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Risk factors of mortality among patients hospitalised with COVID-19 in a critical care or hospital care unit: analysis of the French national medicoadministrative database

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ABSTRACT

Objective To explore mortality risk factors for patients hospitalised with COVID-19 in a critical care unit (CCU) or a hospital care unit (HCU).

Design Retrospective cohort analysis using the French national (*Programme de médicalisation des systèmes d'information*) database.

Setting Any public or private hospital in France.

Participants 98 366 patients admitted with COVID-19 for more than 1 day during the first semester of 2020 were included. The underlying conditions were retrieved for all contiguous stays.

Main outcome measures In-hospital mortality and associated risk factors were assessed using frailty Cox models.

Results Among the 98 366 patients included, 25 765 (26%) were admitted to a CCU. The median age was 66 (IQR: 55–76) years in CCUs and 74 (IQR: 57–85) years in HCUs. Age was the main risk factor of death in both CCUs and HCUs, with adjusted HRs (aHRs) in CCUs increasing from 1.60 (95% CI 1.35 to 1.88) for 46 to 65 years to 8.17 (95% CI 6.86 to 9.72) for ≥85 years. In HCUs, the aHR associated with age was more than two times higher. The gender was not significantly associated with death, aHR 1.03 (95% CI 0.98 to 1.09, p=0.2693) in CCUs. Most of the underlying chronic conditions were risk factors for death, including malignant neoplasm (CCU: 1.34 (95% CI 1.25 to 1.43); HCU: 1.41 (95% CI 1.35 to 1.47)), cirrhosis without transplant (1.41 (95% CI 1.22 to 1.64); 1.27 (95% CI 1.12 to 1.45)) and dementia (1.30 (95% CI 1.16 to 1.46); 1.07 (95% CI 1.03 to 1.12)).

Conclusion This analysis confirms the role of age as the major risk factor of death in patients with COVID-19 irrespective to admission to critical care and therefore supports the current vaccination policies targeting older individuals.

Key messages

- Observational studies have identified age, gender and comorbidities to be the main risk factors of death for patients hospitalised with COVID-19, but most of them did not differentiate patients admitted to a critical care unit from those who were not.
- Analyses pooling data of patients admitted to a critical care unit and those who were not might lead to biased estimates of risks with substantial consequences for prevention strategies such as vaccination targeting populations with a higher risk of severe outcomes.
- This study, one of the largest nationwide COVID-19 cohorts, confirms the role of age as the major risk factor of death and show that mortality risks associated with comorbidities differ between patients admitted to a critical care unit and those who were not.

INTRODUCTION

Unprecedented worldwide efforts have led to the development of several vaccines against the SARS-CoV-2 infection and its associated disease (COVID-19) in less than a year.[1–3] This achievement is an important first step towards controlling the spread of the SARS-CoV-2 pandemic. Further challenges remain in the production of sufficient doses of vaccine and their administration to more than half of the world population to reach 'population immunity'.[4] This goal will be impossible to achieve in the short term given the limited resources to produce and administer the vaccine. An alternative, such as the vaccination of targeted populations with a higher risk of severe outcomes, has already been implemented in many countries.

Studies and meta-analyses have reported mortality rates for patients admitted with COVID-19 to range from 2% to 39%,[5–7] depending on the country and admission

to critical care units (CCUs).[5] Reported mortality risk factors are old age, chronic major comorbidities and male sex.[7 8] Most of the studies included in the published meta-analyses came from Asia and, except for age and gender, the impact of other risk factors, such as comorbidities, varied between them.[5] Their findings are key to guiding target population vaccination strategies and the better they reflect reality, the better they can support health policy decisions.

In France, the epidemic started in late February 2020 and by late March 2021, more than 4.3 million people had been infected for approximately 93 900 deaths.[9] The first epidemic wave started at the end of February 2020, peaked in April 2020 and ended towards the end of June 2020. The country is struggling to control the epidemic with individual physical barrier measures and a series of general population lockdowns, with limited efficacy. Vaccination against SARS-CoV-2 is being progressively implemented, but reliable evidence is needed to support decisions about the populations to target. Studies have reported high mortality rates among men and older patients hospitalised with COVID-19.[10 11] Few studies have assessed clinical risk factors for mortality in patients hospitalised with COVID-19 in France, particularly those stratified according to admission to critical care.

We aimed to explore demographic and clinical risk factors associated with in-hospital mortality in a nationwide cohort of patients admitted with COVID-19 in any hospital in France during the first wave of the pandemic.

METHODS

Study design and French national hospital database

A retrospective cohort study was performed using the French national *Programme de médicalisation des systèmes d'information* (PMSI) database.[12] The PMSI was inspired by the diagnosis-related group classification system developed in the USA in the 1980s. The PMSI is a large, relatively exhaustive, national database that has gathered data transmitted monthly by all public and private hospitals in France since 1997. Initially, the PMSI served to analyse hospital activity and guide healthcare policy. Since 2004, the PMSI has been used to guide health resource allocation following the implementation of an activity-based hospital funding policy. Administrative and medical data are recorded at discharge from hospital for all patient stays. Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10), and procedures performed during hospitalisation are coded according to the Common French Classification of Medical Acts. After anonymisation, the data are uploaded by each hospital to a secure national platform, constituting the PMSI national database.

