BMJ Open

Prognostic Criteria Associated With Survival in Patients Over 60 Admitted to ICU for Severe COVID Infection: the Senior-COVID-Rea Multicentric Survey protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044449
Article Type:	Protocol
Date Submitted by the Author:	04-Sep-2020
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Keywords:	COVID-19, INTENSIVE & CRITICAL CARE, GERIATRIC MEDICINE

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Prognostic Criteria Associated With Survival in Patients Over 60 Admitted to ICU for Severe COVID Infection: the Senior-COVID-Rea Multicentric Survey protocol

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Abstract

Introduction: With the spread of COVID-19 epidemic health plans must be adapted continuously. There is an urgent need to define the best care courses of the patients, and notably the place of ICU admission, according an individualized benefit/risk ratio. Senior-COVID-Rea was designed to evaluate, on health data, in patients over 60 admitted in ICU for severe COVID-19 disease, the impact of age, geriatric parameters (frailty, dependence, malnutrition) and paraclinical parameters on their mortality at 30 days of their admission.

Methods and analysis: This is a multicentric survey protocol to be conducted in 7 hospitals of Auvergne-Rhône-Alpes region, France. All patients over 60 admitted in ICU for severe COVID-19 infection (or their caregiver) will be proposed to enter the study and to fulfill a questionnaire on their functional parameters prior (1 month before) COVID infection: clinical frailty score (CFS), Fried's frailty score, weight loss in the previous 6 months. Paraclinical parameters at ICU admission will be collected: lymphocytes and neutrophils counts, high-fluorescent lymphoid cells and immature granulocytes percentages (Sysmex data), D-dimers, CRP, LDH, creatinine, CT-scan lung extension rate as well as clinical resuscitation scores: PaO2/FiO2 ratio, IGSII/SASPII score and/or SOFA score, and the delay between the first signs of infection and admission to intensive care unit. Primary outcome will be overall survival at day 30. The analysis of factors predicting mortality at day 30 will be carried out by univariate and multivariate logistic regressions. Multivariate logistic regression will consider up to 15 factors.

The ambition of this trial, which focuses on the different approaches of geriatric vulnerability, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination: Study protocol was ethically approved. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT04422340.

Keywords: COVID-19, resuscitation, ICU, age, frailty, Sysmex

Article summary

Strengths and limitations of this study

- This study will provide a cross-sectional analysis of the impact of geriatric parameters, and particularly frailty according CFS and Fried's criteria, on D30 mortality in ICU
- All patients (and relatives) admitted in ICU in 7 hospitals from Auvergne Rhône-Alpes, France will be proposed the study

- A multivariate model will be built, to identify the relative impact of up to 15 covariates

Introduction

With the spread of COVID-19 epidemic since 2019 in Wuhan, China, health plans must be adapted continuously in response to the emergency. The first publications from the Chinese experience demonstrated an increase in the incidence of COVID-19 infections in patients over 60 years of age, a higher frequency of severe forms of the disease and therefore theoretical indications of orientation towards resuscitative care.

However, the first published data from Hubei province suggested a low benefit of resuscitation for patients between 70 and 80 years of age and null in patients over 80 years of age (1). More recent data from Lombardy, Italy, described a 41% mortality rate in patients over 70, 55% in patients over 80 and 100% over 90 (2). These data must question the individual benefit / risk balance of an orientation towards resuscitation for each category of patients, their quality of life and the concept of unreasonable obstinacy.

Among the covariates associated with resuscitation mortality described in the data published to date, cardiovascular comorbidities, certain biological covariates (LDH (3), creatinine, lymphocytes, neutrophils, TP, D-dimers (4), etc.), the time between the first symptoms and the entry into resuscitation have been identified. Cumulative evidence highlights the interest of some additional biological parameters coming from extended complete blood cell count under fluorescence flow cytometry (SYSMEX data, (5–7)).

Another covariate classically proposed to predict patients' outcomes is frailty. Frailty has been defined as "*state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability*". If some consensus has been reached on its definition (8), its operational criteria differ grossly between two views: a multidomain view of frailty, according which frailty is the consequence of the addition of several deficits (9), and a phenotypical view of frailty, according which prefrail and frail patients develop a specific phenotype linked to malnutrition and sarcopenia (10). In an even more pragmatic view of frailty, the CFS (Clinical Frailty Score) was developed, which stratifies older patients in distinct levels of fitness according a rapid "at a glance" assessment for patients' triage (11). According recent evidence from two studies, disease outcomes of COVID-19 patients admitted to hospital would be better predicted by frailty than either age or comorbidity. In an Italian study form the COVID-19 Monza Team members, Frailty Index – a scoring system according the cumulative deficits view of frailty – was able to discriminate retrospectively the patients who recovered from those who either died or were transferred to ICU (12). In the COVID-19 in Older People (COPE) European cohort study, mainly performed in the United Kingdom, the CFS was well correlated with total mortality and day-7 mortality in all patients admitted to hospital for COVID-19 infection (13).

In an intent to better define the individual benefit/risk ratio of ICU admission in each category of patients, the objective of this multicentric observational study is to determine the clinical and biological covariates predictive of mortality in the population of patients over 60 years of age admitted in intensive care unit, with a specific attention paid to a retrospective and declarative assessment of their functional and nutritional parameters 1 month before COVID-19 infection.

Methods and analysis

Objectives

Primary objective

Evaluation of the impact of age on mortality at 30 days after admission to intensive care.

Secondary objective

(i) Evaluation of the impact on 30-day mortality of the following co-variables:

o Co-morbidities (CIRS-G scale), including cardiac and vascular co-morbidities ≥ 2 (1 month prior to infection))

o Functional status of the patient with

- Clinical frailty scale (1 month before infection, collection from caregiver)

- ADL score (1 month before infection, collection from caregiver)

o Nutritional data: weight loss in the last 6 months

o Biological data

- LDH, CRP, creatinine at entry

- Parameters from complete blood count at D1 of intensive care unit entry (lymphocytes, neutrophils counts), SYSMEX data (IG: Immature granulocyte count; HFLC: high fluorescent lymphocyte count) (6-8)

o Chest imaging data :

- COVID-19 lung extension rate on chest CT-scanner (minimal, moderate, extensive, severe, critical according French Radiology Society guidelines (14))

o Resuscitation parameters

- PaO2/FiO2 ratio at intensive care admission

- IGSII/SASPII score (simplified acute physiology score) at D1 of intensive care entry and/or SOFA (sepsis-related organ failure assessment) score: a posteriori estimate based on IGSII/SASPII

- Delay between the first signs of infection and admission to intensive care

(ii) evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on:

- Medical management
    - in the intensive care unit
    - during total hospital stay
- Medical complications
    - in the intensive care unit
    - during hospital stay after intensive care

Study design

Senior-COVID-Rea is a retrospective and prospective multicenter study on health data. Data processing has been approved by the national data protection commission.

Study sites and participants

All patients over 60 admitted between the beginning of COVID wave and 7th May,2020 in intensive care in Senior-COVID-Rea investigations centers (Lyon Sud Hospital, Croix Rousse Hospital, Edouard Herriot Hospital and Lyon Est Hospital from the Hospices Civils de Lyon, Lyon-Villeurbanne Médipôle Nord-Ouest Villefranche-sur-Saône Hospital and Emile Roux Hospital of Le Puy en Velay) will be screened. Individual information explaining the study will be given to the patient. Depending on the clinical condition of the patients, a waiver request is justified in accordance with the ICH (International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use) Harmonized Guideline For Clinical Practice of 9.11.2016: *"In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested"*). In accordance with the regulatory framework, information will be given to the patient's trusted person. As soon as the patient himself is able to read the information leaflet, it will be given to him or her and, in the event of refusal, the patient will be discharged from the study.

If the patient or the close relative does not object to the use of the data, the patient will be assigned an anonymous identification number.

Inclusion criteria are:

- Patient over 60
- sent to an intensive care unit
- whose COVID diagnosis has been established (RT-PCR and / or chest scanner)

Exclusion criteria are:

- Refusal of the patient or his support person to participate in the study

Outcomes and measurements

Primary outcome

The main outcome measure is overall mortality at day 30 after admission in intensive care unit.

