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Original scientific paper

Characteristics of COVID-19 Infection among Nursing Home Residents – A Cross Sectional Study from Croatia

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ABSTRACT

Given high risk of infection-related mortality due to impaired immunity, elderly patients are at increased risk with COVID-19. In its diagnostic procedure clinical laboratory medicine has a pivotal role. The aim of this study was to investigate clinical and laboratory specificities in Croatian population of nursing home residents affected by coronavirus. One hundred and six residents of nursing homes that were hospitalized due to COVID-19 infection, were included in this retrospective study. Clinical and laboratory findings at three time points were extracted from medical records. There were 86 females and 20 males, with median of age 84 (min-max: 47–97) years. Patients were divided into three groups: Survivors (S), patients who are still alive (N=65), In-Hospital Non-Survivors (IHNS), patients who died from coronavirus during hospitalization (N=31) and Out-of-Hospital Non-Survivors (OHNS), patients who recovered from infection but died during the period of three months of the follow-up (N=10). We have established differences between these three groups in laboratory findings ($p<0.05$). At the admission, survivors had lower values of lactate dehydrogenase, aspartate transaminase, sedimentation ratio, ferritin and C-reactive protein, OHNS were in the middle, and IHNS had the highest values. Leukocytes and absolute lymphocyte count were greater in OHNS group, and same between survivors and IHNS. After 7 days, we noticed increase in leukocyte and neutrophils count among IHNS. Assessing of complete blood count, differential blood count, reactants of acute infection and combination of their ratios might predict worse outcome in nursing home residents due to coronavirus infection.

Keywords: *COVID-19, coronavirus, nursing care home, elderly, mortality, laboratory medicine*

Introduction

Since the outbreak of the novel coronavirus in December 2019 in Wuhan, China, SARS-CoV-2 or COVID-19 has spread worldwide at an unexpected rate, becoming a pandemic major concern[1–3]. It is an infectious disease caused by a newly discovered single-stranded RNA coronavirus[2]. Although most human coronavirus infections are mild, former epidemics of the two beta coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV[2,3]. SARS-CoV-2 represents a challenge for both clinicians and scientists with by now almost 47 million confirmed cases and more than 1,205,000 deaths in 216 countries, areas or territories worldwide and no appeasement is in sight[4].

The first detected case of coronavirus in Croatia was imported on February 25th in the capital city of Zagreb, and in Split-Dalmatia County, main region of Dalmatia almost a month later, on 17th March 2020. Despite the fact that the age range of patients has dropped, older patients are still under the high risk. The main problems are the lack of continuous knowledge, asymptomatic spreading of the virus and unpredictable clinical course. According to data from the literature, older age, male sex, and chronic medical conditions, such as diabetes, hypertension, obesity and heart diseases, might be risk factors associated with worse outcomes[5]. Therefore, the nursing home sector has recently seen a disproportionately high number of

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deaths[6]. According to experts, this was connected with the frailty and vulnerability of older people living in nursing care homes and in a part a consequence of the failure of including them in the systematic planning of a response to COVID-19 disease[6]. Despite the fact of aging population – 617 million people are aged 65 and over, some countries, including Croatia, still do not have developed special geriatrics network[4]. Little is known about risk factors associated with COVID-19 in European population. The aim of this study was to elucidate risk and prognostic factors as well as clinical characteristics among nursing care homes residents that were hospitalized in tertiary clinical centre due to COVID-19 infection.

Materials and Methods

Subjects

At the beginning of COVID-19 epidemic in Europe, University Hospital Centre of Split, the second biggest tertiary medical institution in Croatia was rearranged to COVID Hospital, i.e. Respiratory Intensive Centre, regional coronavirus centre for four counties in the region of south Croatia. All adult (older ≥ 18 years) COVID-19 positive nursing care home residents who were admitted to the hospital in the period of March to May 2020 from five different senior homes, were included in this retrospective study. Positive oropharyngeal and nasopharyngeal SARS-CoV2 swabs (COVID 19 RT-PCR test, Cobas 480, Roche, kit LightMix®Modular SARS and Wuhan CoVE-gene and RdRP-gene) were indication for hospitalization regardless of clinical presentation. Criteria for discharge from the hospital were: two consecutive negative SARS-CoV2 swabs within 48 hours, no symptoms, at least 7 days elapsed since the beginning of the disease and last 3 days without fever.

