








RESEARCH ARTICLE

REVISED **Supplemental oxygen in Queen Elizabeth Central Hospital Malawi: a prospective cohort study of patients admitted to medical wards [version 2; peer review: 2 not approved]**

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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 explores predictors and observed time-course of hypoxaemia in order to help 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 February 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). 13 (39%) were 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

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received oxygen for longer than those without. This hypothesis generating study can be used to build a more comprehensive understanding of oxygen supply need at the hospital level.

Keywords

Oxygen, Oxygen therapy, Hypoxaemia, Chest radiograph



This article is included in the [Malawi-Liverpool Wellcome Trust Clinical Research Programme gateway](#).

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REVISED Amendments from Version 1

We would like to thank the peer reviewers for the comments on our manuscript and hope that the changes made reflect some of their feedback.

In particular we have now highlighted clearly the limitations to our study, most importantly the fact it is single centred and has a short period. Whilst we recognize that our results may not be fully generalizable, the results can be used to generate hypothesis and thus have suggested possible relevant future studies.

We have also clarified how 33 participants were included in the study, and that 3 patients or their families declined consent to participation. We have explained how we believe that we have accurately identified all hypoxaemic patients during the study period due to the AETC triage system as well as the daily recordings of oxygen saturations.

Finally, we have corrected our study dates in the abstract and have included the percentage for patients receiving ARV therapy in [Table 1](#).

Any further responses from the reviewers can be found at the end of the article

Introduction

Oxygen reduces morbidity and mortality in hypoxaemic patients, and is listed as an essential drug by the World Health Organization (WHO) ([Sittichanbuncha et al. \(2015\)](#); [World Health Organization, 2015c](#)). If untreated, failure of oxygen supply to tissues precipitates organ failure and death ([Sittichanbuncha et al. \(2015\)](#)). 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., 2012](#); [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., 2012](#)). This prospective cohort study explored the observed time course of hypoxaemia and predictors of supplemental oxygen therapy requirements in medical patients in Blantyre to help 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. Hypoxaemic patients were identified at triage in the emergency department, or from daily pulse oximetry assessment within 48 hours of admission to the medical wards. 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 documented on admission. Diagnoses made by the attending physician and the haemoglobin level were extracted from medical notes. Results of chest radiograph performed at any point during the admission were recorded. 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

Between 18th February 2020 and 11th March 2020 525 patients were admitted under the medical team at QECH. 36 patients were identified by triage in the emergency department and on the medical wards as meeting inclusion criteria, and 33 participants were recruited into the study (3 patients or their families declined participation). Study recruitment was stopped on 11th March due to safety concerns resulting from the evolving Coronavirus-19 pandemic, but all already enrolled participants were followed up until one of the outcomes was achieved. Last day of study follow up was 20th March 2021.

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

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 (81%)
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 %)

Variable	Number (percentage)
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 %)

had previously been treated for it. The most common presenting symptoms were dyspnoea and cough ($n=18$, 55% each). The commonest admission diagnosis was pneumonia ($n=14$, 42%). 14 participants had a chest radiograph (CXR) performed during their admission (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%).

