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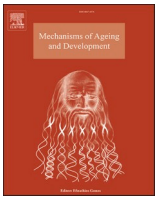

Routine laboratory parameters, including complete blood count, predict COVID-19 in-hospital mortality in geriatric patients

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ABSTRACT

To reduce the mortality of COVID-19 older patients, clear criteria to predict in-hospital mortality are urgently needed. Here, we aimed to evaluate the performance of selected routine laboratory biomarkers in improving the prediction of in-hospital mortality in 641 consecutive COVID-19 geriatric patients (mean age 86.6 ± 6.8) who were hospitalized at the INRCA hospital (Ancona, Italy). Thirty-four percent of the enrolled patients were deceased during the in-hospital stay. The percentage of severely frail patients, assessed with the Clinical Frailty Scale, was significantly increased in deceased patients compared to the survived ones. The age-adjusted Charlson comorbidity index (CCI) score was not significantly associated with an increased risk of death. Among the routine parameters, neutrophilia, eosinopenia, lymphopenia, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein, procalcitonin, IL-6, and NT-proBNP showed the highest predictive values. The fully adjusted Cox regressions models confirmed that high neutrophil %, NLR, derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), and low lymphocyte count, eosinophil %, and lymphocyte-to-monocyte ratio (LMR) were the best predictors of in-hospital mortality, independently from age, gender, and other potential confounders. Overall, our results strongly support the use of routine parameters, including complete blood count, in geriatric patients to predict COVID-19 in-hospital mortality, independent from baseline comorbidities and frailty.

1. Introduction

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recognized as the causative agent for human coronavirus disease (COVID-19). COVID-19 patients are characterized by a high rate of hospitalization, respiratory failure, and ultimately death (Zhou et al., 2020). Italy was the first country in Europe to be heavily affected by high COVID-19 mortality (Onder et al., 2020). To reduce mortality, physicians should establish clear and objective criteria to stratify COVID-19 patients at high risk of in-hospital death, thus improving patient management and resource allocation. Several studies involving large cohorts of hospitalized patients affected by COVID-19, including

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recent studies in the North of Italy – which has been hit hard by the outbreak – investigated the risk factors for severe disease outcomes (Bellan et al., 2020; Geleris et al., 2020; Guan et al., 2020; Hamer et al., 2020; Huang et al., 2020; Richardson et al., 2020; Zanella et al., 2021; Zhou et al., 2020). Overall, older age, male sex, and coexisting conditions, such as diabetes, hypertension, malignancy, chronic obstructive pulmonary disease, obesity, and several immune and inflammatory conditions were identified as risk factors for the most severe outcomes (Chow et al., 2020; Docherty et al., 2020; Guan et al., 2020; Kim et al., 2021; Mehta et al., 2020; Petrilli et al., 2020; Simonnet et al., 2020; Zhang et al., 2021; Zhou et al., 2020).

On the other hand, the role of laboratory medicine in the early detection, diagnosis, prognosis as well as management of COVID-19 patients was highlighted (Lippi and Plebani, 2020). Indeed, the identification of laboratory predictors capable of discriminating disease severity and mortality risk will improve clinical awareness, guide interventional studies, and optimize the allocation of human and technical resources in the in-hospital management of COVID-19 (Henry et al., 2020). Previous reports analyzed the routine laboratory biomarkers at hospital admission for COVID-19, suggesting that the most severe forms of COVID-19 were associated with peripheral lymphocyte and neutrophil subsets alteration (Al Balushi et al., 2021; Cai et al., 2021b; Lu et al., 2021; Reusch et al., 2021; Wang et al., 2020). Similarly, a wide range of metabolic parameters and biomarkers of damage, inflammatory responses, and coagulation system activation have been associated with COVID-19 poor outcomes (Charoenngam et al., 2021; Heer et al., 2021; Khamis et al., 2021; Kitakata et al., 2021; Lv et al., 2020; Manocha et al., 2021; Nurlu et al., 2021; Tang et al., 2021).

Since age is the main risk factor for COVID-19 severe outcomes, geriatric patients should be extensively investigated. A recent study demonstrated that, besides age, immune and laboratory features at hospital admission can affect mortality prediction substantially more than the presence of concomitant clinical comorbidities (Lombardi et al., 2021). In addition, when daily values and trends over time of relevant laboratory parameters were evaluated during the intensive care unit (ICU) stay in association with the severe outcomes in COVID-19 critically ill patients, both daily values or trends over time of parameters associated with acute organ dysfunction, acid-base derangement, coagulation impairment, or systemic inflammation were associated with patient survival (Zanella et al., 2021). However, even if recently consistent evidence of a positive association between a number of routine laboratory biomarkers and COVID-19 severity was provided, further research is needed to clarify whether these results would be consistent across different countries and populations.

Our objective was to examine the association between the most commonly investigated laboratory biomarkers, especially routine blood count parameters, at hospital admission for COVID-19 and in-hospital mortality, in an Italian sample of COVID-19 geriatric patients.

2. Patients and methods

2.1. Study design and participants

The present study used data from the Report-Age COVID project, an observational study conducted at the Italian National Center on Aging (IRCCS INRCA). It aims to deepen our understanding of COVID-19 in older patients hospitalized and diagnosed with COVID-19. All patients aged 65 years and above with confirmed COVID-19 who were admitted to the INRCA hospital from 1st March 2020–24 th June 2021 were included in the study. The only exclusion criterion was the lack of informed consent. The confirmed case was defined as a patient who had been confirmed to be infected with SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction assay regardless of the clinical symptoms.

2.2. Ethics statement

The Report-Age protocol study has been approved by the Ethics Committee of the IRCCS INRCA, Ancona, Italy (reference number CE-INRCA-20008) and registered under the ClinicalTrials.gov database (reference number NCT04348396). All statistical analysis was done with anonymized data. All research was performed in accordance with relevant guidelines and regulations.

2.3. Data collection

Clinical and epidemiological data were collected in a retrospective manner and were anonymized before release. Demographic data including age, sex, and survival status were collected. The categories of comorbidities were assessed including diabetes mellitus, hypertension, heart failure, chronic heart disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, chronic liver disease, connective tissue disease, and dementia. The Charlson comorbidity index (CCIS) was calculated as previously described (Beddhu et al., 2000). The comorbidities associated with COVID-19 were shown as CCI scores.

The Clinical Frailty Scale (CFS) was employed to assess frailty: the CFS is an ordinal 9-point scale in which the assessor makes decisions about the degree of frailty from clinical data (25). The patients are scored from 1 “very fit” to 9 “terminally ill”. Patients were grouped into three groups based on their frailty scores. Patients who were scored at 1–3 on the CFS were defined as not frail (group 1), patients who were scored at 4–6 (group 2) as vulnerable-mildly frail, and patients who scored 7–9 (group 3) as severely frail.

2.4. Routine laboratory biomarkers

Blood concentrations of hemoglobin, C reactive protein (CRP), IL-6, D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP), ferritin, sodium, potassium, procalcitonin, platelet, and withe blood cell count (WBC) were measured by standard procedures.