Secondary outcomes

The secondary outcomes of the study are:

- Mortality proportion in intensive care unit
- Overall survival
- Length of stay (in the intensive care unit, in total with or without readaptation unit)
- Medical management
    - in the intensive care unit: high flow oxygen therapy, non-invasive ventilation, invasive ventilation, prone position, ECMO (extracorporeal membrane oxygenation), catecholamines, extra-renal purification, IHD (intermittent hemodialysis), CVVH (Continuous venovenous hemodiafiltration), short-acting hypnotics, long-acting hypnotics, short-acting analgesics, long-acting analgesics, dexmedetomidine or catapressan, neuroleptic for sedation (levomepromazine, cyamemazine), limiting and stopping active therapeutics (with domain(s) of limitation(s)), anti-infectious therapeutics (antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other), corticosteroids, nutrition (parenteral or enteral feeding, oral nutrition), physiotherapy (passive or active mobilization, armchair bed transfer, edge of the bed sitting, armchair, verticalization).
    - during total hospital stay: oxygen therapy, anti-infectious therapeutics (antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other), corticosteroids, nutrition (parenteral or enteral feeding, oral nutrition), physiotherapy (passive or active mobilization, walk).
- Medical complications

- in the intensive care unit: acquired delirium or confusion, acquired neuropathy, acquired lung infections, catheter-related infections, bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, pulmonary embolism, swallowing disorders, congestion / trouble with ventilation, tracheotomy, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression, multiple intubations (with number), intra-hospital transports (with number).
- during hospital stay after resuscitation: delirium or confusion, post-resuscitation neuropathy, acquired lung infection(s), catheter-related infection(s), bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, swallowing disorders, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression

Sample size calculation

On the basis of the first results of first Chinese retrospective results (1), the hypothesis of Senior-COVID-Rea was the following: considering a single analysis variable (age), with expected mortality of 30% in patients under 70 years of age, and 70% in patients over 70 years of age (with 40% of patients over 70 years of age), it will be necessary to include a total of 130 patients to show a statistically significant difference between these two groups with a power of 90% (bilateral alpha risk test of 5%). Since the analysis considers the integration of several factors, considering 15 factors, hoping for a coefficient of determination of 0.5 of the model, to achieve an optimism of less than 10%, it will be necessary to include 185 patients (criterion 1 of Riley, Snell et al, **(15)**).

After the publication of data on mortality in ICU in Lombardy region, Italy in April 2020 (2), it was considered that a stopping of the trial at 185 patients would impair its statistical power and induce a potential risk of patients' selection bias. As a consequence the scientific committee decided, on the 7th May, that all the patients admitted to ICU before that date - that corresponded to the end of the first COVID wave – should be screened and proposed the study without any patients' number limitation.

This sample size calculation was modified on Clinicaltrials.gov site accordingly (July 28, 2020).

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators to decide whether the data should be corrected or considered as missing data. Any changes in the data will be reported.

Data analyses will be performed by the data management and analysis centre. The analyses will be carried out by an independent statistician with the latest version of the R software environment. All the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the patients included and excluded from the study during the trial time frame (objection to the trial, patient's request to exit from the study) and the characteristics of the patients excluded. Eligibility criteria for included patients will be verified.

Characteristics of the study population and proportions of missing values will be reported. Patient characteristics will be described using mean and standard deviation or median and interquartile range for quantitative variables, and frequencies and distribution for categorical variables.

Primary analysis

The analysis of factors predicting mortality at day 30 will be carried out by univariate and multivariate logistic regressions. Multivariate logistic regression will consider up to 15 factors. In view of the results of the univariate analyses and the correlation between the factors studied, it will be decided which factors will be included in the multivariate analyses. The effect of factors will be quantified by the odds ratio with the associated 95% confidence interval (95% CI).

Secondary analyses

The mortality proportion in intensive care unit will be calculated with its 95 % credible interval in the two groups of patients (less than 70 years old, 70 years old or greater). The overall survival will be described with Kaplan-Meier survival curves in these two groups; the mean and median length of stay in intensive care unit will also be described.

The association of age, and of the frailty scores (using cutoffs) with the medical management and medical complication outcomes will be quantified by an odds ratio with its 95% confidence interval, in an exploratory analysis. In this context, no adjustment will be made for multiple testing.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

According studies on health data, patients leave the study either on a per-protocol basis on day 30 after their admission in intensive care ward or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed by the study.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on April 10, 2020. Data are collecting.

Patients' and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by patients' association (EDS information notice model).

Discussion

Discussion of the study design

This study has an ethical stake in the evaluation of the risk/benefit balance of referring patients over 60 years of age to intensive care procedures, according to their comorbidities and previous functional state as well as the criteria of the seriousness of the pathology at the time of care. Patients over 60 years of age appear to be at risk for COVID-19 infection. The identification of prognostic factors is a major issue in personalizing the care of these patients.

More than chronological age, frailty appears increasingly as a good prognostic marker as it can be defined as a "*medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death*" in response to variable stressors (16). Frailty was previously demonstrated as a good prognostic marker of the ability to overcome resuscitation-associated stress in diverse contexts (17), as well as a predictive marker of complications during noninvasive mechanical ventilation (18), extubation failure (19) resources utilization (20) and poor functional recovery and long-term quality of life (21). It appears logical and ethical that, from a prognostic marker, frailty becomes a tool for adaptation of care courses when the stressor is presumed particularly high as it is with COVID-19 severe infections.

The ambition of this trial, which focuses on the different approaches of frailty, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination

The study sponsor is the Hospices Civils de Lyon. In response to COVID-19 emergency and the regulation on health data, accrual started on April 10,2020. The study protocol (V1.0 of April 7, 2020) was approved by an ethics committee (Comité Scientifique et Éthique des Hospices Civils de Lyon) on June 30, 2020 and declared on ClinicalTrials platform on June 9, 2020. The research will be carried out in accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect non-objection from the patient and/or his relative at the beginning of the procedure (Annexes 1 to 3, in French). This non-objection is logged in the patient's medical chart. The patient can stop the study at any time with an oral information at his investigator or clinical research assistant.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count : 2536

Abbreviations

ADL: Activities of Daily Living; CIRS-G: Cumulative Illness Rating Scale – Geriatric; COVID-19: Coronavirus disease 2019; CFS: Clinical Frailty Score; CRA: Clinical Research Assistant; CVVH: Continuous VenoVenous Hemodiafiltration; ECMO: ExtraCorporeal Membrane Oxygenation; HFLC: High Fluorescent Lymphocyte Count; ICU: Intensive Care Unit; IG: Immature Granulocyte Count; IGS: Indice Gravité Simplifié; IHD: Intermittent HemoDialysis; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment.

Declarations

Acknowledgements

The authors acknowledge the research teams of Lyon Sud Hospital, Croix Rousse Hospital of Lyon, Edouard Herriot Hospital of Lyon, Lyon Est Hospital, Emile Roux hospital center of Puy-en-Velay, Médipôle Lyon-Villeurbanne, and Hôpital Nord Ouest hospital center, who contribute to patient enrolment in this study.

The authors would like to thank patients and their families to contribute to this research despite the urgent and stressful context.

Funding

This work was supported by the Hospices Civils de Lyon, through an internal call for projects "COVID-19" and the decision of the selection committee on May 12,2020. It provided partial funding for statistical analysis and clinical research assistants.

Patient and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by patients' association (information notice model for health data studies).

Availability of data and materials

The final dataset of the Senior-COVID-Rea study will be available on reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Author contributions

All authors participated to the Senior-COVID-Rea protocol conception. CF led the drafting of the manuscript. All authors critically reviewed and approved the final version of the protocol.

