.16	0.7
Interface used on admission				
Nasal canulae	1.00			
Reservoir mask	5.92 1.75 – 20.1	< 0.01*	0.52 0.04 – 6.53	0.6
Simple face mask	0.50 0.17 – 1.48	0.21	0.29 0.03 – 2.74	0.3
Chest radiograph on admission	0.13 0.05 – 0.37	< 0.01*	0.08 0.02 – 0.30	< 0.01*

Table 4. Likelihood of requiring oxygen therapy at end of study if requiring oxygen on given day. Calculated by conditional survival analysis.

If requiring supplemental oxygen on day	Likelihood of requiring supplemental oxygen at end of study	95 % CI
1	0.12	0.02 – 0.31
2	0.16	0.03 – 0.39
3	0.21	0.04 – 0.48
5	0.27	0.05 – 0.56
7	0.38	0.05 – 0.74
10	0.67	0.02 – 0.96

Due to the global coronavirus-19 pandemic, planned recruitment and follow up was curtailed, and our sample size was not reached. Despite high completeness of follow-up, this therefore limits the results of the regression analysis.

Conclusions

It has previously been demonstrated that programmatically introducing oxygen in paediatric populations is beneficial (Duke *et al.*, 2008), however data from adult practice are few. Further research should outline how oxygen demand can be met in health centres that encounter hypoxaemic patients. Efficacy data are required to inform formal health economic analysis, but it is unlikely that these can be ethically determined. Instead, relative cost-efficiency estimates could help policymakers in decisions to deploy oxygen solutions. Our data provide some patient-level data which describe periods of treatment, required flow rates, and outcomes which could inform such plans.

Data availability

Underlying data

DataCat: Supplemental oxygen in Queen Elizabeth Central Hospital Malawi: a prospective cohort study of patients admitted to medical wards, http://dx.doi.org/10.17638/datacat.liverpool.ac.uk/1211 (Stolbrink *et al.*, 2021).

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