Participants

All patients admitted to any hospital for COVID-19 between 1 January and 30 June 2020 and discharged at the latest on 30 September 2020 were included, regardless of their age. We selected patients whose care sequence contained at least one of the following ICD-10 diagnosis codes for COVID-19, adapted from those defined by the WHO: U07.1, U07.10, U07.11, U07.12, U07.14 and U07.15.[13] The care sequence for a patient was defined as the sum of all contiguous hospital stays (with less than 1 day in between). The starting date of the care sequence was the admission date for the first stay, and the end date was the date of discharge or death. We excluded care sequences lasting less than 1 day unless the patient died. Only the first care sequence per patient was considered.

Outcome

The primary outcome was in-hospital mortality defined as death occurring during hospital stay. In-hospital mortality was collected using a variable of the PMSI describing mortality and the destination at discharge.

Covariates

The following variables were assessed for each included patient: age, gender, body mass index (BMI), underlying illnesses, admission to a CCU or hospital care unit (HCU) and death. Critical care regroups all levels of intensive care units. Patients treated in both a CCU and HCU were considered to be in a CCU.

Age groups were categorised as follows: <18, 18–45, 46–65, 66–70, 71–84 and ≥85 years The age categories were defined based on literature review strengthened by Chi-square Automatic Interaction Detector method (SIPINA software V.3.12).[14] The BMI was defined by ICD-10 codes (online supplemental table S1) and categorised as: <30, 30–39 and ≥40 kg/m².

A team of physicians experienced in medical information reviewed the ICD-10 codes and classified underlying illnesses as chronic conditions (ascertained during the entire care sequence or within any previous hospitalisation 2 years before admission) or acute conditions (ascertained during the current entire care sequence). The definitions and ICD-10 codes used to specify comorbidities are listed in online supplemental table S1. Chronic conditions included hypertension, chronic cardiac disease, diabetes (type 1 and 2), chronic kidney disease, asthma, chronic pulmonary disease, malignant neoplasm, dementia, solid organ transplant, HIV/AIDS, dyslipidaemia, cirrhosis without transplant, coronary artery disease and history of stroke. The Charlson comorbidity index without age was computed as global measure of comorbidity.[15] Acute conditions included acute pulmonary failure, acute respiratory distress syndrome, acute pulmonary infection (excluding viral infections), shocks (including hypovolaemic shock, cardiogenic shock and septic shock), myocardial infarction, acute pulmonary embolism, thrombophlebitis, acute liver failure and acute kidney injury.

COVID-19 cases were classified based on ICD-10 codes as asymptomatic (U07.12), with respiratory symptoms (U07.1, U07.10 or U07.11) or with other symptoms

(U07.14 or U07.15). U07.10, U07.12 and U07.14 were used to define laboratory-confirmed COVID-19 cases and U07.11 and U07.15 for clinically or radiologically diagnosed cases. A code hierarchy was used if there was more than one U07.X code during the same care sequence as follows: U0710 >U0714>U0712>U0711>U0715.

Statistical analysis

Continuous variables are described as medians and IQR and categorical variables as frequencies and percentages.

The Kaplan-Meier method was used to estimate the cumulative probability of death stratified by age group, gender and admission or not to a CCU. As mentioned previously, the care sequences had to end by 30 September to allow for a relatively complete follow-up for the patients included in this study. The duration of follow-up was the difference between the hospital admission date and discharge or death date. Discharged patients were considered to no longer be at risk of in-hospital death.

Multivariate Cox frailty models, using the last department of the hospitalisation as a random intercept, were used to investigate risk factors associated with in-hospital mortality. The analysis was stratified according to admission to a CCU or HCU, with separate presentation of the results. HIV/AIDS and the Charlson comorbidity index were not included in multivariate analyses, the former because of a few patients concerned and the latter to avoid colinearity with the comorbidities. Covariates were retained in the final model if significant ($\alpha \leq 5\%$). Gender, chronic cardiac disease and solid organ transplant were forced into the final model. First-order interactions between admission to CCU and either age, gender or BMI were investigated and proportional hazards assumptions explored.

Sensitivity analyses were performed including alternative modelling and subgroups analyses: (1) alternative modelling using logistic regressions (online supplemental table S3); (2) frailty Cox model excluding length of stay (LOS) outliers defined as LOS longer than 60 days (online supplemental table S4); and (3) frailty Cox model with age in continuous variable (online supplemental table S5).

All tests were two sided. Analyses were performed using SAS Enterprise Guide V.8.3 software and R V.3.5.2 (packages: survival, survminer, forestplot).

Patient and public involvement

Neither patients nor the public were involved in the design, conduct or reporting of this study. Anonymised patient discharge data were used to address a national research priority question in the context of urgency and rapid progression of the COVID-19 pandemic.