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Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2
Protocol version	3	Date and version identifier	12 (Ethics and dissemination)
Funding	4	Sources and types of financial, material, and other support	13 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2 (Authors' list) 13 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12 (Ethics and dissemination) 13 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 (Data management and statistical analyses) 10 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11 (End of protocol) And N/A (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A And 11 (Patients' and public involvement)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A (no visit – health data study)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10 (End of protocol)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethics and dissemination)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethics and dissemination) 11 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10 (Ethical and legal considerations)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	12 (Ethics and dissemination), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annexes 1 & 2 (in French)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04422340
Date of registration in primary registry	June 9, 2020
Secondary identifying numbers	
Source(s) of monetary or material support	Hospices Civils de Lyon
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Senior-COVID-Rea Multicentric Survey
Scientific title	Prognostic Criteria Associated With Survival in Patients Over 60 Admitted to ICU for Severe COVID Infection: the Senior-COVID-Rea Multicentric Survey
Countries of recruitment	France
Health condition(s) or problem(s) studied	Severe COVID
Intervention(s)	N/A
Key inclusion and exclusion criteria	Inclusion Criteria: • Patient over 60 • sent to a resuscitation unit (or an intensive care unit) • whose COVID diagnosis has been established (RT-PCR and / or chest scanner) Exclusion criteria are: • Refusal of the patient or his support person to participate in the studyExclusion Criteria:
Study type	Cohort study Allocation: N/A Intervention model: Single Group Assignment Masking: None (Open Label) Primary purpose: Prognostic model

Data category	Information
Date of first enrolment	Avril 10th, 2020
Target sample size	> 185
Recruitment status	Recruiting
Primary outcome(s)	Impact of age on mortality at 30 days after admission to intensive care.
Key secondary outcomes	(i) Impact on 30-day mortality of the following co-variables: ▪ Co-morbidities (CIRS-G scale), including cardiac and vascular co-morbidities at ≥ 2 (1 month prior to infection)) ▪ Functional status of the patient with ○ Clinical frailty scale (1 month before infection, collection from caregiver) ○ ADL score (1 month before infection, collection from caregiver) ▪ Nutritional data: weight loss in the last 6 months ▪ Biological data ○ LDH, CRP, creatinine at entry ○ Parameters from complete blood count at D1 of resuscitation entry (lymphocytes, neutrophils counts), SYSMEX data (IG: Immature granulocyte count; HFLC: high fluorescent lymphocyte count) ▪ Radiological data: ○ COVID-19 lung extension rate (minimal, moderate, extensive, severe, critical according French Radiology Society guidelines) • Resuscitation parameters ○ PaO2/FiO2 ratio at resuscitation admission ○ IGSII/SASPII score (simplified acute physiology score) at D1 of resuscitation entry and/or SOFA (sepsis-related organ failure assessment) score: a posteriori estimate based on IGSII/SASPII ○ Delay between the first signs of infection and admission to resuscitation (ii) Evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on: ▪ Medical management ○ in the Resuscitation unit ○ during total hospital stay ▪ Medical complications ○ Resuscitation unit ○ During hospital stay after resuscitation

BMJ Open

Risk factors associated with day-30 mortality in patients over 60 admitted in ICU for severe COVID-19: the Senior-COVID-Rea Multicentre Survey protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044449.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Mar-2021
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Geriatric medicine, Infectious diseases
Keywords:	COVID-19, INTENSIVE & CRITICAL CARE, GERIATRIC MEDICINE

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Risk factors associated with day-30 mortality in patients over 60 admitted in ICU for severe COVID-19: the Senior-COVID-Rea Multicentre Survey protocol

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Abstract

Introduction: With the spread of COVID-19 epidemic health plans must be adapted continuously. There is an urgent need to define the best care courses of COVID-19 patients, especially in intensive care units (ICU), according to their individualised benefit/risk ratio. Since older age is associated with poorer short- and long-term outcomes, prediction models are needed, that may assist clinicians in their ICU admission decision. Senior-COVID-Rea was designed to evaluate, in patients over 60 admitted in ICU for severe COVID-19 disease, the impact of age, geriatric and paraclinical parameters on their mortality 30 days after ICU admission.

Methods and analysis: This is a multicentre survey protocol to be conducted in 7 hospitals of the Auvergne-Rhône-Alpes region, France. All patients over 60 admitted in ICU for severe COVID-19 infection (or their legally acceptable representative) will be proposed to enter the study and to fill in a questionnaire regarding their functional and nutritional parameters 1 month before COVID-19 infection. Paraclinical parameters at ICU admission will be collected: lymphocytes and neutrophils counts, high-fluorescent lymphoid cells and immature granulocytes percentages (Sysmex data), D-dimers, CRP, LDH, creatinine, CT-scan lung extension rate as well as clinical resuscitation scores, and the delay between the first signs of infection and ICU admission. The primary outcome will be the overall survival at day 30 post-ICU admission. The analysis of factors predicting mortality at day 30 will be carried out using univariate and multivariate logistic regressions. Multivariate logistic regression will consider up to 15 factors.

The ambition of this trial, which takes into account the different approaches of geriatric vulnerability, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination: The study protocol was ethically approved. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT04422340.

Keywords: COVID-19; resuscitation; intensive care unit; age; frailty; Sysmex.

Article summary

Strengths and limitations of this study

- This study will provide a cross-sectional analysis of the impact of geriatric parameters, and particularly frailty according to CFS and Fried's criteria, on mortality at day 30 after ICU admission.
- This study will provide critical information regarding the personalised benefit/risk balance of ICU admission in patients over 60.
- These results will provide a factual illustration of a real-life situation.
- As knowledge and techniques regarding the management of COVID-19 patients change rapidly, mortality and ICU capacities may differ over time.
- Mortality rates will depend on the ICU techniques and local uses that may vary from one centre to another.

Introduction

Since the outbreak of the COVID-19 epidemic (2019, Wuhan, China), health plans have been continuously adapted in response to the emergency of the sanitary situation, especially regarding the intensive care units (ICU) capacities. The first studies were based on data from the Chinese population and demonstrated a more elevated incidence of COVID-19 infections in older people (≥60 years old) compared to younger people, as well as a higher frequency of severe forms of the disease (1) and therefore more theoretical indications of ICU admission. However, the first published data from the Hubei province suggested a low benefit of resuscitation for patients between 70 and 80 years old and a null benefit for patients over 80 (1). More recent data from Lombardy, Italy, reported a 41% mortality rate in patients over 70, 55% in patients over 80, and 100% in patients over 90, even though they admitted in ICU (2). Consequently, the individual benefit/risk balance of an orientation towards resuscitation for each age category should be considered in terms of quality of life and taking into account the limit unreasonable obstinacy.

So far, cardiovascular comorbidities, some laboratory parameters (LDH (3), creatinine, lymphocytes, neutrophils, TP, D-dimers (4), etc.), and the time between the symptom onset and the entry into resuscitation have been identified as covariates associated with resuscitation mortality. Cumulative evidence highlights the interest of some additional biological parameters extracted from extended complete blood cell count under fluorescence flow cytometry (SYSMEX data, (5–7)).

Another covariate classically proposed to predict patient outcomes is frailty. Frailty has been defined as a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability (8). Although some consensus has been reached regarding its definition, its operational criteria differ grossly between a multidomain view, according to which frailty is the

consequence of the addition of several deficits (9), and a phenotypical view, according to which prefrail and frail patients develop a specific phenotype related to malnutrition and sarcopenia (10). The Frailty Index – a scoring system according the cumulative deficits view of frailty – has been used in an Italian study from the COVID-19 Monza Team members to discriminate retrospectively the patients who recovered from those who either died or were transferred to ICU (11). Such results suggest that the outcomes of COVID-19 patients admitted to the hospital are better predicted by frailty than either age or comorbidities. The CFS (Clinical Frailty Score) enables the stratification of older patients into distinct levels of fitness using a rapid "at-a-glance" assessment (12). Using this score, the COVID-19 in Older People (COPE) European cohort study, mainly performed in the United Kingdom, was able to correlate frailty with the total mortality and the day-7 mortality in all patients admitted to hospital for COVID-19 infection (13). On March 20th, 2020, the United Kingdom's National Institute for Health and Care Excellence (NICE) published a COVID-19 Rapid Guideline (critical care). According to it, only patients with a CFS less than five should be considered for critical care (14), as this threshold was previously shown to predict a higher mortality in (non-COVID) older patients admitted in ICU (15).

