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# Biased and unbiased estimation of the average length of stay in intensive care units in the Covid-19 pandemic

Nathanael Lapidus<sup>1\*</sup>, Xianlong Zhou<sup>2,3</sup>, Fabrice Carrat<sup>1</sup>, Bruno Riou<sup>4</sup>, Yan Zhao<sup>2,3</sup>  
and Gilles Hejblum<sup>5</sup>

## Abstract

**Background:** The average length of stay (LOS) in the intensive care unit (ICU\_ALOS) is a helpful parameter summarizing critical bed occupancy. During the outbreak of a novel virus, estimating early a reliable ICU\_ALOS estimate of infected patients is critical to accurately parameterize models examining mitigation and preparedness scenarios.

**Methods:** Two estimation methods of ICU\_ALOS were compared: the average LOS of already discharged patients at the date of estimation (DPE), and a standard parametric method used for analyzing time-to-event data which fits a given distribution to observed data and includes the censored stays of patients still treated in the ICU at the date of estimation (CPE). Methods were compared on a series of all COVID-19 consecutive cases ( $n = 59$ ) admitted in an ICU devoted to such patients. At the last follow-up date, 99 days after the first admission, all patients but one had been discharged. A simulation study investigated the generalizability of the methods' patterns. CPE and DPE estimates were also compared to COVID-19 estimates reported to date.

**Results:** LOS  $\geq 30$  days concerned 14 out of the 59 patients (24%), including 8 of the 21 deaths observed. Two months after the first admission, 38 (64%) patients had been discharged, with corresponding DPE and CPE estimates of ICU\_ALOS (95% CI) at 13.0 days (10.4–15.6) and 23.1 days (18.1–29.7), respectively. Series' true ICU\_ALOS was greater than 21 days, well above reported estimates to date.

**Conclusions:** Discharges of short stays are more likely observed earlier during the course of an outbreak. Cautious unbiased ICU\_ALOS estimates suggest parameterizing a higher burden of ICU bed occupancy than that adopted to date in COVID-19 forecasting models.

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**Keywords:** COVID-19, Pandemics, Intensive care units, Statistical models, China

## Introduction

The spread of a novel coronavirus (SARS-CoV-2) has brought about a pandemic referred to as the COVID-19

pandemic [1]. This pandemic has resulted in a worldwide crisis with unprecedented decisions of restrictive non-pharmacological mitigation interventions taken at local, regional, or national levels. A major aim of these measures is lessening as much as possible the daily number of new individuals requiring an admission in intensive care units (ICU) in order to be able to appropriately manage them in the healthcare system and sustain an appropriate management for the rest of

\*Correspondence: nathanael.lapidus@inserm.fr

<sup>1</sup> Sorbonne Université, INSERM, Institut Pierre Louis D'Épidémiologie Et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Unité de Santé Publique, 27 Rue Chaligny, 75571 Paris Cedex 12, France  
Full list of author information is available at the end of the article

the population [2]. A fast inflow of new admissions in the ICU has critical consequences within a short time. For example, between March 19 and April 2 2020 in France, the number of ICU beds occupied by COVID-19 infected persons dramatically increased from 1002 to 6305 [3], corresponding to an average daily increase of 14% additional beds. Such a situation requires a massive and rapid increase of ICU facilities and the French Minister of Health announced on March 28 that the nationwide capacity had been increased from 5000 to 10,000 critical beds [4]. The underlying mathematics are simple: an average unbalanced increase of 15% during 14 days implies that at day 14, the resulting occupancy would be that of day 0 multiplied by a factor 7.08 since  $1.15^{(14 \text{ days})} = 7.08$ . The system is highly sensitive to a sustained unbalance: even an average increase as low as 2% during 2 weeks, a likely situation after outbreak peak, would nevertheless require increasing occupancy at day 14 by 32%.

The average length of stay (ALOS) in ICU is an important estimate relating to the stability of the healthcare system in terms of ICU bed occupancy. For instance, hypothesizing an ICU ALOS of 10 days in patients infected with a new emerging agent, the daily probability of a bed discharge would be  $1/\text{ALOS} = 1/10 = 0.10$ . This implies that whenever the rate of required admissions would exceed the 10% ALOS-dependent threshold, the global number of beds occupied or required would increase and possibly overwhelm capacity.

