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

Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

# Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score☆

Giusy Tiseo [1], Ili Margalit [2], Marco Ripa [3], Vanni Borghi [4], Hefziba Green [5,6], Virginie Prendki [7,8], Niccolò Riccardi [1], Yael Dishon [9], Giovanni Battista Perego [10], Alessandro Grembiale [11], Laura Galli [3], Marco Tinelli [12], Antonella Castagna [3], Cristina Mussini [13], Dafna Yahav [14], Mical Paul [9], Marco Falcone [1,*], on behalf of the ESCMID Study Group for Infections in the Elderly (ESGIE)

[1] *Infectious Diseases Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*
[2] *Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel*
[3] *Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy*
[4] *Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy*
[5] *Department of Medicine A, Kaplan Medical Center, Rehovot, Israel*
[6] *Faculty of Medicine, Hebrew University of Jerusalem Jerusalem, Israel*
[7] *Division of Internal Medicine for the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland*
[8] *Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland*
[9] *Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel*
[10] *IRCCS Istituto Auxologico Italiano, San Luca Hospital, Milan, Italy*
[11] *Azienda Sanitaria Friuli Occidentale, 'Santa Maria degli Angeli' Hospital, Pordenone, Italy*
[12] *Istituto AuxologicoItaliano, IRCCS, San Luca Hospital, Milan, Italy*
[13] *Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Italy*
[14] *Infectious Diseases Unit, Sheba Medical Center, Ramat-Gan, Israel*

ARTICLE INFO

*Article history:*
Received 17 July 2022
Received in revised form
20 September 2022
Accepted 22 September 2022
Available online xxx

Editor: L. Leibovici

*Keywords:*
COVID-19
Dependency
Elderly
SARS-CoV-2
Survival

ABSTRACT

*Objective:* To identify predictors of 30-day survival in elderly patients with coronavirus disease 2019 (COVID-19).

*Methods:* Retrospective cohort study including patients with COVID-19 aged ≥65 years hospitalized in six European sites (January 2020 to May 2021). Data on demographics, comorbidities, clinical characteristics, and outcomes were collected. A predictive score (FLAMINCOV) was developed using logistic regression. Regression coefficients were used to calculate the score. External validation was performed in a cohort including elderly patients from a major COVID-19 centre in Israel. Discrimination was evaluated using the area under the receiver operating characteristic curve (AUC) in the derivation and validation cohorts. Survival risk groups based on the score were derived and applied to the validation cohort.

*Results:* Among 3010 patients included in the derivation cohort, 30-day survival was 74.5% (2242/3010). The intensive care unit admission rate was 7.6% (228/3010). The model predicting survival included independent functional status (OR, 4.87; 95% CI, 3.93–6.03), a oxygen saturation to fraction of inspired oxygen ($SpO_2/FiO_2$) ratio of >235 (OR, 3.75; 95% CI, 3.04–4.63), a C-reactive protein level of <14 mg/dL (OR, 2.41; 95% CI, 1.91–3.04), a creatinine level of <1.3 (OR, 2.02; 95% CI, 1.62–2.52) mg/dL, and absence of fever (OR, 1.34; 95% CI, 1.09–1.66). The score was validated in 1174 patients. The FLAMINCOV score ranges from 0 to 15 and showed good discrimination in the derivation (AUC, 0.79; 95% CI, 0.77–0.81; $p < 0.001$) and validation cohorts (AUC, 0.79; 95% CI, 0.76–0.81; $p < 0.001$). Thirty-day survival ranged

☆ FLAMINCOV score takes its name from the project entitled "Role of inFLAMmatory markers as predictors of mortality IN elderly patients with COVid-19 (FLAMINCOV)".

* Corresponding author. Marco Falcone, Infectious Diseases Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria Pisana, Via Paradisa 2, 56124, Pisa, Italy.
*E-mail address:* marco.falcone@unipi.it (M. Falcone).

https://doi.org/10.1016/j.cmi.2022.09.019

from 39.4% (203/515) to 95.3% (634/665) across four risk groups according to score quartiles in the derivation cohort. Similar proportions were observed in the validation set.

*Discussion:* The FLAMINCOV score identifying elderly with higher or lower chances of survival may allow better triage and management, including intensive care unit admission/exclusion. **Giusy Tiseo, Clin Microbiol Infect 2022;▪:1**



## Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, the elderly have been identified as one of the most vulnerable patient groups [1,2]. Mortality rates change across age categories, ranging from 9.5% in patients aged 60–69 years up to 29.6% in those aged >80 years [3]. The highest mortality rates are reported in elderly patients admitted to the intensive care unit (ICU) [4,5]. Thus, intensivists were initially discouraged to admit elderly patients to the ICU, and age has been often considered the only determining factor in ICU triage decisions. This approach raised ethical concerns because the poor outcome reported in the elderly in some studies has been related to the delayed ICU admission of these patients [6]. The clinical frailty scale (CFS) seems to better predict the outcome of elderly patients instead of age itself [7]. However, the use of CFS for critical care decisions has been debated because mildly frail older adults may still have enough intrinsic capacity to withstand the stressors of hospitalization and achieve clinical success [8]. Thus, identification of elderly patients with COVID-19 who have a higher chance of survival might be useful to better decide treatments and allocation of these patients while reducing the risk of therapeutic obstinacy in those with a reduced probability of recovery.

The aim of our study was to identify predictors of 30-day survival in a large cohort of elderly patients with COVID-19 and stratify patients according to their probability to survive.