RESULTS

Study population

Among the 111 940 patients hospitalised with COVID-19 in France between January and June 2020, 98 366 (88%) were included in this study. In total, 13 574 (12%) patients who were discharged alive after a LOS of <1 day were excluded. Among the patients included, 82 764 (84%) had a sequence of care with one hospital stay and 15 602 (16%) had more than one hospital stay (figure 1).

Overall, 25 765 (26%) were admitted to a CCU at any time, with a median care sequence LOS of 15 days (IQR:

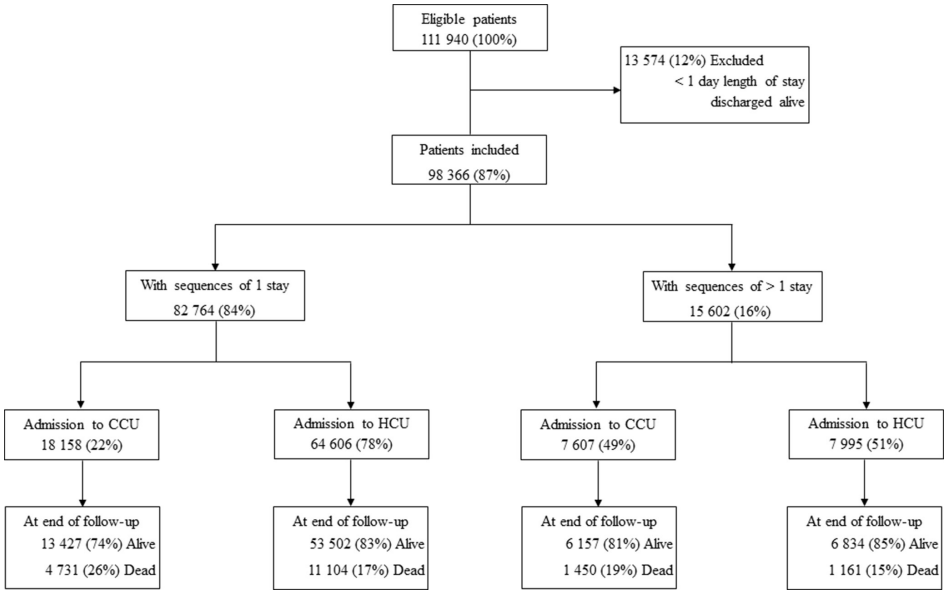

Figure 1 Study patient selection flow chart. The selection process of the patients included in our analysis is presented. The care sequence was defined as the sum of all contiguous hospital stays (with less than 1 day in between). Patients were excluded if the length of stay (LOS) was less than 1 day and they were discharged alive. CCU, critical care unit; HCU, hospital care unit.

Table 1 Survival and follow-up characteristics of 98 366 patients hospitalised with COVID-19 in France between 1 January and 30 June 2020 (data are presented as n (%) unless otherwise indicated)

	Overall (n=98 366)	Patients admitted to a CCU (n=25 765)	Patients admitted to an HCU (n=72 601)	P value
Median length of stay in days (IQR)	9 (4–16)	15 (8–28)	8 (4–13)	<0.0001
Median survival time in days (95% CI*)				
Overall	61 (59 to 64)	77 (72 to 83)	48 (46 to 52)	<0.0001
By gender and age				
Male				
<18	–	–	–	
18–45	142 (125 to NA)	142 (125 to NA)	81 (62 to NA)	
46–65	127 (109 to NA)	154 (119 to NA)	72 (63 to NA)	
66–70	77 (67 to 93)	82 (71 to 107)	61 (48 to 85)	
71–84	41 (38 to 43)	45 (41 to 50)	37 (34 to 41)	
≥85	23 (22 to 24)	22 (19 to 25)	23 (22 to 25)	
Female				
<18	–	–	–	
18–45	–	–	84 (68 to NA)	
46–65	122 (94 to NA)	122 (94 to NA)	83 (64 to NA)	
66–70	87 (77 to NA)	89 (72 to NA)	81 (65 to NA)	
71–84	57 (50 to 67)	53 (47 to 67)	57 (49 to 72)	
≥85	43 (41 to 47)	32 (27 to 40)	46 (43 to 52)	
Survival time				
≤60 days	96 466 (98.1)	24 267 (94.2)	72 199 (99.4)	
>60 days	1 900 (1.9)	1 498 (5.8)	402 (0.6)	
Status at the end of follow-up				
Discharged	79 920 (81.2)	19 584 (76.0)	60 336 (83.1)	
Died in hospital	18 446 (18.8)	6 181 (24.0)	12 265 (16.9)	

*CIs were obtain from R survfit function using log transformation.
CCU, critical care unit; HCU, hospital care unit; NA, not available.

8–28) and 72 601 (74%) were admitted to a HCU with a median LOS of 8 days (IQR: 4–13) (table 1). Among the patients admitted to a CCU, 18 158 (70%) stayed in one hospital and 7607 (30%) were hospitalised in more than one hospital (figure 1).

Demographic and clinical characteristics

The demographic and clinical characteristics of the patients are presented in table 2.