This example demonstrates that estimating the ICU ALOS of a population infected by an emergent virus constitutes a very critical information to modelers and decision-makers for guiding adaptations of the local capacities in the context of the outbreak. Such an estimate is expected to be provided as soon as possible. However, when examining the situation within a short delay after the beginning of the outbreak, only few cases are likely to be already discharged from the ICU. The patients still in ICU referred to as censored cases must be considered in any unbiased estimation relating to the length of stay (LOS). In this study, we present a detailed examination of the timeline of the whole cohort of consecutive COVID-19 patients admitted to a devoted ICU of the Zhongnan hospital of Wuhan University (ZHWU) in which we investigated the evolution of the ALOS estimation according to the accumulation of the cases, using two methods of estimation. Our results indicate that even considering a last follow-up date corresponding to the date when two-thirds of the admitted patients would have been discharged, the ICU ALOS estimated with the biased method would be nearly half of that issued from the unbiased method.

In the light of these investigations, the estimates relating to ICU LOS of COVID-19 cases that have been reported to date [5–8], likely underestimate the real values. Such estimates being also used in forecasting models [9–13], the present study has practical implications for improving prediction scenarios to guide public decision.

## Methods

### Ethics

This study was approved by the Medical Ethics Committee, ZHWU (Clinical Ethical Approval No. 2020005). The informed consent was waived by the Medical Ethics Committee for emerging infectious disease.

### Setting

As in many locations, the organization of the ZHWU (Hubei province, People's Republic of China) for managing COVID-19 patients was subjected to several changes during the course of the COVID-19 outbreak. First, on December 30 2019, at a time when the outbreak emerged frankly, two initial ICU, one depending on emergency and the other from surgery, were reorganized for constituting a single entity of 31 beds devoted to the management of patients with COVID-19 requiring critical care. Second, on March 12 2020, at a time when the outbreak had declined, all COVID-19 ICU patients were transferred to another ICU in Leishenshan hospital, the largest newly built facility for COVID-19 patients with 1600 beds, while ICU admissions were reorganized for other pathologies than COVID-19 at ZHWU. Third, on April 15, Leishenshan hospital was definitively closed and patients initially admitted at ZHWU were retransferred to this hospital.

### Patients

All consecutive patients with a confirmed diagnosis of COVID-19 by PCR and initially admitted to the above-mentioned ICU of 31 beds at ZHWU from December 30 2019 to March 12 2020 ( $n = 57$ ) were included in the study. Patients admitted to this ICU during this period also included 10 consecutive patients for which there was a radiological evidence of viral pneumonia [14] while RT-PCR test of throat swabs had remained negative for several times, and these patients were also considered as eligible for the study. Last follow-up of patients was made on April 8 2020, 91 and 34 days after the first and the last admission, respectively. The file of each patient along his/her hospital course was cautiously reviewed, including whenever the patient was transferred to another hospital. The following data were collected for each patient: age, sex, date of admission and discharge in the hospital as well as the vital status at discharge (dead or alive), date

of admission and discharge in the ICU as well as the vital status at discharge (dead or alive), beginning and end dates of mechanical invasive or noninvasive ventilation procedures. Whenever a patient was transferred from the ICU in a given hospital to the ICU of another hospital, we considered that such a continuum constituted a single ICU stay.

Since the objective of this study was an assessment of the ALOS in ICU of COVID-19 patients, 8 of the above-mentioned 67 stays were excluded from the analysis: first, one of the 57 patients with a confirmed RT-PCR positive test had contracted COVID-19 at the hospital while this patient was hospitalized for post-complications after a kidney transplantation, and the record file highly suggested an ICU stay relating more to these complications than to COVID-19 infection. Conversely, only three of the ten patients with the radiological evidence of viral pneumonia were included in the analysis: seven patients had clinical characteristics suggesting that the ICU stay might be not mainly related to COVID-19 (e.g., liver lesions, massive cerebral infarction, ...), and were therefore excluded from the study.

### Statistical analyses

Data are expressed as mean (95% confidence interval (CI)) or median [interquartile range (IQR)], and represented according to the Kaplan–Meier estimator [15]. In addition, we examined how the ICU ALOS estimates of COVID-19 patients issued from two estimation methods evolve and compare while the cumulative number of available stays increases along the course of the outbreak. All analyses were made with R statistical software version 3.6.1 and censored data were fitted with the use of the *flexsurv* package. The two methods compared were the following.

#### Discharged patients' estimation (DPE)

This first method applies a straight-forward calculation: all ICU stays of the series for which the discharge date is before or equal to a given follow-up date of interest were considered (and only such stays were considered). Reported ALOS estimate was the mean LOS of those already discharged patients. Reported LOS median and quartiles were calculated on the same patients.