## Methods

### *Patient cohort and study design*

This is a retrospective study including hospitalized patients aged ≥65 years with COVID-19 at six sites (University Hospital of Pisa, Italy; Rabin Medical Center, Beilinson Hospital, Israel; Istituto Auxologico Italiano, Milan, Italy; Hospital of Modena, Italy; San Raffaele Scientific Institute, Milan, Italy; and Geneva University Hospitals, Switzerland) from January 2020 to May 2021. The inclusion criteria were as follows: 1) an age ≥65 years; 2) laboratory-confirmed COVID-19, diagnosed by a positive SARS coronavirus 2 real-time polymerase chain reaction test result on a nasopharyngeal swab. Model development and reporting followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement and published recommendations for prediction models [9,10]. Patients who met the inclusion criteria constituted the population of interest and were included in the derivation set to develop a score for survival prediction in elderly patients. The derived score was validated in a validation set of elderly patients hospitalized in the Rambam Health Care Campus, Haifa, Israel, from April 2020 to January 2022. The inclusion criteria used for the derivation population were used to select patients for the validation set.

This study is part of a project entitled "Role of inFLAMmatory markers as predictors of mortality IN elderly patients with COVid-19 (FLAMINCOV)". The protocol was approved by the medical ethics committee of Area Vasta Nord Ovest (ID 19283) and the institutional ethics review boards of participating hospitals. Written informed consent was obtained from participants according to local rules.

### *Data collection and potential predictive variables*

Epidemiological and demographic information, medical history, comorbidities, information on clinical symptoms on admission, treatments, and interventions received during the hospital course, including the need for oxygen or invasive mechanical ventilation support, were collected from medical records using a prespecified case report form.

Functional capacity was evaluated according to the patient's ability to perform activities of daily living by using the Norton scale on admission (Table S1) [11]. Clinical signs and symptoms included fever (body temperature of >38°C), dyspnoea, and confusion/altered mental status on admission. Oxygen saturation ($SpO_2$) values on admission were collected and oxygen saturation to fraction of inspired oxygen ratio ($SpO_2/FiO_2$) was also calculated [12]. A $SpO_2/FiO_2$ ratio was categorized as >235 or ≤235 because of its correlation with a arterial oxygen partial pressure to fraction of inspired oxygen ($PiO_2/FiO_2$) ratio of 200> or ≤200 [13]. Laboratory findings on admission included white blood cell count, lymphocyte, platelet counts, C-reactive protein (CRP), procalcitonin, D-dimer, and ferritin levels. Data about treatments (steroids and immunosuppressive drugs) and interventions (low-flow oxygen, high-flow oxygen therapy, non-invasive and invasive mechanical ventilation) were collected.

The clinical information used to calculate the prognostic score was obtained on the day of admission to the hospital.

### *Outcome*

The primary outcome measure was 30-day survival.

### *Statistical analysis*

Continuous variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as frequencies and proportions. The comparison between patients who survived and those who did not was performed using the Mann-Whitney U test, Pearson's chi-squared test, or Fisher's exact test, as appropriate. Continuous variables were dichotomized according to Classification and Regression Tree analysis, apart from $SpO_2/FiO_2$ ratio (categorized as >235 or ≤235) and the $PiO_2/FiO_2$ ratio (categorized as >200 or ≤200).

To explore factors associated with survival, univariable and multivariable logistic regression models were used. A multivariable analysis was performed to identify factors independently associated with 30-day survival using a forward regression model. Variables with statistical significance ($p < 0.05$) on univariate analysis were included in the multivariable model. Details about the

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019

included variables and score selection are reported in Supplementary Materials. OR and 95% CI were calculated.

All patients from the six participating centres were included in the derivation cohort. The predictive score (FLAMINCOV that takes its name from the study project, as above specified) was developed using the regression coefficients as in Sullivan's scoring system by dividing each regression coefficient by the smallest and rounding to the nearest unit. Imputation for missing variables was considered if missing values were less than 20%. We assessed discrimination by using the area under the receiver operating characteristic curve (AUC). A value of 0.5 indicates no predictive ability, 0.7–0.8 is considered good, 0.8–0.9 is considered excellent, and >0.9 is considered outstanding [14]. The Lemeshow–Hosmer goodness-of-fit test was used to evaluate calibration. The cohort was split into quartiles on the basis of the regression probabilities, and survival rates were calculated for the four risk groups both in the derivation and validation cohorts.

The variables required for calculating the FLAMINCOV score were collected for external validation. The AUC, Lemeshow–Hosmer goodness-of-fit test, and 30-day survival by risk groups, defined by the same score thresholds as in the derivation cohort, were calculated also for the validation cohort. All statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corp), and were considered significant at a p value of <0.05 (two-tailed).

## Results

### *Study population*

A total of 3010 elderly patients were included in the derivation cohort. Table 1 shows the demographic and clinical characteristics for the derivation cohort. The median age was 77 years (IQR, 70–84); 42.2% of the patients were women. The 30-day survival rate was 74.5% (2242/3010 patients). A progressive increase in 30-day mortality rates was observed during the course of the study (Fig. 1). Overall, 228/3010 (7.6%) patients were hospitalized in the ICU. Time from emergency department (ED) admission to ICU transfer was 2 (IQR, 0–6) days. Data on co-infections on hospital admission were available in 1886/3010 (62.6%) patients. Among them, co-infections were detected in 7.4% of the patients (140/1886) and represented by respiratory bacterial infections ($n$ = 101/1886, 5.4%), urinary tract infections ($n$ = 19/1886, 1%), and other types (one *Clostridium difficile* infection, one *Enterococcus faecalis* bacteraemia).