In this study, 54% of the hospitalised patients were men, with a higher proportion of men admitted to CCUs than HCUs (65% vs 50%). The median age was 66 years (IQR: 55–76) for the patients in CCUs and 74 years (IQR: 57–85) for those in HCUs. Patients in CCUs were younger, with a higher proportion <70 years of age (61% *vs* 44%) and a lower proportion of patients aged 85 years and older (9% vs 27%). Approximately 18% of the patients in CCUs had a BMI >30 kg/m² compared with 8% in HCUs.

Among the 98 366 patients, 87 940 (89%) had respiratory symptoms of COVID-19. The proportion of respiratory presentation was significantly higher for patients admitted to CCUs (94% vs 88%). The proportion of patients with at least one chronic underlying condition was 89%. A higher proportion of patients in CCUs had a comorbidity score ≥3 for the Charlson comorbidity index (23% vs 18%). The most common chronic underlying conditions were hypertension (47%), diabetes (24%), chronic cardiac disease (16%) and coronary artery disease (14%). Patients in CCUs had a significantly higher proportion of chronic underlying conditions, except for malignant neoplasm, chronic kidney disease and dementia. Fewer patients with dementia were admitted to CCUs (4% vs 14%). The most common underlying

Table 2 Demographic characteristics and underlying conditions of 98 366 patients hospitalised with COVID-19 in France between 1 January and 30 June 2020 (data are presented as n (%) unless otherwise indicated)

	Overall (n=98 366)	Patients admitted to a critical care unit (n=25 765)	Patients admitted to a hospital care unit (n=72 601)	P value
Age, years				<0.0001
Median (IQR)	71 (56–83)	66 (55–76)	74 (57–85)	
<18	1571 (1.6)	599 (2.3)	972 (1.3)	
18–45	11 065 (11.2)	2527 (9.8)	8538 (11.8)	
46–65	19 579 (19.9)	6733 (26.1)	12 846 (17.7)	
66–70	15 783 (16.0)	5997 (23.3)	9786 (13.5)	
71–84	28 249 (28.7)	7490 (29.1)	20 759 (28.6)	
≥85	22 119 (22.5)	2419 (9.4)	19 700 (27.1)	
Gender				<0.0001
Female	45 444 (46.2)	8898 (34.5)	36 546 (50.3)	
Male	52 922 (53.8)	16 867 (65.5)	36 055 (49.7)	
Body mass index, kg/m²				<0.0001
<30	87 959 (89.4)	21 183 (82.2)	66 776 (92.0)	
30–39	8316 (8.5)	3655 (14.2)	4661 (6.4)	
≥40	2091 (2.1)	927 (3.6)	1164 (1.6)	
Clinical presentation				<0.0001
Asymptomatic	4335 (4.4)	496 (1.9)	3839 (5.3)	
Respiratory symptoms	87 940 (89.4)	24 328 (94.4)	63 612 (87.6)	
Other symptoms	6091 (6.2)	941 (3.7)	5150 (7.1)	
Chronic underlying conditions				
Charlson comorbidity index‡				<0.0001
0	42 366 (43.1)	9649 (37.5)	32 717 (45.1)	
1–2	37 077 (37.7)	10 182 (39.5)	26 895 (37.0)	
≥3	18 923 (19.2)	5934 (23.0)	12 989 (17.9)	
Hypertension				<0.0001
No	51 891 (52.8)	12 718 (49.4)	39 173 (54.0)	
Yes	46 475 (47.2)	13 047 (50.6)	33 428 (46.0)	
Chronic cardiac disease				<0.0001
No	82 558 (83.9)	21 405 (83.1)	61 153 (84.2)	
Yes	15 808 (16.1)	4360 (16.9)	11 448 (15.8)	
Coronary artery disease				<0.0001
No	84 568 (86.0)	21 674 (84.1)	62 894 (86.6)	
Yes	13 798 (14.0)	4091 (15.9)	9707 (13.4)	
Diabetes (types 1 and 2)				<0.0001
No	74 397 (75.6)	18 462 (71.7)	55 935 (77.0)	
Yes	23 969 (24.4)	7303 (28.3)	16 666 (23.0)	
Chronic kidney disease				0.0020
No	85 167 (86.6)	22 453 (87.1)	62 714 (86.4)	
Yes	13 199 (13.4)	3312 (12.9)	9887 (13.6)	
Asthma				<0.0001
No	93 790 (95.3)	24 414 (94.8)	69 376 (95.6)	
Yes	4576 (4.7)	1351 (5.2)	3225 (4.4)	
Chronic pulmonary disease				<0.0001