However, the geriatric community promptly reacted to these guidelines, pointing out the risk of drift in assessing the CFS, designed to be performed by trained geriatricians (16,17) and the ethical dilemma of transforming the frailty spectrum into a binary covariate, considering that the inter-rater variability may be high between CFS scores 4 and 5 (17). Moreover, two studies evaluating the impact of CFS score in COVID-19 versus non-COVID-19 populations stated that CFS is not a good discriminator of prognosis in COVID-19 infected population (18,19).

Nevertheless, and independently of COVID-19, there has been growing interest in the specificities of the older population in ICUs, due to generally more deleterious short- and

long-term outcomes and the identification of predictive risk factors that may assist clinicians in their ICU admission decision (15,20,21).

In an intent to better define the individual benefit/risk ratio of ICU admission for each age category of patients, the objective of this multicentre observational study is to determine the clinical and laboratory covariates predictive of mortality among COVID-19 patients over 60 years old admitted in ICU and depending on their age. A specific attention will be paid to their functional and nutritional parameters (retrospective and declarative assessment) 1 month before infection.

Methods and analysis

Objectives

Primary objective

Evaluation of the impact of age on mortality at day 30 after admission to ICU.

Secondary objective

(i) Evaluation of the impact of the following co-variables on mortality at day 30: comorbidities 1 month prior to infection (grade ≥ 2, scored on the cumulative illness rating scale-geriatric [CIRS-G] (22)) and more specifically cardiac and vascular comorbidities (grade ≥ 2 on the CIRS-G); the functional status 1 month before infection, assessed by the caregiver using the CFS and the ADL (activity of daily living) (23) and IADL (instrumental ADL) (24) scores; nutritional data (weight at hospital and ICU admission, weight loss in the last 1 and 6 months before infection, presence of mild or severe anorexia); laboratory data at ICU admission (LDH, CRP, and creatinine levels, as well as lymphocytes and neutrophils count, and SYSMEX data [IG: immature granulocyte count; HFLC: high fluorescent lymphocyte count] (6-8)); chest imaging data (COVID-19 lung extension rated as minimal,

moderate, extensive, severe, or critical according to the French Radiology Society guidelines (25)); and resuscitation parameters at ICU admission (PaO2/FiO2 (arterial oxygen pressure/fraction of inspired oxygen) ratio, IGS II/SASP II (*indice de gravité simplifié II*/ simplified acute physiology score II (26)) and/or SOFA (sepsis-related organ failure assessment) score (*a posteriori* estimate based on IGS II/SASP II, (27)), and delay between the first signs of infection and admission to ICU(ii) Evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on: medical management in the ICU and during the total hospital stay; and on medical complications in the ICU and during the hospital stay after ICU discharge.

Study design

Senior-COVID-Rea is a retrospective and prospective multicentre study analysing data from patient charts. Patients were retrospectively included from the starting of COVID-19 pandemic in France (February 2020) to 10th April 2020, and prospectively from 10th April 2020. Data processing has been approved by the *Commission nationale de l'informatique et des libertés* (CNIL: French data protection commission). The study is registered on ClinicalTrials.gov under the number NCT04422340.

Study centres and participants

All patients over 60 admitted between February 2020 (the beginning of the COVID-19 outbreak in France) and 7th May, 2020 in ICUs from the Senior-COVID-Rea investigation centres (Hôpital Lyon Sud, Hôpital de la Croix-Rousse, Hôpital Edouard Herriot, and Hôpital Lyon Est from the *Hospices Civils de Lyon*, and the Médipôle Lyon-Villeurbanne, Hôpital Nord-Ouest Villefranche-sur-Saône, and Hôpital Emile Roux in Le Puy-en-Velay) are eligible for inclusion.

Inclusion criteria are: being aged 60 years or more, being admitted to an ICU, and having a COVID-19 diagnosis confirmed by RT-PCR or chest scanner. The sole exclusion criterion is refusal to participate in the study.

Individual information explaining the study will be given to the patients. Depending on their clinical condition, a waiver request is justified in accordance with the ICH (International council for harmonisation of technical requirements for pharmaceuticals for human use) harmonized guidelines for clinical practice of 9.11.2016: *"In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested"*). In accordance with the regulatory framework, information will be given to the patient's legally acceptable representative. The information leaflet will be given to patients as soon as they are able to read it; in the event of refusal to participate, the patient will be removed from the study.

Each included patient will be assigned an anonymous identification number.

Outcomes and measurements

Primary outcome

The primary outcome is the overall mortality at day 30 after admission in ICU.

Secondary outcomes

The secondary outcomes of the study are: (i) the mortality in ICU, (ii) the overall survival, the length of stay (in the ICU, in total, in a rehabilitation when applicable), (iii) the medical management in the ICU (high flow oxygen therapy, non-invasive ventilation, invasive ventilation, prone position, extracorporeal membrane oxygenation [ECMO], catecholamines, extra-renal purification, intermittent hemodialysis [IHD], continuous venovenous hemodiafiltration [CVVH], short-acting hypnotics, long-acting hypnotics, short-acting

analgesics, long-acting analgesics, dexmedetomidine or catapressan, neuroleptic for sedation [levomepromazine, cyamemazine], withholding or withdrawing life-sustaining treatments (specifying the limited intervention(s)), anti-infectious treatments [antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other], corticosteroids, nutrition [parenteral or enteral feeding, oral nutrition], physiotherapy [passive or active mobilisation, armchair bed transfer, edge of the bed sitting, armchair, verticalization]) and during the total hospital stay (oxygen therapy, anti-infectious treatments [antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other], corticosteroids, nutrition [parenteral or enteral feeding, oral nutrition], physiotherapy [passive or active mobilisation, walk]), and (iv) the medical complications in the ICU (acquired delirium or confusion, acquired neuropathy, acquired lung infections, catheter-related infections, bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, pulmonary embolism, swallowing disorders, congestion/trouble with ventilation, tracheotomy, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression, multiple intubations and their count, intra-hospital transports and their count) and during the hospital stay after resuscitation (delirium or confusion, post-resuscitation neuropathy, acquired lung infection(s), catheter-related infection(s), bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, swallowing disorders, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression).

Sample size calculation

To assess the effect of age on mortality in ICU, it is planned to compare mortality between patients under and over 70 years of age. Based on the results from a Chinese retrospective study (1), the hypothesis of the Senior-COVID-Rea study was the following: considering a single analysis variable (age), and an expected mortality of 30% for patients under 70 and 70% for

patients over 70 (patients over 70 years representing 40% of the study population), it will be necessary to include a total of 130 patients to show a statistically significant difference between these two groups with a power of 90% (bilateral alpha risk test of 5%). Since the analysis considers the integration of several factors, considering 15 factors, hoping for a coefficient of determination of 0.5 of the model, to achieve an optimism of less than 10%, it will be necessary to include 185 patients (criterion 1 of Riley, Snell *et al.* **(28)**).

After the publication of data on mortality in ICU from Lombardy, Italy in April 2020 (2), it was considered that closing the inclusion process after 185 inclusions would impair the statistical power of the study and induce a potential patient selection bias. As a consequence, the scientific committee decided on the 7th May, 2020 that all the patients admitted to ICU before that date - that corresponded to the end of the first COVID-19 wave in France – were eligible and proposed no limitation in terms of number of inclusions for this study. This sample size calculation was modified on Clinicaltrials.gov site accordingly (28th July, 2020).

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators who will decide whether the data should be corrected or considered as missing. All changes in the data will be notified.

The analyses will be carried out by an independent statistician using R (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

All the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the process of patient inclusion and exclusion (refusal to participate, patient's request to terminate participation in the study) during the trial time frame and the characteristics of the patients excluded.

The characteristics of the study population and the proportion of missing values will be reported. Patient characteristics will be expressed as mean (± standard deviation) or median [interquartile range] for quantitative variables and counts and percentages for categorical variables.