Compared with patients who survived within 30 days from admission, non-survivors were significantly older and more frequently men (Table 1). Dependent functional status, diabetes mellitus, cardiovascular disease, and chronic kidney failure were more common in non-survivors. Survivors were more likely to

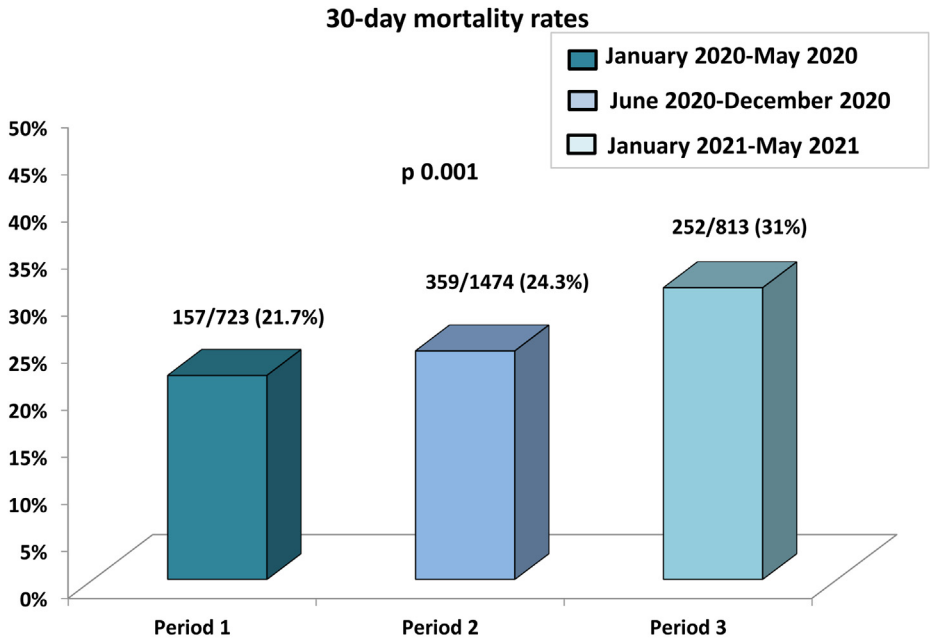
**Table 1**
Comparison of elderly patients with COVID-19 who died and those who did not within 30 days from hospital admission

| | Total ($n$ = 3010) | 30-day survivors ($n$ = 2242) | Non-survivors ($n$ = 768) | p |
|---|---|---|---|---|
| Age (y), median (IQR) | 77 (70–84) | 75 (69–82) | 82 (75–87) | **<0.001** |
| Female sex, n (%) | 1270 (42.2) | 982 (43.8) | 288 (37.5) | **0.002** |
| Functional status, n/N (%) | | | | |
| Independent functional status | 1454/2879 (50.5) | 1275/2112 (60.4) | 179/767 (23.3) | **<0.001** |
| BMI, median (IQR) | 27 (24–30.5) | 27.9 (24.8–31.2) | 25.9 (23.3–28.9) | **<0.001** |
| Comorbidities, n (%) | | | | |
| Diabetes mellitus | 861 (28.6) | 615 (27.4) | 246 (32) | **0.015** |
| Cardiovascular disease | 1090 (36.2) | 762 (34) | 328 (42.7) | **<0.001** |
| Hypertension | 1256 (41.7) | 946 (42.2) | 310 (40.4) | 0.375 |
| Cerebrovascular disease | 311 (10.3) | 218 (9.7) | 93 (12.1) | 0.061 |
| Chronic pulmonary disease | 307 (10.2) | 220 (9.8) | 87 (11.3) | 0.231 |
| Chronic kidney disease | 319 (10.6) | 189 (8.4) | 130 (16.9) | **<0.001** |
| Chronic liver disease | 38 (1.3) | 29 (1.3) | 9 (1.2) | 0.794 |
| Solid cancer | 415 (13.8) | 295 (13.2) | 120 (15.6) | 0.087 |
| Immunosuppressive treatment before admission, n (%) | 355 (11.8) | 260 (11.6) | 95 (12.4) | 0.567 |
| Clinical presentation on admission, n/N (%) | | | | |
| Absence of fever | 2091/2988 (70) | 1603/2228 (71.9) | 488/760 (64.2) | **<0.001** |
| Normal mental status | 2562 (85.1) | 2032 (90.6) | 530 (69) | **<0.001** |
| Absence of dyspnoea | 1925 (64) | 1561 (69.6) | 364 (47.4) | **<0.001** |
| $PaO_2/FiO_2$ > 200 | 1561/2791 (55.9) | 1350/2023 (66.7) | 211/768 (27.5) | **<0.001** |
| $SpO_2/FiO_2$ > 235 | 1495 (49.7) | 1303 (58.1) | 192 (25) | **<0.001** |
| Physical examination on admission, n/N (%) | | | | |
| Absence of hypotension | 2815/2959 (95.1) | 2126/2191 (97) | 689/768 (89.7) | **<0.001** |
| No tachycardia (HR < 100) | 2370/2896 (81.8) | 1787/2182 (81.9) | 583/714 (81.7) | 0.883 |
| No tachypnoea (RR < 20) | 2132/2747 (77.6) | 1731/2173 (79.7) | 401/574 (69.9) | **<0.001** |
| SOFA score, $n$ = 2746 | 3 (3–4) | 3 (3–4) | 3 (3–4) | 0.716 |
| Laboratory exams at ED | | | | |
| Creatinine, mg/dL, median (IQR) | 1 (0.8–1.3) | 1 (0.9–1.2) | 1 (0.8–1.7) | **<0.001** |
| Creatinine <1.3 mg/dL, n (%) | 2385 (79.2) | 1886 (84.1) | 49 (65) | **<0.001** |
| Lymphocytes >800/mcL, n (%) | 2138 (71) | 1651 (73.6) | 487 (63.4) | **<0.001** |
| Platelet count >150 × $10^3$/mcL, n/N (%) | 2295/2918 (78.6) | 1744/2154 (81) | 551/764 (72.1) | **<0.001** |
| Ferritin <1325 ng/mL, n/N (%) | 1183/1431 (82.7) | 906/1068 (84.8) | 277/363 (76.3) | **<0.001** |
| D-dimer < 1650 mg/L, n/N (%) | 1307/1949 (67.1) | 1037/1421 (73) | 270/528 (51.1) | **<0.001** |
| C-reactive protein <14 mg/dL, n/N (%) | 2086/2613 (79.8) | 1617/1919 (84.3) | 469/694 (67.6) | **<0.001** |
| COVID-19 treatment, n (%) | | | | |
| Low molecular weight heparin | 2496 (82.9) | 1861 (83) | 635 (82.7) | 0.837 |
| Remdesivir | 489 (16.2) | 380 (16.9) | 109 (14.2) | 0.074 |
| Steroids | 1700 (56.5) | 1195 (53.3) | 505 (65.8) | **<0.001** |
| Convalescent plasma | 58 (1.9) | 44 (2) | 14 (1.8) | 0.808 |
| Immunomodulatory drugs[a] | 365 (12.1) | 266 (11.9) | 99 (12.9) | 0.452 |

