The African Covid-19 Critical Care Outcomes Study (ACCCOS)

An African, multi-centre evaluation of patient care and clinical outcomes for patients with COVID-19 admitted to high-care or intensive care units

Study protocol version 2.0

23 April 2020

(Statistical analysis plan version 1: Interim analysis)

(Added 8 September 2020)

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Introduction

The infectious disease COVID-19, caused by coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has been declared a pandemic and an international healthcare emergency by the World Health Organization (WHO). It has spread across the globe, overwhelming healthcare systems by causing high rates of critical illness. Mortality from COVID-19 exceeds 4%, with older people with comorbidities being extremely vulnerable.[1] It is expected that between 50-80% of the world's population may contract SARS-CoV-2 over the next two years.

We expect the outcomes to be potentially worse in Africa, because firstly, there is a limited workforce,[2] and secondly there are limited intensive care facilities and critical care resources across Africa to provide sufficient care. It is estimated that there are 0.8 (95% confidence interval 0.3 to 1.45) critical care beds per 100,000 population in Africa.[3] It is likely that the volume of unplanned admissions associated with COVID-19 will further adversely affect critical care outcomes in Africa,[4] especially as the ability of healthcare systems in Africa to adapt and expand during the pandemic to meet the clinical workload is unknown. Furthermore, the patient outcomes in critical care is poorly documented in this under-resourced environment.

Most countries in Africa are still in the early phase of the epidemic which provides the opportunity to study the utilization of critical care resources and their impact on patient outcomes. It is important therefore to establish what resources, comorbidities and interventions are potentially associated with either mortality or survival in Africa. Rapid dissemination of these findings may help inform appropriate resource prioritisation and utilisation during the COVID-19 pandemic in Africa. These points provide the rationale for the African Covid-19 Critical Care Outcomes Study (ACCCOS).

Research questions

Primary outcome

The primary outcome is in-hospital mortality in adult patients referred to intensive care or high-care units following suspected or known COVID-19 infection in Africa.

Secondary outcomes

To determine the risk factors (resources, comorbidities and interventions) associated with mortality in adult patients with suspected or known COVID-19 infection in Africa.

The research questions to be addressed are the following. In patients with suspected or known COVID-19 infection in Africa;

1. What are the critical care resources associated with survival?
2. What patient comorbidities and other risk factors are associated with in-hospital mortality?
3. What hospital interventions are associated with in-hospital survival?

Methods

An African national multi-centre prospective observational cohort study of adult (≥18 years) patients referred to intensive care or high-care units in Africa with suspected or known COVID-19 infection in Africa. Patient follow up will be for a maximum of 30 days in-hospital.

This study will run between April to December 2020, with an interim analysis after 250 to 300 deaths registered in the study, or in June or July 2020 if this number of deaths has not been reported in the study. The reason for the interim analysis, is to potentially provide data which may be associated with improved outcomes in Africa, in timeous manner for possible implementation during this COVID-19 pandemic.

This study will be registered on ClinicalTrials.gov.

Inclusion criteria

All consecutive patients at participating centres referred for high-care unit or intensive care unit admission who have suspected or known COVID-19.

Exclusion criteria

None

Centres

Our plan is to recruit as many centres as possible in Africa and ask them to include all eligible patients in the study.

Ethics approval

Ethics approval will be obtained from each university centre. Steering committee members will ensure ethics approval is obtained from their respective centres. Centres will not be permitted to record data unless ethics approval or an equivalent waiver is in place.