Primary analysis

The analysis of factors predicting mortality at day 30 will be carried out using univariate and multivariate logistic regressions. The multivariate logistic regression will consider up to 15 factors. In view of the results of the univariate analyses and the correlation between the factors studied, it will be decided which factors will be included in the multivariate analyses. Multicollinearity will be analysed by Venn diagram and variance inflation factors. The effect of each factor will be quantified and expressed as the odds ratio and the associated 95% confidence interval (95% CI).

Secondary analyses

The mortality proportion in ICU and the 95% confidence interval will be calculated for the two groups of patients (dead vs alive, and according to age). The overall survival will be described using Kaplan-Meier survival curves in these two groups; the mean and median length of stay in intensive care unit will also be reported.

The association of age and of the frailty scores (using cutoffs) with the medical management and medical complication outcomes will be quantified and expressed as odds ratio and the associated 95% CI in an exploratory analysis. In this context, no adjustment will be made for multiple testing.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures the compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

According to studies analysing data from patient charts, and according to French regulation, patients leave the study either on a per-protocol basis on day 30 after their admission in intensive care ward or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on 10th April, 2020. Data are being collected.

Patients' and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by a patients' association (EDS information notice model).

Discussion

Discussion of the study design

This study has an ethical stake in the evaluation of the risk/benefit balance of referring patients over 60 to intensive care procedures, according to their comorbidities and pre-infection functional state, as well as to the severity of the pathology at the time of care. Patients over 60 years old appear to be at risk of developing severe forms of COVID-19 infection. The identification of prognostic factors is a major issue for the personalisation of care of these patients.

More than chronological age, frailty appears as a good prognostic marker in response to variable stressors (29). Frailty has been previously demonstrated as a good prognostic marker of the ability to overcome resuscitation-associated stress in diverse contexts (30), as well as a predictive marker of complications during non-invasive mechanical ventilation (31), extubation failure (32), resources utilization (33), and poor functional recovery and long-term quality of life (34). Therefore, using frailty as a prognostic marker and as a tool for the adaptation of care management appears logical and ethical, especially in contexts of high stress, such as COVID-19 severe infections.

The ambition of this trial, which takes into account the different approaches of frailty, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination

The study sponsor is the *Hospices Civils de Lyon*. In response to the COVID-19 emergency and the regulation on health data, accrual started on 10th April, 2020. The study protocol (V1.0 of 7th April, 2020) was approved by an ethics committee (*Comité Scientifique et Éthique des Hospices Civils de Lyon*) on 30th June, 2020 and declared on ClinicalTrials platform on 9th June,

2020. The research will be carried out in accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills the SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect non-objection from patients and/or their relatives at the beginning of the procedure (Annexes 1 to 3, in French). This non-objection is logged in the patient's medical chart. The patient can withdraw his/her consent for participation in the study at any time with an oral information to the investigator or clinical research assistant.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count: 2857

Abbreviations

ADL: Activities of Daily Living; CIRS-G: Cumulative Illness Rating Scale – Geriatric; COVID-19: Coronavirus disease 2019; CFS: Clinical Frailty Score; CRA: Clinical Research Assistant; CVVH: Continuous VenoVenous Hemodiafiltration; ECMO: ExtraCorporeal Membrane Oxygenation; HFLC: High Fluorescent Lymphocyte Count; ICU: Intensive Care Unit; IG: Immature Granulocyte Count; IGS: Indice Gravité Simplifié; IHD: Intermittent HemoDialysis; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment.

Declarations

Acknowledgements

The authors acknowledge the research teams from the Senior-COVID-Rea investigation centres (Hôpital Lyon Sud, Hôpital de la Croix-Rousse, Hôpital Edouard Herriot, and Hôpital Lyon Est from the *Hospices Civils de Lyon*, and the Médipôle Lyon-Villeurbanne, Hôpital Nord-Ouest Villefranche-sur-Saône, and Hôpital Emile Roux in Le Puy-en-Velay) who contribute to the enrolment of patients in this study.

The authors would like to thank patients and their families to contribute to this research despite the urgent and stressful context. They also thank Hélène Boyer (DRCI, Hospices Civils de Lyon) for help in manuscript preparation.

Patient and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by patients' association (information notice model for health data studies).

Availability of data and materials

The final dataset of the Senior-COVID-Rea study will be available upon reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interest.

Consent for publication

Not applicable

Author contributions

All authors (CF, AM, MR, FS, JB, CB, JD, CR, LB, PA, VC, BB, SG, CG, EG, LA, DD, LJ, AL, JBP, AF, FT) participated to the Senior-COVID-Rea protocol conception. CF led the drafting of the manuscript. All authors critically reviewed and approved the final version of the protocol.

Funding statement

This work was supported by the *Hospices Civils de Lyon*, and was selected through an internal call for projects "COVID-19" (decision of the selection committee on 12th May, 2020). It provided partial funding for statistical analysis and clinical research assistants.

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Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2
Protocol version	3	Date and version identifier	12 (Ethics and dissemination)
Funding	4	Sources and types of financial, material, and other support	13 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2 (Authors' list) 13 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12 (Ethics and dissemination) 13 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 (Data management and statistical analyses) 10 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11 (End of protocol) And N/A (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A And 11 (Patients' and public involvement)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A (no visit – health data study)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10 (End of protocol)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethics and dissemination)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethics and dissemination) 11 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10 (Ethical and legal considerations)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	12 (Ethics and dissemination), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annexes 1 & 2 (in French)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov NCT04422340
Date of registration in primary registry	9th June, 2020
Secondary identifying numbers	
Source(s) of monetary or material support	Hospices Civils de Lyon
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
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Public title	Senior-COVID-Rea Multicentric Survey
Scientific title	Prognostic Criteria Associated With Survival in Patients Over 60 Admitted to ICU for Severe COVID Infection: the Senior-COVID-Rea Multicentric Survey
Countries of recruitment	France
Health condition(s) or problem(s) studied	Severe COVID
Intervention(s)	N/A
Key inclusion and exclusion criteria	Inclusion Criteria: • being aged 60 years or more • being admitted into a resuscitation unit (or an intensive care unit) • having a COVID-19 diagnosis established by RT-PCR and/or chest scanner Exclusion criterion: • Refusal of the patient or his/her caregiver to participate in the study
Study type	Cohort study Allocation: N/A Intervention model: Single Group Assignment

Data category	Information
	Masking: None (Open Label) Primary purpose: Prognostic model
Date of first enrolment	10th April, 2020
Target sample size	> 185
Recruitment status	Recruiting
Primary outcome(s)	Impact of age on mortality at day 30 after admission to intensive care.
Key secondary outcomes	(i) Impact on mortality at day 30 day of the following co-variables: ▪ Comorbidities (CIRS-G scale): total number of comorbidities grade ≥ 2 , and number of cardiac and vascular comorbidities grade ≥ 2 (1 month prior to infection)) ▪ Functional status 1 month before infection (information collected from the caregiver) ○ Clinical frailty scale ○ ADL score ▪ Nutritional data: weight change in the last 6 months ▪ Laboratory data at ICU admission ○ LDH, CRP, creatinine ○ Parameters from complete blood count (lymphocytes, neutrophils counts), SYSMEX data (IG: Immature granulocyte count; HFLC: high fluorescent lymphocyte count) ▪ Radiological data: ○ COVID-19 lung extension rate (minimal, moderate, extensive, severe, critical according to the French Radiology Society guidelines) • Resuscitation parameters at ICU admission ○ PaO2/FiO2 ratio ○ IGS II/SASP II score (simplified acute physiology score) and/or SOFA (sepsis-related organ failure assessment) score (*a posteriori* estimate based on IGS II/SASP II) ○ Delay between the first signs of infection and admission into ICU (ii) Evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on: ▪ Medical management

Data category	Information
	○ in the ICU ○ during total hospital stay ▪ Medical complications ○ during ICU stay ○ during hospital stay after ICU discharge

BMJ Open

Risk factors associated with day-30 mortality in patients over 60 admitted in ICU for severe COVID-19: the Senior-COVID-Rea Multicentre Survey protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044449.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Apr-2021
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Geriatric medicine, Infectious diseases
Keywords:	COVID-19, INTENSIVE & CRITICAL CARE, GERIATRIC MEDICINE

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Risk factors associated with day-30 mortality in patients over 60 admitted in ICU for severe COVID-19: the Senior-COVID-Rea Multicentre Survey protocol

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Abstract

Introduction: With the spread of COVID-19 epidemic health plans must be adapted continuously. There is an urgent need to define the best care courses of COVID-19 patients, especially in intensive care units (ICU), according to their individualised benefit/risk ratio. Since older age is associated with poorer short- and long-term outcomes, prediction models are needed, that may assist clinicians in their ICU admission decision. Senior-COVID-Rea was designed to evaluate, in patients over 60 admitted in ICU for severe COVID-19 disease, the impact of age, geriatric and paraclinical parameters on their mortality 30 days after ICU admission.