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,

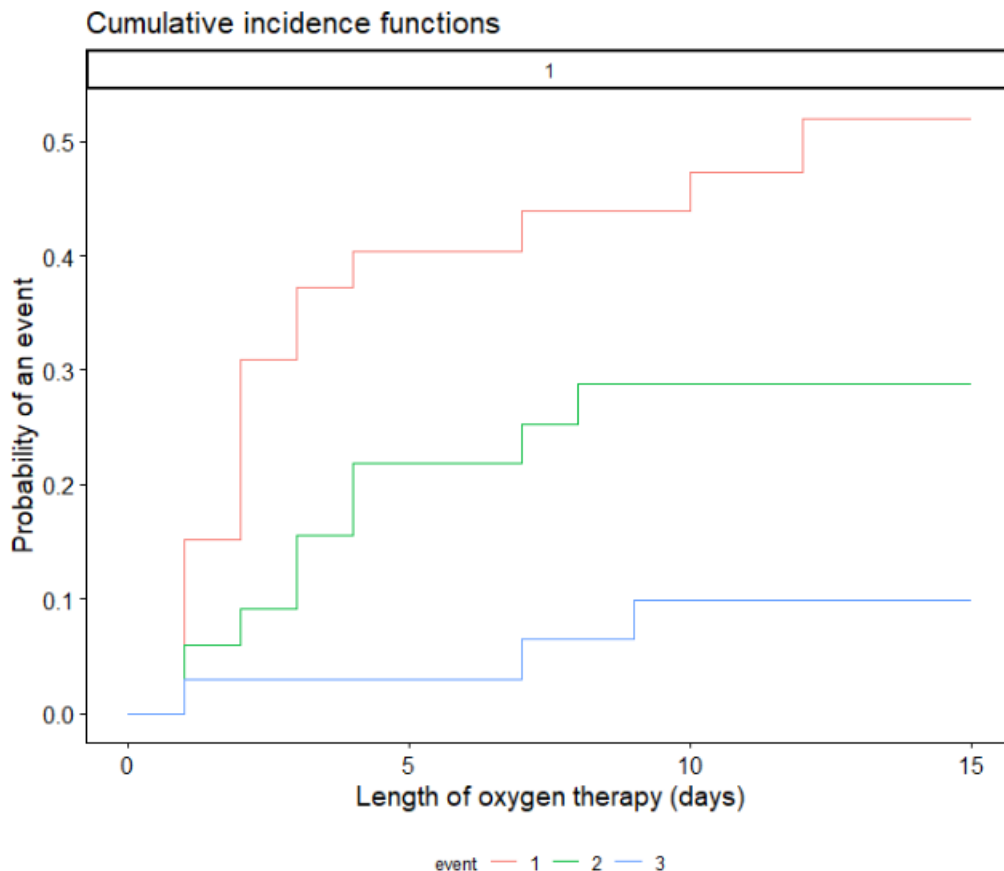


Figure 1. Competing interest graph of the probability of death (red), discharge (green) or inpatient without supplemental oxygen at study end (blue) by length of oxygen therapy (days). Calculated using cumulative incidence functions. Baseline comparison: inpatient on day 15 requiring supplemental oxygen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

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 %)