Methods

Relevant anamnestic data, description of clinical presentation and standard laboratory parameters, performed in routine analyses, were reviewed from the electronical medical records. This included complete blood count and absolute count of differential blood count, biochemical parameters of kidney, heart and liver function, markers of acute infection, coagulogram and urine analysis. According to complete blood count several ratios were calculated: neutrophils to lymphocyte (N/L); neutrophil/lymphocyte × platelet (N/LP) and platelet, neutrophil, and lymphocyte ratio (PNLR). All tests were measured by standard laboratory methods.

Three time points of laboratory sampling were chosen for this research: at the admission, after 7 days respecting pathophysiological peak in viral load and after relief of symptoms, i.e. at the time of discharge or death[7]. The primary endpoint was in-hospital mortality, and secondary endpoint was out of hospital mortality in the period of three months of the follow-up. Study was conducted according to Helsinki declaration and was approved by local ethics committee. No additional blood sampling or any other procedure was needed for this study, so informed consent was not obtained from each patient.

Statistical analysis

Statistical significance was set at $p < 0.05$, and all confidence intervals (CI) were at the 95 % level. We performed descriptive statistics including means ± standard deviations and medians and interquartile, respectively. Analysis of statistical significance of differences in several numerical variables was performed with the Kruskal-Wallis test and of differences between the two groups with the Mann-Whitney and Dunn test. Other tests used in this research were χ^2 test and Fisher's exact test. To compare the risk of in-hospital death of patients with COVID-19 we performed multiple linear regression and logistic regression models. Receiver operating characteristic (ROC) curves were performed to calculate cut-off values significant for in – hospital mortality. Statistical analysis was performed using National Council for the Social Studies (NCSS) 2020 software.

Results

One hundred and six COVID 19 positive nursing care home residents were hospitalized in regional COVID hospital in south Croatia and all of them were later included in this study. There were 86 (81.13%) females and 20 (18.87%) males, with median of age 84 (min-max: 47–97) years. Patients were divided into three groups: Survivors (S), patients who are still alive, In-Hospital Non-Survivors (IHNS), patients who died during hospitalization and Out-of-Hospital Non-Survivors (OHNS), patients who were discharged from hospital, but died during the period of three months of the follow-up. Table 1 shows demographic characteristics of all participants.

Patients did not differ by age, but there was a significant difference in sex distribution. Males were represented equally to females in OHNS group, in contrast to S and INHS groups, where women predominated. Patients from senior homes were characterized with high prevalence of comorbid diagnoses of arterial hypertension (63.21%), diabetes (29.25%), cardiovascular diseases (coronary artery disease or heart failure) (36.79%) and neurological complications including dementia and recent cerebrovascular incidents with residual neurological deficits (48.11%). Out of hospital non-survivors more often suffered from arterial hypertension and dementia, while diabetes and cardiovascular comorbidities were more common in in-hospital non-survivors group. Clinical presentation of COVID 19 infection was diverse, but mostly consisted of fever, dyspnoea and non-productive cough. Detailed view of various symptoms is presented in Table 2. Thirty patients did not have any symptom of infection on the admission, but most of them developed/continued with fever or dyspnoea during hospitalization. Three patients (2.83%) remained asymptomatic all the time. Radiological findings proven by X-ray and MSCT of thorax differed between

TABLE 1

DEMOGRAPHIC CHARACTERISTICS AND COMORBIDITIES OF COVID 19 POSITIVE NURSING CARE HOME RESIDENTS, N (%)

Variable N (%)	Total (N=106)	Survivor (N=65)	In-Hospital Non-Survivor (N=31)	Out-of-Hospital Non-Survivor (N=10)	χ^2	p
Age*	84 (11)	84 (7)	86 (14)	82 (11.25)	/	0.214**
Sex	86F, 20M	57F, 8M	24F, 7M	5M, 5F	18.536	0.005
BMI: Underweight	21(19.81)	8 (12.30)	7 (22.58)	6 (60)	17.918	0.009
Normal weight	67 (63.21)	54 (83.08)	10 (32.26)	3 (30)		
Overweight + obesity	18 (16.98)	3 (4.62)	14 (45.16)	1 (10)		
Diabetes mellitus type 2	31 (29.25)	16 (24.62)	12 (38.71)	3 (30)	13.308	0.038
Arterial hypertension	67 (63.21)	39 (60)	20 (64.52)	8 (80)	12.975	0.043
Hyperlipidaemia	2 (1.89)	1 (1.54)	1 (3.23)	0 (0)	12.011	0.062
CVD	39 (36.79)	18 (27.69)	16 (51.61)	5 (50)	17.290	0.009
COPD	9 (8.49)	4 (6.15)	4 (12.90)	1 (10)	12.545	0.051
CKD	6 (5.66)	1 (1.54)	3 (9.68)	2 (20)	17.397	0.008
Active malignant disease	4 (3.77)	3 (4.62)	1 (3.23)	0 (0)	12.251	0.057
Neurological disease	51 (48.11)	28 (43.07)	16 (51.61)	7 (70)	14.113	0.028