Estimated Glomerular Filtration Rate (eGFR) was estimated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009).

2.5. Statistical analysis

Continuous variables were reported as either mean and standard deviation or median and interquartile range based on their distribution (assessed using the Shapiro-Wilk test). Comparison of variables between groups was performed by unpaired Student’s *t*-test or Mann-Whitney U test as appropriate. Tertiles of laboratory parameters were calculated and, as other categorical variables, were expressed as absolute numbers and percentages and analyzed by Chi-square test.

The association between tertiles of % Neutrophils, % Lymphocytes, neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (dNLR, calculated as neutrophil count divided by the result of WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), and in-hospital death was initially investigated by Kaplan Meier curves. Therefore, we built Cox proportional hazards analysis to derive unadjusted (Model 1), age- and gender-adjusted (Model 2) and age- gender- and Clinical Frailty Scale (CFS)-adjusted (Model 3) hazard ratios (HR) and 95% confidence intervals (95% CI) of the association between all independent variables and study outcome. The length of hospital stay was used as the time to failure variable for the model. Schoenfeld’s test was used to test proportional hazards assumptions.

Finally, six multivariable models were estimated adjusting for confounders that resulted statically significant in the previous step. Independent variables for these models were tertiles of % Neutrophils and % Lymphocytes (model a); tertiles of # Neutrophils and # Lymphocytes

(model b); tertiles of NLR (model c); tertiles of dNLR (model d); tertiles of PLR (model e); tertiles of LMR (model f).

Sequential imputation using chained equations with ordered logistic regression method was applied in case of missing values in covariates. The imputation model included the variables with the highest correlation with those registered for imputation. The number of missing values for each variable has been reported in Supplementary Table 1. Categorization of the variables into tertiles was done prior to the imputation of the missing data. Augmented regressions were performed in the presence of perfect prediction for all categorical imputation variables. A two-tailed P value < 0.05 was considered significant. Data were analyzed using STATA version15.1 Statistical Software Package for Windows (Stata Corp, College Station, TX).

3. Results

A total of 641 consecutive geriatric patients (mean age 86.6 ± 6.8) who were hospitalized at the INRCA hospital (Ancona, Italy) due to COVID-19 were included in the analysis. 34% (220/641) of the enrolled patients were deceased during the in-hospital stay. The mean number of days from hospital admission to discharge for the recovered patients was 17.3 ± 11.1, and that for the deceased patients was 12.8 ± 9.2. The

Table 1
Sample description.

	Total n = 641	Survived n = 421	Deceased n = 220	p
Age, mean ± sd	86.6 ± 6.8	85.6 ± 7.2	88.5 ± 5.5	**< 0.001**
Male gender, n (%)	266 (41.5%)	159 (37.8%)	107 (48.6%)	**0.008**
CCI, n (%)				0.736
0	285 (44.5%)	190 (45.1%)	95 (43.2%)	
1	200 (31.2%)	127 (30.2%)	73 (33.2%)	
2 or more	156 (24.3%)	104 (24.7%)	52 (23.6%)	
CFS categories, n (%)				**< 0.001**
0–3	103 (16.1%)	78 (18.5%)	25 (11.4%)	
4–6	151 (23.6%)	112 (26.6%)	39 (17.7%)	
7–9	278 (43.4%)	159 (37.8%)	119 (54.1%)	
NA	109 (17.0%)	72 (17.1%)	37 (16.8%)	
Comorbidities, n (%)				
Hypertension	223 (34.8%)	144 (34.2%)	79 (35.9%)	0.667
Chronic heart failure	54 (8.4%)	34 (8.1%)	20 (9.1%)	0.660
Diabetes mellitus	75 (11.7%)	51 (12.1%)	24 (10.9%)	0.652
History of MI	10 (1.6%)	6 (1.4%)	4 (1.8%)	0.703
History of stroke	10 (1.6%)	6 (1.4%)	4 (1.8%)	0.703
COPD	37 (5.8%)	27 (6.4%)	10 (4.6%)	0.336
Dementia	133 (20.8%)	85 (20.2%)	48 (21.8%)	0.629
Cancer	21 (3.3%)	12 (2.9%)	9 (4.1%)	0.402
Liver disease	2 (0.3%)	1 (0.2%)	1 (0.5%)	0.640
Renal diseases	60 (9.4%)	37 (8.8%)	23 (10.5%)	0.492
Symptoms, n (%)				
Cough	160(25.0%)	107(25.4%)	53(24.2%)	0.772
Dyspnea	350(54.6%)	195(46.3%)	156(70.9%)	**< 0.001**
Diarrhea	63(9.9%)	44(10.5%)	19(8.6%)	0.524
Nausea	22(3.4%)	17(4.1%)	4(2.0%)	0.249
Vomit	30(4.7%)	21(5.1%)	9(4.0%)	0.595
Conjunctivitis	4(0.7%)	3(0.7%)	2(0.7%)	0.989
Ageusia	13(2.0%)	10(2.4%)	3(1.3%)	0.448
Anosmia	10(1.6%)	7(1.7%)	3(1.3%)	0.756
Glucocorticoids, n (%)	462 (72.1%)	301 (71.5%)	161 (73.2%)	0.652
Heparin, n (%)	556 (86.7%)	367 (87.2%)	189 (85.9%)	0.654
Hemoglobin, median (IQR)	11.70 (10.40–13.00)	11.70 (10.30–12.80)	11.90 (10.60–13.45)	0.062
Neutrophils (%), median (IQR)	80.2 (70.3–87.7)	75.2 (66.7–83.4)	87.5 (81.0–92.0)	**< 0.001**
Neutrophils ($\times 10^3$/ μL), median (IQR)	6.17 (4.29–9.49)	5.53 (3.99–7.83)	8.10 (5.07–12.51)	**< 0.001**
Lymphocytes (%), median (IQR)	12.80 (7.30–20.80)	16.10 (10.30–23.00)	7.35 (3.80–13.05)	**< 0.001**
Lymphocytes ($\times 10^3$/ μL), median (IQR)	1.01 (0.66–1.44)	1.13 (0.78–1.53)	0.76 (0.46–1.13)	**< 0.001**
Eosinophils (%), median (IQR)	0.1 (0.0–0.8)	0.3 (0.0–1.2)	0.0 (0.0–0.2)	**< 0.001**
Eosinophils ($\times 10^3$/ μL), median (IQR)	0.02 (0.00–0.07)	0.03 (0.00–0.10)	0.00 (0.00–0.02)	**< 0.001**
Basophils (%), median (IQR)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.0–0.2)	**0.004**
Basophils ($\times 10^3$/ μL), median (IQR)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.01 (0.00–0.02)	0.936
D-dimer, median (IQR)	1170 (680–2440)	1120 (660–2180)	1440 (790–4080)	**0.002**
eGFR, median (IQR)	67 (43–84)	77 (53–86)	48.5 (28–78)	**< 0.001**
Glycaemia, median (IQR)	109 (88–142)	105 (86–133)	118.5 (93–160)	**< 0.001**
Sodium, median (IQR)	140 (137–143)	139 (137–142)	142 (137–148)	**< 0.001**
Potassium, median (IQR)	4.2 (3.8–4.6)	4.2 (3.8–4.6)	4.2 (3.7–4.7)	0.535
NT-proBNP, median (IQR)	1538 (567.5–4169.5)	1093 (410–2655)	2973 (1400–8631)	**< 0.001**
CRP, median (IQR)	3.97 (1.55–9.56)	2.86 (1.13–6.77)	7.78 (3.34–13.77)	**< 0.001**
PCT, median (IQR)	0.09 (0.05–0.28)	0.05 (0.05–0.16)	0.27 (0.10–0.85)	**< 0.001**
IL-6, median (IQR)	35.3 (14.1–78.5)	31.15 (12.3–65.1)	55.4 (21.6–114.3)	**< 0.001**
Ferritin, median (IQR)	548.5 (310.0–973.0)	521.0 (283.0–886.0)	669.0 (367.0–1411.0)	**0.001**
NLR, median (IQR)	6.07 (3.61–11.34)	4.87 (3.05–7.79)	10.74 (5.92–21.60)	**< 0.001**
dNLR, median (IQR)	2.10 (0.85–4.80)	2.00 (0.93–3.86)	3.17 (0.59–7.19)	**0.005**
PLR, median (IQR)	228.26 (144.66–340.00)	204.42 (142.61–305.00)	280.05 (154.87–436.81)	**< 0.001**
LMR, median (IQR)	2.14 (1.41–3.25)	2.35 (1.65–3.37)	1.60 (1.17–2.89)	**< 0.001**