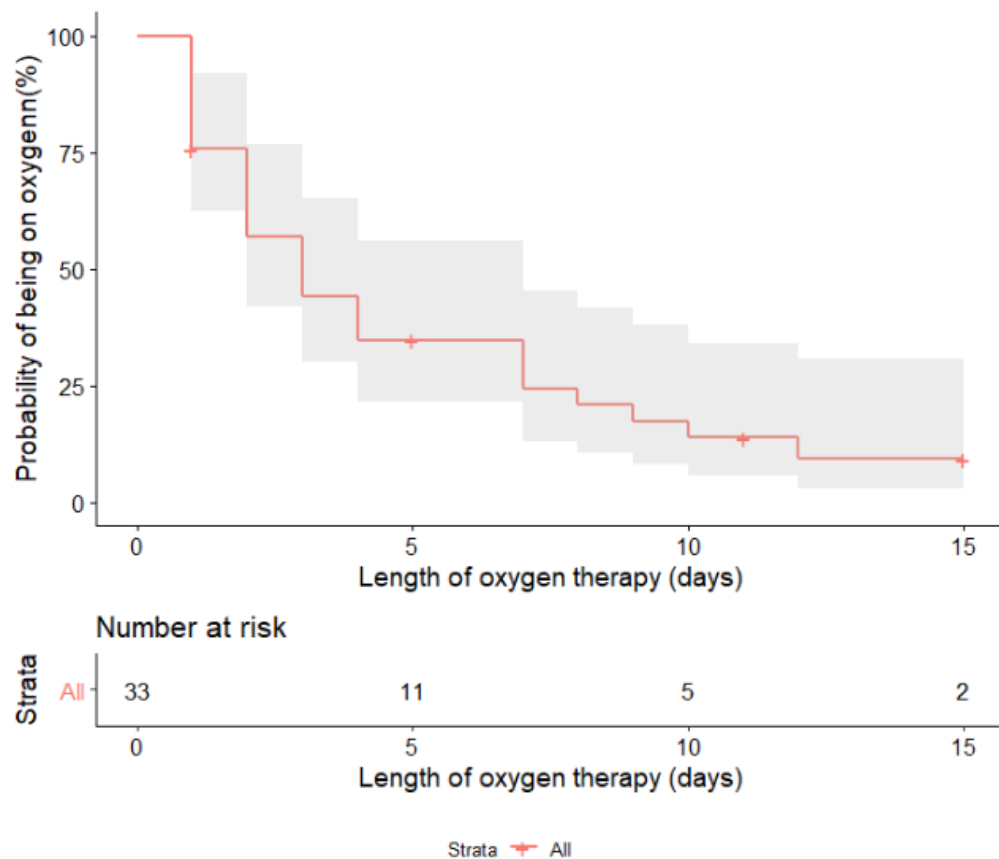


Figure 2. Kaplan-Meier curve of overall probability of receiving supplemental oxygen (%) and length of oxygen therapy (days). Censored data appear as crosses, grey area: 95 % confidence interval.

$p < 0.01$). 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 underlying pathology. It recapitulates previous observations where hypoxaemia was 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 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. Oxygen cylinders are used preferentially across Africa, as they are cheaper to purchase and easier to use than concentrators (Belle *et al.*, 2010; 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 or even over-oxygenation. Whilst hyperoxaemia is associated with excess mortality (Chu *et al.*, 2018; Kane *et al.*, 2013), the most common diagnoses in our cohort were pneumonia, TB and heart failure (14(42%), 5(15%) and 5(15%) respectively). Pneumonia, sepsis and heart failure were the commonest causes of death (6, 3 and 3 cases respectively). Hence hyperoxaemia is unlikely to have affected mortality.

The median duration of supplemental oxygen therapy was three days, which was influenced by the large number of early