*median (IQR); **Kruskal Wallis test; BMI – body mass index, CVD – cardiovascular disease, COPD – chronic obstructive pulmonary disease, CKD – chronic kidney disease

TABLE 2

CLINICAL AND RADIOLOGICAL PRESENTATION OF COVID 19 INFECTION AMONG NURSING CARE HOME RESIDENTS, N (%)

Variable	Total (N=106)	Survivor (N=65)	In-Hospital Non-Survivor (N=31)	Out-of-Hospital Non-Survivor (N=10)	$\chi 2$	p
Chest pain	4 (3.77)	2 (3.08)	1 (3.23)	1 (10)	12.201	0.058
Abdominal pain	1 (0.94)	1 (1.58)	0 (0)	0 (0)	12.320	0.055
Diarrhoea	6 (5.66)	4 (6.15)	1 (3.23)	1 (10)	13.055	0.160
Vomiting and nausea	6 (5.66)	3 (4.62)	3 (9.68)	0 (0)	13.424	0.037
Loss of sense of smell and taste	7 (6.60)	6 (9.23)	1 (3.23)	0 (0)	15.976	0.192
Sore throat	5 (4.72)	5 (7.69)	0 (0)	0 (0)	16.382	0.174
Weakness	14 (13.21)	8 (12.31)	4 (12.90)	2 (20)	11.742	0.068
Arthralgia and myalgia	5 (4.72)	2 (3.08)	2 (6.45)	1 (10)	12.441	0.053
Headache	3 (2.83)	2 (3.08)	0 (0)	1 (10)	14.275	0.027
Dyspnoea	25 (23.58)	12 (18.46)	9 (29.03)	4 (40)	14.148	0.028
Cough	35 (33.02)	25 (38.46)	7 (22.58)	3 (30)	13.859	0.031
Fever	42 (39.62)	23 (35.38)	14 (45.16)	5 (50)	12,663	0.049
Respiratory insufficiency dependent on mechanical ventilation	15 (14.15)	1 (1.54)	14 (45.16)	0 (0)	44.750	0.000
Radiological findings: Normal	53 (50)	38 (58.46)	10 (32.26)	5 (50)		
Unilateral pneumonia	21 (19.81)	14 (21.54)	6 (19.35)	1 (10)	21.410	0.045
Bilateral pneumonia	30 (28.30)	12 (18.46)	14 (45.16)	4 (40)		
Ground glass opacity	2 (1.87)	1 (1.54)	1 (3.23)	0 (0)		
Average days of hospitalization*	23.5±11.79	25.08±8.97	18.48±14.81	28.8±13.52	15.153	0.001

*mean ± standard deviation

each group (p=0.045), ranging from normal, through unilateral or bilateral inhomogeneous shading to typical ground glass opacity with crazy paving appearance, air space consolidation, bronchovascular thickening in the lesion and traction bronchiectasis (Table 2). Average days of hospitalization were 23.5±11.79. In post-hoc analysis patients who survived differed from those who died during hospitalisation (p<0.001, Z=–3.667) in duration of treatment, but not from those who died during the follow-up period (p=0.634, Z=0.476). The two groups of non-survivors differed in days of hospitalization (p=0.007, Z=2.675) (Table 2). Oxygen supplementation through nasal cannulas was needed for 28 patients (12, 12, 4, respectively) (p=0.010, χ^2=16.713) and mechanical ventilation for 15 patients (p=0.000, χ^2=44.750) predominately (93.33%) in in-hospital non-survivor group. Serial laboratory tests were performed for each patient.