CFS, Clinical Frailty Scale; CCI, Charlson Comorbidity Index; CRP, C Reactive Protein; PCT, procalcitonin; IL-6, interleukin-6; NLR, neutrophil- to-lymphocyte ratio; dNLR, derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count); NT-proBNP, N-terminal pro-brain natriuretic peptide; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; IQR, interquartile range. In bold significant variables.

minimum number of days for which patients in the recovered group remained hospitalized was 1 day, while the maximum number was 92 days for survived patients and 56 days for deceased patients.

With respect to medication use, most of the patients received corticosteroids during their hospital stays (n 462, 72.1%); with no significant difference (p = 0.652) between deceased (n. 161, 73.2%) and survived (n. 301, 71.5%).

The clinical and laboratory characteristics of the study cohort (total patients= 641; survived patients = 421 and deceased patients = 221) upon admission are reported in Table 1. Deceased patients were significantly older than survivors, and the male sex was significantly more common among deceased patients.

The most frequent comorbidities among the cohort of patients were hypertension, dementia, and diabetes (Table 1). Surprisingly, the proportions of subjects in each tertile of CCI score were not significantly different between survived and deceased patients, as well as single comorbidities. As expected, the proportions of patients with severe frailty, classified as CFS 7–9, were significantly increased in deceased patients (54.1% in deceased vs 37.8% in the survived patients). Among patients with a CFS score of 7, which indicates severe frailty but no imminent risk of death, the observed mortality was 35.3%. On the other hand, mortality for patients with CFS scores of 8 and 9 was 44.2% and 52.4%, respectively. All the routine laboratory variables analyzed in this cohort were significantly different between deceased and survived patients, except for hemoglobin, basophil count, and serum potassium (Table 1).

All the continuous variables reported in Table 1 were then categorized into tertiles, as reported in Table 2. Regarding the WBC differential counts and the derived indexes – neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (dNLR), calculated as neutrophil count divided by the result of WBC count minus neutrophil count, platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) – deceased and survived patients were characterized by significantly different distributions among tertiles. The proportion of patients with the highest neutrophil counts, both absolute and relative, was significantly higher among the deceased patients, whereas an opposite trend was observed for lymphocytes. Notably, also eosinopenia was significantly more frequent in deceased than surviving patients (Table 2).

Receiver Operating Characteristic (AuROC) curves were computed to assess the ability of neutrophil and lymphocyte percentage counts, as well as NLR, to predict in-hospital mortality (Fig. 1 and Supplementary Fig. 1 for variables categorized into tertiles or considered as continuous, respectively). The area under the curve (AUC) was 0.77 for both neutrophil and lymphocyte counts, and 0.75 for NLR, suggesting good predictive performances.

Regarding the other biochemical variables, a significantly higher proportion of deceased patients was characterized by increased levels of D-dimer, glucose, sodium, potassium, NT-proBNP, CRP, procalcitonin, IL-6, ferritin, and reduced eGFR.

Subsequently, three different univariate Cox regression models that were unadjusted (model 1), age- and gender-adjusted (model 2), and age-, gender-, and CFS-adjusted (model 3), were computed for each variable (Table 3). The risk of mortality of patients in the highest tertile of neutrophil % at hospital admission was five to six-fold higher compared to the lowest tertile. Similar results were obtained for eosinopenia, and lymphopenia (%). Overall, neutrophilia, eosinopenia, and lymphopenia (%) had the best ability in predicting in-hospital death.

NLR score showed a good predictive performance, whereas the other derived indices, i.e., dNLR, PLR, and LMR showed reduced predictive values. The Kaplan-Meier survival estimates and log-rank tests for comparison for the abovementioned parameters are reported in Fig. 2.

Among the routine biochemical parameters, CRP, procalcitonin, IL-6, and NT-proBNP showed the highest predictive values (Table 3 and Supplementary Table 2).

Finally, fully adjusted Cox regressions models evaluating the predictive value of (a) neutrophil, lymphocyte and eosinophils percentage

Table 2
Proportions of surviving and deceased COVID-19 patients according to tertiles of selected complete blood count parameters and biochemical variables.