p value were calculated using Mann-Whitney U test for continuous variables and chi-square test for categorical variables; p < 0.05 are highlighted in bold. BMI, body mass index; COVID-19, coronavirus disease 2019; ED, Emergency Department; HR, hazard ratio; IQR, interquartile range; PiO2/FiO2: partial pressure arterial oxygen to fraction of inspired oxygen ratio; RR respiratory rate; SaO2/FiO2: oxygen saturation to fraction of inspired oxygen ratio; SOFA: sequential Organ Failure Assessment.

[a] Either tocilizumab or baricitinib.

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019




| PERIOD 1<br>January 2020-May 2020 | PERIOD 2<br>June 2020-December 2020 | PERIOD 3<br>January 2021-May 2021 |
|---|---|---|
| 157/723 (21.7%) | 359/1474 (24.3%) | 252/813 (31%) |

**Fig. 1.** Thirty-day mortality rates across the different periods.

present with no fever, normal mental status, no dyspnoea, and a $SpO_2/FiO_2$ ratio of >235 on hospital admission. Furthermore, survivors had less frequent lymphopenia, thrombocytopenia, and high ferritin and CRP values on admission (Table 1).

*Determinants of survival and derivation of the FLAMINCOV score*

The FLAMINCOV score was derivated in 2586/3010 (85.9%) patients with complete data. The study flow chart is reported in Fig. 2. Comparison between patients with missing data and those included showed that missing data occurred more commonly among younger patients and those with fewer comorbidities; 30-day survival was higher among patients with missing data (Table S2). The 30-day survival rate was 73.5% (1901/2586).

On multivariable analysis (Table 2), independent functional status (OR, 4.87; 95% CI, 3.93–6.03; $p < 0.001$), a $SpO_2/FiO_2$ ratio >235 (OR, 3.75; 95% CI, 3.04–4.63; $p < 0.001$), CRP <14 mg/dL (OR, 2.41; 95% CI, 1.91–3.04; $p < 0.001$), a creatinine level of <1.3 mg/dL (OR, 2.02; 95% CI, 1.62–2.52; $p < 0.001$) and absence of fever (OR, 1.34; 95% CI, 1.09–1.66; p 0.006) were factors independently associated with 30-day survival. These findings were confirmed also considering time periods and centres as variables in the multivariable model (Table S3).

Table 2 shows the FLAMINCOV score and designation of points. The score ranged from 0 to 15. The AUC of our model was 0.79 (95%