The consent process and data inclusion in the study will be the following. We expect that for most patients, consenting at the time of admission to critical care will be inappropriate due to the patient's condition and the critical care management needed. Therefore, in most cases we will only be able to explain the study to the patient following clinical improvement from their critical condition. We will also be able to explain the study to a legal representative or proxy, once the patient's management has been stabilised in the critical care. For these reasons, we are applying for:

i) 'Delayed consent' for patients admitted to critical care, which can be given by the patient (following stabilisation or recovery in critical care) or a legal representative or proxy (should the patient be unable to provide consent).

ii) If there is no opportunity to acquire 'delayed consent' (i.e. the patient does not recover sufficiently to provide consent, and there is no legal representative or proxy to provide consent for participation) before the study outcome is reached (i.e. 30 days in hospital, or the patient dies in hospital), then we request that the ethics committee considers permission to include the patient's data in the study.

The justifications for this consent process and data inclusion are the following. We expect that almost all critical care admissions will be urgent or emergent. Attempts to obtain traditional consent in predominantly urgent and emergent critical care admissions, which may include patients with a decreased level of consciousness may lead to non-consecutive patient enrolment in the study. It is likely that this would lead to a biased sample, with artificially low estimates of adverse outcomes in African Covid-19 critical care patients, and data which is not generalisable to the majority of African Covid-19 critical care patients. Finally, generating biased and poorly generalizable data would not address the research question, and thus would dishonour the contributions of the other included patients, and would be wasteful research in a resource-limited environment.

Data collection and collation

Data will be collected in individual centres on paper case record forms (CRFs) for every patient recruited. Paper CRFs will be stored within a locked office in each centre as they will include identifiable patient data in order to allow follow-up of clinical outcomes. Data will then be pseudo-anonymised by generation of a unique numeric code and transcribed by local investigators onto an internet based electronic CRF. Each patient will only be identified on the electronic CRF by their numeric code; thus the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A participant (patient) list will be used in each centre to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points. Access to the data entry system will be protected by username and password delivered during the registration process for individual local investigators. All electronic data transfer between participating centres and the co-ordinating centre will be encrypted using a secure protocol (HTTPS/SSL 3.0 or better). Data will be anonymised during the transcription process using the Research Electronic Data Capture (REDCap) tools hosted by Safe Surgery South Africa (SSSA). REDCap is a secure, we-based application designed to support data capture for research studies.[5] Soft limits will be set for data entry, prompting investigators when data were entered outside these limits. In countries with poor internet access, paper case record forms may be forwarded to SSSA, for entry by SSSA.

Pseudo-anonymised (coded) data may also be sent by **e-**mail to the coordinating centre if necessary.

Each centre will maintain a secure trial file including a protocol, local investigator delegation log, ethics approval documentation, the participant list, etc.

A final summary printout of included patients with major variables should be produced for each centre together with final data submission to double check for completeness and accuracy.

Dataset

A realistic data set will be fundamental to the success of the investigation, and this was confirmed in previous studies e.g. EuSOS study where nearly complete data was available on 46 000 patients,[6] and ASOS in a resource limited African environment had complete data in over 95% of participants.[2] We have adopted a leaner dataset than used in EuSOS or ASOS, and therefore believe that these key data points will not discourage centres from participating because of an excessive burden of data collection.

Centre co-ordinators may request the addition of a limited number of data points to support the ACCCOS data collection and for subsequent regional analyses. All additional data points must be discussed with the co-principal investigators and if necessary the steering committee.

Centre specific data will be collected once for each hospital including: secondary/tertiary centre, number of hospital beds, number and level of critical care beds, details about the reimbursement status of the hospital and public holidays or other local factors affecting patient care during study period e.g. nurse to patient ratio.

The case record form (CRF) will be completed for every eligible patient admitted to the high-care unit or the intensive care unit during the study period (appendix 1). Patients will be followed up until hospital discharge. This will be censored at thirty days i.e. patients will be followed up until discharge or for thirty days whichever is the shorter period.

Sample size calculation

The sample size will depend upon the number of centres recruited and their respective caseloads. Each centre will also complete a screening tool of all eligible patients during study participation. The duration of enrolment at a site will be determined by the local lead investigator, and the circumstances allowing participation during the COVID-19 pandemic.