	Total n = 641	Survived n = 421	Deceased n = 220	p
Hemoglobin, n (%)				0.198
1 (6.9–10.8)	215 (33.5%)	148 (35.2%)	67 (30.5%)	
2 (10.9–12.5)	216 (33.7%)	145 (34.4%)	71 (32.3%)	
3 (12.6–18.9)	210 (32.8%)	128 (30.4%)	82 (37.3%)	
% Neutrophils, n (%)				**< 0.001**
1 (29.0–73.7)	215 (33.5%)	189 (44.9%)	26 (11.8%)	
2 (73.8–85.4)	214 (33.4%)	153 (36.3%)	61 (27.7%)	
3 (85.5–97.8)	212 (33.1%)	79 (18.8%)	133 (60.5%)	
# Neutrophils, n (%)				**< 0.001**
1 (0.57–4.82)	214 (33.4%)	162 (38.5%)	52 (23.6%)	
2 (4.85–7.95)	214 (33.4%)	160 (38.0%)	54 (24.6%)	
3 (7.98–46.60)	213 (33.2%)	99 (23.5%)	114 (51.8%)	
% Lymphocytes, n (%)				**< 0.001**
1 (0.7–8.9)	216 (33.7%)	84 (20%)	132 (60%)	
2 (9.0–17.5)	213 (33.2%)	156 (37.1%)	57 (25.9%)	
3 (17.6–54.9)	212 (33.1%)	181 (43%)	31 (14.1%)	
# Lymphocytes, n (%)				**< 0.001**
1 (0.12–0.77)	217 (33.9%)	102 (24.2%)	115 (52.3%)	
2 (0.78–1.26)	211 (32.9%)	147 (34.9%)	64 (29.1%)	
3 (1.27–12.99)	213 (33.2%)	172 (40.9%)	41 (18.6%)	
% Eosinophils, n (%)				**< 0.001**
1 (0–0.09)	255 (39.8%)	124 (29.5%)	131 (59.5%)	
2 (0.1–0.5)	184 (28.7%)	121 (28.7%)	63 (28.6%)	
3 (0.6–11.1)	202 (31.5%)	176 (41.8%)	26 (11.8%)	
# Eosinophils, n (%)				**< 0.001**
1 (0.00)	247 (38.5%)	108 (25.6%)	139 (63.2%)	
2 (0.01–0.05)	194 (30.3%)	414 (33.5%)	53 (24.1%)	
3 (0.06–0.71)	200 (31.2%)	172 (40.9%)	28 (12.7%)	
% Basophils, n (%)				**0.004**
1 (0.0–0.1)	363 (56.6%)	221 (52.5%)	142 (64.5%)	
2 (0.2)	146 (22.8%)	99 (23.5%)	47 (21.4%)	
3 (0.3–2.3)	132 (20.6%)	101 (24%)	31 (14.1%)	
# Basophils, n (%)				**0.023**
1 (0.00–0.01)	416 (64.9%)	280 (66.5%)	136 (61.8%)	
2 (0.02)	121 (18.9%)	67 (15.9%)	54 (24.6%)	
3 (0.03–0.29)	104 (16.2%)	74 (17.6%)	30 (13.6%)	
D-dimer, n (%)				**0.019**
1 (190–830)	172 (33.5%)	129 (35.6%)	43 (28.5%)	
2 (840–1930)	170 (33.1%)	126 (34.8%)	44 (29.1%)	
3 (1940–35000)	171 (33.3%)	107 (29.6%)	64 (42.4%)	
eGFR, n (%)				**< 0.001**
1 (3–51)	216 (33.7%)	98 (23.3%)	118 (53.6%)	
2 (52–80)	213 (33.2%)	154 (36.6%)	59 (26.8%)	
3 (81–90)	212 (33.1%)	169 (40.1%)	43 (19.5%)	
Glycaemia, n (%)				**0.004**
1 (39–95)	161 (33.6%)	119 (37.3%)	42 (26.3%)	
2 (96–128)	163 (34%)	112 (35.1%)	51 (31.9%)	
3 (129–880)	155 (32.4%)	88 (27.6%)	67 (41.9%)	
Sodium, n (%)				**< 0.001**
1 (115–138)	261 (40.7%)	192 (45.6%)	69 (31.4%)	
2 (139–142)	190 (29.6%)	148 (35.2%)	42 (19.1%)	
3 (143–173)	190 (29.6%)	81 (19.2%)	109 (49.5%)	
Potassium, n (%)				**0.017**
1 (2.0–3.9)	220 (34.3%)	138 (32.8%)	82 (37.3%)	
2 (4.0–4.5)	231 (36%)	168 (39.9%)	63 (28.6%)	
3 (4.6–7.9)	190 (29.6%)	115 (27.3%)	75 (34.1%)	
NT-proBNP, n (%)				**< 0.001**
1 (14–796)	166 (33.5%)	144 (40.7%)	22 (15.5%)	
2 (798–2579)	165 (33.3%)	120 (33.9%)	45 (31.7%)	
3 (2580–70000)	165 (33.3%)	90 (25.4%)	75 (52.8%)	
CRP, n (%)				**< 0.001**
1 (0.1–2.1)	210 (33.3%)	175 (42%)	35 (16.4%)	
2 (2.2–7.1)	210 (33.3%)	146 (35%)	64 (30%)	
3 (7.2–34.6)	210 (33.3%)	96 (23%)	114 (53.5%)	
PCT, n (%)				**< 0.001**
1 (0.05)	215 (40.2%)	187 (51.5%)	28 (16.3%)	
2 (0.06–0.19)	147 (27.5%)	103 (28.4%)	44 (25.6%)	
3 (0.20–189.55)	173 (32.3%)	73 (20.1%)	100 (58.1%)	
IL-6, n (%)				**< 0.001**
1 (1.5–20.5)	129 (33.5%)	106 (37.6%)	23 (22.3%)	
2 (20.6–57.5)	128 (33.2%)	99 (35.1%)	29 (28.2%)	
3 (57.9–804.2)	128 (33.2%)	77 (27.3%)	51 (49.5%)	

(*continued on next page*)

Table 2 (*continued*)

	Total n = 641	Survived n = 421	Deceased n = 220	p
Ferritin, n (%)				**0.011**
1 (15–397)	161 (33.4%)	124 (35.3%)	37 (28.2%)	
2 (403–804)	162 (33.6%)	125 (35.6%)	37 (28.2%)	
3 (805–7514)	159 (33%)	102 (29.1%)	57 (43.5%)	
NLR, n (%)				**< 0.001**
1 (0.43–4.22)	214 (33.4%)	178 (42.3%)	36 (16.4%)	
2 (4.25–9.23)	214 (33.4%)	161 (38.2%)	53 (24.1%)	
3 (9.27–73.10)	213 (33.2%)	82 (19.5%)	131 (59.5%)	
dNLR, n (%)				**< 0.001**
1 (−605 to 1.31)	214 (33.4%)	140 (33.2%)	74 (33.8%)	
2 (1.32–3.64)	213 (33.3%)	170 (40.4%)	43 (19.6%)	
3 (3.68–274)	213 (33.3%)	111 (26.4%)	102 (46.6%)	
PLR, n (%)				**< 0.001**
1 (4.56–165.79)	214 (33.4%)	154 (36.6%)	60 (27.3%)	
2 (165.83–294.23)	214 (33.4%)	154 (36.6%)	60 (27.3%)	
3 (296.12–1660.00)	213 (33.2%)	113 (26.8%)	100 (45.4%)	
LMR, n (%)				**< 0.001**
1 (0.26–1.63)	215 (33.5%)	103 (24.5%)	112 (50.9%)	
2 (1.64–2.84)	213 (33.2%)	161 (38.2%)	52 (23.6%)	
3 (2.85–38.21)	213 (33.2%)	157 (37.3%)	56 (25.5%)	

Note, #, absolute count; eGFR, estimated Glomerular Filtration Rate; CRP, C Reactive Protein; CT, procalcitonin; IL-6, interleukin-6; NLR, neutrophil- to-lymphocyte ratio; dNLR, derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count); PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio. In bold significant variables.