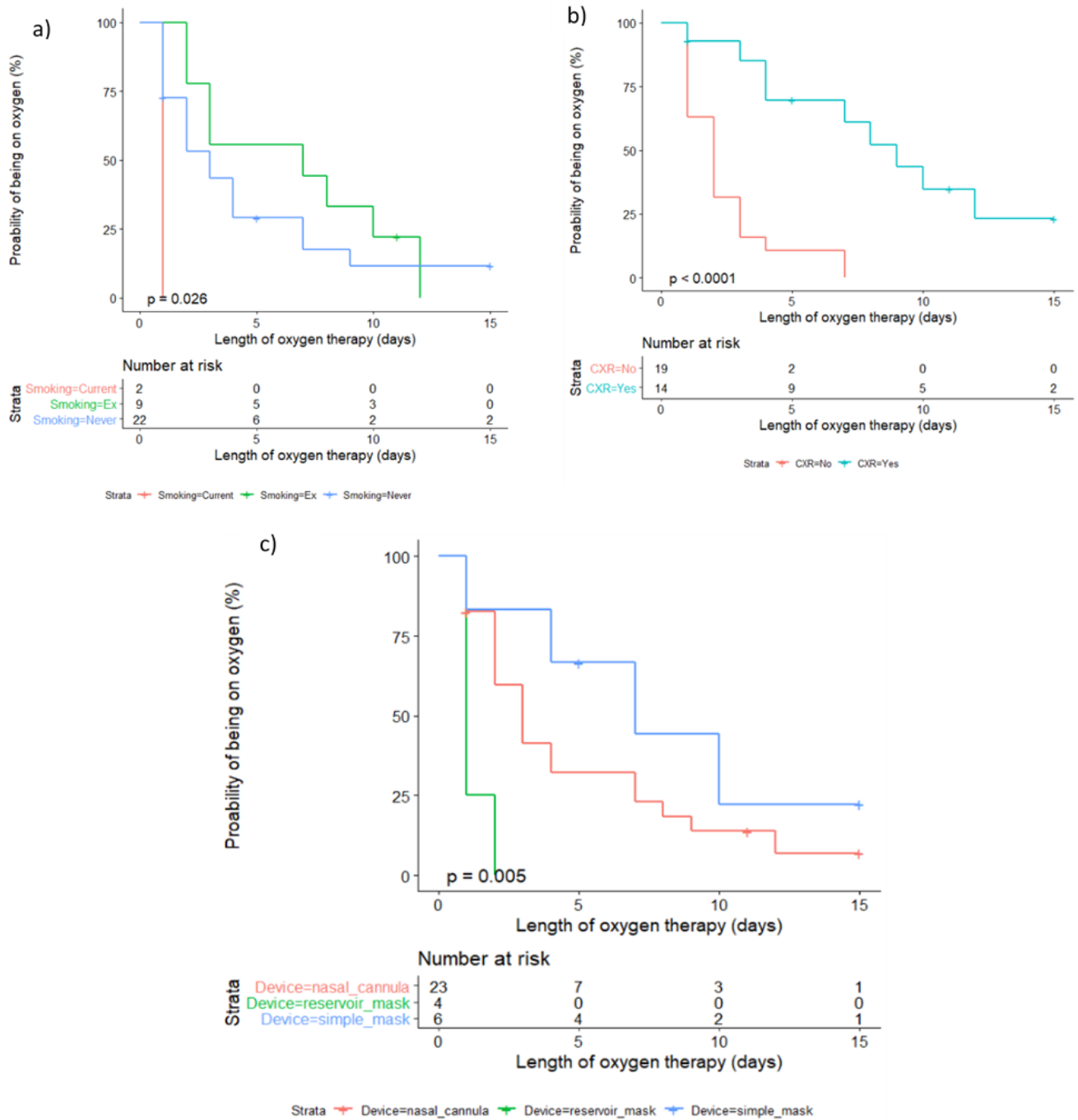


Figure 3. Kaplan-Meier curves of probability of receiving supplemental oxygen and length of oxygen therapy (days) by **a)** smoking status, **b)** having a chest radiograph and **c)** initial device used to deliver oxygen. Censored data appears as crosses, grey area: 95% confidence interval.

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

deaths. Two participants required continuous, supplemental oxygen for more than two weeks. These observations could be tentatively 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.*, 2012).

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.

Limitations

We recognize that this study was single centered with a relatively small sample size, and thus may only provide a ‘snapshot’ of the situation. It is liable to be affected by random error as well as selection bias. It was conducted over a short study

period that only represents one of the seasonal variations that are known to affect the number of admissions and severity of illness, and thus in turn the need for oxygen. It was also not possible to longitudinally follow flow rates for individual patients due to frequent switches between delivery devices as well as broken equipment.

During our recruitment period 535 patients were admitted to medicine, 36 of whom we identified as being hypoxaemic (7% admissions). We are confident that we have included the majority of patients who were hypoxaemic during the study period due to the thorough admission triage process as well as close collaboration with staff to identify any newly hypoxaemic patients on the wards via daily saturation readings. Whilst the results may not be wholly generalizable, they can be used to shape further hypothesis. For example, future work may explore the association of sharing oxygen devices and complications such as nosocomial infections or acute desaturating events. There could also be further exploration into the cost of oxygen supply methods which could better inform formal health economic 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. Our study provides some patient-level data which describe periods of treatment, and outcomes which could help generate further hypothesis to better inform oxygen demand.

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).

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Open Peer Review

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Reviewer Report 21 June 2021

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 **Kathryn Maitland** 

Faculty of Medicine, Imperial College London, London, UK

Thank you for considering my appraisal of the study and including these in the response and revisions to the manuscript.

I do note that the authors still have not fully corrected the final statement ' It has previously been demonstrated that programmatically introducing oxygen in paediatric populations is beneficial ([Duke et al., 2008](#))...' with respect to my comments. There are quite a number of limitations of this study that does not justify the strength of this statement. May I also point the authors to another recent publication, DOI 10.1007/s00134-021-06385-3; that I think would be appropriate to reflect on.

With respect to the recent publication I have indicated I am the lead author of that manuscript, however I do think its findings, albeit inconclusive, should be reflected upon as well as the accompanying editorial (DOI 10.1007/s00134-021-06406-1).