#### Censored patients' estimation (CPE)

This second method takes into account the inherent censored characteristic of longitudinal data: considering a given follow-up date of estimation, all previously admitted patients were considered, whether or not they were already discharged. A parametric distribution (e.g., exponential, gamma or Weibull) was fitted to the whole set of patients. Such a method for appropriately

analyzing time-to-event censored data belongs to the standard framework of methods of survival analysis [15, 16]. Reported ALOS estimates, as well as LOS medians and quartiles, are predictions based on this parametric model.

#### Additional comparisons

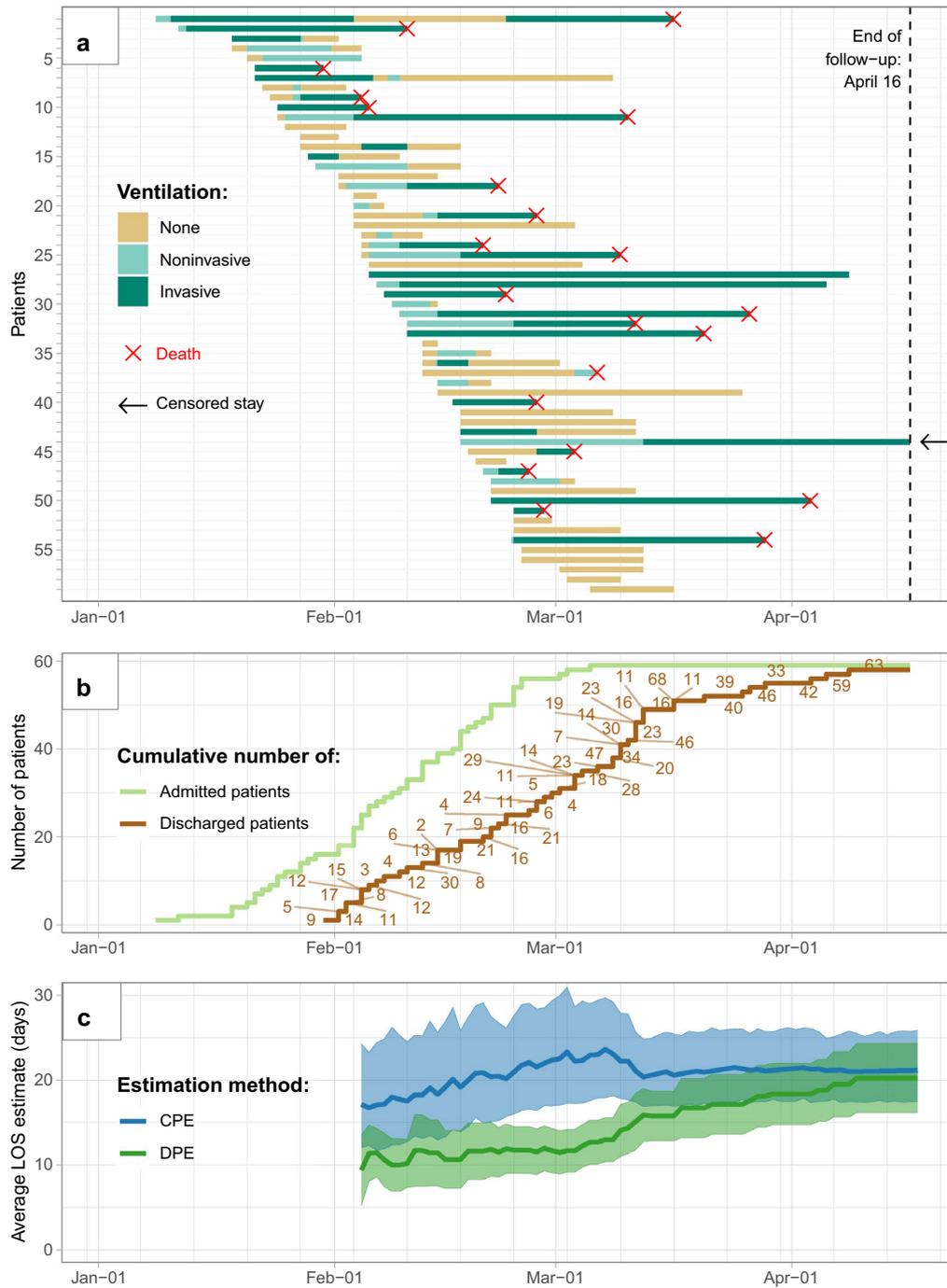
In order to demonstrate the generalizability of our results, these two methods were also compared using two simulation studies. Both considered a 30-bed ICU with as many patients admitted on day 0 and new patients admitted as soon as the previous ones were discharged. In the first study, simulated LOS were sampled with replacement from the 59 observed LOS in ZHWU. Such a simulation allows to be free from the observed schedule in practice, including the order of occurrence of the lengths of stay observed. The simulation forces the ICU to be initiated in an already saturated functioning admitting COVID-19 patients. The LOS of the patient still in the ICU at the date of last follow-up was imputed. In the second study, LOS were sampled from a parametric gamma distribution in order to explore how estimates evolve with time in a situation where the true distribution is known.