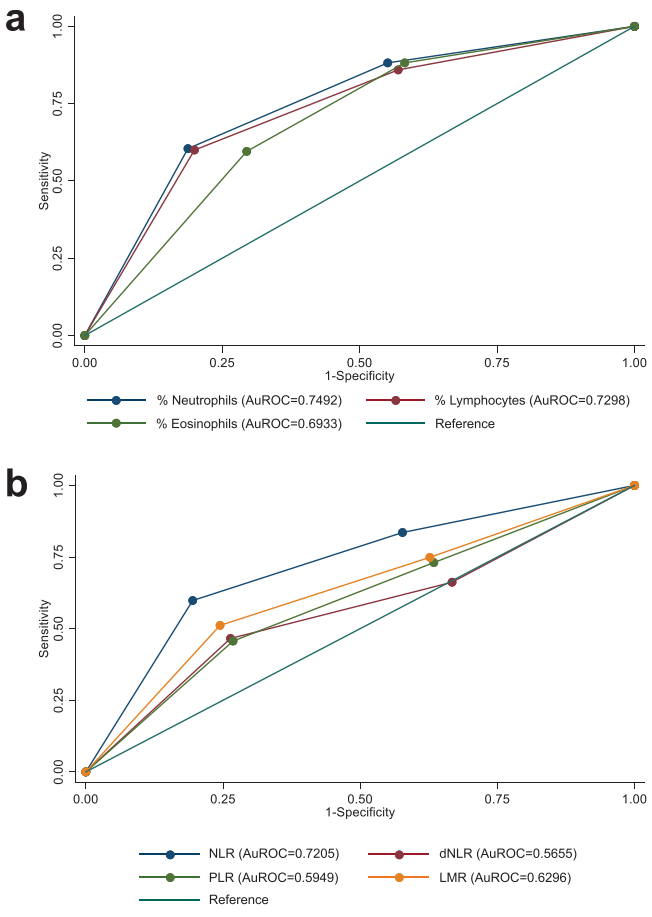

Fig. 1. Area under the Receiver Operating Characteristic (AuROC) curve comparison for the ability of **(a)** neutrophil %, lymphocyte %, eosinophil %, and **(b)** neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (MLR), categorized into tertiles, to discriminate between deceased and survivor COVID-19 patients.

Table 3
Univariate Cox Regression survival analysis.

	Model 1: Unadjusted HR (95%CI)	Model 2: Adj. for age and gender HR (95%CI)	Model 3: Model 2 +CFS-adjusted HR (95%CI)
Hemoglobin, ref. 1 (6.9–10.8)			
2 (10.9–12.5)	1.19 (0.85–1.67)	1.25 (0.89–1.75)	1.29 (0.91–1.80)
3 (12.6–18.9)	1.66 (1.19–2.29)	1.61 (1.16–2.23)	1.69 (1.21–2.35)
% Neutrophils, ref. 1 (29.0–73.7)			
2 (73.8–85.4)	2.73 (1.72–4.33)	2.58 (1.63–4.10)	2.49 (1.57–3.96)
3 (85.5–97.8)	6.68 (4.38–10.18)	5.92 (3.87–9.05)	5.66 (3.69–8.69)
# Neutrophils, ref. 1 (0.57–4.82)			
2 (4.85–7.95)	0.97 (0.66–1.42)	0.88 (0.60–1.30)	0.88 (0.60–1.29)
3 (7.98–46.60)	2.48 (1.78–3.45)	2.06 (1.47–2.88)	1.98 (1.41–2.78)
% Lymphocytes, ref. 1 (0.7–8.9)			
2 (9.0–17.5)	0.35 (0.26–0.48)	0.37 (0.27–0.51)	0.36 (0.26–0.50)
3 (17.6–54.9)	0.20 (0.13–0.29)	0.23 (0.15–0.34)	0.24 (0.16–0.37)
# Lymphocytes, ref. 1 (0.12–0.77)			
2 (0.78–1.26)	0.52 (0.38–0.70)	0.56 (0.41–0.76)	0.57 (0.42–0.77)
3 (1.27–12.99)	0.30 (0.21–0.43)	0.34 (0.24–0.49)	0.35 (0.25–0.51)
% Eosinophils, ref. 1 (0–0.09)			
2 (0.1–0.5)	0.53 (0.39–0.71)	0.51 (0.38–0.69)	0.51 (0.38–0.69)
3 (0.6–11.1)	0.16 (0.10–0.25)	0.17 (0.11–0.26)	0.17 (0.11–0.26)
# Eosinophils, ref. 1 (0.00)			
2 (0.01–0.05)	0.38 (0.28–0.52)	0.37 (0.27–0.51)	0.37 (0.27–0.51)
3 (0.06–0.71)	0.16 (0.10–0.24)	0.16 (0.10–0.24)	0.16 (0.11–0.25)
% Basophils, ref. 1 (0.0–0.1)			
2 (0.2)	0.86 (0.62–1.20)	0.84 (0.61–1.17)	0.85 (0.61–1.19)
3 (0.3–2.3)	0.59 (0.40–0.87)	0.66 (0.45–0.97)	0.69 (0.46–1.02)
# Basophils, ref. 1 (0.00–0.01)			
2 (0.02)	1.21 (0.88–1.66)	1.21 (0.88–1.66)	1.22 (0.89–1.67)
3 (0.03–0.29)	0.84 (0.56–1.24)	0.86 (0.58–1.28)	0.86 (0.58–1.28)
D-dimer, ref. 1 (190–830)			
2 (840–1930)	0.98 (0.68–1.42)	0.95 (0.66–1.37)	0.95 (0.66–1.38)
3 (1940–35000)	1.27 (0.89–1.82)	1.23 (0.86–1.76)	1.18 (0.83–1.69)
eGFR, ref. 1 (3–51)			
2 (52–80)	0.49 (0.36–0.67)	0.49 (0.36–0.67)	0.54 (0.39–0.74)
3 (81–90)	0.29 (0.21–0.42)	0.35 (0.24–0.50)	0.35 (0.24–0.51)
Glucose, ref. 1 (39–95)			
2 (96–128)	1.15 (0.77–1.73)	1.11 (0.74–1.65)	1.12 (0.75–1.67)
3 (129–880)	1.65 (1.13–2.43)	1.65 (1.13–2.41)	1.58 (1.08–2.32)
Sodium, ref. 1 (115–138)			

(*continued on next page*)

Table 3 (*continued*)