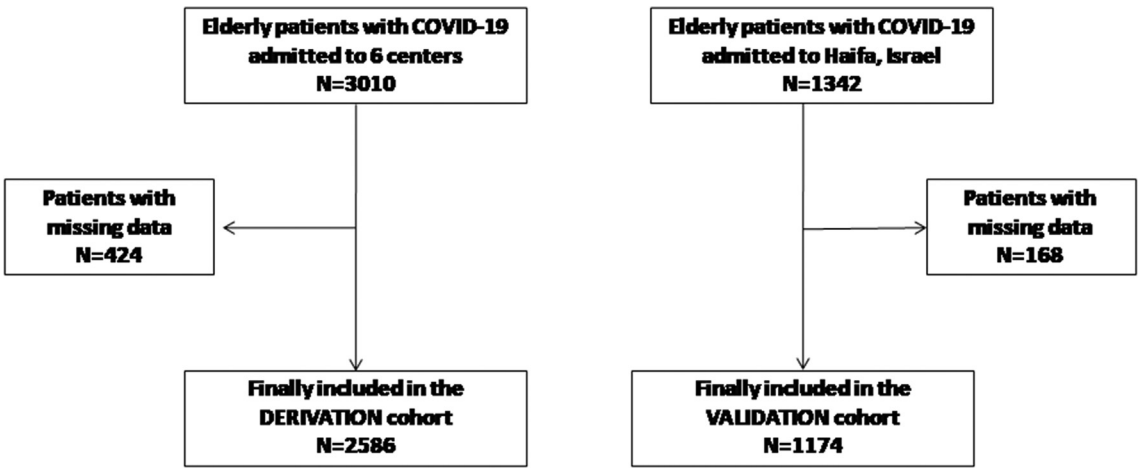



**Fig. 2.** Study flow chart (both derivation and validation cohort). COVID-19, coronavirus disease 2019.

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019

**Table 2**
Multivariate logistic regression analysis of factors independently associated with 30-day survival and score points

| | β coefficient | OR (95% CI) | p | Point-based risk score |
|---|---|---|---|---|
| Independent functional status | 1.584 | 4.87 (3.93–6.03) | <0.001 | +5 |
| SaO2/FiO2 > 235 | 1.322 | 3.75 (3.04–4.63) | <0.001 | +4 |
| CRP <14 mg/dL | 0.881 | 2.41 (1.91–3.04) | <0.001 | +3 |
| Creatinine <1.3 mg/dL | 0.705 | 2.02 (1.62–2.52) | <0.001 | +2 |
| Absence of fever | 0.296 | 1.34 (1.09–1.66) | 0.006 | +1 |

Multivariable analysis was performed using a forward regression model. The variables entered but not retained were age, female sex, diabetes mellitus, and normal mental status. CRP, C-reactive protein; $SaO_2/FiO_2$: oxygen saturation to fraction of inspired oxygen ratio

CI, 0.77–0.81; p < 0.001) (Fig. 3, panel a). The goodness-of-fit Hosmer–Lemeshow $\chi^2$ was 3.6 (p 0.822), indicating a good calibration.

The FLAMINCOV score was classified into four risk groups according to percentiles of the score: 1) risk group 1 (score, ≤5; observed 30-day survival, 39.4%), risk group 2 (score, 6–9; observed survival, 65.8%), risk group 3 (score, 10–11; observed survival, 85.9%), and risk group 4 (score, 12–14; observed 30-day survival, 95.3%). Survival rates across the different risk groups are reported in Fig. 4, panel A.

*External validation*

The external population from the Rambam Health Care Campus, Haifa (Israel) included 1342 elderly patients. The FLAMINCOV score was validated in 1174/1342 (87.5%) patients with complete data (Fig. 2). A comparison between patients with missing data and those included showed that missing data occurred among patients with fewer comorbidities but lower 30-day survival and a short time to death (Table S4). The 30-day survival rate was 68.1% (799/1174 patients). The AUC of the model was 0.77 (95% CI, 0.75–0.8; p < 0.001) (Fig. 3, panel b). The goodness-of-fit Hosmer–Lemeshow $\chi^2$ was 7.9 (p 0.340), indicating reasonable calibration. When applying the FLAMINCOV score risk group definitions in the validation cohort, 30-day survival rates were as follows: 38.4% in risk group 1, 60.2% in risk group 2, 77.8% in risk group 3, and 94.5% in risk group 4 (Fig. 4, panel B).

## Discussion

In this multi-centre observational cohort study, we propose the FLAMINCOV score to predict 30-day survival in elderly patients with COVID-19 and guide clinicians to their optimal management and allocation. The score comprises variables easily obtainable at the ED before patient triage.

During the first wave when hospitals faced with significant challenges, elderly patients were usually excluded from ICU care because advanced age appeared to be strongly associated with poorer outcomes [15]. In a survey from 21 countries, one-third of the responders declared that elderly patients were not candidates