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 27 April 2021

<https://doi.org/10.21956/wellcomeopenres.18182.r43199>

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**Kristina E. Rudd**

Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Thank you for the opportunity to review this manuscript. The authors' objective was to describe the demographics, management, and outcomes of adults admitted to medical wards with hypoxemia in a single center in Malawi over a 1-month time period in early 2020. I agree with the authors that it is important to study the needs of patients with hypoxemia in low-resource settings in order to inform future oxygen resource allocation. A strength of the work includes its prospective design. The study is limited by the fact that it is single-center, does not include denominator data (specifically, what portion of all patients admitted to the hospital at that time did and did not have hypoxemia?), and is very small, with only 33 patients. Unfortunately this very small sample size, along with the other limitations of the study, make it impossible to generalize the findings in any meaningful way. The paper is interesting, but should be considered hypothesis-generating work. I think one of the most helpful findings is the authors' documentation of the frequency with which oxygen delivery devices were shared between patients – perhaps further examining this practice (which indeed is commonplace in many resource-limited settings though not well studied in the medical literature) in a larger future study would be interesting? Relevant work could include investigating the association between oxygen device sharing and complications such as nosocomial infection or acute desaturation events, and outcomes such as hospital mortality or secondary organ dysfunction.

Major Comments:

1. The authors state that part of their objective was to “explore the observed time course of hypoxemia and predictors of supplemental oxygen therapy requirements in medical patients...to inform needs assessment of oxygen at the hospital level.” I worry that, given the very high mortality rate in this study, difficulty determining individual patients' oxygen flow rates, and severely limited resources, the use / provision of supplemental oxygen in this study does not reflect the requirements for oxygen. Therefore any analyses of predictors of duration of oxygen therapy at best difficult to interpret and at worst completely misleading. For example, in such a resource-limited setting, perhaps it was actually the healthier patients with a better chance of survival who received a longer duration of oxygen therapy? Or perhaps, given the very small sample size and brief study duration, length of oxygen therapy simply reflects provider variation? I would strongly suggest removing all of these regression analyses and K-M curves. The authors seem to make causal conclusions here that are not substantiated by the results.
2. The Results state that 525 patients were admitted under the medical team during the study

period. The paper's quality is significantly diminished by the fact that the authors do not include a CONSORT diagram showing the reasons why only 33 people were recruited for this study. How many were hypoxic but didn't receive oxygen? How many were both hypoxic and received oxygen, but declined consent?

Minor Comments:

1. The abstract states that the study took place January – March 2020, but the methods state it was 18 Feb – 20 March (actually 18 Feb – 11 March per the results). Please correct whichever sections are incorrect.
2. Why is no percentage included for the patients receiving ARV therapy (Table 1)?

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pulmonary and Critical Care clinical research, epidemiology of sepsis and critical illness in resource-limited settings.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 25 May 2021

Helen Thomson, Malawi Liverpool Wellcome Trust, Blantyre, Malawi

Many thanks for the review of the manuscript. Your comments have been reviewed and hopefully you can see the reflection of this in our most recent submission.

Of note, we perhaps did not clearly highlight the limitations to our study, and thus have added a paragraph about this. We agree this paper is likely hypothesis generating work and

have suggested possible relevant future work.

Whilst we have not included a consort diagram, we hopefully have explained in the discussion that of the 525 patients admitted under the medical team 36 patients were identified as being hypoxaemic and 3 patients/their families declined consent, leading to 33 participants in the study. We believe that both the triage system in AETC as well as the daily recording of oxygen saturations allowed us to highlight all the hypoxaemic patients during the study period.

We have corrected the study dates in the abstract and have included the percentage for patients receiving ARV therapy.

Competing Interests: No competing interests were disclosed.

Reviewer Report 09 March 2021

<https://doi.org/10.21956/wellcomeopenres.18182.r42646>

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Kathryn Maitland 

Faculty of Medicine, Imperial College London, London, UK

The introduction starts with a bold statement 'Oxygen reduces morbidity and mortality in hypoxaemic patients and then goes on to state 'failure of oxygen supply to tissues precipitates organ failure and death'. The two references supporting these are a 'before and after' observational study conducted in Papua New Guinea (Duke *et al.*) in early 2000's in children with hypoxaemia implying that better use of oxygen (although not actually recorded rate/volume of oxygen used) resulted in better outcomes - has numerous potential biases to draw on as definitive evidence. The second reference is to a case report (Goldhill) of an elderly gentleman admitted with severe pneumonia who received oxygen, escalated to CPAP and the ICU care but died 24 days into admission. Perhaps the authors may be more speculative or provide better references to support this statement.