Methods and analysis: This is a multicentre survey protocol to be conducted in 7 hospitals of the Auvergne-Rhône-Alpes region, France. All patients over 60 admitted in ICU for severe COVID-19 infection (or their legally acceptable representative) will be proposed to enter the study and to fill in a questionnaire regarding their functional and nutritional parameters 1 month before COVID-19 infection. Paraclinical parameters at ICU admission will be collected: lymphocytes and neutrophils counts, high-fluorescent lymphoid cells and immature granulocytes percentages (Sysmex data), D-dimers, CRP, LDH, creatinine, CT-scan lung extension rate as well as clinical resuscitation scores, and the delay between the first signs of infection and ICU admission. The primary outcome will be the overall survival at day 30 post-ICU admission. The analysis of factors predicting mortality at day 30 will be carried out using univariate and multivariate logistic regressions. Multivariate logistic regression will consider up to 15 factors.

The ambition of this trial, which takes into account the different approaches of geriatric vulnerability, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination: The study protocol was ethically approved. The results of the primary and secondary objectives will be published in peer-reviewed journals. ClinicalTrials registration: NCT04422340.

Keywords: COVID-19; resuscitation; intensive care unit; age; frailty; Sysmex.

Article summary

Strengths and limitations of this study

- This study will provide a cross-sectional analysis of the impact of geriatric parameters, and particularly frailty according to CFS and Fried's criteria, on mortality at day 30 after ICU admission.
- This study will provide critical information regarding the personalised benefit/risk balance of ICU admission in patients over 60.
- Broad inclusion criteria and systematic screening will limit inclusion biases.
- As knowledge and techniques regarding the management of COVID-19 patients change rapidly, mortality and ICU capacities may differ over time.
- Differences in COVID-19 management may also differ depending on the different ICU teams.

Introduction

Since the outbreak of the COVID-19 epidemic (2019, Wuhan, China), health plans have been continuously adapted in response to the emergency of the sanitary situation, especially regarding the intensive care units (ICU) capacities. The first studies were based on data from the Chinese population and demonstrated a more elevated incidence of COVID-19 infections in older people (≥60 years old) compared to younger people, as well as a higher frequency of severe forms of the disease (1) and therefore more theoretical indications of ICU admission. However, the first published data from the Hubei province suggested a low benefit of resuscitation for patients between 70 and 80 years old and a null benefit for patients over 80 (1). More recent data from Lombardy, Italy, reported a 41% mortality rate in patients over 70, 55% in patients over 80, and 100% in patients over 90, even though they admitted in ICU (2). Consequently, the individual benefit/risk balance of an orientation towards resuscitation for each age category should be considered in terms of quality of life and taking into account the limit unreasonable obstinacy.

So far, cardiovascular comorbidities, some laboratory parameters (LDH (3), creatinine, lymphocytes, neutrophils, TP, D-dimers (4), etc.), and the time between the symptom onset and the entry into resuscitation have been identified as covariates associated with resuscitation mortality. Cumulative evidence highlights the interest of some additional biological parameters extracted from extended complete blood cell count under fluorescence flow cytometry (SYSMEX data, (5–7)).

Another covariate classically proposed to predict patient outcomes is frailty. Frailty has been defined as a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability (8). Although some consensus has been reached regarding its definition, its operational criteria differ grossly between a multidomain view, according to which frailty is the

consequence of the addition of several deficits (9), and a phenotypical view, according to which prefrail and frail patients develop a specific phenotype related to malnutrition and sarcopenia (10). The Frailty Index – a scoring system according the cumulative deficits view of frailty – has been used in an Italian study from the COVID-19 Monza Team members to discriminate retrospectively the patients who recovered from those who either died or were transferred to ICU (11). Such results suggest that the outcomes of COVID-19 patients admitted to the hospital are better predicted by frailty than either age or comorbidities. The CFS (Clinical Frailty Score) enables the stratification of older patients into distinct levels of fitness using a rapid "at-a-glance" assessment (12). Using this score, the COVID-19 in Older People (COPE) European cohort study, mainly performed in the United Kingdom, was able to correlate frailty with the total mortality and the day-7 mortality in all patients admitted to hospital for COVID-19 infection (13). On March 20th, 2020, the United Kingdom's National Institute for Health and Care Excellence (NICE) published a COVID-19 Rapid Guideline (critical care). According to it, only patients with a CFS less than five should be considered for critical care (14), as this threshold was previously shown to predict a higher mortality in (non-COVID) older patients admitted in ICU (15).

However, the geriatric community promptly reacted to these guidelines, pointing out the risk of drift in assessing the CFS, designed to be performed by trained geriatricians (16,17) and the ethical dilemma of transforming the frailty spectrum into a binary covariate, considering that the inter-rater variability may be high between CFS scores 4 and 5 (17). Moreover, two studies evaluating the impact of CFS score in COVID-19 versus non-COVID-19 populations stated that CFS is not a good discriminator of prognosis in COVID-19 infected population (18,19).

Nevertheless, and independently of COVID-19, there has been growing interest in the specificities of the older population in ICUs, due to generally more deleterious short- and

long-term outcomes and the identification of predictive risk factors that may assist clinicians in their ICU admission decision (15,20,21).

In an intent to better define the individual benefit/risk ratio of ICU admission for each age category of patients, the objective of this multicentre observational study is to determine the clinical and laboratory covariates predictive of mortality among COVID-19 patients over 60 years old admitted in ICU and depending on their age. A specific attention will be paid to their functional and nutritional parameters (retrospective and declarative assessment) 1 month before infection.

Methods and analysis

Objectives

Primary objective

Evaluation of the impact of age on mortality at day 30 after admission to ICU.

Secondary objective

(i) Evaluation of the impact of the following co-variables on mortality at day 30: comorbidities 1 month prior to infection (grade ≥ 2, scored on the cumulative illness rating scale-geriatric [CIRS-G] (22)) and more specifically cardiac and vascular comorbidities (grade ≥ 2 on the CIRS-G); the functional status 1 month before infection, assessed by the caregiver using the CFS and the ADL (activity of daily living) (23) and IADL (instrumental ADL) (24) scores; nutritional data (weight at hospital and ICU admission, weight loss in the last 1 and 6 months before infection, presence of mild or severe anorexia); laboratory data at ICU admission (LDH, CRP, and creatinine levels, as well as lymphocytes and neutrophils count, and SYSMEX data [IG: immature granulocyte count; HFLC: high fluorescent lymphocyte count] (6-8)); chest imaging data (COVID-19 lung extension rated as minimal,

moderate, extensive, severe, or critical according to the French Radiology Society guidelines (25)); and resuscitation parameters at ICU admission (PaO2/FiO2 (arterial oxygen pressure/fraction of inspired oxygen) ratio, IGS II/SASP II (*indice de gravité simplifié II*/ simplified acute physiology score II (26)) and/or SOFA (sepsis-related organ failure assessment) score (*a posteriori* estimate based on IGS II/SASP II, (27)), and delay between the first signs of infection and admission to ICU(ii) Evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on: medical management in the ICU and during the total hospital stay; and on medical complications in the ICU and during the hospital stay after ICU discharge.

