



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



The importance of revealing data on limitation of life sustaining therapy in critical ill elderly Covid-19 patients

Hans Flaatten, MD PhD^{a,*}, Bertrand Guidet, MD^b, Dylan W. de Lange, MD PhD^c, Michael Beil, MD PhD^d, Susannah K. Leaver, MD PhD^e, Jesper Fjølner, MD^f, Peter Vernon van Heerden, MD PhD^g, Sviril Sigal, MD^h, Wojciech Szczeklik, MDⁱ, Christian Jung, MD PhD^j

^a Department of Anaesthesia and Intensive Care Medicine, Haukeland University Hospital, Bergen, Norway

^b Hôpital Saint-Antoine, Service de Réanimation, GRC Respire SU, Paris, France

^c Department of Intensive Care Medicine, University Medical Center, University Utrecht, Utrecht, the Netherlands

^d Hadassah University Hospital, Intensive Care, Jerusalem, Israel

^e Department of Adult Critical Care, St George's Healthcare NHS Foundation Trust, London, UK

^f Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark

^g General Intensive Care Unit, Hadassah-Hebrew University Hospital, Jerusalem, Israel

^h MPH Medical Intensive Care Unit, Hadassah-Hebrew University Hospital, Jerusalem, Israel

ⁱ Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland

^j Department of Cardiology, Pulmonary Diseases, and Vascular Medicine, Medical Faculty, Heinrich Heine University of Duesseldorf, Germany

1. Introduction

There is a strong link between limiting life-sustaining treatments (LST) and short-term outcomes, as is illustrated in a recent publication in this journal from Germany [1].

Once a patient has been admitted to the intensive care unit (ICU), limitation of LST is frequently discussed and applied. In the current pandemic, such information is of particular importance given the ongoing discussions in many countries about triage of (elderly) COVID-19 patients [2].

In this short communication we present data on the impact of limitation of LST on the outcome of elderly COVID-19 patients in Europe.

2. Methods

During the present COVID-19 pandemic we conducted a prospective multicentre observational study in elderly patients (≥ 70 years) with COVID-19 who were admitted to ICUs in Europe ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04321265) ID: NCT04321265) [3]. The main aim was to analyse the ICU, 30-day and 90-day mortality rates. We also recorded limitation of LST during the ICU stay, either as withholding or withdrawal of active treatment. No common definition of limitation of LST was applied as each ICU followed

Abbreviations: LST, life sustaining therapy; OR, Odds ratio; VIP, Very old Intensive care Patients studies; PCR, polymerase chain reaction; CFS, Clinical Frailty Scale; SOFA, Sequential Organ Failure Assessment.

* Corresponding author at: Haukeland University Hospital, Dep of Anesthesia and Intensive Care, N-5021 Bergen, Norway.

E-mail addresses: hans.flaatten@uib.no (H. Flaatten), bertrand.guidet@aphp.fr (B. Guidet), deLange-3@umcutrecht.nl (D.W. de Lange), beil@doctors.org.uk (M. Beil), susannahleaver@nhs.net (S.K. Leaver), jesperfjolner@clin.au.dk (J. Fjølner), vernon@hadassah.org.il (P.V. van Heerden), Sigals1@hadassah.org.il (S. Sigal), wojciech.szczeklik@uj.edu.pl (W. Szczeklik), jungc@uni-duesseldorf.de (C. Jung).

national guidelines. Patients were included in the study if they had a PCR-verified SARS-CoV-2 infection and if their age was ≥ 70 years. A pre-defined list of variables was collected at admission: comorbidities, frailty using the Clinical Frailty Scale (CFS) organ dysfunction (SOFA score) and medication [4]. We also collected information on usual ICU procedures such as mode of ventilation, cardiovascular and renal support. Patients with complete data on treatment limitations, frailty and 30-day survival were included in this study.

3. Results

The study included 1266 patients with a mean age of 75 years, from 138 ICUs in 28 countries, admitted between 19th March and 26th May 2020. [Table 1](#) shows data subdivided into two subgroups according to the presence or absence of limitation of LST during the ICU admission. Patients with limitation of LST were older, with a higher SOFA score and were more often frail (CFS of 4 or more). The overall 30-day mortality for the entire patient cohort was 43%. The number of patients, where limitation of LST was applied, was 466 (37%), most frequently due to withholding LST. The 30-day mortality of elderly patients with limitation of LST was 79%, where as the mortality of patients without such limitations was 23%. The cumulative number of deaths until day 90 in each group is shown in [Fig. 1](#) as unadjusted Kaplan Meier survival curves.

4. Discussion

In this large international study, we found that the crude mortality in elderly patients with covid-19 is hugely influenced by the application of limitation of LST. This is not unexpected, and while several confounding factors are undoubtedly at play, the bottom line is that applying limitations on LST is strongly associated with outcome. Hence, the absence of

Table 1
Data on patients with (LST+) and without (LST-). Data given as median and IQR or %.

