Clinical factors affecting short- and long-term mortality in older patients with COVID-19: a retrospective cohort study

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ABSTRACT

The majority of fatal cases of SARS-CoV-2 was concentrated among older patients. We aimed at assessing risk factors contributing to mortality in this population. A retrospective study including 584 COVID-19 patients aged ≥80 years hospitalized between October 10th 2020 to May 4th 2021 at Ospedale di Circolo (Varese, Italy) and Ospedale Galmarini (Tradate, Italy) was conducted. Evaluation of risk factors associated with in-hospital mortality was the primary endpoint. 509 patients were considered. Median age was 86 [82-89] years. Almost half of the patients (n=241) suffered from ≥3 comorbidities. Overall in-hospital mortality was 39.7% (n=202). Age, chronic kidney disease (CKD), peripheral oxygen saturation at admission, and high-flow oxygen during hospital stay independently predicted in-hospital mortality. Overall mortality at 6 months was 57.8% (n=294) and increased with increasing age and number of comorbidities (P<0.05). Age, CKD, and dementia independently predicted 6-month mortality. Age and comorbidities predicted short- and long-term mortality in older patients (≥80 years). Stratification of patients according to age and comorbidities might provide critical information for a better management of elderly patients.

Introduction

Coronavirus disease 2019 (COVID-19) carried an unprecedented challenge because of its high fatality rate and its burden on healthcare systems worldwide.[1] Italy was severely hit in the first phases of COVID-19 pandemic ac-

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Contributions: AB, AMM, conceived the study design; FR, MaMe, BP, MG, MB, PMT, CB, FR collected data; AB, performed statistical analyses; FR, MaMe, BP, AB, drafted the first version of the manuscript; AB, AMM, MaMo, DDG, FD, critically revised the manuscript. All authors read and approved the final version to be published.

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Ethical approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki (revised version 2000) and approved by the local Institutional Review Board (Valutazione dell'efficacia di parametri clinici, laboratoristici e radiologici nella predizione dell'efficacia delle terapie in uso per il trattamento della sindrome da distress respiratorio acuta secondaria ad infezione da SARS-CoV-2 [REgistro COvid-19 asST settE LAghi, RECOSTELA; study number 150/2021).

Availability of data and material: data and materials are available by the authors.

Informed consent: patients signed a written informed consent before enrolment. For those who could not sign due to his/her medical condition, a verbal consent with a witness was collected.

Conference presentation: a part of the results herein provided has been discussed as an oral presentation during the 28th annual congress of Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) held in Milan (Italy).

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counting for a net increase in mortality across all age groups.[2] However, the majority of fatal cases was primarily concentrated among older patients, in particular those aged ≥80 years.[3] The clinical impact and the prevalence of mortality among the elderly affected by SARS-CoV-2 have led to dramatic consequences so that COVID-19 is turning out to be a novel geriatric condition.[4] This clarifies the efforts made by the medical community to identify the role of clinical characteristics, preexisting comorbidities and other potential prognostic factors, such as age and frailty, which are related to a higher risk of poor outcomes.[5,6] To this end, Gemes *et al.* have shown that the analysis of chronic conditions may figure out a projection of COVID-19 for a specific population in a specific area, thus stressing the importance to understand why elderly people are more prone to be infected by the virus and experience poor outcomes.[7] Accordingly, the stratification of older people according to disease burden could optimize the management and allocation of financial resources management and preventive strategies against COVID-19.[8]

Studies specifically looking at older patients (≥80 years) are few.[9] The need for a better understanding of the mechanisms through which COVID-19 affects this portion of patients is still an open question, despite the vaccination campaign improved the burden of the disease. In this study, we aimed at describing the prevalence of short- and long-term mortality among patients aged ≥80 years and associated clinical factors.

Materials and Methods

Study design

This is a retrospective study that collected data from 584 patients aged ≥80 years hospitalized because of COVID-19 [laboratory real-time-polymerase chain reaction (RT-PCR) SARS-CoV-2 positivity]. Patients were included on a consecutive basis in a period ranging from October 10th 2020 to May 4th 2021 from the COVID-19-dedicated Internal Medicine Divisions of the Ospedale di Circolo e Fondazione Macchi (Varese, Italy) and Ospedale Galmarini (Tradate, Italy) that are both part of the same local network (ASST Sette Laghi, Varese, Italy).