Continued

Table 2 Continued

	Overall (n=98 366)	Patients admitted to a critical care unit (n=25 765)	Patients admitted to a hospital care unit (n=72 601)	P value
No	88 708 (90.2)	23 020 (89.3)	65 688 (90.5)	
Yes	9658 (9.8)	2745 (10.7)	6913 (9.5)	
Malignant neoplasm				<0.0001
No	86 056 (87.5)	22 778 (88.4)	63 278 (87.2)	
Yes	12 310 (12.5)	2987 (11.6)	9323 (12.8)	
Dementia				<0.0001
No	87 104 (88.6)	24 758 (96.1)	62 346 (85.9)	
Yes	11 262 (11.4)	1007 (3.9)	10 255 (14.1)	
Solid organ transplant				<0.0001
No	97 171 (98.8)	25 265 (98.1)	71 906 (99.0)	
Yes	1195 (1.2)	500 (1.9)	695 (1.0)	
HIV/AIDS				0.0018
No	97 727 (99.4)	25 563 (99.2)	72 164 (99.4)	
Yes	639 (0.6)	202 (0.8)	437 (0.6)	
Dyslipidaemia				<0.0001
No	87 410 (88.9)	22 264 (86.4)	65 146 (89.7)	
Yes	10 956 (11.1)	3501 (13.6)	7455 (10.3)	
Cirrhosis without transplant				<0.0001
No	96 841 (98.4)	25 283 (98.1)	71 558 (98.6)	
Yes	1525 (1.6)	482 (1.9)	1043 (1.4)	
History of stroke				
No	92 174 (93.7)	24 199 (93.9)	67 975 (93.6)	0.0950
Yes	6192 (6.3)	1566 (6.1)	4626 (6.4)	
Acute underlying conditions				
Acute pulmonary failure				<0.0001
No	67 549 (68.7)	10 522 (40.8)	57 027 (78.5)	
Yes	30 817 (31.3)	15 243 (59.2)	15 574 (21.5)	
Acute respiratory distress syndrome				<0.0001
No	86 724 (88.2)	16 101 (62.5)	70 623 (97.3)	
Yes	11 642 (11.8)	9664 (37.5)	1978 (2.7)	
Acute pulmonary infection*				<0.0001
No	83 413 (84.8)	18 232 (70.8)	65 181 (89.8)	
Yes	14 953 (15.2)	7533 (29.2)	7420 (10.2)	
Shock†				<0.0001
No	92 732 (94.3)	20 649 (80.1)	72 083 (99.3)	
Yes	5634 (5.7)	5116 (19.9)	518 (0.7)	
Myocardial infarction				<0.0001
No	97 712 (99.3)	25 379 (98.5)	72 333 (99.6)	
Yes	654 (0.7)	386 (1.5)	268 (0.4)	
Acute pulmonary embolism				<0.0001
No	94 331 (95.9)	23 596 (91.6)	70 735 (97.4)	
Yes	4035 (4.1)	2169 (8.4)	1866 (2.6)	
Thrombophlebitis				<0.0001

Continued

Table 2 Continued

	Overall (n=98 366)	Patients admitted to a critical care unit (n=25 765)	Patients admitted to a hospital care unit (n=72 601)	P value
No	96 057 (97.7)	24 413 (94.8)	71 644 (98.7)	
Yes	2309 (2.3)	1352 (5.2)	957 (1.3)	
Acute liver failure				<0.0001
No	97 517 (99.1)	25 183 (97.7)	72 334 (99.6)	
Yes	849 (0.9)	582 (2.3)	267 (0.4)	
Acute kidney injury				<0.0001
No	85 545 (87.0)	19 382 (75.2)	66 163 (91.1)	
Yes	12 821 (13.0)	6383 (24.8)	6438 (8.9)	

*Acute pulmonary infection, excluding viral infections.
†Shock includes hypovolaemic shock, cardiogenic shock or infectious shock.
‡Charlson comorbidity index without age.

acute conditions were acute pulmonary failure (31%), acute pulmonary infection (15%), acute kidney injury (13%) and acute respiratory distress syndrome (12%).

Follow-up and survival

Overall, 79 920 (81%) patients were alive at discharge and 18 446 (19%) died in hospital. The cumulative proportion of death was higher for patients admitted to CCUs than those to HCUs (24% vs 17%) (table 1). The proportion of deaths was the highest (26%) for those who were admitted to a CCU and stayed in only one hospital (figure 1). Median survival was 77 days (95% CI 72 to 83) and 48 days (95% CI 46 to 52) for patients in CCUs and HCUs, respectively (table 1). About 6% of the patients admitted to CCU had a survival time >60 days versus 0.6% for those admitted to HCU.

Older men had a lower probability of survival. The probability of survival decreased with increasing age for patients in CCUs, especially men (figure 2A,C). Very few deaths occurred for patients <18 years old, with no difference according to gender. For men admitted to CCUs, median survival decreased from 154 days for the 46–65 years group to 22 days (IQR: 19–25) for those ≥85 years of age. For women admitted to CCUs, median survival decreased from 122 days in the 46–65 years group to 32 days (IQR: 27–40) for those ≥85 years of age (table 1).

Among patients admitted to HCUs, survival was less correlated with age, particularly for men and women ≥85 years of age, who had the lowest probability of survival (figure 2B,D). Men had a median survival of 23 days (IQR: 22–25), whereas that of women was 46 days (IQR: 43–52). For women aged below 70 years, median survival was essentially the same: approximately 80 days (table 1).

Risk factors of mortality

Cox proportional adjusted HRs (aHRs) for the variables that remained in the final multivariable model are presented in figure 3. Results of univariable and initial multivariable models are available in online supplemental table S2.