Study design

Senior-COVID-Rea is a retrospective and prospective multicentre study analysing data from patient charts. Patients were retrospectively included from the starting of COVID-19 pandemic in France (February 2020) to 10th April 2020, and prospectively from 10th April 2020. Data processing has been approved by the *Commission nationale de l'informatique et des libertés* (CNIL: French data protection commission). The study is registered on ClinicalTrials.gov under the number NCT04422340.

Study centres and participants

All patients over 60 admitted between February 2020 (the beginning of the COVID-19 outbreak in France) and 7th May, 2020 in ICUs from the Senior-COVID-Rea investigation centres (Hôpital Lyon Sud, Hôpital de la Croix-Rousse, Hôpital Edouard Herriot, and Hôpital Lyon Est from the *Hospices Civils de Lyon*, and the Médipôle Lyon-Villeurbanne, Hôpital Nord-Ouest Villefranche-sur-Saône, and Hôpital Emile Roux in Le Puy-en-Velay) are eligible for inclusion.

Inclusion criteria are: being aged 60 years or more, being admitted to an ICU, and having a COVID-19 diagnosis confirmed by RT-PCR or chest scanner. The sole exclusion criterion is refusal to participate in the study.

Individual information explaining the study will be given to the patients. Depending on their clinical condition, a waiver request is justified in accordance with the ICH (International council for harmonisation of technical requirements for pharmaceuticals for human use) harmonized guidelines for clinical practice of 9.11.2016: *"In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested"*). In accordance with the regulatory framework, information will be given to the patient's legally acceptable representative. The information leaflet will be given to patients as soon as they are able to read it; in the event of refusal to participate, the patient will be removed from the study.

Each included patient will be assigned an anonymous identification number.

Outcomes and measurements

Primary outcome

The primary outcome is the overall mortality at day 30 after admission in ICU.

Secondary outcomes

The secondary outcomes of the study are: (i) the mortality in ICU, (ii) the overall survival, the length of stay (in the ICU, in total, in a rehabilitation when applicable), (iii) the medical management in the ICU (high flow oxygen therapy, non-invasive ventilation, invasive ventilation, prone position, extracorporeal membrane oxygenation [ECMO], catecholamines, extra-renal purification, intermittent hemodialysis [IHD], continuous venovenous hemodiafiltration [CVVH], short-acting hypnotics, long-acting hypnotics, short-acting

analgesics, long-acting analgesics, dexmedetomidine or catapressan, neuroleptic for sedation [levomepromazine, cyamemazine], withholding or withdrawing life-sustaining treatments (specifying the limited intervention(s)), anti-infectious treatments [antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other], corticosteroids, nutrition [parenteral or enteral feeding, oral nutrition], physiotherapy [passive or active mobilisation, armchair bed transfer, edge of the bed sitting, armchair, verticalization]) and during the total hospital stay (oxygen therapy, anti-infectious treatments [antibiotherapy lines, remdesivir, lopinavir/ritonavir, hydroxychloroquine, azithromycin, other], corticosteroids, nutrition [parenteral or enteral feeding, oral nutrition], physiotherapy [passive or active mobilisation, walk]), and (iv) the medical complications in the ICU (acquired delirium or confusion, acquired neuropathy, acquired lung infections, catheter-related infections, bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, pulmonary embolism, swallowing disorders, congestion/trouble with ventilation, tracheotomy, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression, multiple intubations and their count, intra-hospital transports and their count) and during the hospital stay after resuscitation (delirium or confusion, post-resuscitation neuropathy, acquired lung infection(s), catheter-related infection(s), bacteremia, pressure sore, necrosis of the extremities, deep vein thrombosis, swallowing disorders, joint stiffening, neurological deficit secondary to stroke, peripheral nerve compression).

Sample size calculation

To assess the effect of age on mortality in ICU, it is planned to compare mortality between patients under and over 70 years of age. Based on the results from a Chinese retrospective study (1), the hypothesis of the Senior-COVID-Rea study was the following: considering a single analysis variable (age), and an expected mortality of 30% for patients under 70 and 70% for

patients over 70 (patients over 70 years representing 40% of the study population), it will be necessary to include a total of 130 patients to show a statistically significant difference between these two groups with a power of 90% (bilateral alpha risk test of 5%). Since the analysis considers the integration of several factors, considering 15 factors, hoping for a coefficient of determination of 0.5 of the model, to achieve an optimism of less than 10%, it will be necessary to include 185 patients (criterion 1 of Riley, Snell *et al.* **(28)**).

After the publication of data on mortality in ICU from Lombardy, Italy in April 2020 (2), it was considered that closing the inclusion process after 185 inclusions would impair the statistical power of the study and induce a potential patient selection bias. As a consequence, the scientific committee decided on the 7th May, 2020 that all the patients admitted to ICU before that date - that corresponded to the end of the first COVID-19 wave in France – were eligible and proposed no limitation in terms of number of inclusions for this study. This sample size calculation was modified on Clinicaltrials.gov site accordingly (28th July, 2020).

Data management and statistical analyses

Data are monitored by a clinical research associate (CRA). Inconsistencies will be reported to the study investigators who will decide whether the data should be corrected or considered as missing. All changes in the data will be notified.

The analyses will be carried out by an independent statistician using R (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

All the characteristics collected will be subjected to a descriptive analysis.

Descriptive analyses

A flow-chart diagram will describe the process of patient inclusion and exclusion (refusal to participate, patient's request to terminate participation in the study) during the trial time frame and the characteristics of the patients excluded.

The characteristics of the study population and the proportion of missing values will be reported. Patient characteristics will be expressed as mean (± standard deviation) or median [interquartile range] for quantitative variables and counts and percentages for categorical variables.

Primary analysis

The analysis of factors predicting mortality at day 30 will be carried out using univariate and multivariate logistic regressions. The multivariate logistic regression will consider up to 15 factors. In view of the results of the univariate analyses and the correlation between the factors studied, it will be decided which factors will be included in the multivariate analyses. Multicollinearity will be analysed by Venn diagram and variance inflation factors. The effect of each factor will be quantified and expressed as the odds ratio and the associated 95% confidence interval (95% CI).

Secondary analyses

The mortality proportion in ICU and the 95% confidence interval will be calculated for the two groups of patients (dead vs alive, and according to age). The overall survival will be described using Kaplan-Meier survival curves in these two groups; the mean and median length of stay in intensive care unit will also be reported.

The association of age and of the frailty scores (using cutoffs) with the medical management and medical complication outcomes will be quantified and expressed as odds ratio and the associated 95% CI in an exploratory analysis. In this context, no adjustment will be made for multiple testing.

Data monitoring

The successful completion of the database is ensured by the hospital CRA. The hospital CRA also ensures the compliance with the study protocol. The sponsor CRA verifies that the rights of the participants are respected.

End of protocol

According to studies analysing data from patient charts, and according to French regulation, patients leave the study either on a per-protocol basis on day 30 after their admission in intensive care ward or at any time during the conduct of the study if they no longer wish to participate. However, as indicated in the information letter to the patients/caregivers, the data collected before exclusion may be used as part of the study.

Confidentiality

Correspondence tables will be kept in a separate file that does not contain clinical data. The access to the nominative information is protected by a password and confidentiality is guaranteed.

Protocol amendments

Any important modifications requiring a new ethics committee approval will be communicated in future publications. Any potential impact of protocol modifications on the results will be discussed as appropriate.

Trial status

Patient enrolment began on 10th April, 2020. Data are being collected.

Patients' and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by a patients' association (EDS information notice model).

Discussion

Discussion of the study design

This study has an ethical stake in the evaluation of the risk/benefit balance of referring patients over 60 to intensive care procedures, according to their comorbidities and pre-infection functional state, as well as to the severity of the pathology at the time of care. Patients over 60 years old appear to be at risk of developing severe forms of COVID-19 infection. The identification of prognostic factors is a major issue for the personalisation of care of these patients.