There are approximately 25 to 30 variables in the dataset which may be associated with mortality in COVID-19 patients requiring critical care admission. We plan to do an interim analysis once 250 to 300 deaths are registered in the trial, to allow assessment of these risk factors in a logistic regression analysis, allowing for approximately 10 events per variable.[7] Should this milestone not be reached by June or July 2020, a limited logistic regression will be conducted to provide some data to inform further management in Africa during COVID-19.

Statistical analysis

Data will be presented at a national level and at a continental African level. All institutional level data will be anonymised prior to publication. Categorical variables will be described as proportions and will be compared using chi-square tests. Continuous variables will be described as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed. Comparisons of continuous variables between groups will be performed using t-tests, one-way ANOVA or equivalent non parametric tests as appropriate. Univariate analysis will be performed to test factors associated with postoperative complications, critical care admission and in-hospital death.

Single-level and hierarchical multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into the models

based on their univariate relation to outcome ($p<0.05$), biological plausibility and low rate of missing data.

Results of logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals. The models will be assessed through the use of sensitivity analyses to explore possible interacting factors and examine any effect on the results. A single final analysis is planned at the end of the study.

Primary outcome measure

Incidence of in-hospital mortality in adult patients referred to intensive care or high-care units following suspected or known COVID-19 infection in Africa.

Secondary outcome measures

To determine the risk factors (resources, comorbidities and interventions) associated with mortality in adult patients with suspected or known COVID-19 infection in Africa.

Organisation

ACCCOS is performed under the auspices of the Critical Care Society of South Africa (CCSSA). The Steering Committee will be chaired by BB and PDG. The Critical Care Society of South Africa is represented by PDG. The study management team will be appointed by the Steering Committee and led by BB and PDG. The duties of this team will include administration of all project tasks, communication between project partners (including funders, steering committee members, national and local co-ordinators, etc.), data collation and management and preparation of reports for individual study sites. The Steering Committee is responsible for the scientific conduct and consistency of the project. The Steering Committee will ensure communication between the funder(s), study management team and co-ordinators as necessary.

Country co-ordinators

Country co-ordinators will be appointed by the steering committee to lead the project within individual countries and:

- Identify local co-ordinators in participating hospitals
- Assist with translation of study paperwork as required
- Ensure distribution of research manuals, eCRF and other materials
- Ensure necessary regulatory approvals are in place prior to the start date
- Ensure good communication with the participating sites in his/her country

Local co-ordinators

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of eCRFs
- Communicate with the relevant national coordinator

Data management and ownership

On behalf of the Steering Committee, the Safe Surgery South Africa (SSSA) will act as custodian of the data. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to conduct secondary analyses. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summary data will be presented publicly and all institutional and patient level data will be strictly anonymised. Individual patient data provided by participating hospitals remain the property of the respective institution. Once each local co-ordinator has confirmed the data provided from their hospital are both complete and accurate, they will be provided with a spreadsheet of the raw (un-cleaned) data for their hospital.

The complete ACCCOS dataset, anonymised with respect to participating patients and hospitals, will be made freely and publicly available two years following publication of the main scientific report. Prior to this, the steering committee is not under any obligation to release data to any collaborator or third party if they believe this is not in keeping with the wider aims of the ACCCOS project.

Publication plan

The steering committee will appoint a writing committee to draft the scientific report(s) of this investigation, which will be disseminated in a timely manner. The group will be known as 'The ACCCOS Investigators'. It is anticipated that a number of secondary analyses will be performed. ACCCOS investigators will be given priority to lead such analyses and are encouraged to do so. Participation and authorship opportunities will be based on contribution to the primary study. The steering committee will consider the scientific validity and the possible effect on the anonymity of participating centres prior to granting any such requests. Where necessary, a prior written agreement will set out the terms of such collaborations. The steering committee must approve the final version of all manuscripts including ACCCOS data prior to submission. In the event of disagreement within the steering committee, the co-

principal investigators will make a ruling. Any analysis incorporating ACCCOS data from two or more study sites will be considered a secondary analysis and subject to these rules. The Steering Committee must approve the final version of all manuscripts prior to submission, whether they relate to part or all of the ACCCOS dataset.