At the admission IHNS had higher values of median (IQR) of lactate dehydrogenase than S (p=0.005) and OHNS (p=0.047), 273 (182) U/L and 189 (83.5) U/L and 173.5 (94.75) U/L respectively, RR: 25-241 U/L). Median (IQR) of aspartate transaminase was higher in both IHNS (37 (25) U/L) and OHNS (32 (28.25) U/L) than in S group (25 (16) U/L) (p=0.009 and p=0.046, respectively, RR: 11–38 U/L). Fibrinogen level (RR: 1.8 – 3.5 g/L) differed only between non – survivors and survivors (6.2 (2.5) g/L) p=0.049 and p=0.036, respectively, but not between in and out of hospital non – survivors, p=1.000, (3.9 (0.6) and 4.05 (3.85) g/L). Sedimentation ratio (RR: 4–24 mm/3.6ks) differed only between survivors and IHNS (p=0.042), 52.5 (46.75) mm/3.6ks and 91 (32.25) mm/3.6ks, respectively. At the admission IHNS had higher values of median (IQR) of ferritin than S (p<0.001) and OHNS (p<0.001), 2325 (626) ng/ml, 246 (479.5) and 82 (203) respectively, RR: 10–120 ng/ml).

In Table 3 only medians of those laboratory parameters that significantly differed between groups in at least two or all three analyses are presented. In post hoc analysis subgroups of patients were correlated to each other. Between Survivors and In Hospital Non-Survivors group, there were statistically significant differences in all parameters presented in Table 3 (all p<0.05) except for haemoglobin 2 levels.

Table 4 shows medians (IQR) of differential blood count in COVID-19 positive patients. Parameters that differed between survivors and non-survivors were higher leukocytes with absolute neutrophils and lymphocyte counts in

TABLE 3

MEDIANS OF LABORATORY FINDINGS IN COVID 19 POSITIVE PATIENTS IN TRIPLE CONSECUTIVELY SAMPLING: AT THE ADMISSION (1), AFTER 7 DAYS (2) AND BEFORE DISCHARGE/DEATH (3)

	Survivor (N=65)			In-Hospital Non-Survivor (N=31)			Out-of-Hospital Non-Survivor (N=10)			p		
Laboratory measurement	1.	2.	3.	1.	2.	3.	1.	2.	3.	p1	p2	p3
Haematology												
Leukocytes (1e9/L)	5.9	6.3	6.4	5.9	9.5	12.7	7.1	6.5	10.1	0.311	0.001	<0.001
Erythrocytes (1e12/L)	4.42	4.3	4.23	3.9	3.8	3	4.51	4.4	3.8	0.002	0.013	0.003
Haemoglobin (g/L)	132	128	124	122.5	119	93	134.5	132.5	117.5	0.025	0.045	0.004
RDW (%)	14.4	14.3	14.7	15.2	15.1	15.8	14.4	14.1	14.1	0.047	0.004	0.003
Neutrophils (1e9/L)	3.5	4.2	4	3.7	7.4	11	4.6	4.1	7.6	0.185	<0.001	<0.001
Lymphocytes (1e9/L)	1.3	1.9	1.4	0.9	0.9	0.8	1.5	1.3	1.3	0.006	0.042	0.002
Biochemistry												
Urea (mmol/L)	7.1	7.5	6.7	11.2	15.9	14.1	10.3	10.5	5.7	0.029	<0.001	<0.001
Uric acid (μmol/L)	320	319	289	481	617	467	427	618	156	0.192	0.013	0.034
Albumins (g/L)	34	32	31	30.5	26	21	35	36	29	0.049	0.027	0.043
CRP (mg/L)	19.4	23.1	14.15	72.9	105.2	118.5	42.6	62.4	65.2	<0.001	<0.001	<0.001
Procalcitonin (ng/mL)	0.1	0.09	0.08	0.2	0.17	0.6	0.2	NA	0.1	0.138	0.002	<0.001
Hs-Troponin T (ng/L)	21.4	28.9	24.7	47.8	62	176.4	38.7	NA	55.6	0.038	0.028	0.346
Ratios												
N/LP	1.11	1.29	0.87	2.2	3.7	3.74	1.31	1.1	1.5	0.011	0.005	0.001
N/L	2.8	3.71	2.93	4.3	8.3	6.36	3	2.75	7.1	0.042	0.001	0.000
PNLR	540.4	788.2	932.5	765.7	1902.5	1632.1	744.5	702.1	2566.3	0.237	0.007	0.001
L/CRP	0.05	0.05	0.09	0.01	0.01	0.01	0.05	0.02	0.02	0.002	0.026	0.002