Patients admitted to such Divisions with COVID-19 symptoms whose nasopharyngeal swab came negative or with medical records not available or incomplete for >50% of the hospital stay were not considered. Patients who did not consent to participate in the study were excluded. The study flow chart is summarized in *Supplementary Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (revised version 2000) and approved by the local Institutional Review Board (Valutazione dell'efficacia di parametri clinici, laboratoristici e radiologici nella predizione dell'efficacia delle terapie in uso per il trattamento della sindrome da distress respiratorio acuta secondaria ad infezione da SARS-CoV-2 [REgistro COvid-19 asST settE LAghi, RECOSTELA; study number 150/2021). Patients signed a written informed consent before enrolment. For those who could not sign due to his/her medical condition, a verbal consent with a witness was collected.

Data collection

The following medical information was collected in the database using the wHospital® InPatient electronim platform (wHealth-Lutech Group, Cinisello Balsamo, Milan, Italy): age, sex, length of hospital stay, past medical history, peripheral oxygen saturation (SpO_2) at the time of hospital admission, hospital therapy, oxygen support, survival/death state, discharge site, and hospital of admission (Varese or Tradate). As arterial blood gas analysis was not available for all patients, we considered the fraction of inspired oxygen (FiO_2) as a proxy of the degree of respiratory failure.

Patient outcomes (survival or death) during the 6-month follow-up were retrieved from the electronic database of Lombardy region (Sistema Informativo Socio Sanitario, SISS). This system was also queried to double-check patient outcomes during the time of hospital stay.

All patients were stratified according to the Clinical frailty scale (CFS),[10] that evaluates subjects according to their functional capacity, level of dependence and comorbidities in a range from 1 to 9. Patients were categorized into three groups according to the score: fit (score 1 to 3), pre-frail (score 4), frail (score 5 to 9) as previously reported.[11]

Study endpoints

The primary endpoint of the study was the evaluation of risk factors associated with in-hospital mortality. Secondary endpoints included the evaluation of clinical factors predicting 6-month mortality and the impact of frailty on such patients.

Statistical analysis

Normality of continuous variables was evaluated using Shapiro-Wilk test and Q-Q plots. Continuous variables that did not follow a Gaussian distribution were expressed as median and interquartile range (IQR), while categorical variables are presented as numbers and percentages (%). Continuous, independent variables were analyzed through a Mann-Whitney U test, whereas categorical, independent variables were compared via a Chi-squared test or Fisher's exact test, as appropriate. Comparisons between continuous variables were performed using Wilcoxon signed rank test or Kruskal-Wallis test, as appropriate. The McNemar's test was used for comparison of coupled categorical variables, as appropriate. Cox proportional hazards model expressed as hazard ratio (HR) with the corresponding 95% confidence interval (CI) using a stepwise backward elimination model (level of significance $P<0.10$ for inclusion and exclusion) was used to evaluate the prognostic impact of clinical variables with regard to in-hospital and 6-month mortality.

A two-sided P-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Mac, version 27.0 (IBM CO., Armonk, NY, USA) and GraphPad Prism, version 8.2 for Windows (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

Results

Baseline characteristics of the cohort

Out of 584 patients, 509 patients were considered. Reasons for exclusion are shown in *Supplementary Figure 1*. No differences were encountered in terms of sex and age between included and excluded patients (P= not significant). Median age was 86 (IQR 82-89, range 80-99) years and 16% (n=83) of the cohort was older than 90 years, with a prevalence of women (59.7%, n=304) (*Supplementary Table 1*).

The burden of comorbidities was high, with almost half of the cohort (n=241) suffering from three or more comorbidities (*Supplementary Figure 2*). A stable distribution of comorbidities across age groups was recorded (*Supplementary Figure 3*). Hypertension was the most frequent comorbidity (78%, n=396), followed by dementia (30%, n=152), atrial fibrillation (27%, n=137), and diabetes (24%, n=120) (*Supplementary Table 1*).

The large majority of patients were classified as frail (70.8%, n=358) (*Supplementary Figure 4*). No differences were recorded in terms of demographics and comorbidities across CFS groups (*Supplementary Table 2*).