### Results

The median age of the patients was 62 years [IQR 52–70] and 38 (64%) were men. The time-course of the ICU stays of the 59 COVID-19 patients is shown in Fig. 1a. At the date of last follow-up, April 16, one patient was still in the ICU, 21 deaths (36%) had occurred in the ICU, and the 37 patients discharged alive from the ICU were also all discharged alive from the hospital.

Invasive mechanical ventilation procedures concerned 40 (68%) patients: stays involving only noninvasive ventilation concerned 11 patients, stays involving only mechanical invasive ventilation concerned 12 patients, and 17 patients had shifted from one type of ventilation to another during the course of their stay. The mean and median estimates for the duration of mechanical invasive ventilation was 21.6 days (95% CI 15.4–28.7) and 12.0 days [IQR 8.5–31 days], respectively. The corresponding estimates for noninvasive ventilation were 5.6 days (95% CI 3.9–7.8) and 3.5 [IQR 1.9–3.0], respectively.

Figure 1b shows the cumulative number of admissions and discharges according to time. At the date of last follow-up, over 3 months (99 days) had passed since the date of the first admission, January 8. Figure 1c shows the evolution of DPE and CPE-based ALOS estimates according to the accumulating data that become available as time passes. Exponential,



**Fig. 1** Timeline of the 59 COVID-19 cases treated in the intensive care unit (ICU). **a** For each case are plotted admission and discharge dates, periods of ventilation, and vital status at discharge. **b** Cumulative numbers of admissions and discharges according to time, with discharged patients' lengths of stay (LOS). **c** Evolution of the estimates of ICU average LOS issued from the two methods of estimation according to the date chosen for estimation. The expected estimate is shown together with the corresponding 95% confidence interval. CPE, method including censored cases; DPE, method considering only stays for which the patient was already discharged from ICU at the date of estimation. Whenever some patients of the cohort remain treated in the ICU at the date of follow-up, **c** indicates that DPE yields a biased underestimation of ALOS: discharges observed early are more likely to concern patients with a short LOS or conversely, the discharges occurring at the end of the process are more likely to concern patients with a long LOS. **b** illustrates the latter pattern: nine out of the 10 first occurring discharges concern LOS < 15 days, while eight out of the 10 last occurring discharges concerned LOS > 30 days

Weibull, and gamma distributions led to similar fits of the data—with a delayed convergence for the exponential distribution—and we retained the gamma distribution for reporting CPE. On February 8, 1 month after the first admission date, 11 (19%) patients had been discharged from the ICU and the corresponding estimate of ALOS with DPE was 18.0 days (95% CI 12.2–27.0), nearly twice that of DPE which was 10.0 days (95% CI 6.9–13.1). On March 8, 2 months after the first admission date, 38 (64%) patients had been discharged and the estimate of ALOS issued from DPE and CPE at that date was 13.0 days (95% CI 10.4–15.6) and 23.1 days (95% CI 18.1–29.7), respectively. Under the assumption that the parametric distribution used in CPE is well fitted to the data, the two methods should converge towards a similar estimate when no censoring data remain, i.e., when all patients of the cohort have been discharged: while only one patient remained in the ICU at the last date of follow-up, April 16, ALOS with CPE and DPE was 21.1 days (95% CI 17.5–25.3) (which constitutes the most accurate estimate on the study data set) and 20.2 days (95% CI 16.2–24.3), respectively. CPE estimate of hospital ALOS was 30.6 days (95% CI 26.2–35.3) and median duration of hospital LOS was 27.0 days [IQR 16.5–39.0]. Whenever some patients of the cohort remain treated in the ICU at the date of follow-up, DPE yields a biased underestimation of ALOS: discharges observed early are more likely to concern patients with a short LOS or conversely, the discharges occurring at the end of the process are more likely to concern patients with a long LOS. Figure 1b, in which the LOS corresponding to each discharged patient is indicated along the discharge curve, illustrates this pattern: 9 out of the 10 first occurring discharges concern LOS < 15 days, while eight out of the 10 last occurring discharges concerned LOS > 30 days. In the end, the simulations shown in Additional file 1: Appendix S1 demonstrate the generalizability of the biased pattern of DPE, and the unbiased pattern of CPE.