Group	LST+	LST-
N	466 (37%)	800 (64%)
Age (year)	76 (73–80)	74 (72–77)
ICU LOS (days)	11 (4.8–21.2)	11.3 (5–22.9)
SOFA score	6 (3–8)	5 (3–8)
Frailty (CFS ≥ 4) ¹	61%	39%
Diabetes	160 (25%)	294 (37%)
Pulmonary Disease	114 (24%)	186 (23%)
Chronic heart failure	78 (17%)	117 (15%)
Hypertension	304 (85%)	464 (58%)
Mortality 30d ²	79%	23%
Mortality 90d ³	86%	32%

^{1,2,3} $p < 0.0001$.

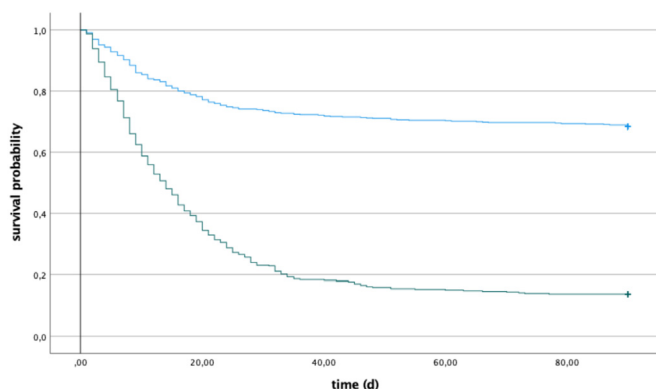


Fig. 1. Kaplan Meyer survival curves: Patients with limitation of LST (LST+, bottom curve) and no limitation (LST-, upper curve).

such information in current published COVID-19 studies on outcome is surprising, especially in critically ill old patients. In fact, we have not found any recent major studies on outcome during the present pandemic where a detailed description of the use of limitation of LST is given [4,5]. This issue was neither revealed nor discussed in a recent meta-analysis. This is probably as the majority of studies included (91%) were retrospective in nature and medical records rarely document limitation of LST [6]. Limitation of LST is considered a controversial issue with a number of cultural challenges. It is therefore difficult to study and might be left out in order not to complicate the analysis. This is illustrated by the fact that there is a large variation between (European) countries in how often limitation of LST is instigated [7]. Additionally, the implementation of LST have been shown to change over time and was reported recently to have increased in some countries [8].

5. Conclusion

Limitation of LST was frequently found in this large European population of critically ill elderly COVID-19 patients and was strongly linked with mortality. We therefore would encourage the research community to reveal the use of limitation of LST in all cohort studies of critically ill

patients where the main objective is outcome. Without such data it is difficult to assess the association of any other ICU variable or treatment modality in relation to short term outcomes. Both our data and the study by Bruno et al. [1] in this journal are a reminder of this.

Ethics approval and consent to participate

The study was carried out in 28 countries, mainly European, and each country received permission from national or regional research ethical committees and informed consent, when necessary.

Availability of data and materials

The dataset used and analysed during the study can be made available from the corresponding author on reasonable request.

Funding

This study was supported in France by a grant from Fondation Assistance Publique-Hôpitaux de Paris pour la recherche. In Norway, the study was supported by a grant from the Health Region West. In addition, the study was funded by a grant from the European Open Science Cloud (EOSC), EOSCsecretariat.eu has received funding from the European Union's Horizon Programme call H2020-INFRAEOSC-05-2018-2019, grant Agreement number 831644.

Declaration of Competing Interest

All authors declare no conflict of interest.

Acknowledgement

The COVIP study group including all national and local investigators from 138 ICUs are thanked for their continuing support during the present pandemic.

References

- [1] Bruno RR, Wernly B, Beil M, et al. Therapy limitation in octogenarians in German intensive care units is associated with a longer length of stay and increased 30 days mortality: A prospective multicenter study. *J Crit Care.* 2020;60:58–63. <https://doi.org/10.1016/j.jccr.2020.07.024>.
- [2] DeJong C, Chen AH, Lo B. An ethical framework for allocating scarce inpatient medications for COVID-19 in the US. *JAMA.* 2020;323(23):2367–8.
- [3] Jung C, Flaatten H, Fjølner J, et al. The impact of frailty on survival in elderly intensive care patients with COVID-19—the COVIP Study. *Crit Care.* 2021;25(149). <https://doi.org/10.21203/rs.3.rs-245592/v1>.
- [4] Richardson S, JS Hirsch JS, M Narasimhan, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the new York City area. *JAMA.* 2020;323(20):2052–9.
- [5] Hewitt J, Carter B, Vilches-Moraga A, et al; COPE study collaborators. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health.* 2020;8:e444–51.
- [6] Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: A comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. *PLoS One.* 2020;15(12):e0243191.
- [7] Guidet B, Flaatten H, Boumendil A, et al. Withholding or withdrawing of life-sustaining therapy in older adults (≥ 80 years) admitted to the intensive care unit. *Intensive Care Med.* 2018 May 17;43(1–11):1–12.
- [8] Sprung CL, Ricou B, Hartog CS, et al. Changes in end-of-life practices in European intensive care units from 1999 to 2016. *JAMA.* 2019;322(17):1–12.