Respiratory parameters and management of COVID-19-related respiratory failure

Median SpO_2 at admission to COVID-19-dedicated internal medicine divisions was 95 [92-97] % in the whole cohort (*Supplementary Table 3*). Most of patients presented with respiratory failure at emergency department admission. Almost 40% of them were on oxygen support other than nasal cannulas [130 (25.7%) patients on Ventimask, 73 (14.5%) patients on non-rebreather mask, and 22 (4.4%) on continuous positive air pressure (CPAP)] (*Supplementary Table 3*).

Systemic glucocorticoids were administered in a large part of the cohort (71.9%, n=366) (*Supplementary Table 4*). Due to changing recommendations based on completed studies in that period, different doses were used. Intravenous dexamethasone 6 mg daily was the most used formulation (40.4%, n=205), while high-dose dexamethasone (20 mg daily for 5 days, followed by 10 mg daily for 5 days based on the paper by Villar *et al.*) was administered in 20.9% (n=106) of patients (*Supplementary Table 4*).[12]

In-hospital mortality

The overall mortality during hospital stay was 39.7% (n=202; *Supplementary Figure 5*). Mortality rate proportionally increased across age groups (Figure 1) and the presence of at least one comorbidity was associated with an increasing risk of death as well (Figure 2) (P<0.05 for both).

When grouping our cohort by survival status during hospital stay, those who died were older and frail and more frequently suffered from chronic kidney disease (CKD) (Table 1). In addition, they presented more frequently SpO_2 <85% at admission and needed non-rebreather mask and CPAP either at admission or as maximum oxygen support throughout the hospital stay (Table 2).

Variables of clinical interest were put into a Cox proportional hazards model followed by a stepwise backward regression to look for predictors of in-hospital mortality. At this point, age, CKD, SpO_2 at admission, and FiO2 ≥31% (*i.e.*, use of Ventimask, non-rebreather mask, or CPAP) as maximum oxygen support during hospital stay were found to independently predict death during hospitalization (Table 3).

Six-month mortality

Overall mortality at 6 months was 57.8% (n=294; *Supplementary Figure 5*). As observed for in-hospital mortality, the proportion of patients who died progressively increased with age (P<0.001; Figure 1) and the number of comorbidities (P<0.001; Figure 2). When comparing the cohort by survival status after 6 months from hospitalization, those who died were older (age >90 years) and more frequently suffered from dementia (*Supplementary Table 5*).

In the adjusted Cox proportional hazards model, age, CKD, and dementia came out to independently predict 6-month mortality (Table 3).

Discussion and Conclusions

The main results of our study are: i) elderly people hospitalized for SARS-CoV-2 infection during the pre-vaccination era experienced an increased mortality rate both at the time of hospitalization and after 6 months; ii) age, CKD, and severe respiratory failure independently predicted in-hospital mortality; iii) age, CKD, and dementia represented independent predictors of long-term mortality.

The increased mortality rate observed in our cohort of eld-

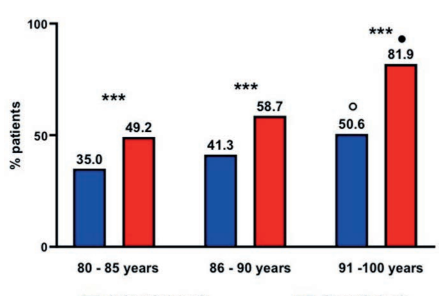

Figure 1. Overall mortality across age groups. A progressive increase in in-hospital and 6-month mortality was observed for increasing age. ***P<0.001 comparing in-hospital *vs.* 6-month mortality. °P=0.037 across age groups for in-hospital mortality; •P<0.001 across age groups for 6-month mortality.

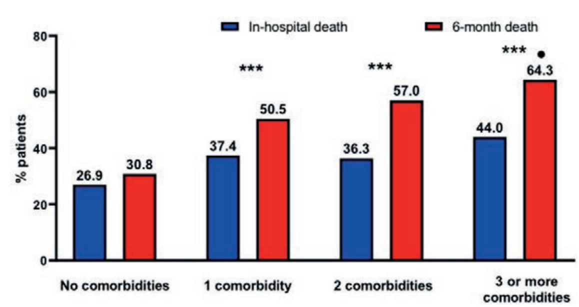

Figure 2. Overall mortality according to the number of comorbidities. An increasing mortality rate was observed for both in in-hospital and 6-month time points parallel to the number of comorbidities. ***P<0.001 comparing in-hospital *vs.* 6-month mortality; •P<0.001 across number of comorbidities for 6-month mortality.