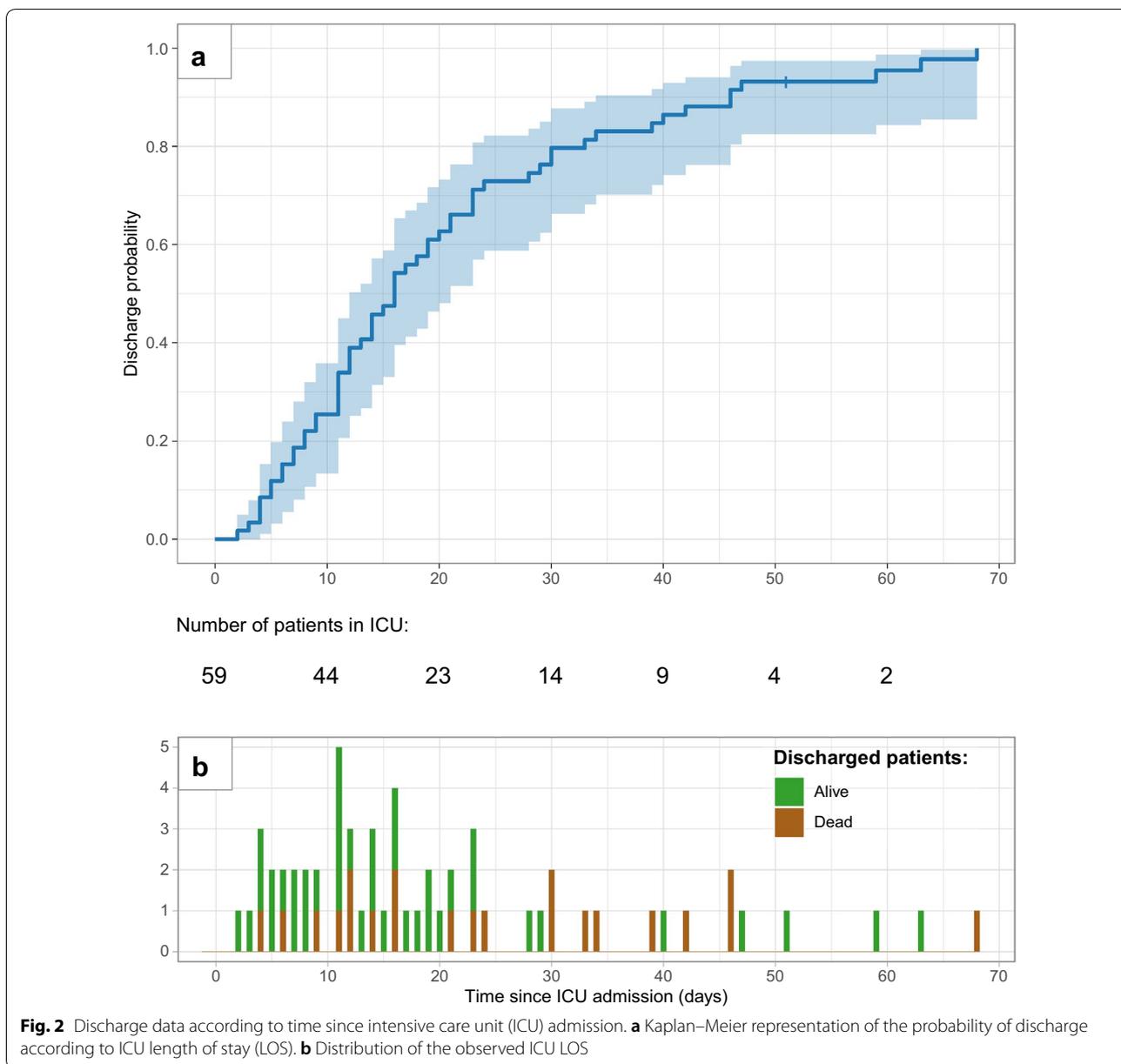
Figure 2a presents a Kaplan–Meier estimator and indicates that the median ICU LOS is around 16 days. The corresponding estimate issued from CPE is slightly higher, at 17.4 days, because the corresponding parametric fit is impacted by the substantial frequency of very long stays: Fig. 2b shows the LOS distribution and 14 out of the 59 patients (24%) had a length of stay  $\geq 30$  days. The relatively high frequency of such patients with a very long LOS explains why the expected estimates of ALOS shown in Fig. 1c requires a substantial delay until remaining stable. Interestingly, among the 14 patients with a LOS  $\geq 30$  days, 8 had died while the total number of observed deaths in the cohort was 21. The fact that 38% (8/21) of the deaths observed