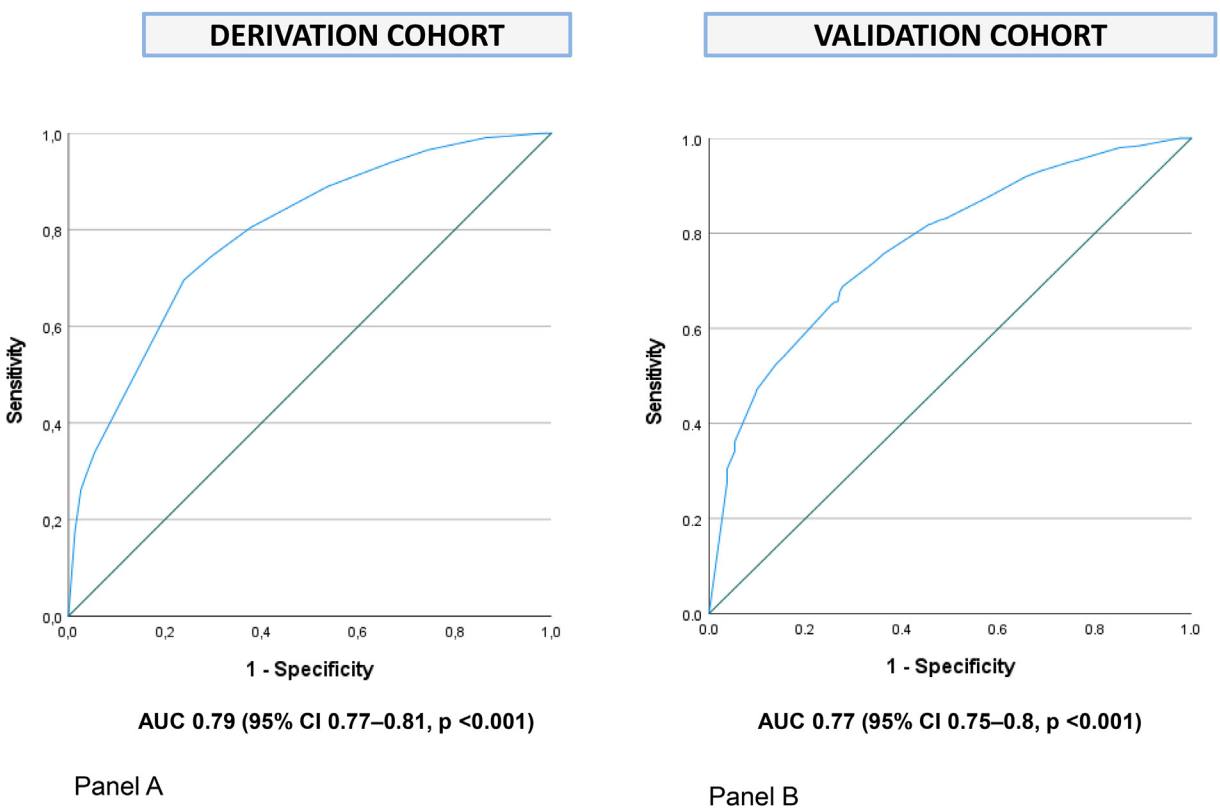
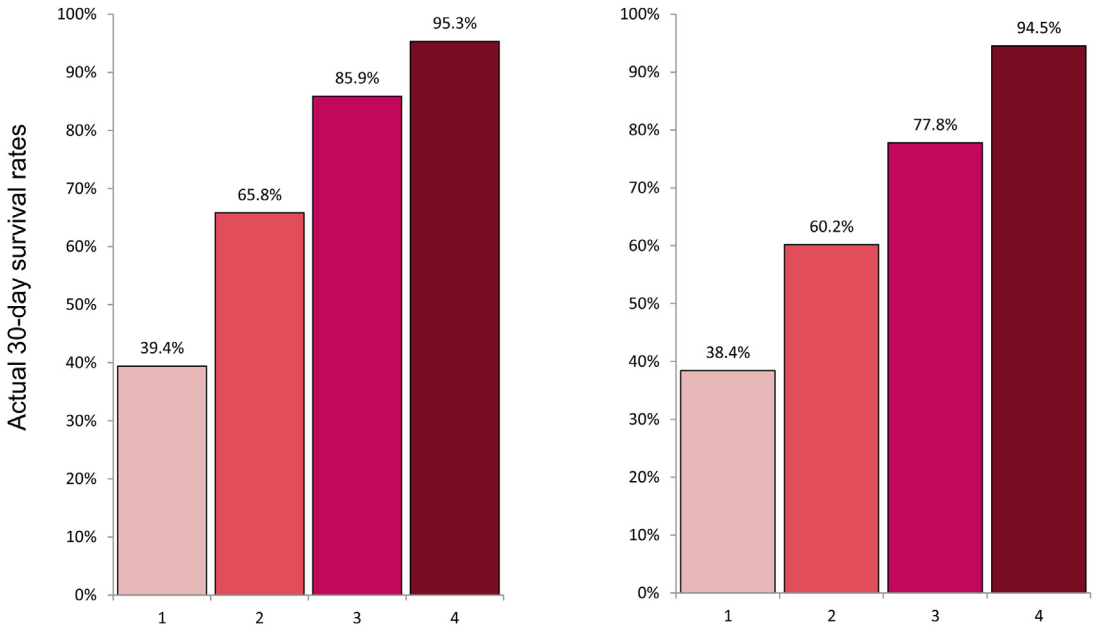



**Fig. 3.** Receiver operating characteristic curve of the FLAMINCOV score in the derivation cohort (panel A) and the validation cohort (panel B). AUC, area under the receiver operating characteristic curve.

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019




| Derivation cohort (N=2586) | | | | |
|---|---|---|---|---|
| Points-risk score | 0-5 | 6-9 | 10-11 | 12-15 |
| Surviving patients | 203/515 | 469/713 | 595/693 | 634/665 |

Panel A, derivation cohort

| External validation cohort (N=1174) | | | |
|---|---|---|---|
| 0-5 | 6-9 | 10-11 | 12-15 |
| 102/265 | 191/314 | 263/338 | 243/257 |

Panel B, validation cohort

**Fig. 4.** Thirty-day rates across different risk groups of the FLAMINCOV score (the risk groups were calculated according to the percentiles of the score) in the derivation and validation cohorts; 1 represents low probability of survival, 2 represents low-intermediate probability of survival, 3 represents low-high probability of survival, and 4 represents high probability of survival. FLAMINCOV Project: Role of inFLAMmatory markers as predictors of mortality IN elderly patients with COVid-19.

for ICU care in their hospitals [16]. The allocation of patients based only on age generated some concerns. There is evidence that age on its own can be misleading in outcome prediction, and scientific societies advocated the use of CFS in clinical decisions for elderly patients with COVID-19 [8,17]. However, the use of frailty alone as an instrument to decide patient allocation is questionable, because in many studies, categorization of CFS was arbitrary. Compared with the Norton scale used in our study, CFS is more specific to evaluate frailty; however, it has not been specific for patients with COVID-19 in this special population.