erly patients appears in line with the published evidence.[9,13,14] However, we found a large proportion (nearly 40%) of patients who died during the index hospital admission, that is similar to what found by Regvat *et al.*,[15] but different from Steinmeyer *et al.*, who reported data from Geriatric divisions in France with an in-hospital mortality of 18%, that is much lower compared to ours (39.7%).[9] Similar proportions of in-hospital mortality are recorded in the COVIP (COronavirus disease in Very elderly Intensive care Patients) study,[11] although this study was conducted among elderly patients admitted to the intensive care unit (ICU). With this regard, our data provided a peculiar overview on older patients admitted to an acute division – internal medicine divisions that were repurposed to treat COVID-19 patients. For this reason, our setting of care cannot be compared with ICUs and this represents a novelty of our work, as data on older COVID-19 patients managed in non-intensive divisions are scarce in the literature.

Age resulted an independent risk factor both for in-hospital and 6-month mortality in our cohort. Accordingly, this effect was even larger across age groups. The finding is confirmatory of what reported in early studies of COVID-19 eld-

Table 1. Baseline characteristics of the overall cohort according to survival status during hospital stay.

	Survived n=307	Deceased n=202	P
Age, years	85 [82-89]	87 [83-90]	0.002
80-85 years, n (%)	165 (53.7)	89 (44.1)	0.037
86-90 years, n (%)	101 (32.9)	71 (35.1)	0.632
91-100 years, n (%)	41 (13.4)	42 (20.8)	0.028
Sex			
Male, n (%)	125 (40.7)	80 (39.6)	0.854
Female, n (%)	182 (59.3)	122 (60.4)	
Comorbidities			
Hypertension, n (%)	242 (78.8)	154 (76.2)	0.514
Type 2 diabetes, n (%)	69 (22.5)	51 (25.2)	0.522
Coronary artery disease, n (%)	48 (15.6)	36 (17.8)	0.543
Atrial fibrillation, n (%)	86 (28.0)	51 (25.2)	0.540
Heart failure, n (%)	35 (11.4)	34 (16.8)	0.086
Valvular heart disease, n (%)	30 (9.8)	20 (9.9)	1.000
Previous stroke, n (%)	30 (9.8)	28 (13.9)	0.157
COPD, n (%)	45 (14.7)	31 (15.3)	0.899
Dementia, n (%)	83 (27.0)	69 (34.2)	0.093
Chronic kidney disease, n (%)	43 (14.0)	44 (21.8)	0.030
Chronic liver disease, n (%)	6 (2.0)	8 (4.0)	0.267
Active cancer, n (%)	28 (9.1)	13 (6.4)	0.320
Hypothyroidism, n (%)	35 (11.4)	25 (12.4)	0.779
Clinical Frailty Scale	5 [4-7]	6 [5-7]	0.068
CFS 1 to 3 (fit), n (%)	55 (17.9)	26 (12.9)	0.139
CFS 4 (vulnerable), n (%)	45 (14.7)	22 (10.9)	0.231
CFS 5 to 9 (frail), n (%)	205 (66.8)	152 (75.2)	0.048
Length of hospital stay, days	10 [6-16]	7 [4-12]	<0.001

CFS, Clinical frailty scale; COPD, chronic obstructive pulmonary disease.

Table 2. Respiratory parameters according to survival status during hospital stay.

	Survived (n=307)	Deceased (n=202)	P
SpO_2 at admission	96 [94-97]	94 [91-96]	<0.001
SpO_2 >95%, n (%)	156 (53.4)	66 (35.3)	<0.001
SpO_2 91 to 95%, n (%)	110 (35.8)	79 (39.1)	0.455
SpO_2 85 to 90%, n (%)	21 (6.8)	30 (14.9)	0.004
SpO_2 <85%, n (%)	5 (1.7)	12 (6.4)	0.010
Oxygen support at admission			
Nasal cannulas, n (%)	97 (31.9)	43 (21.4)	0.011
Ventimask, n (%)	76 (25.0)	54 (26.9)	0.678
Non-rebreather mask, n (%)	22 (7.2)	51 (25.4)	<0.001
CPAP, n (%)	5 (1.6)	17 (8.5)	<0.001
Maximum oxygen support during hospital stay			
Nasal cannulas, n (%)	103 (33.6)	25 (12.4)	<0.001
Ventimask, n (%)	72 (23.6)	29 (14.4)	0.012
Non-rebreather mask, n (%)	44 (14.5)	100 (49.5)	<0.001
CPAP, n (%)	16 (5.2)	41 (20.3)	<0.001