occurred in patients who had an ICU stay  $\geq 30$  days also indicates that obtaining a reliable estimate of the mortality rate in the patients admitted to the ICU as well as obtaining a reliable ALOS of the individuals dying in the ICU also requires waiting a substantial delay after the beginning of the outbreak.

## Discussion

Taking the COVID-19 outbreak as an emblematic example of the first outbreak of a threatening pandemic due to a novel infectious agent, the present study demonstrates the importance of obtaining a reliable estimate of the ICU ALOS in such situations. The study also recalls that appropriate methods of estimation require the inclusion of censored cases in the analysis, and we also demonstrate the important bias associated with calculations only based on the stays of already discharged patients. Importantly, the bias inherent of the latter method is not at all sensitive to sample size or to the consideration of factors potentially associated with ICU ALOS value (e.g., variability from one center to another). For example, whatever the number of patients and the variability of the numerous centers involved in the studies of Guan et al. [17] based on National data from China and in the study of Grasselli et al. [5] based on 72 hospitals from Lombardy mentioned in Table 1, the provided estimates were biased. Finally, whenever patients of the population treated in the ICU with a long LOS are observed at a substantial frequency, as was observed in the present reported series, the bias relating to inappropriate methods might be especially important.

Although the present study shows that ALOS constitutes an important parameter, we failed to find any observational study of COVID-19 cases published in the early phase of the epidemic that reported ALOS. Nevertheless, several of these studies had reported median estimates of ICU LOS and such a choice is perfectly understandable: since ICU LOS is not normally distributed, a reporting of median and IQR instead of the mean is recommended. The medians of ICU LOS reported [6–8, 17, 18] (see Table 1) often concern a particular sub-population (e.g., patients who died, patients who survived), ranged from 4 days (estimate considering six patients who died in the ICU) to 11 days (estimate reported in the same study and based on 12 patients discharged alive from the ICU) [18], and raise concerns in terms of the potential bias of the reported estimates (see Table 1). These concerns may be then extended to modeling studies [9, 10, 12, 13, 18] that will naturally parameterize their forecasts according to the observational data reported (Table 1). The data of the series reported here yielded an estimate of ICU ALOS at 21.1 days (95% CI 17.5–25.3) and a median



ICU LOS at 17.4 days [IQR 9.6–28.7]. These estimates are well above estimates that were reported in the early phase of the epidemic. They are associated with several strengths. First the whole study time-course lasted 99 days, enough time had passed for allowing a last date of follow-up at which all patients but one were discharged. To our knowledge, such a resulting quasi-complete distribution of the LOS observed in a given series of COVID-19 cases (see Fig. 2b) has not been reported to date, and in addition, such a data set is indeed appropriate for assessing estimation methods since the target value of the estimate is nearly perfectly known (only

one stay remained censored). Second, the high values reported here are based on a reasonable sample size ( $n = 59$ ) and our study demonstrates that an unbiased estimate at a reasonable distance from the beginning of the epidemic is inherently higher than that issued from a biased calculation a short time after the beginning of the outbreak. Nevertheless, our study also has some limitations. The study is monocentric and therefore, the extrapolation of our estimates to other settings is questionable. The gamma distribution-based CPE method allowed a reasonable ALOS estimate at the beginning of the epidemic, but other distributions might better