In our study, the absence of dependency and not age itself is the most important factor associated with survival. Several studies have highlighted the importance of prioritizing functional capacity as a principal endpoint in the care of elderly patients admitted to the hospital for different diseases [18,19]. Among different available scales, the Norton scale is a simple assessment tool traditionally used for the assessment of the risk of pressure ulcers but may also be useful in predicting other complications and in-hospital mortality [11]. Recent single-centre observational studies including 186 and 375 elderly patients with COVID-19 showed that functional status predicts death in hospitalized patients with COVID-19 [20,21]. The poor prognosis of elderly patients with COVID-19 and functional dependency may be related to different factors, including comorbidity burden, poor nutritional status, impaired cell-mediated immunity, cytokine production, and phagocytosis [22].

We found that increases in CRP serum levels were associated with higher risks of mortality. Several factors may explain this correlation: 1) CRP is directly related to the production of interleukin 6, which might reflect the activation of immune response and cytokine storm [23]; 2) the inflammatory state illustrated by CRP elevation may reflect the activation of the coagulation cascade and pro-thrombotic state [24,25]; 3) CRP may be the marker of a pre-existing chronic activation of an innate immune system [26].

The FLAMINCOV score has some strengths. It allows the prediction of 30-day survival according to different classes of risk: low, intermediate-low, intermediate-high, and high probability to survive. Patients were well distributed across risk classes both in the derivation and validation cohorts. Thus, it may be useful from a clinical point of view because it properly reflects the variety of patients admitted to the hospital. This stratification may support clinicians because it allows the identification of elderly patients with high or low chances to survive. Patients with less severe diseases are usually at low risk of a fatal outcome and are not candidates for the ICU. Conversely, the FLAMINCOV score may be more useful in patients with severe COVID-19. In this category, a low FLAMINCOV score may help physicians to exclude patients from intensive care, whereas patients included in the intermediate or high FLAMINCOV classes (e.g. a patient with independent functional status and no significant increase in inflammatory markers) should not be excluded only on an age-based evaluation. Surprisingly, we found an increase in mortality across three different periods. Although this is not an objective of the study, it should be underlined that this finding is in line with those in previous studies [6]. This may be due to several reasons, including changes in the treatment of COVID-19 with the widespread use of steroids, which

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019

remains debated in the elderly [2] and reduced access to intensive care with the increase in the absolute number of patients with COVID-19 and reduced hospital capacity.

Our study has several limitations. First, the retrospective nature of this study may have affected data collection. There are some missing data (for example, procalcitonin values were unavailable for a large percentage of patients and we could not establish whether this was a prognostic biomarker too and data about 'Do not resuscitate order' were not available for all centres). However, we excluded cases with missing data and provided their description. Second, the evaluation of functional status at the ED was not a multi-parametric assessment and we used the Norton scale, which is not a specific scale to evaluate frailty [27]. Anyway, this reflects the real-world experience and we tried to provide a specific tool for the elderly with COVID-19 admitted to the ED. Third, the vaccination campaigns together with the spread of new variants of concern changed the severity of COVID-19 in elderly patients. In this context, the FLAMINCOV score may have reduced applicability. However, access to vaccination is not equal all over the world, and as Omicron spreads globally, the majority of people in low-income countries remain unvaccinated and unprotected against COVID-19. Moreover, elderly patients may have a reduced response to vaccines and continue to represent subjects at high risk of progression [28]. Finally, the score did not consider therapies, and some heterogeneity in the COVID-19 treatment might have been present among centres. Some treatments, such as steroids, may affect the parameters of the score, including CRP. Although we collected all laboratory findings on admission, we did not take into account the impact of treatments started at home. A further study should be planned to evaluate the impact of treatments on the outcome of this special patient population.

In conclusion, we developed the FLAMINCOV score to identify elderly patients with COVID-19 with different probabilities to survive. The FLAMINCOV score may be useful to better triage elderly patients with severe COVID-19, allowing the identification of patients with low and those with intermediate or high probabilities to survive, which may beneficiate from intensive care.

## Author contributions

MF, DY, CM, VP, MT, and MP designed the study. GT created the case report form and developed the database. GT, IM, MR, VB, HG, VP, NR, YD, GBP, AG, and LG collected the data. GT analysed and interpreted the data. GT, MF, and MP performed statistical analysis of the data. GT and MF wrote the manuscript; MT, AC, CM, DY, MP, and MF revised and contributed to the critical revision of the final manuscript.

## Transparency declaration

MF received grants and/or has been on the speakers' bureau from Angelini, Menarini, Pfizer, ThermoFisher, GSK, MSD, Gilead, and Shionogi. All conflicts of interest are outside the submitted work and did not influence its results. All other authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.09.019.

## References

[1] Lian J, Jin X, Hao S, Cai H, Zhang S, Zheng L, et al. Analysis of epidemiological and clinical features in older patients with coronavirus Disease 2019 (COVID-19) outside Wuhan. Clin Infect Dis 2020;71:740–7.

[2] Prendki V, Tiseo G, Falcone M. ESCMID study group for infections in the elderly (ESGIE). Caring for older adults during the COVID-19 pandemic. Clin Microbiol Infect 2022;28:785–91.

[3] Bonanad C, García-Blas S, Tarazona-Santabalbina F, Sanchis J, Bertomeu-González V, Fácila L, et al. The effect of age on mortality in patients with Covid-19: a meta-analysis with 611,583 subjects. J Am Med Dir Assoc 2020;21:915–8.