CPAP, continuous positive air pressure; SpO_2, peripheral oxygen saturation.

erly patients from China.[16,17] The greater susceptibility of the elderly in developing a severe form of SARS-CoV-2 infection could be explained by various factors. Physiological changes affecting the respiratory system determine a decrease in the pulmonary reserve and the defensive barrier function.[18] In addition, elderly people are known to experience inflammaging, *i.e.*, a phenomenon for which levels of pro-inflammatory cytokines (especially interleukin-1, interleukin-6, and tumor necrosis factor) rise with increasing age.[19] This couple with immunosenescence, as advancing age leads to the disruption of both innate and adaptive immunity.[20] Accordingly, in elderly patients the increased reactivity and the impairment of the immune system contribute to an unbalanced inflammatory response, where persistent and self-sustained hyperinflammation triggers catastrophic events which predispose to multiple organ failure.[21,22]

The large burden of comorbidities in our cohort is related to older age. According to a survey by the Italian Institute of Statistics, almost half of people aged >65 years suffers from ≥3 chronic diseases, in agreement with the results of our study. Interestingly, our findings show that the burden of comorbidities has no role on in-hospital survival, while a negative impact on 6-month survival was evident. In particular, we have observed a trend for increased mortality along with the number of comorbidities. This is in line with a Chinese study where the presence of more comorbidities was associated with an increased risk of death (HR from 1.7 for at least one comorbidity up to 2.6 for ≥2 comorbidities).[23] While cardiovascular comorbidities were the most common among patients with COVID-19, as confirmed by several studies,[24,25] we were not able to confirm this finding.

CKD was independently associated with short- and long-term mortality in our cohort. This finding appears in line with what reported in systematic reviews and meta-analyses, where CKD increased mortality among elderly patients with COVID-19.[26,27] A possible explanation could be represented by the ability of SARS-CoV-2 to infect endothelial cells, including kidney cells. Indeed, CKD and/or the presence of immunosuppression in patients who underwent renal transplantation have been indicated as risk factors for severe COVID-19.[28]

In our study, dementia showed no correlation with mortality during hospitalization, while it represented the main predictor of long-term mortality. Patients affected by dementia are susceptible to COVID-19, although causes are partially unclear. A large meta-analysis including 119,218 hospitalized patients with SARS-CoV-2 infection found that 9% of them had dementia and experienced almost a 4-fold increased death rate.[29] The increased mortality in patients with dementia may be explained by several factors. These patients frequently suffer from multiple comorbidities with poor prognosis. In addition, patients with neurodegenerative diseases presented augmented basal cytokine levels, which may predispose to a more severe course of COVID-19.[29] Several studies report that COVID-19 may present with atypical manifestations in people with dementia,[30] thus delaying in diagnostic and therapeutic approach. Finally, especially in the first phases of COVID-19 pandemic, living in long-term care facilities and the inability to keep adequate prevention measures and isolation might have provided an additional risk of SARS-CoV-2 infection.[31]

Frailty is a known predictor of all-cause and cause-specific mortality.[32] In a meta-analysis, frailty was independently associated with in-hospital mortality among COVID-19 patients.[33] Differently from the available literature, we were not able to prove an association between frailty and mortality, that was, however, an exploratory analysis. The substantial difference between the 16 retrospective studies included in the meta-analysis and our study primarily concerns the median age of recruited patients, which is significantly lower than ours (68 *vs*. 86 years). It is then possible that age provided the greatest influence on mortality prediction, since our cohort included very old patients.