Age was a strong risk factor associated with death for patients hospitalised with COVID-19 in both CCUs and HCUs. The aHR for death varied from 1.60 (95% CI 1.35 to 1.88) for patients aged 46–65 years to 8.17 (95% CI 6.86 to 9.72) for those aged 85 years and above for patients in CCUs. The aHR of death associated with age was more than two times higher for patients admitted to HCUs than those admitted to CCUs, varying from 3.29 (95% CI 2.48 to 4.37) in the 46–65 years group to 18.21 (95% CI 13.90 to 23.86) for those ≥85 years of age.

Gender was not significantly associated with death for patients admitted to CCUs in multivariable analysis, aHR 1.03 (95% CI 0.98 to 1.09, p=0.2504). The main chronic conditions associated with death were cirrhosis without transplant, aHR 1.41 (95% CI 1.21 to 1.64, p<0.001), malignant neoplasm, 1.34 (95% CI 1.25 to 1.43), p<0.001, and dementia, 1.30 (95% CI 1.16 to 1.46, p<0.001). A BMI ≥40 kg/m², history of stroke, coronary artery disease, diabetes and chronic pulmonary disease were also risk factors of death, with moderate aHRs. Hypertension was associated with a decreased risk of death, aHR 0.81 (95% CI 0.76 to 0.85, p<0.001). The main acute conditions associated with death were shock, aHR 1.64 (95% CI 1.54 to 1.74, p<0.001), acute respiratory distress syndrome, 1.60 (95% CI 1.50 to 1.70, p<0.001), acute liver failure, 1.54 (95% CI 1.37 to 1.74, p<0.001)) and acute kidney injury, 1.34 (1.26 to 1.42, p<0.001)) (figure 3).

Among patients admitted to HCUs, men had a higher risk of death, aHR: 1.28 (95% CI 1.23 to 1.33, p<0.001). As for patients admitted to CCUs, the main chronic conditions associated with death were malignant neoplasm, aHR 1.41 (95% CI 1.35 to 1.4, p<0.001) and cirrhosis without transplant, 1.27 (95% CI 1.12 to 1.45, p<0.001). A history of stroke, chronic kidney disease and dementia were factors associated with a moderate risk of death. Diabetes and chronic pulmonary disease were not

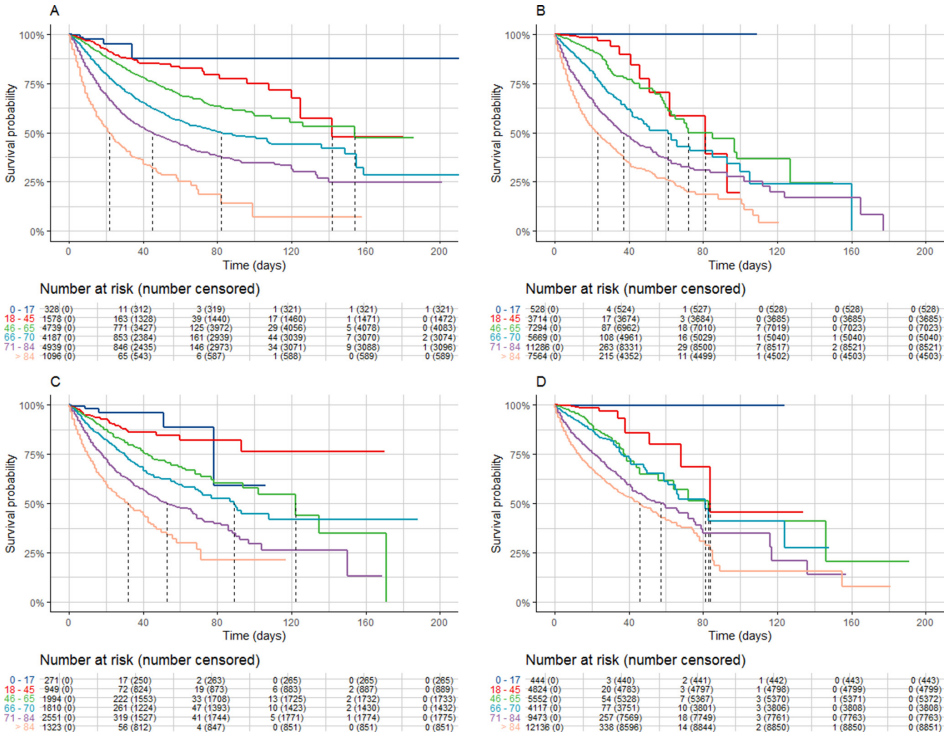

Figure 2 Probability of survival according to gender and admission to a critical care or hospital care unit Kaplan-Meier estimates for six age groups (<18, 18–45, 46–65, 66–70, 71–84 and ≥85) by sex and admission to critical care unit. (A) Survival curves by age group for men admitted to a critical care unit. (B) Survival curves by age group for men admitted to a hospital care unit. (C and D) Survival curves for women admitted to a critical care unit and those admitted to a hospital care unit, respectively. A survival table showing the number of patients at risk and the number censored is shown below each graph.

significantly associated with death. Asthma was associated with a reduced risk of death, aHR 0.76 (95% CI 0.68 to 0.85, p<0.001). Acute respiratory distress syndrome, aHR 3.95 (95% CI 3.73 to 4.18, p<0.001), acute pulmonary failure, 3.16 (95% CI 3.05 to .28, p<0.001) and shock 2.91 (95% CI 2.63 to 3.23, p<0.001) were associated with a higher risk of death (figure 3).