Deliverables

The main deliverables will be scientific reports of preliminary findings for general and specialty journals, abstracts for presentation to national and international meetings including those of the supporting societies and a final report summarising the overall findings.

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Appendix 1

The African Covid-19 Critical Care Outcomes Study (ACCCOS) case record form

African Covid-19 Critical Care Outcomes Study (ACCCOS)

Age ☐☐☐ years Sex ☐ M ☐ F (Measured or estimated) Mass (kg) ☐☐☐ Height (cm) ☐☐☐

COVID-19 ☐ Positive ☐ Suspected (If suspected, was patient later COVID-19 positive ☐ Y ☐ N ☐ COVID-19 testing not done)

Chronic co-morbid disease (tick all that apply): Coronary artery disease ☐ Y ☐ N Congestive heart failure ☐ Y ☐ N
Hypertension ☐ Y ☐ N Stroke or Transient ischaemic attack ☐ Y ☐ N Diabetes mellitus ☐ Y ☐ N Cancer ☐ Y ☐ N
Current smoker ☐ Y ☐ N Chronic Lung Disease ☐ Y ☐ N Active TB ☐ Y ☐ N Chronic Liver Disease ☐ Y ☐ N
HIV/AIDS ☐ Y ☐ N If yes, Antiretroviral therapy ☐ Y ☐ N Chronic/ malaria within 3 months ☐ Y ☐ N Chronic kidney disease ☐ Y ☐
Location before critical care referral: ☐ Emergency Department ☐ In-hospital ward ☐ Transfer from another hospital/health facility Any surgery prior to 2 weeks of critical care admission ☐ Y ☐ N
Cardiorespiratory arrest in 24 hours prior to critical care referral ☐ Y ☐ N
Quick SOFA score on referral: SBP≤100mmHg ☐ Y ☐ N Resp rate≥22 breathes/min ☐ Y ☐ N GCS≤14 ☐ Y ☐ N
SOFA score on referral/ admission (mark 0 to 4 for each category or unable to calculate due to missing data):

NOTE: See table below. Use worst values recorded from 24hrs prior to referral to 1hr after admission to Critical Care

SOFA score CNS ☐ or unable to calculate (mark X) ☐ SOFA score CVS ☐ or unable to calculate (mark X) ☐

SOFA score Respiratory ☐ or unable to calculate (mark X) ☐ SOFA score Renal ☐ or unable to calculate (mark X) ☐

SOFA score Liver ☐ or unable to calculate (mark X) ☐ SOFA score Haem ☐ or unable to calculate (mark X) ☐

Admission decision: Admitted to (tick one): ☐ ICU ☐ HCU ☐ 'other area for critical care'

Was admission delayed due to lack of resources (e.g. bed, staffing etc) ☐ Y ☐ N Nurse to patient ratio: ☐ nurses to ☐ patients

Ability to provide invasive ventilation for patient if required ☐ Y ☐ N Physician available on site 24/7 for patient ☐ Y ☐ N

ICU or HCU Admission time (24h) & date: [h][h] : [m][m] [d][d] [m][m] [2][0][2][0]

Organ support indication for admission to 'other area for critical care', HCU or ICU admission:

Respiratory support ☐ Y ☐ N Cardiovascular support ☐ Y ☐ N Renal support ☐ Y ☐ N Other ☐ Y ☐ N

Management in ICU or HCU (check all that apply throughout stay): Respiratory: Oxygen mask ☐ Y ☐ N ☐ Not available

CPAP ☐ Y ☐ N ☐ Not available HFNO (high-flow nasal oxygen) ☐ Y ☐ N ☐ Not available