**Table 1 LOS estimates reported in the literature**

Reference, journal, date of line publication	Summary of important elements relating to the estimate provided	Estimate provided (ALOS, average length of stay; MLOS, median length of stay; IQR, interquartile range)
Wang et al., <i>Jama</i> , Feb 7 2020 [6]	Monocentre study (Wuhan, China). 138 consecutive patients admitted in the hospital from Jan 1 to Jan 28 2020. Last date of follow-up was Feb 3. At this date, of the 36 patients admitted to the ICU, 11 were still in the ICU, 9 had been discharged to home, 10 had been transferred to the general wards, and 6 had died. Censored data are not considered	Hospital MLOS [IQR] = 10 days [7.0–14.0] for those who were discharged at the date of last follow-up (n = 47 out of the 138 patients of the series, including 25 out of the 36 ICU patients)
Yang et al., <i>Lancet Respir Med</i> , Feb 21 2020 [7]	Monocentre (Wuhan, China): 52 patients admitted to the ICU between late December 2019 and January 26 2020. At the date of last follow-up, February 3 2020, there were 32 deaths and 20 survivors among which 12 were not discharged. Censored data are not considered	ICU MLOS in patients who died = 7 days
Guan et al., <i>New Engl J Med</i> , Feb 28 2020 [17]	Multicentre study from China. National data of hospitalized patients between Dec 1 and Jan 29. At the date of last follow-up, January 31, 1029 out of the 1099 patients included in the study were still hospitalized (93%), and 154 out of the 173 patients (89%) categorized as severe were still hospitalized. Censored data are not considered	Hospital MLOS [IQR] of severe patients: 13 days [11.5–17]
Cao et al., <i>Intensive Care Med</i> , Mar 2 2020 [18]	Monocentre (Wuhan, China): 18 patients transferred to the ICU out of 102 patients hospitalized between January 3 and February 1, 2020. At the date of last follow-up February 15, the 102 patients were discharged. Estimation based on all stays (n = 18)	ICU MLOS = 11 days for patients who survived (n = 12), ICU MLOS = 4 days for the patients who died (n = 6)
Zhou et al., <i>Lancet</i> , Mar 9 2020 [8]	Two centers (Wuhan, China), 51 ICU patients admitted at hospital between December 29 2019 and January 31 2020, and discharged before Jan 31 out of 813 patients admitted at hospital before January 31. Censored data are not considered	ICU MLOS [IQR] = 8 days [4–12]
IHME COVID-19 team <i>Medrxiv</i> , Mar 30 2020 [13]	Modeling study. Uses values reported by Zhou et al. [8]	ICU MLOS = 8 days
Moghadas et al., <i>PNAS</i> Apr 03 2020 [9]	Modeling study. Authors indicate that the ICU ALOS for survivors was based on ventilation data reported by Chen et al. and Wang et al. [6], while ICU ALOS for patients dying in the ICU is derived from Yang et al. [7] (n.b., 7 days was reported as the MLOS, not as the ALOS)	ICU ALOS = 13.25 days for survivors ICU ALOS = 7 days for patients dying in the ICU
Grasselli et al., <i>Jama</i> , April 6 2020 [5]	ICU network of 72 hospitals in Lombardy Italy. 1591 admitted to the ICU between February 20 and March 18, 2020. At the date of final follow-up, March 25, 920 patients (58%) were still in the ICU, 256 patients had been discharged alive (16%), and 405 (25%) patients had died, 10 patients with missing data. Censored data are not considered	ICU MLOS = 9 days considering all patients, ICU MLOS = 10 days for those still in the ICU ICU MLOS = 8 days for those discharged ICU MLOS = 7 days for those who died
Weissman et al., <i>Ann Intern Med</i> , April 7 2020 [10]	Modeling study. ICU ALOS from Hill's model ( <a href="https://alhill.shinyapps.io/COVID19seir/">https://alhill.shinyapps.io/COVID19seir/</a> ) which source is Zhou et al. [8] (n.b., 8 days was reported as the MLOS, not as the ALOS)	ICU ALOS = 8 days