Patients herein described were affected by interstitial pneumonia causing acute respiratory failure and the most critical cases developed acute respiratory distress syndrome (ARDS). Our findings confirmed that SpO_2 detected at the time of admission was an independent risk factor associated with mortality. In addition, increased FiO_2 values detected both on admission and as a maximum value delivered to the patient during the hospitalization were independently correlated with mortality. Our findings appear confirmatory of data

Table 3. Predictive factors for the occurrence of death during hospital stay and at 6-month follow-up according to adjusted Cox proportional hazards model.

In-hospital mortality	HR	95% IC	P
Age	1.08	1.05-1.12	<0.001
Chronic kidney disease	1.51	1.05-2.17	0.025
SpO_2 at admission	0.92	0.89-0.95	<0.001
FiO_2 ≥31% at hospital admission	1.37	0.96-1.95	0.087
FiO_2 ≥31% as maximum oxygen support during hospital stay	2.84	1.77-4.56	<0.001
6-month mortality	**HR**	**95% IC**	**P**
Age	1.08	1.05-1.10	<0.001
Chronic kidney disease	1.39	1.04-1.86	0.026
Chronic liver disease	1.73	0.97-3.10	0.063
Dementia	1.64	1.29-2.08	<0.001

Factors included into the model for in-hospital mortality: age, sex, hypertension, type 2 diabetes, coronary artery disease, atrial fibrillation, heart failure, previous stroke, COPD, dementia, chronic kidney disease, chronic liver disease, active cancer, SpO_2 at admission, FiO_2 ≥31% (*i.e.*, use of Ventimask, non-rebreather mask, and CPAP) either at hospital admission and as maximum oxygen support during hospital stay. Factors included into the model for 6-month mortality: age, sex, hypertension, type 2 diabetes, coronary artery disease, atrial fibrillation, heart failure, previous stroke, COPD, dementia, chronic kidney disease, chronic liver disease, active cancer. HR, hazard ratio; CI, confidence interval; SpO_2, peripheral oxygen saturation.

on patients treated for COVID-19-related ARDS, that however derive from ICUs.[34] Our study highlighted the increased death rate for patients needing, especially those on CPAP. Indeed, a study conducted in older adults admitted to the ICU with need of mechanical ventilation experienced a mortality rate close to 97%.[35] Based on these results, an accurate reflection on the risk-benefit ratio related to the use of non-invasive-ventilation in elderly patients is warranted.

Our study has different strengths. The main one deals with the large number of elderly patients enrolled at two centers severely hit by COVID-19 (Varese district, Lombardy region, Italy), so that the data herein presented might be considered representative of a portion of the Italian population. In addition, we had full access to data regarding 6-month mortality through a chart-level review of the local healthcare database, thus providing information about short-term mortality. Some limitations, however, need to be acknowledged while reading our manuscript. The retrospective nature may account for selection bias and ascertainment bias due to missing data. Because of the retrospective nature of our analysis, it was not possible to obtain and elaborate parameters relating to pre-hospitalization renal function, neither was made a distinction between patients on conservative therapy and hemodialysis. Stratification of patients by CKD degree might help understanding how CKD influences the outcome of patients with SARS-CoV-2 disease. As our cohort included older patients suffering from severe COVID-19, this might have increased the mortality rate. Finally, the follow-up was limited to 6 months, and possibly some complications might not be captured, especially cardiovascular ones.

In conclusion, the elderly have been disproportionately hit by COVID-19 pandemic. Age and comorbidities provide relevant prognostic information in this subset of patients with COVID-19. The research, development and promotion of vaccination campaigns led to a reduction in disease severity and mortality rates, also among the elderly. Crucially, stratification of patients could have important implications to guide clinical decisions, choose the most appropriate treatment and improve the outcome of older people.

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Online supplementary material:

Table S1. Baseline characteristics of the overall cohort.

Table S2. Baseline characteristics of the overall cohort according to Clinical frailty scale.

Table S3. Respiratory parameters during hospital stay in the whole cohort.

Table S4. Pharmacological management of respiratory failure in the whole cohort.

Table S5. Baseline characteristics of the overall cohort according to survival status at 6-month follow-up.

Figure S1. Study flow chart.

Figure S2. Number of comorbidities in the whole cohort.

Figure S3. Distribution of comorbidities across age groups. No differences in terms of proportions of comorbities was observed in the three age groups. P not significant for Chi-square test.

Figure S4. Frailty distribution in the overall cohort.

Figure S5. Overall mortality during hospital admission and after 6 months.