Proned while not ventilated ☐ Y ☐ N Proned on mech ventilation ☐ Y ☐ No, not indicated ☐ No, not practised

Non-invasive ventilation ☐ Y ☐ N ☐ Not available Invasive ventilation ☐ Y ☐ N ☐ Not available

Intubation: ☐ Pre-admission ☐ Post admission ☐ No intubation

If patient intubated, was intubation: ☐ Elective intubation ☐ Emergency intubation, and was the patient extubated ☐ Y ☐ N

Other: Inotropes/ vasoconstrictors ☐ Y ☐ N Dialysis ☐ Y ☐ N Therapeutic anticoagulation ☐ Y ☐ N

Steroid therapy ☐ Y ☐ N Repurposed/ experimental Covid-19 drug therapy ☐ Y ☐ N ECMO ☐ Y ☐ N ☐ Not available

Patient outcome:

Consent: ☐ Consent obtained ☐ Patient included in study as unable to obtain 'delayed' consent (e.g. no proxy/ died)

Status at hospital discharge or 30 days after critical care admission ☐ Alive & discharged ☐ Alive & in hospital ☐ Dead

Status at critical care discharge: ☐ Alive ☐ Dead Length of stay in critical care: ☐☐ days

Decision to limit therapy ☐ Y ☐ N Withdrawal of life support ☐ Y ☐ N

ACCCOS unique patient ID ☐☐☐☐☐☐☐☐☐☐

✂- -

Patient name: ______________________________ DOB [d][d] [m][m] [y][y][y][y]

Patient hospital number : ______________________ CRF v2.0

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Statistical analysis plan version 1

(Interim analysis)

8 September 2020

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Introduction

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We expect the outcomes to be potentially worse in Africa, because firstly, there is a limited workforce,[2] and secondly there are limited intensive care facilities and critical care resources across Africa to provide sufficient care. It is estimated that there are 0.8 (95% confidence interval 0.3 to 1.45) critical care beds per 100,000 population in Africa.[3] It is likely that the volume of unplanned admissions associated with COVID-19 will further adversely affect critical care outcomes in Africa,[4] especially as the ability of healthcare systems in Africa to adapt and expand during the pandemic to meet the clinical workload is unknown. Furthermore, the patient outcomes in critical care is poorly documented in this under-resourced environment.

Most countries in Africa are still in the early phase of the epidemic which provides the opportunity to study the utilization of critical care resources and their impact on patient outcomes. It is important therefore to establish what resources, comorbidities and interventions are potentially associated with either mortality or survival in Africa. Rapid dissemination of these findings may help inform appropriate resource prioritisation and utilisation during the COVID-19 pandemic in Africa. These points provide the rationale for the African Covid-19 Critical Care Outcomes Study (ACCCOS).

Statistical analysis plans

Primary outcome

The primary outcome is in-hospital mortality in adult patients referred to intensive care or high-care units following suspected or known COVID-19 infection in Africa.

Statistical analysis plan for primary objective

We will present the incidence and 95% CI for these data.

Secondary outcomes

To determine the risk factors (resources, comorbidities and interventions) associated with mortality in adult patients with suspected or known COVID-19 infection in Africa.

The research questions to be addressed are the following. In patients with suspected or known COVID-19 infection in Africa;

4. What are the critical care resources associated with survival?
5. What patient comorbidities and other risk factors are associated with in-hospital mortality?
6. What hospital interventions are associated with in-hospital survival?

Statistical analysis plan

Categorical variables will be described as proportions and compared using chi-square tests, Fisher's exact tests, Pearson's chi-square tests or chi-square tests with Yates correction, as appropriate. Continuous variables will be described as mean and standard deviation if normally distributed or otherwise median and interquartile range (IQR). Comparisons of continuous variables between groups will be performed using unpaired t-tests or one-way ANOVA as appropriate. Univariate analysis will be performed to test for risk factors associated with in-hospital death.