	Model 1: Unadjusted HR (95%CI)	Model 2: Adj. for age and gender HR (95%CI)	Model 3: Model 2 +CFS-adjusted HR (95%CI)
2 (139–142)	0.89 (0.61–1.31)	0.92 (0.63–1.36)	0.94 (0.64–1.38)
3 (143–173)	3.19 (2.35–4.33)	2.83 (2.07–3.88)	2.73 (1.99–3.75)
Potassium, ref. 1 (2.0–3.9)			
2 (4.0–4.5)	0.71 (0.51–0.98)	0.78 (0.56–1.08)	0.79 (0.57–1.10)
3 (4.6–7.9)	1.06 (0.77–1.45)	1.16 (0.85–1.59)	1.19 (0.86–1.63)
NT-proBNP, ref. 1 (14–796)			
2 (798–2579)	1.92 (1.24–2.98)	1.76 (1.13–2.74)	1.69 (1.08–2.65)
3 (2580–70000)	3.37 (2.27–5.01)	2.77 (1.84–4.16)	2.67 (1.77–4.04)
CRP, ref. 1 (0.1–2.1)			
2 (2.2–7.1)	1.84 (1.22–2.77)	1.69 (1.12–2.55)	1.62 (1.07–2.46)
3 (7.2–34.6)	3.92 (2.69–5.71)	3.58 (2.45–5.21)	3.31 (2.26–4.85)
PCT, ref. 1 (0.05)			
2 (0.06–0.19)	2.05 (1.33–3.15)	1.87 (1.21–2.89)	1.84 (1.19–2.84)
3 (0.20–189.55)	4.31 (2.92–6.38)	4.06 (2.74–6.02)	3.96 (2.65–5.90)
IL-6, ref. 1 (1.5–20.5)			
2 (20.6–57.5)	1.39 (0.86–2.26)	1.27 (0.79–2.05)	1.17 (0.72–1.90)
3 (57.9–804.2)	2.10 (1.33–3.32)	1.93 (1.23–3.03)	1.86 (1.17–2.94)
Ferritin, ref. 1 (15–397)			
2 (403–804)	1.03 (0.70–1.51)	0.99 (0.68–1.44)	0.98 (0.67–1.43)
3 (805–7514)	1.64 (1.14–2.35)	1.60 (1.10–2.31)	1.53 (1.05–2.22)
NLR, ref. 1 (0.43–4.22)			
2 (4.25–9.23)	1.57 (1.03–2.41)	1.47 (0.96–2.26)	1.42 (0.92–2.17)
3 (9.27–73.10)	4.50 (3.10–6.55)	3.85 (2.64–5.64)	3.65 (2.48–5.36)
dNLR, ref. 1 (−605 to 1.31)			
2 (1.32–3.64)	0.74 (0.51–1.08)	0.74 (0.51–1.08)	0.73 (0.50–1.06)
3 (3.68–274)	2.07 (1.53–2.81)	1.99 (1.46–2.70)	1.89 (1.39–2.57)
PLR, ref. 1 (4.56–165.79)			
2 (165.83–294.23)	1.03 (0.72–1.48)	1.00 (0.70–1.44)	1.02 (0.71–1.47)
3 (296.12–1660.00)	2.00 (1.45–2.77)	2.03 (1.47–2.81)	1.91 (1.38–2.64)
LMR, ref. 1 (0.26–1.63)			
2 (1.64–2.84)	0.46 (0.33–0.64)	0.48 (0.35–0.67)	0.52 (0.37–0.73)
3 (2.85–38.21)	0.50 (0.36–0.69)	0.55 (0.40–0.77)	0.56 (0.40–0.78)

Notes, CFS, clinical frailty scale; #, absolute count; CRP, C Reactive Protein; PCT, procalcitonin; IL-6, interleukin-6; NLR, neutrophil- to-lymphocyte ratio; dNLR, derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count); PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

counts as well as (b) absolute counts, (c) NLR, (d) dNLR, (e) PLR, and (f) LMR, were fitted adjusting for age, gender, and tertiles of the variables significant at the univariate level. The results, reported in Table 4 and Supplementary Table 3, showed that high neutrophil % (HR=2.48 [95% CI: 1.41–4.35]), NLR (HR=2.36 [95% CI: 1.53–3.66]), dNLR (HR=1.63 [95% CI: 1.15–2.30]), PLR (HR=2.34 [95% CI: 1.64–3.32]), and low lymphocyte count (HR=2.08 [95% CI: 1.37–3.13]), low eosinophiles (%) (HR=3.12 [95% CI: (1.92–5.01]), and low LMR (HR=1.59 [95% CI: 1.12–2.27]) were the best independent predictors of in-hospital mortality in geriatric patients affected by COVID-19.

4. Discussion

The coronavirus disease 2019 (COVID-19) is characterized by a high rate of hospitalization, respiratory failure, and death, especially in the oldest patients. Intensive efforts were undertaken to early predict the most severe COVID-19 outcomes, ideally at the point of hospital admission.

Early prediction of COVID-19 in-hospital mortality relies usually on age and patients' preexisting comorbidities (Kim et al., 2021). We enrolled a cohort of more than 600 COVID-19 patients with a mean age of 86 years, aimed to evaluate the role of routinely measured biomarkers of immunity and inflammation, in predicting in-hospital mortality. Growing evidence supports the relevant role played by inflammation in the progression of various viral pneumonia infectious, including COVID-19, since severe inflammatory responses contribute to weak adaptive immune response. In this framework, circulating biomarkers that can represent immune status and inflammation could predict COVID-19 prognosis.

Our results demonstrate that in geriatric patients admitted to hospital for COVID-19 the blood count parameters and some circulating biomarkers of inflammation have the best performance in predicting short-term mortality. We confirmed that COVID-19 outcomes were predicted by baseline frailty, i.e. before the onset of COVID 19 disease, estimated with the use of CFS. A number of recent studies demonstrated that the presence of severe frailty can stratify patients with COVID-19 at increased risk of in-hospital death, thus suggesting that the evaluation of frailty can support decision making about medical care in adult patients admitted to hospital with COVID-19 (Covino et al., 2021; Marengoni et al., 2021; Rebora et al., 2021; Saragih et al., 2021; Yang et al., 2021; Zhang et al., 2021).

Surprisingly, preexisting comorbidities, evaluated through the age-adjusted CCI score, were not significantly associated with an increased risk of death in our cohort of older patients. Our results are in line with those reported recently in older patients affected by COVID-19 (Lombardi et al., 2021). Additionally, about half of the enrolled patients had CCI equal to or greater than 1 and about 25% had CCI equal to or greater than 2 in our study, thus suggesting that the overall comorbidity burden may have reduced discriminatory capacity in such a complex population of older frail patients. The percentage of patients with severe frailty was higher in deceased than in survived COVID-19 patients, confirming that frailty more than comorbidities is associated with in-hospital mortality. In this real-world population, prognostic factors different from those highlighted in other younger cohorts are likely to emerge.

Overall, these data suggest that the oldest patients admitted to hospital for COVID-19 with severe frailty and imbalanced blood cell counts and increased inflammatory circulating biomarkers are characterized by a significantly increased risk of death, independently from preexisting comorbidities.