NA – not applicable, N – neutrophils, L – lymphocytes, P – Platelets, CRP – C reactive protein, RDW – Red Cell Distribution Width

TABLE 4

COMPLETE BLOOD COUNT DIFFERENCES BETWEEN SURVIVORS AND NON-SURVIVORS

	Total (N=106)		Survivor (N=65)		In-Hospital Non-Survivors (N=31)		Out-of-Hospital Non-Survivors (N=10)		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	p
Leu1	6	2.95	5.9	2.75	5.9	6.48	7.1	1.25	NS
Ne1	3.6	2.96	3.465	2.53	3.67	5.49	4.59	1.77	NS
Ly1	1.26	0.81	1.32	0.82	0.94	0.60	1.53	0.79	0.006
Mo1	0.45	0.26	0.45	0.25	0.42	0.35	0.51	0.33	NS
Eo1	0.04	0.07	0.05	0.08	0.02	0.05	0.06	0.16	NS
Ba1	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.02	NS
Er1	4.35	0.83	4.42	0.87	3.86	0.94	4.51	0.29	0.002
Pl1	218	122	221	120.5	190	165	229	81	NS
Leu2	6.8	3.7	6.3	3.5	9.5	7.7	6.45	3.35	0.001
Ne2	4.75	3.81	4.24	2.96	7.42	7.47	4.14	2.68	<0.001
Ly2	1.18	0.69	1.19	0.77	0.93	0.67	1.31	0.62	0.049
Mo2	0.51	0.32	0.48	0.32	0.57	0.25	0.55	0.56	NS
Eo2	0.07	0.13	0.08	0.13	0.03	0.12	0.06	0.15	NS
Ba2	0.02	0.01	0.02	0.02	0.02	0.02	0.03	0.02	NS
Er2	4.2	0.9	4.3	0.77	3.82	1.39	4.39	0.63	0.013
Pl2	261.5	151,8	269	145	255	125	262.5	151.25	NS
Leu3	7.1	5.8	6.35	2.85	12.7	10.7	10.05	1.6	<0.001
Ne3	4.88	5.1	4	2.44	11.02	10.59	7.65	1.69	<0.001
Ly3	1.29	0.7	1.4	0.58	0.84	0.72	1.31	0.57	0.002
Mo3	0.52	0.29	0.5	0.25	0.48	0.63	0.67	0.54	NS
Eo3	0.12	0.16	0.13	0.11	0.08	0.19	0.24	0.26	0.049
Ba3	0.03	0.03	0.03	0.02	0.04	0.04	0.04	0.04	NS
Er3	4.09	1.18	4.23	1.07	3.03	3.12	3.84	0.67	0.003
Pl3	297	162	297	121.75	238	176	382	199.75	0.038

Leu – leukocytes, Ne – neutrophils, Ly – lymphocytes, Mo – monocytes, Ba – basophils, Eo – eosinophils, Er – erythrocytes, Pl – platelets

those who died. Eosinophils count was the highest in out of hospital non-survivors group in the third sampling (p=0.049) but it did not differ in previous two samplings. When patients were divided into two groups – those with and without bacterial co-infection, they did not differ in any finding of differential blood counts in the first two samplings (all p>0.05), only in leukocytes (p=0.003) and neutrophils absolute count in the third sampling (p=0.001) which both were higher in the group with bacterial superinfection.

In the further analysis prognosis of in-hospital lethal outcome was performed using different regression models. The results confirmed that basic laboratory findings including higher leukocytes, neutrophils, C-reactive protein and several ratios: neutrophils to lymphocyte (N/L), neutrophil/lymphocyte × platelet (N/LP) and platelet, neutrophil, and lymphocyte ratio (PNLR) were connected with poor outcome in elderly COVID-19 positive patients (Table 5).