[4] Dres M, Hajage D, Lebbah S, Kimmoun A, Pham T, Béduneau G, et al. Characteristics, management, and prognosis of elderly patients with COVID-19 admitted in the ICU during the first wave: insights from the COVID-ICU study: prognosis of COVID-19 elderly critically ill patients in the ICU. Ann Intensive Care 2021;11:77.

[5] Guillon A, Laurent E, Godillon L, Kimmoun A, Grammatico-Guillon L. Long-term mortality of elderly patients after intensive care unit admission for COVID-19. Intensive Care Med 2021;47:710–2.

[6] Jung C, Fjølner J, Bruno RR, Wernly B, Artigas A, Pinto BB, et al. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. Crit Care 2021;25:344.

[7] Covino M, Russo A, Salini S, De Matteis G, Simeoni B, Polla DD, et al. Frailty assessment in the emergency department for risk stratification of COVID-19 patients aged ≥80 years. J Am Med Dir Assoc 2021;22:1845–18452.e1.

[8] Chong E, Chan M, Tan HN, Lim WS. COVID-19: use of the clinical frailty scale for critical care decisions. J Am Geriatr Soc 2020;68:E30–2.

[9] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.

[10] Leibovici L, Rodríguez-Baño J, Chemaly RF, Cutler S, Huttner A, Kalil AC, et al. Prediction models in CMI. Clin Microbiol Infect 2022;28:311–2.

[11] Leshem-Rubinow E, Vaknin A, Sherman S, Justo D. Norton scale, hospitalization length, complications, and mortality in elderly patients admitted to internal medicine departments. Gerontology 2013;59:507–13.

[12] Catoire P, Tellier E, de la Rivière C, Beauvieux MC, Valdenaire G, Galinski M, et al. Assessment of the $SpO_2/FiO_2$ ratio as a tool for hypoxemia screening in the emergency department. Am J Emerg Med 2021;44:116–20.

[13] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, National Institutes of Health. National heart, lung, and blood Institute ARDS network. Comparison of the $SpO_2/FIO_2$ ratio and the $PaO_2/FIO_2$ ratio in patients with acute lung injury or ARDS. Chest 2007;132:410–7.

[14] Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5:1315–6.

[15] Lewis EG, BreckonsM, Lee RP, Dotchin C, Walker R. Rationing care by frailty during the COVID-19 pandemic. Age Ageing 2021;50:7–10.

[16] Tiseo G, Yahav D, Paul M, Tinelli M, Gavazzi G, Mussini C, et al. What have we learned from the first to the second wave of COVID-19 pandemic? An international survey from the ESCMID Study Group for Infection in the Elderly (ESGIE) group. Eur J Clin Microbiol Infect Dis 2022;41:281–8.

[17] National Institute for Health and Care Excellence. COVID-19 rapid guideline: critical care. Accessed 6 April 2020. Available at: www.nice.org.uk/guidance/ng159.

[18] Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, et al. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2017;135:e894–918.

[19] O'Neill D, Forman DE. The importance of physical function as a clinical outcome: assessment and enhancement. Clin Cardiol 2020;43:108–17.

[20] Plotnikov G, Waizman E, Tzur I, Yusupov A, Shapira Y, Gorelik O. The prognostic role of functional dependency in older inpatients with COVID-19. BMC Geriatr 2021;21:219.

[21] Laosa O, Pedraza L, Álvarez-Bustos A, Carnicero JA, Rodriguez-Artalejo F, Rodriguez-Mañas L. Rapid assessment at hospital admission of mortality risk from COVID-19: the role of functional status. J Am Med Dir Assoc 2020;21:1798–1802.e2.

[22] Bencivenga L, Rengo G, Varricchi G. Elderly at time of coronavirus disease 2019 (COVID-19): possible role of immunosenescence and malnutrition. Geroscience 2020;42:1089–92.

[23] Bartleson JM, Radenkovic D, Covarrubias AJ, Furman D, Winer DA, Verdin E. SARS-CoV-2, COVID-19 and the ageing immune system. Nat Aging 2021;1:769–82.

[24] Cangemi R, Calvieri C, Falcone M, Cipollone F, Ceccarelli G, Pignatelli P, et al. Comparison of thrombotic events and mortality in patients with community-acquired pneumonia and COVID-19: a multicenter observational study. Thromb Haemost 2022;122:257–66.

[25] Mengozzi A, Georgiopoulos G, Falcone M, Tiseo G, Pugliese NR, Dimopoulos MA, et al. The relationship between cardiac injury, inflammation and coagulation in predicting COVID-19 outcome. Sci Rep 2021;11:6515.

[26] Pirabe A, Heber S, Schrottmaier WC, Schmuckenschlager A, Treiber S, Pereyra D, et al. Age related differences in monocyte subsets and cytokine pattern during acute COVID-19-a prospective observational longitudinal study. Cells 2021;10:3373.

[27] Pilotto A, Azzini M, Cella A, Cenderello G, Castagna A, Pilotto A, et al. The multidimensional prognostic index (MPI) for the prognostic stratification of older inpatients with COVID-19: a multicenter prospective observational cohort study. Arch GerontolGeriatr 2021;95:104415.

[28] Riccardi N, Falcone M, Yahav D. Vaccination for SARS-CoV-2 in hematological patients. Acta Haematol 2022;145:257–66.

Please cite this article as: Tiseo G et al., Predictors of survival in elderly patients with coronavirus disease 2019 admitted to the hospital: derivation and validation of the FLAMINCOV score, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.09.019