Sensitivity analyses yielded similar results to those of the main analysis.

DISCUSSION

Principal findings

In this study, we investigated in-hospital mortality and the associated risk factors in a large cohort of patients hospitalised with COVID-19 in France. Age was the major independent risk factor of death for both patients in CCUs and those in HCUs. However, patients in HCUs had a higher risk of death associated with age than those in CCUs. Mortality increased was strongly correlated with age for men and women in CCUs and men ≥85 years of age had the highest probability of death. Among patients admitted to HCUs, mortality was less correlated with age, especially for women.

Comparison with other studies

We stratified our analysis according to CCU or HCU admission, as the patients and care differ between CCUs and HCUs. This was illustrated by the larger survival times for patients in CCU compared with those in HCU, consequence of a higher proportion of 'outlier' survival times (>60 days) in CCU and selection bias regarding age and dementia. Older patients with a higher proportion of dementia were less likely admitted to CCU.

The proportion of patients admitted to CCUs (26% in our study) was in the range of that previously reported.[8 10 16] We found a higher proportion of men admitted to CCUs, consistent with studies in the UK reporting 67%–70% men in intensive care.[17 18] As shown previously, men hospitalised with COVID-19 were more likely to have comorbidities and have a higher risk of worse outcomes; thus, they were logically more likely to be admitted to CCUs.[16 19 20] We found a lower proportion of patients with dementia in CCUs, as they are more often ≥85 years of age, consistent with the findings of a study in a centre within the highest health and wealth band in the UK.[18] The risk–benefit balance of admitting older patients with dementia to CCUs is a larger and openly debated question, although it is more challenging in the context of the COVID-19 epidemic. Similarly to studies in the UK, we found a lower proportion of malignant neoplasm and chronic kidney disease in patients admitted to CCUs.[17 18]

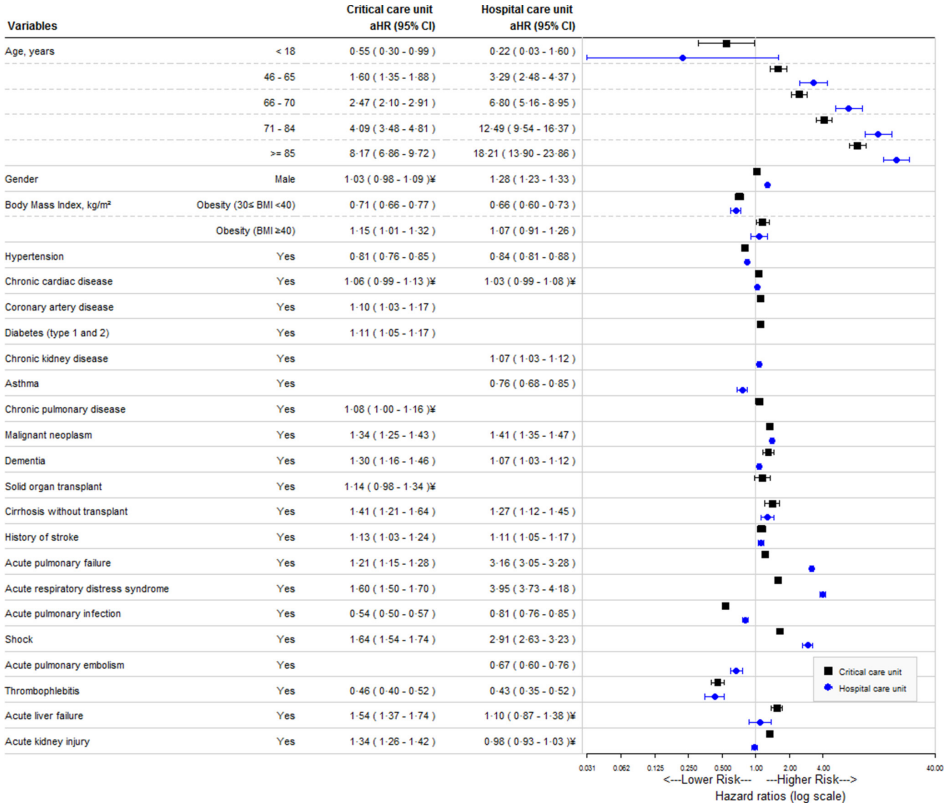

Figure 3 Factors associated with in-hospital mortality stratified by admission to critical care in a cohort of patients hospitalised with COVID-19 in France between 1 January and 30 June 2020 forest plot showing Cox proportional multivariable adjusted HRs (aHRs) in the subpopulation of patients admitted to a critical care unit, represented by black squares, and those admitted to a hospital care unit, represented by blue circles. The bars on each side of the squares or circles represent the 95% CIs. The aHRs and corresponding 95% CI are shown on a log-scale on the plot. The aHRs are reported in columns 3 and 4. The reference groups were: 18–45 for age and <30 kg/m² for body mass index (BMI). ¥aHR with p value >0.01