In-hospital mortality was related to older age (p<0.001, 95%CI: 0.002–0.004) and chronic comorbidities such as diabetes [OR] 0.245, p=0.043, 95%CI 0.003–15.801, hyperlipidaemia (p=0.045, [OR] 5.110, 95%CI: 1.881–13.886), cardiovascular diseases (p=0.013, [OR] 2.412, 95%CI: 1.022–5.691), arterial hypertension (p=0.043, [OR] 2.667, 95%CI: 2.362–2.365) and neurological comorbidities (p=0.028, [OR] 2.467, 95%CI: 2.465–2.468). Angiotensin converting enzyme inhibitors use, which was recorded in 29 patients, was not associated with lethal outcome (p=0.904). Addiction to mechanical ventilation was significantly connected with lethal outcome (p<0.001, [OR] 53.449, 95%CI: 6.501–439.477). Receiver operating characteristic (ROC) curve with area under curve (AUC) were

TABLE 5

RISK FACTORS ASSOCIATED WITH IN-HOSPITAL COVID-19 MORTALITY

	RC1	p1	Lower 95% CI limit1	Upper 95% CI limit1	RC2	p2	Lower 95% CIlimit2	Upper 95% CI limit2	RC3	p3	Lower 95% CI limit3	Upper 95% CI limit3
						Haematology						
Leukocytes	0.060	0.036	0.004	0.114	0.064	<0.001	0.032	0.096	0.059	<0.001	0.036	0.084
Erythrocytes	–0.489	0.001	–0.761	–0.217	–0.318	0.009	–0.555	–0.081	–0.439	<0.001	–0.669	–0.209
Haemoglobin	–0.012	0.013	–0.022	–0.003			NS		–0.015	0.001	–0.023	–0.001
RDW	0.157	0.005	0.048	0.266	0.163	0.005	0.049	0.276	0.156	0.004	0.052	0.260
Neutrophils	0.075	0.012	0.017	0.133	0.072	<0.001	0.038	0.107	0.079	<0.001	0.051	0.107
Lymphocytes			NS				NS				NS	
						Biochemistry						
Urea			NS		0.041	<0.001	0.022	0.059	0.048	<0.001	0.031	0.065
Uric acid			NS		0.002	0.003	0.001	0.004	0.002	0.012	0.001	0.004
Albumins	–0.086	0.029	–0.162	–0.009			NS		–0.079	0.019	–0.143	–0.015
CRP	0.006	<0.001	0.003	0.008	0.006	<0.001	0.004	0.009	0.008	<0.001	0.006	0.009
Procalcitonin			NS		0.786	0.004	0.268	1.303	0.026	0.044	0.001	0.051
Hs-Troponin T			NS				NS				NS	
						Ratios						
N/LyP	0.138	0.003	0.049	0.226	0.149	<0.001	0.072	0.226	0.013	0.042	0.001	0.026
N/Ly	0.059	0.004	0.019	0.098	0.079	<0.001	0.041	0.118	0.026	0.004	0.009	0.043
PNLR	0.0002	0.013	3.47E–05	0.0003	0.0002	0.001	8.16E–05	0.0003	0.0003	<0.001	0.0002	0.0005
Ly/CRP			NS		–1.933	0.045	–3.826	–0.041	–0.776	0.033	–1.487	–0.064
Days of hospitalization	–0.018	0.017	–0.032	–0.003								

*RC– regression coefficient

used to establish cut-off values of complete blood count to differentiate patients who recovered or died in the hospital of coronavirus. Combination of higher neutrophils and leukocytes count accompanied with ratios showed specificity in predicting lethal outcome (Table 6). At the admission, N/L ≥ 3.32, N/LP ≥ 1.78 and PNLR ≥ 621.5 were associated with higher in-hospital mortality ratio. After 7 days, i.e. in the peak of viremia those ratios increased to 4.14, 2.65 and 1600.24, respectively.