Strong evidence has been accumulated since the beginning of the COVID-19 pandemic that neutrophils play an important role in the pathogenesis of severe disease course and that neutrophilia represents a feasible and inexpensive biomarker of COVID-19 severity (Wu et al., 2020). In COVID-19 patients, neutrophilia associated with lymphopenia was observed in patients with increased disease severity and with poor prognosis (Picchi et al., 2021; Yang et al., 2020; Zhu et al., 2021). A number of studies showed a correlation between markers derived from standard blood count tests, such as neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (dNLR, neutrophil count divided by the result of WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) and systematic

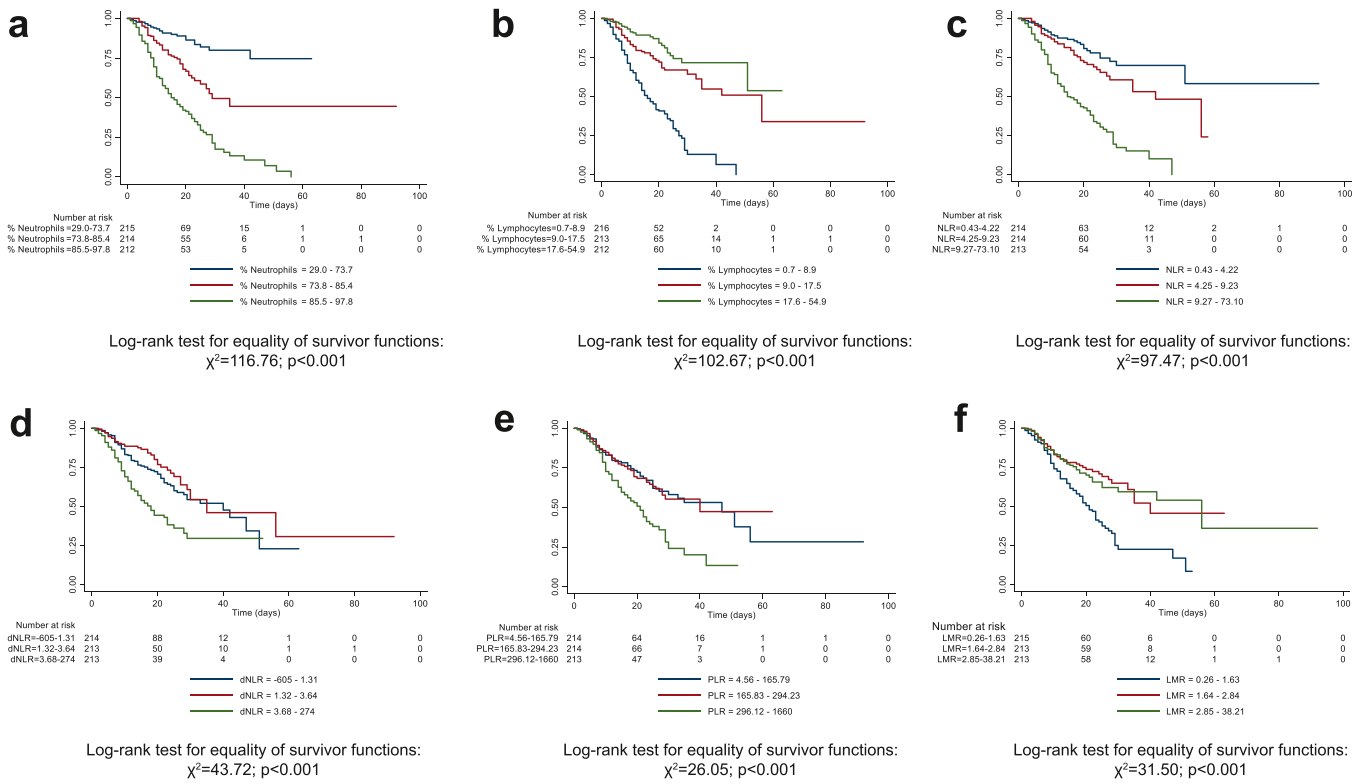

Fig. 2. Kaplan-Meier survival estimates for (a) neutrophil %, (b) lymphocyte %, (c) neutrophil-to-lymphocyte ratio (NLR), (d) derived NLR (dNLR), (e) platelet-to-lymphocyte ratio (PLR), (f) lymphocyte-to-monocyte ratio (LMR).

inflammatory response in a number of age-related diseases, including cancer (Xu et al., 2021; Ying et al., 2014), type 2 diabetes mellitus (T2DM) (Tong et al., 2004), cardiovascular diseases (CVD) (Bhat et al., 2013; Ji et al., 2021), and stroke (Cai et al., 2021a).

A recent meta-analysis including 7482 COVID-19 patients found significantly higher NLR in advanced stages compared to earlier stages of COVID-19 with good accuracy to diagnose and predict the disease outcome, especially mortality prediction (Alkhatip et al., 2021).

These results could be explained, almost in part, by taking into account the physio-pathological roles played by neutrophils. Neutrophils may not only damage host tissue, but they can also suppress the adaptive immune response, a role described for the so-called granulocytic myeloid-derived suppressor cells (MDSC), originally identified in cancer (Bronte et al., 2016). MDSC cells have been described to inhibit lymphocyte proliferation via depletion of arginine by Arginase-1 (Rodriguez et al., 2009) or through the expression of PD-L1 in viral chronic infections, such as HCV (Zhai et al., 2017), and HIV (Cloke et al., 2012). Considering the key role of neutrophil-induced tissue damage and fine-tuned suppression of the adaptive immune response in the pathology of COVID-19, targeting the effector functions or the extravasation of neutrophils in the lungs could be a promising opportunity for pharmacological intervention also in geriatric patients.

Recent reports suggested that steroid therapies can impair the use of NLR as a marker of outcome and disease severity in COVID-19 patients, and its use should be limited to naïve patients before starting potential interfering therapies (Gelzo et al., 2021). No significant impact on mortality was observed in our cohort based on steroid therapies after admission, while no data were available on steroid therapies before hospital admission. In October 2020, the Italian Medicines Agency (AIFA) recommended the use of glucocorticoids, especially dexamethasone, in COVID-19 patients who required supplemental oxygen therapy and ventilation, after the positive findings of the RECOVERY trial (The RECOVERY Collaborative Group et al., 2021). Before this recommendation, the use of glucocorticoids was dependent upon clinical judgment, and in some cases even contraindicated due to negative interactions with the innate immune response in the context of a viral infection (Sarzani et al., 2021). We enrolled COVID-19 positive patients admitted at INRCA hospital from 1st March 2020–24 th June 2021. For this reason, about 28% of COVID-19 patients did not receive glucocorticoids, with no significant difference between deceased and survived. Of note, the proportion of patients treated with glucocorticoids is in line with previous reports describing an increasing trend in the use of dexamethasone and other corticosteroids between March and September 2020 (Ioannou et al., 2022).

Interestingly, our results showed a significant association between low eosinophil counts and COVID-19 severe outcomes. It was suggested that eosinophils could play beneficial functions in COVID-19 patients, probably contributing by controlling the exacerbated inflammation induced by neutrophils (Cortes-Vieyra et al., 2021). Even if the role of eosinophils in inflammation remains controversial, recent evidence suggested that different eosinophils subpopulations in the same tissue could differentially modulate inflammatory responses (Kanda et al., 2021). The anti-inflammatory role of eosinophils was observed in murine models, demonstrating that eosinophils can locally produce anti-inflammatory and pro-resolving lipid mediators, such as protectin D1 and resolvin E3, through a 12/15-lipooxygenase-mediated biosynthetic route, thus promoting resolution by counter-regulating the neutrophil influx and stimulating the ingestion of apoptotic neutrophils by macrophages, as well as increasing phagocyte clearance into draining lymph nodes (Yamada et al., 2011). Our results are in line with the historical role of the eosinophil count as a non-specific biomarker of acute infection (Abidi et al., 2008). Indeed, in our cohort, normal eosinophil counts have been associated with more favorable outcomes, and this observation may reflect a markedly reduced infection severity and stress response, as well as a reduced incidence of bacterial superinfections in survivor patients.