Patients admitted to CCUs had more severe acute conditions and a higher cumulative mortality rate. Consistent with previous studies, age was the strongest risk factor for death for patients hospitalised with COVID-19.[10 16 19–21] The risk of death associated with age was more than two times higher for patients admitted to HCUs than those admitted to CCUs. Patients admitted to CCUs were kept alive and followed much longer in care. Mortality was markedly correlated with age among both men and women in CCUs. A previous study demonstrated an exponential relationship between mortality and age in patients with COVID-19.[22] Gender was not significantly associated with death in CCUs, whereas men had a higher risk of death in HCUs. Although the results of published studies were not stratified according to admission to CCUs,[16 19–21 23] a study in New York also found no association between mortality and gender after adjusting for vital signs and laboratory parameters.[21] The cumulative mortality rate in our study was in the range of those of other studies.[10 16 21]

Published studies have reported several comorbidities to be risk factors of mortality for patients hospitalised with COVID-19.[8 10 16 17 19–21] We found a higher risk of mortality for patients with malignant neoplasm, cirrhosis without transplant and dementia in both CCUs and HCUs. These results are consistent with previous findings.[10 16 20 24] Dementia had a higher effect on mortality for patients admitted to CCUs than those admitted to HCUs. The management of COVID-19 for patients with dementia is an issue that requires further focused analyses.[25 26] Definitions of comorbidities vary widely, which made it difficult to interpret comparisons across studies.

In addition to the age and comorbidities, other factors associated with mortality such as early access to care and treatment have been explored.[27 28] Data about the time between onset of illness and hospitalisation were not available. Thus, we were not able to account for access to care at the individual level, but we took into account the variability of care at the departmental level through random effects in modelling. The analysis stratification according to admission to CCU contributes to control potential biases due to differences in care delivery, assuming that patients admitted to CCU benefit from recent treatment regimens such as steroids, tocilizumab or non-invasive ventilation.

Strengths and limitations of study

The strengths of this analysis were its reliance on the analysis of the entire sequence of care and stratification

according to admission to critical care. Unlike previous studies,[11 19] we did not analyse the hospital stay within one hospital but used the complete sequence of hospitalisation. Indeed 16% of patients were transferred to at least one other hospital. If this had not been done, we would have underestimated the mortality rate and LOS and introduced a bias in the risk factor analysis. In addition, stratification of the results according to CCU admission was crucial, as we show that the risk of death and its risk factors were different according to the type of unit of hospitalisation.

Our study had several limitations. First, we used the PMSI database, which is a large nationwide database with a risk of variability in coding of the underlying conditions. To mitigate this risk, we relied on a team of physicians with experience in medical information who selected the ICD-10 codes included in our analysis, taking the coding rules and the reliability of the information into account. To enhance the completeness of the description of chronic underlying conditions, we expanded our research to 2 years before the hospitalisation with COVID-19. Second, as we did not have the date linked to the codes, we were unable to ascertain the precise moment of occurrence of the acute conditions. Combining the PMSI and other local or national health databases may be interesting to explore the relationship between mortality and acute event leading to admission or treatments. Third, we did not have direct measures of severity. Thus, we stratified our analysis according to admission to critical care. In addition, we used the Charlson comorbidity index as a proxy of disease burden. We did not include this index in the multivariate analysis as we were interested in exploring the independent effect of several comorbidities on mortality. Fourth, we might have underestimated or overestimated mortality, as we included patients with an ICD-10 of COVID-19, irrespective of the reason of their admission. However, our study focused on the first epidemic wave of SARS-CoV-2 in France, during which most of the screening tests were carried out on symptomatic patients. Sensitivity analysis in which we varied the COVID-19 case definition resulted in an insignificant impact on our findings. Fifth, as we included the first care sequence per patient, we did not consider in-hospital deaths occurring in a later care sequence. This could have led to biased results if patients with multiple care sequences differed in terms of mortality risk factors from those with a unique care sequence.

CONCLUSIONS AND POLICY IMPLICATIONS

In accordance with previous findings, our study confirmed the fact that age is the major risk factor of death for patients hospitalised with COVID-19. Gender is an additional risk factor of death for patients admitted to HCUs, with a higher risk among older men. Comorbidities also play a role, with an increasing risk of death for patients with malignant neoplasms, cirrhosis without transplant and dementia in both CCUs and HCUs. These results are reassuring in terms of current vaccination policies that target older individuals. Mortality risk factors may have changed with successive waves of the epidemic due to increasing knowledge about the infection, the impact of preventive measures and changes in population behaviour. A comparison of patient characteristics between the successive waves of the epidemic and their association with severe outcomes should make it possible to assess the management of the crisis in France and guide subsequent decisions in the current context of continuous adaptation of policies to control the epidemic.

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