Discussion

In a short period of time, SARS-CoV2 infection has become the world's leading health problem. Combining assessment of imaging diagnostic methods with clinical and laboratory findings could facilitate early diagnosis of COVID-19 complications. In this study we have proven differences in clinical and laboratory findings, outcomes and risk factors for death in European COVID-19 nursing home residents among survivors and both in– and out of hospital non-survivors. Residents at nursing care homes represent a specific elderly population, generally characterized by higher comorbidity than community adults and higher vulnerability to infections[8]. There is a higher likelihood for spread of virus because of closer contacts between them in view of aerosol transmission as main pathway of infection, insufficient isolation opportunities, inadequate hygiene, and cognitive impairment and immune-supressed states[8]. All of our participants had one or more comorbidities and nationwide studies from China confirmed that COVID-19 positive patients with any comorbidity yielded poorer clinical outcomes than those without. The risk was higher when greater number of comorbidities was present[9]. Hypertension, diabetes, COPD and malignancy correlated with poorer clinical outcomes in accordance with our data[9]. Furthermore, more than 60% of non-survivors were either underweight or overweight. Patients, who were obese, mostly died during hospitalization, and those with lower body weight after discharge. In clinical practice, only 3 to 5% of hospitalized population is diagnosed with malnutrition, although real numbers are even 10 times higher[10]. Bencivenga et al. have proposed that correction of nutritional deficits may attenuate the age-dependent alterations of the innate and adaptive immune system which participate in the in-

TABLE 6

RECOMMENDED CUT-OFF VALUES FOR SIGNIFICANT MARKERS FOR THE PREDICTION OF IN – HOSPITAL MORTALITY IN COVID-19 PATIENTS

	AUC	p	95% CI lower limit	95%CI upper limit	Cut-off value	Sensitivity %	Specificity %
Ne1	0.630	0.023	0.486	0.742	≥3.75	65	64
Leu2	0.760	<0.001	0.621	0.853	≥8.40	70	84
Ne2	0.798	<0.001	0.672	0.879	≥5.47	78	70
Leu3	0.729	0.001	0.541	0.848	≥9.30	71	75
Ne3	0.768	<0.001	0.582	0.878	≥6.18	71	74
N/LP1	0.631	0.103	0.385	0.793	≥1.78	82	73
N/LP2	0.714	0.013	0.469	0.856	≥2.65	75	70
N/LP3	0.788	<0.001	0.553	0.907	≥2.39	73	85
N/L1	0.686	0.039	0.420	0.843	≥3.32	69	69
N/L2	0.788	0.002	0.494	0.920	≥4.14	73	75
N/L3	0.871	<0.001	0.686	0.949	≥4.08	91	73
PNLR1	0.835	<0.001	0.614	0.934	≥621.5	64	61
PNLR2	0.719	0.016	0.455	0.867	≥1600.24	73	73
PNLR3	0.733	0.011	0.466	0.878	≥1287.9	72	78

creased susceptibility and poor outcome among elderly COVID-19 patients[11]. Obesity, on the other hand, may aggravate COVID-19 because it might be connected with overactive inflammation and immune response, increased expression of ACE2, increased abdominal pressure, limited chest expansion and insufficient respiratory compensatory function[12]. Inhomogeneous bilateral shading was typical radiological finding for non-survivors in our sample, while interestingly about 50 % of patients in each group had normal presentation on repeated radiological diagnostic imaging methods. According to the data from literature, even asymptomatic patients might have pneumonia manifested with chest CT imaging abnormalities[13]. Rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1–3 weeks was typical for coronavirus positive patients emphasizing the necessity of continuous supervisions[13].

Among laboratory findings, leukocytes and absolute lymphocyte counts were greater in OHNS group, as well as between survivors and IHNS. After 7 days, we noticed an increase in leukocyte and neutrophils counts among IHNS. Separately, we analysed patients with and without proven bacterial co-infection at the admission, and we noticed a significant difference in complete and differential blood count neither at the admission nor after 7 days. Our results e, therefore, indicated higher leukocytes and neutrophils counts in older COVID-19 positive patients with worse outcome unrelated to bacterial infection. According to literature, leucocytosis and neutrophilia are observed in a minority of COVID-19 infected patients, and they mostly follow bacterial superinfection, although neutrophilia might be also the consequence of the cytokine storm, a hyperinflammatory state and it is accompanied with severe form of the disease[14]. In contrary, lymphopenia is a typical finding in 35–75% of COVID-19 positive patients, mostly those with fatal outcome, and it is believed it represents a defective immune response to the virus[15]. Researchers have discovered geographic variability in the percentage of COVID-19 patients who developed lymphopenia, e.g. among Chinese more often than in Italian or Singapore populations and that might be explain why it was not typical in our cohort[16,17]. Among Chinese population leukopenia, lymphocytopenia and eosinophil cytopenia are the most typical peripheral blood count findings[18]. C reactive protein, the most common used reactant of acute infection, is increased in 75%–93% of patients with COVID-19 infection, particularly in severe form of disease, including viremia[19]. In our study CRP differed at all time points between the three groups, from the highest in IHNS to the lowest in S group. At the admission, survivors had lower values of lactate dehydrogenase, aspartate transaminase, sedimentation ratio and C-reactive protein, OHNS were in the middle, and IHNS had the highest values. According to the data from literature, high lactate dehydrogenase level, serum ferritin, cardiac and muscle injury, liver and kidney function, hyperglycaemia and coagulation measures seem to be independent predictors of in-hospital mortality and more severe forms of infection in patients with COVID-19[20–22]. A meta-analysis in Asian population compared laboratory findings between severe and non-severe COVID 19 positive patients. The results showed a significant decrease in lymphocyte, monocyte, and eosinophil, haemoglobin, platelet, albumin, serum sodium, lymphocyte to C-reactive protein ratio, and an increase in the neutrophil, alanine aminotransferase, as-