More than chronological age, frailty appears as a good prognostic marker in response to variable stressors (29). Frailty has been previously demonstrated as a good prognostic marker of the ability to overcome resuscitation-associated stress in diverse contexts (30), as well as a predictive marker of complications during non-invasive mechanical ventilation (31), extubation failure (32), resources utilization (33), and poor functional recovery and long-term quality of life (34). Therefore, using frailty as a prognostic marker and as a tool for the adaptation of care management appears logical and ethical, especially in contexts of high stress, such as COVID-19 severe infections.

The ambition of this trial, which takes into account the different approaches of frailty, is to define the respective abilities of different operational criteria of frailty to predict patients' outcomes.

Ethics and dissemination

The study sponsor is the *Hospices Civils de Lyon*. In response to the COVID-19 emergency and the regulation on health data, accrual started on 10th April, 2020. The study protocol (V1.0 of 7th April, 2020) was approved by an ethics committee (*Comité Scientifique et Éthique des Hospices Civils de Lyon*) on 30th June, 2020 and declared on ClinicalTrials platform on 9th June,

2020. The research will be carried out in accordance with the Helsinki Declaration and ICH GCP Guidelines. Trial protocol fulfills the SPIRIT 2013 checklist (Supplementary table 1) and World Health Organization Trial Registration Data Set (Supplementary table 2). The study complies with the principles of the data protection act in France and with the General Data Protection Regulations in force in Europe. Each investigator must collect non-objection from patients and/or their relatives at the beginning of the procedure (Annexes 1 to 3, in French). This non-objection is logged in the patient's medical chart. The patient can withdraw his/her consent for participation in the study at any time with an oral information to the investigator or clinical research assistant.

The results of the primary and secondary objectives will be published in peer-reviewed journals. All authors of future publications will have to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

Total words count: 2857

Abbreviations

ADL: Activities of Daily Living; CIRS-G: Cumulative Illness Rating Scale – Geriatric; COVID-19: Coronavirus disease 2019; CFS: Clinical Frailty Score; CRA: Clinical Research Assistant; CVVH: Continuous VenoVenous Hemodiafiltration; ECMO: ExtraCorporeal Membrane Oxygenation; HFLC: High Fluorescent Lymphocyte Count; ICU: Intensive Care Unit; IG: Immature Granulocyte Count; IGS: Indice Gravité Simplifié; IHD: Intermittent HemoDialysis; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment.

Declarations

Acknowledgements

The authors acknowledge the research teams from the Senior-COVID-Rea investigation centres (Hôpital Lyon Sud, Hôpital de la Croix-Rousse, Hôpital Edouard Herriot, and Hôpital Lyon Est from the *Hospices Civils de Lyon*, and the Médipôle Lyon-Villeurbanne, Hôpital Nord-Ouest Villefranche-sur-Saône, and Hôpital Emile Roux in Le Puy-en-Velay) who contribute to the enrolment of patients in this study.

The authors would like to thank patients and their families to contribute to this research despite the urgent and stressful context. They also thank Hélène Boyer (DRCI, Hospices Civils de Lyon) for help in manuscript preparation.

Patient and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The information notice was written according a model validated by patients' association (information notice model for health data studies).

Availability of data and materials

The final dataset of the Senior-COVID-Rea study will be available upon reasonable request after publication of the primary objective. Data requests can be submitted to the corresponding author.

Competing interest

The authors declare that they have no competing interest.

Consent for publication

Not applicable

Author contributions

All authors (CF, AM, MR, FS, JB, CB, JD, CR, LB, PA, VC, BB, SG, CG, EG, LA, DD, LJ, AL, JBP, AF, FT) participated to the Senior-COVID-Rea protocol conception. CF led the drafting of the manuscript. All authors critically reviewed and approved the final version of the protocol.

Funding statement

This work was supported by the *Hospices Civils de Lyon*, and was selected through an internal call for projects "COVID-19" (decision of the selection committee on 12th May, 2020). It provided partial funding for statistical analysis and clinical research assistants.

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Supplementary table 1: SPIRIT 2013checklist of the trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 2
Protocol version	3	Date and version identifier	12 (Ethics and dissemination)
Funding	4	Sources and types of financial, material, and other support	13 (Funding)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2 (Authors' list) 13 (Authors' contributions)
	5b	Name and contact information for the trial sponsor	Supplementary table 2

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12 (Ethics and dissemination) 13 (Funding)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 (Data management and statistical analyses) 10 (Data monitoring)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11 (End of protocol) And N/A (no dose modifications)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A And 11 (Patients' and public involvement)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A (no visit – health data study)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9 (Sample size calculation)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A (no problem for accrual)
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10 (End of protocol)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 (Data management and statistical analyses)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10 (Data management and statistical analyses)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10 (Data Monitoring)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10 (Ethics and dissemination)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10 (Ethics and dissemination) 11 (Protocol amendments)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10 (Ethical and legal considerations)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11 (Confidentiality)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13 (Competing interests)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13 (Availability of data and materials)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15 (Dissemination policy)
	31b	Authorship eligibility guidelines and any intended use of professional writers	12 (Ethics and dissemination), N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Annexes 1 & 2 (in French)

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary table 2: All items from the World Health Organization Trial Registration Data Set (SPIRIT item 2b)

Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov NCT04422340
Date of registration in primary registry	9th June, 2020
Secondary identifying numbers	
Source(s) of monetary or material support	Hospices Civils de Lyon
Primary sponsor	Hospices Civils de Lyon
Secondary sponsor(s)	
Contact for public queries	David Dayde, +33.4.78.86.37.74, david.dayde@chu-lyon.fr
Contact for scientific queries	Claire Falandry, +33.4.78.86.66.34, claire.falandry@chu-lyon.fr
Public title	Senior-COVID-Rea Multicentric Survey
Scientific title	Prognostic Criteria Associated With Survival in Patients Over 60 Admitted to ICU for Severe COVID Infection: the Senior-COVID-Rea Multicentric Survey
Countries of recruitment	France
Health condition(s) or problem(s) studied	Severe COVID
Intervention(s)	N/A
Key inclusion and exclusion criteria	Inclusion Criteria: • being aged 60 years or more • being admitted into a resuscitation unit (or an intensive care unit) • having a COVID-19 diagnosis established by RT-PCR and/or chest scanner Exclusion criterion: • Refusal of the patient or his/her caregiver to participate in the study
Study type	Cohort study Allocation: N/A Intervention model: Single Group Assignment

Data category	Information
	Masking: None (Open Label) Primary purpose: Prognostic model
Date of first enrolment	10th April, 2020
Target sample size	> 185
Recruitment status	Recruiting
Primary outcome(s)	Impact of age on mortality at day 30 after admission to intensive care.
Key secondary outcomes	(i) Impact on mortality at day 30 day of the following co-variables: ▪ Comorbidities (CIRS-G scale): total number of comorbidities grade ≥ 2 , and number of cardiac and vascular comorbidities grade ≥ 2 (1 month prior to infection)) ▪ Functional status 1 month before infection (information collected from the caregiver) ○ Clinical frailty scale ○ ADL score ▪ Nutritional data: weight change in the last 6 months ▪ Laboratory data at ICU admission ○ LDH, CRP, creatinine ○ Parameters from complete blood count (lymphocytes, neutrophils counts), SYSMEX data (IG: Immature granulocyte count; HFLC: high fluorescent lymphocyte count) ▪ Radiological data: ○ COVID-19 lung extension rate (minimal, moderate, extensive, severe, critical according to the French Radiology Society guidelines) • Resuscitation parameters at ICU admission ○ PaO2/FiO2 ratio ○ IGS II/SASP II score (simplified acute physiology score) and/or SOFA (sepsis-related organ failure assessment) score (*a posteriori* estimate based on IGS II/SASP II) ○ Delay between the first signs of infection and admission into ICU (ii) Evaluation of the impact of age and frailty scores (CFS and Fried's frailty score) on: ▪ Medical management

Data category	Information
	○ in the ICU ○ during total hospital stay ▪ Medical complications ○ during ICU stay ○ during hospital stay after ICU discharge