The main model will only include patients with complete outcome data (i.e. patients who are still in hospital receiving therapy, and have not reached the outcome definition of death, discharge, or in-hospital at 30 days will be excluded). Generalized linear mixed models using a logit link will be used to identify independent risk factors for the binary outcome of mortality. We will use a three-level generalized mixed model, with patients being at the first level, hospital at the second and country at the third level, to account for the expected correlation in outcomes within hospitals and countries. We will exclude patients with missing values for potential risk predictors, and only use a complete case analysis if there are <5% of the dataset with incomplete potential clinical risk predictors.[8] All risk factors will be entered into the model, unless the number of reported deaths is insufficient to provide 10 events (deaths) per variable.[7] Should the events per variable be <10, then variables with a univariate association of $p<0.05$, and variables with biological plausibility and a low rate of missing data will be used.

Variables to be considered for inclusion in the model;

i. Age
ii. Sex
iii. BMI
iv. COVID-19 positive or suspected (sensitivity only known positive)
v. Coronary artery disease
vi. Congestive heart failure
vii. Hypertension
viii. Stroke or Transient ischaemic attack
ix. Diabetes mellitus
x. Cancer
xi. Current smoker
xii. Chronic Lung Disease
xiii. Active TB
xiv. Chronic Liver Disease
xv. HIV/AIDS (no, yes, yes on anti-retrovirals)
xvi. Chronic/previous malaria
xvii. Chronic kidney disease
xviii. Cardiorespiratory arrest in 24 hours prior to critical care referral
xix. Quick SOFA score on referral
xx. SOFA score on referral/ admission
xxi. Was admission delayed due to lack of resources (e.g. bed, staffing etc)
xxii. Nurse to patient ratio
xxiii. Ability to provide invasive ventilation for patient if required
xxiv. Physician available on site 24/7 for patient
xxv. Indication for admission (number of organ system support i.e. none, one, two, three or more)
xxvi. Respiratory support (None, Oxygen mask, HFNO, CPAP)
xxvii. Proned (None, not ventilated, on mech ventilation)
xxviii. Ventilation (None, Non-invasive ventilation, Invasive ventilation)
xxix. Intubation (no, yes elective, yes emergency)
xxx. Inotropes/ vasoconstrictors
xxxi. Dialysis
xxxii. Therapeutic anticoagulation
xxxiii. Steroid therapy
xxxiv. Repurposed/ experimental Covid-19 drug therapy
xxxv. ECMO

Collinearity will be assessed using the variance inflation factor. If collinearity is detected, then variables will either be excluded or combined. The model fit will be evaluated.

Results of the logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). The models will be assessed through the use of sensitivity analyses to explore possible interacting factors and examine any effect on the results.

A single final analysis is also planned at the end of the study.

Univariate and multivariate statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) version 24 (SPSS Inc., Chicago, IL, USA).

Sensitivity analyses for the secondary outcome

1. Analysis of confirmed Covid-19 positive patients only
2. Analysis which excludes all patients who had withdrawal of life support or decision to limit therapy

Additional analyses

Description of participating sites will include the following;

1. Number of hospital beds
2. Number of critical care beds allowing invasive ventilation
3. Number of critical care and high-care beds not allowing invasive ventilation
4. Nurse to patient ratio for critical care patients during the day
5. Nurse to patient ratio for critical care patients during the night
6. Number of specialist intensivists managing patients in critical care unit
7. Number of other specialist doctors managing patients in critical care unit
8. Number of non-specialist doctors managing patients in critical care unit
9. Doctor to patient ratio for critical care patients
10. Doctor on site in the critical care unit after hours
11. How many extra ventilators could be used for a critical care surge?
12. ICU type ventilators
13. Operating room type ventilators
14. ECMO
15. Proning during mechanical ventilation
16. Pulse oximetry for all, some or no patients
17. Ability to do arterial blood gases

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