In addition to cell counts, we also observed that increased levels of PCT, IL-6, CRP, and NT-proBNP were associated with in-hospital

Table 4
Fully adjusted Cox regression analysis.

Model	Independent variables	HR (95%CI)
a	% Neutrophils, ref. 1 (29.0–73.7)	
	2 (73.8–85.4)	1.75 (1.03–2.99)
	3 (85.5–97.8)	2.53 (1.44–4.45)
	% Lymphocytes, ref. 1 (0.7–8.9)	
	2 (9.0–17.5)	0.60 (0.42–0.86)
	3 (17.6–54.9)	0.60 (0.35–1.02)
	% Eosinophils, ref. 1 (0–0.09)	
	2 (0.1–0.5)	0.59 (0.42–0.82)
	3 (0.6–11.1)	0.32 (0.20–0.51)
b	# Neutrophils, ref. 1 (0.57–4.82)	
	2 (4.85–7.95)	0.87 (0.58–1.30)
	3 (7.98–46.60)	1.38 (0.94–2.02)
	# Lymphocytes, ref. 1 (0.12–0.77)	
	2 (0.78–1.26)	0.54 (0.38–0.76)
	3 (1.27–12.99)	0.45 (0.29–0.68)
	# Eosinophils, ref. 1 (0.00)	
	2 (0.01–0.05)	0.45 (0.31–0.65)
	3 (0.06–0.71)	0.23 (0.14–0.36)
c	NLR, ref. 1 (0.43–4.22)	
	2 (4.25–9.23)	1.29 (0.82–2.03)
	3 (9.27–73.10)	2.44 (1.56–3.83)
d	dNLR, ref. 1 (−605 to 1.31)	
	2 (1.32–3.64)	0.80 (0.53–1.19)
	3 (3.68–274)	1.60 (1.12–2.26)
e	PLR, ref. 1 (4.56–165.79)	
	2 (165.83–294.23)	1.50 (1.02–2.21)
	3 (296.12–1660.00)	2.39 (1.67–3.42)
f	LMR, ref. 1 (0.26–1.63)	
	2 (1.64–2.84)	0.64 (0.44–0.92)
	3 (2.85–38.21)	0.62 (0.44–0.89)

Notes: #, absolute count. Model a adjusted for age, gender and tertiles of, % Basophils, D-dimer, eGFR, Glycaemia, Sodium, Potassium, NT-proBNP, CRP, Procalcitonin, IL-6, Ferritin. Model b adjusted for age, gender and tertiles of, # Basophils, D-dimer, eGFR, Glycaemia, Sodium, Potassium, NT-proBNP, CRP, Procalcitonin, IL-6, Ferritin. Models c, d, e, f adjusted for age, gender, Clinical Frailty Scale and tertiles of % Eosinophils, % Basophils, D-dimer, eGFR, Glycaemia, Sodium, Potassium, NT-proBNP, CRP, Procalcitonin, IL-6 Ferritin.

mortality for COVID-19. Traditionally, PCT has been used in clinical practice as a diagnostic marker of bacterial infection, aiding clinical decisions surrounding the use of antibiotics. A recent meta-analysis including a total of 7716 patients demonstrated that patients with elevated procalcitonin on admission were at a higher risk of severe and critical COVID-19, although the underlying pathophysiological mechanisms were not clarified (Shen et al., 2021). It was postulated that this positive association could reflect bacterial co-infection, although currently, there is insufficient evidence to validate this hypothesis (Heer et al., 2021; Liu et al., 2020).

In a recent study on patients admitted for COVID-19, PCT elevation was associated with several clinical, radiological, and laboratory characteristics of disease severity. However, PCT elevation was strongly associated with hospital mortality only in subjects older than 75 years (Ticinesi et al., 2021).

Regarding IL-6 levels and COVID-19 mortality, in a recent prospective meta-analysis of clinical trials of patients hospitalized for COVID-19, including 10,930 patients with a median age of 61 years, the administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2021). Notably, IL-6 was recognized as the best circulating biomarker of inflammaging, and increased IL-6 levels were observed in several age-related diseases (reviewed in Olivieri et al., 2021).

NT-proBNP has been used in clinical practice as a diagnostic marker of heart failure, a condition commonly observed in older patients. However, increased NT-proBNP circulating levels can be observed in association with conditions characterized by an exacerbation of inflammation. Recent evidence suggested that NT-proBNP is frequently elevated in COVID-19 and it is strongly and independently associated with mortality (Caro-Codon et al., 2021). Recent evidence suggested that, besides age, the evaluation of NT-proBNP, IL-6, and lactate dehydrogenase (LDH) can predict in-hospital mortality of COVID-19 patients regardless of other comorbidities (Ruscica et al., 2021).

Our study has some limitations that need to be addressed, most notably its retrospective nature and single-center design. Moreover, interpretations of our findings could be limited by the sample size. However, clinical and laboratory data were collected and analyzed for all the admitted patients, in adherence to the original Report-Age COVID-19 protocol. Nonetheless, by including all the patients admitted at the INRCA-IRCCS facilities between March 2020 to June 2021 we believe that data from our study population could represent a fair estimate of the outcomes of COVID-19 in geriatric patients. An additional limitation may be represented by the difficulty of discriminating deaths due to COVID-19 from deaths associated with COVID-19. We believe that, especially in older patients, estimation of mortality should take into account also preexisting comorbidities that are exacerbated by the systemic inflammatory status induced by the disease, and also by the less known direct effects of SARS-CoV-2 on organs other than the lung (Gupta et al., 2020). Furthermore, the documented large excess of deaths during the COVID-19 pandemic period (Wang et al., 2022) clearly indicates that even without severe lung involvement and hypoxia, the inflammatory context of the viral infection and other overlapped infections can precipitate cardiovascular events, including atherothrombotic manifestations and venous thromboembolism. Therefore, in designing our analyses we decided to consider the all-cause mortality as the primary endpoint.

5. Conclusions

Overall, baseline laboratory abnormalities reflect both the extent of baseline vulnerability at the time of admission and the degree of disease severity. The interaction between these two factors, which act synergistically in determining the likelihood of in-hospital mortality, can be highlighted by the prompt assessment of routine laboratory parameters. Our results strongly support the use of these laboratory tests, including complete blood cell count, available within minutes to hours after hospital admission, in addition to clinical evaluation, to assess the degree of disease severity and to predict in-hospital mortality in the setting of geriatric patients with COVID-19, independently from preexisting comorbidities.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2022.111674.

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