fit data from other settings. Because it is unbiased, the CPE method should nevertheless always be preferred, and the choice of associated simple parametric distributions should be favored as compared to more complex distributions whenever corresponding fittings are similar. The estimate issued from Wuhan data is also inherently adjusted for many co-factors with a likely influence on ICU LOS that may vary from one place to another and/or with time. For example, one may think about the impact of disease knowledge on triage decisions and on the decision to withdraw early mechanical ventilation based on refinement of prognostic factors (ethical issues), bed availability and pressure of this threatening epidemic on the organization of the health-care system likely modifies the characteristics of admitted patients as well as various specific characteristics of the units (including cultural behaviors), accumulating experience with COVID-19 patients likely improves management procedures according to time. Ideally, estimates for different spatiotemporal settings should be based on observational data directly collected in corresponding settings for guarantying estimates appropriately adjusted with co-factors. However, such generalizability issues relating to estimate variability according to spatiotemporal conditions also stands for most studies reported to date, and devising a universal validated model able to adjust for any spatiotemporal condition worldwide is a very ambitious work, far beyond the object of the present study. The main outcome of this study is alerting the community about three elements. First, all scientists working on COVID-19 must realize that when dealing with data relating to LOS, they should imperatively use appropriate methods devoted to the analysis of censored data. Such methods are not original, they belong to the standard tools used in the domain of survival analysis and are easily available in any statistical software. There is no reason for avoiding their usage, and the reader will find an illustrative computer code in Additional file 2: Appendix S2. An additional strength of these methods—illustrated in Additional file 2: Appendix S2—is their ability to fit individual characteristics of patients with multivariable models to predict LOS adjusted to co-factors explicitly considered in the model formula. Such a modeling strategy may for example be deployed for documenting variations between different recruitment settings or for providing estimates in specific strata of the population. A side result of the analyses made in the present study suggests that the fatality rate of COVID-19 patients in the ICU might also be underestimated, and on this topic, the present study shares many perspectives with the work of Lipsitch et al. on the biases associated with the estimation of case-fatality risks [19]. Second, in the

context of the first outbreak of a novel infectious agent, some estimates concerning time-to-event data such as hospital LOS, ICU LOS, duration of ventilation, time of illness onset to ICU admission, etc., constitute a kind of critical food required to feed forecast models and these models are very important in many issues such as exploring and comparing mitigation scenarios, or optimizing preparedness. Therefore, enhancing the quality of the above-mentioned estimates is an important concern and our study suggests that there is room for such enhancements in the analyses of COVID-19 epidemic. Third and to conclude, whenever the estimates reported in this study would be generalizable to other settings, then this is bad news: long ICU LOS as reported here imply that occupied beds remain unavailable for a long time and this adds additional pressure to the surge in ICU beds encountered in many places worldwide.

## Conclusion

Based on this complete series of consecutive cases together with simulated cases, the present work demonstrates that ICU\_ALOS estimates used in most models to date may be importantly underestimated. In such a context of novel infectious agent, this work advocates for an urgent application of widespread survival analysis tools to properly estimate ICU\_ALOS and other critical parameters relying on censored time-to-event data. Accurate estimation of these parameters, on which rely forecast models, is crucial to ensure consistency of mitigation and preparedness scenarios, as attested by the worldwide concern over ICU bed occupancy in the current COVID-19 crisis.

## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s13613-020-00749-6>.

**Additional file 1: Appendix S1.** Simulation study.

**Additional file 2: Appendix S2.** Unbiased average length of stay estimation—an illustrative example.

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Not applicable

## Authors' contributions

The decision of performing the study emerged from informal discussions involving NL, XZ, FC, BR, YZ, and GH. Study conception and design: NL and GH. Data acquisition: XZ and YZ had full access to all of the raw data in the study and can take responsibility for the integrity of the data. Analysis: NL and GH. Interpretation of data: NL, XZ, FC, BR, YZ, and GH. First draft of the article: NL and GH. All authors read and approved the final manuscript.

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#### Availability of data and materials

All data used in this article are explicitly shown in Figs. 1 and 2 of the article. Any request for additional details must be sent to Drs. Zhao and Zhou.

#### Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee, ZHWU (Clinical Ethical Approval No. 2020005). The informed consent was waived by the Medical Ethics Committee for emerging infectious disease.

#### Consent for publication

Not applicable.

#### Competing interests

Prof. Carrat reports personal fees from SANOFI, personal fees from IMAXIO, outside the submitted work. The other authors have nothing to disclose.

#### Author details

<sup>1</sup> Sorbonne Université, INSERM, Institut Pierre Louis D'Épidémiologie Et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Unité de Santé Publique, 27 Rue Chaligny, 75571 Paris Cedex 12, France. <sup>2</sup> Emergency Center, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei, China. <sup>3</sup> Hubei Clinical Research Center for Emergency and Resuscitation, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei, China. <sup>4</sup> Sorbonne Université, UMR INSERM 1166, IHU ICAN, and AP-HP, GH Pitié-Salpêtrière, Service d'Accueil des Urgences, 75013 Paris, France. <sup>5</sup> Sorbonne Université, INSERM, Institut Pierre Louis D'Épidémiologie Et de Santé Publique, 75012 Paris, France.

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