The introduction also includes a study conducted in the same hospital (Evans *et al.* 2016) in 144 adults including 14 eligible to receive oxygen therapy. Some of the same issues that the current paper discusses were brought out.

I noticed that the short period of the study from 18th February 2020 and 20th March 2020 and refer the authors (some being co-authors of the Evans paper) to the limitations highlighted in that study. *'as a 24-hour cross-sectional study it only provides a brief snapshot and is open to random error as well as information and selection bias. Malawi essentially has three seasons: hot and wet, hot and temperate. As a result, there are seasonal variations in the number of admissions as well as the severity*

of illness with a consequent impact on the need for oxygen'.

My concern is about generalisability. I understand that the study halted as a result of COVID – why was it not possible to restart it once recruitment was allowed? There needs to be some more reflection on this limited window of the study.

I note that median O₂ sats were 84% on admission and that on oxygen (all received oxygen therapy, despite many having to share the supply) median O₂ sats were normal 98% (95 – 99). The conclusion that sharing oxygen resource needs to be tempered by this fact.

The authors 'show' that having a chest X-ray reduced the risk of dying. This is reported as 'CXR on admission'. Does that mean CXR taken AT admission time (to hospital) or if a CXR was ever taken during admission was included in this variable. This is rather problematic both ways. First the patients who got a CXR AT admission were probably more likely to be less critically sick hence less likely to die. If this parameter includes CXR at any time then since most deaths occurred <72 hours of admission and likely to be to critical sick to send off for an X-ray it is mostly that these deaths did not have a CXR i.e. only those who were able to survive long enough to get a chest X-ray had a better outcome. Unless the authors have an alternative explanation?

The authors have reported overall use of oxygen used in the study. Is it possible that the authors could report median (and interquartile range) of oxygen use per patient in those with known flow rates (although assumptions may have to be made that this flow rate may not have been constant over time)? In addition, it would be very good to provide, based on the cost of a bottle of oxygen, how much oxygen therapy cost – other variable costs to include would be mask, tubing etc. There is very little published on the 'costs' of oxygen therapy.

When discussing the issues of difficulties in providing sustainable sources of oxygen there are some references they may want to include¹. These include a survey of oxygen supply and associated infrastructure that was performed at 231 health centres and hospitals in twelve African countries and some more discussion based on this paper for the challenges of using Oxygen concentrators, the WHO preferred option, when electricity supplies as reported in this survey at most centres was very unreliable. Our research group has also reported on this².

At the beginning of the discussion the authors note that despite correction of oxygen saturations there was a high mortality. It would be good to see some speculation over whether hypoxaemia was on the causal pathway to mortality? Oxygen therapy can have risks and benefits - perhaps these could be weighed up^{3, 4}?

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emergencies. *Crit Care*. 2013; **17** (2): 313 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Critical illness in resource poor hospitals in Africa.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 25 May 2021

Helen Thomson, Malawi Liverpool Wellcome Trust, Blantyre, Malawi

Many thanks for the review of the manuscript. Your comments have been reviewed and hopefully you can see the reflection of this in our most recent submission.

We have now changed our references in our introduction that provide stronger evidence to support our statements. We now reference a Thai study including nearly 100,000 patients that demonstrate low oxygen saturations to be significantly associated with pre-hospital mortality.

We have also added a section exploring the limitations of our study, including the fact it is single-centred and has a short period that does not account for seasonal variation in Malawi. We recognise that whilst our results may not be fully generalizable, the results can be used to generate hypothesis, and we have made suggestions of future relevant work.

In the discussion we have a paragraph related to the presence of a CXR and length of oxygen therapy received (*'Patients who were investigated with a CXR received oxygen for longer*

than those who had no radiography performed. A CXR may...). We agree that there is potential for confounding bias in our findings and have hopefully explained this.

Whilst we would have liked to explore the longitudinal relationship of individual patients oxygen use, this was not possible due to broken equipment and frequent switching of patients oxygen delivery devices. We have referenced the *Belle et al.* study of oxygen supply and associated infrastructure to highlight difficulties in providing sustainable sources of oxygen.

Competing Interests: No competing interests were disclosed.