partate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, lactate dehydrogenase, fibrinogen, prothrombin time, D-dimer, glucose level, and neutrophil to lymphocyte ratio in the severe group compared with the non-severe group[23]. No significant changes in white blood cells, creatine kinase, troponin I, myoglobin, IL-6 and K between the two groups were observed[23]. Results of several studies confirmed that increased neutrophil to lymphocyte ratio could be an independent predictor of in-hospital death in Chinese COVID-19 patients, while NLR over 4 predicted transfer to intensive care unit among Italian patients[24–26]. In addition to NLR, we showed that in our sample higher N/LP and PNLR were also connected to worse outcome.

In conclusion, in spite of numerous studies published in a short period of time willing to elucidate pathophysiology, risk factors, outcome, treatment options and all other aspects of this novel global threat, we still have a lot of doubts. The question arises whether Chinese results can be applied globally? Are there differences among different populations caused by ethnicity, geographical position or genetic variability? Is there the same sort of SARS-CoV2 in the whole world? In our study we have compared easily available clinical and laboratory parameters among south Croatian population in recognizing COVID-19 patients at higher risk that can be helpful in everyday clinical practice in implementing increased surveillance among them. In the future, novel studies are needed on larger samples, especially taking into account the effectiveness of potential vaccines. COVID-19 pandemic has highlighted the urgency of building a global system that can support both routine and pandemic adult immunization, as a strategy to preserve and improve medical, social, and economic outcomes, including maintaining functional ability that benefits older adults, their families, and communities[27]. Combined strategy of education and prevention of illness with finding effective, but harmless vaccine might be a solution for preventing outbreaks in nursing home residents caused by a variety of infectious agents including SARS-CoV2[8].

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OBILJEŽJA INFEKCIJE COVID-19 MEĐU ŠTIĆENICIMA DOMOVA ZA STARIJE – PRESJEČNA STUDIJA IZ HRVATSKE

S A Ž E T A K

S obzirom na visok rizik od smrtnosti povezane s infekcijom zbog oslabljenog imuniteta, stariji pacijenti imaju povećan rizik od zaraze COVID-19. U dijagnostičkom postupku klinička laboratorijska medicina ima ključnu ulogu. Cilj ovog istraživanja bio je istražiti kliničke i laboratorijske specifičnosti u hrvatskoj populaciji štićenika domova za starije pogođenih koronavirusom. U ovu retrospektivnu studiju uključeno je 106 štićenika domova za starije koji su hospitalizirani zbog infekcije COVID-19. Klinički i laboratorijski nalazi u tri vremenska razdoblja izvučeni su iz medicinske evidencije. Istraživanje je uključilo 86 žena i 20 muškaraca, srednje dobi 84 (min-max: 47–97) godine. Pacijenti su podijeljeni u tri skupine: preživjeli (S), pacijenti koji su još uvijek živi (N = 65), (IHNS), pacijenti koji su umrli od koronavirusa tijekom hospitalizacije (N = 31) i (OHNS), pacijenti koji su se oporavili od infekcije, ali su umrli tijekom razdoblja od tri mjeseca praćenja (N = 10). Utvrdili smo značajne razlike između ove tri skupine u laboratorijskim nalazima ($p < 0,05$). Istraživanje pokazuje da procjene kompletne krvne slike, diferencijalne krvne slike, reaktanata akutne infekcije i kombinacija njihovih omjera mogu ukazivati na lošiji ishod štićenika domova za starije zbog infekcije koronavirusom.