Characteristics and Outcomes of Patients Infected with SARS-CoV-2 in Israel: Correlation between Laboratory Findings on Admission to Emergency Department and Subsequent Respiratory Failure

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ABSTRACT **Background:** There is limited clinical information on coronavirus disease-19 (COVID-19) patients in Israel.

Objectives: To describe the characteristics, outcomes, and potential associations of hospitalized COVID-19 patients in Israel.

Methods: We conducted a single-center, retrospective study of 58 consecutive laboratory-confirmed COVID-19 patients admitted to Laniado Hospital, Israel, between 14 March 2020 and 14 May 2020. Demographic, clinical, and laboratory data on admission were collected and analyzed, and the association to subsequent respiratory failure was assessed.

Results: Mean age of patients was 70.7 ± 16.9 years (53% males, 47% females.); 74% had at least one co-morbidity. Most patients were of Jewish Ashkenazi descent. During hospitalization 15 patients (mean age 78.18 ± 10.35 years); 80% male, 73% Sephardi descent developed respiratory failure with a mortality rate of 60% occurring on average 10.6 days following intubation. Laboratory tests at admission displayed a significant increase in C-reactive protein (CRP) and creatine kinase (CK) and a decrease in absolute lymphocyte count (ALC) in patients who eventually developed respiratory failure (163.97 mg/L, 340.87 IU/L, 0.886 K/µl vs. 50.01 mg/L, 123.56 IU/L, 1.28 K/µl, respectively). Multivariate logistic analysis revealed an integrated parameter of CRP, CK, and ALC highly correlated with respiratory failure. Receiver operating characteristic curve revealed the area under the curve of CK, ALC, and the integrated parameter to be 0.910, 0.784, 0.754, and 0.913, respectively. CRP was the strongest predictor to correlate with respiratory failure.

Conclusions: CRP, CK, and ALC levels on admission could possibly be used to detect high-risk patients prone to develop respiratory failure.

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KEY WORDS: coronavirus disease-19 (COVID-19), C-reactive protein (CRP), creatine kinase (CK), lymphopenia, respiratory failure

In December 2019, a respiratory illness termed coronavirus disease-19 (COVID-19), caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in Wuhan, China, and spread rapidly worldwide. SARS-CoV-2 has become the third coronavirus in the past two decades to cause a major global public health crisis, after the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). While the spread of infection for the current outbreak is occurring more rapidly than in the SARS and MERS epidemic, the overall case fatality ratio (CFR) appears to be lower.

Whereas MERS and SARS displayed mortality rates of 35% and 9%, respectively, the SARS-CoV-2 mortality rate varies by country but ranges from 2.3% (China) to 7.2% (Italy) [1,2]. The variations in SARS-CoV-2 CFR could be explained in part by population characteristics that increase vulnerability. Such demographic and epidemiological factors associated with disease severity have been identified and include male sex, advanced age, and the presence of co-morbidities [3]. Many laboratory features such as decreased absolute lymphocyte count (ALC), increased C-reactive protein (CRP) and creatine kinase (CK) and electrolytes abnormalities have also been associated with COVID-19 disease severity [4,5]. Furthermore, despite being currently under reported, ethnicity might similarly affect disease outcome as seen in minority ethnic communities in previous pandemics [6].

SARS-CoV-2 infection can lead to a wide range of clinical manifestations from asymptomatic or mild illness (fever and shortness of breath) to respiratory failure and the need for invasive mechanical ventilation [7]. In this study we described the demographic, clinical, and laboratory characteristics of patients with confirmed COVID-19 infection admitted to our hospital in central Israel from the beginning of the outbreak. Moreover, since blood biomarkers can be used to predict disease outcome in infectious disease settings such as influenza [8],

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we were interested to determine the correlation between laboratory findings on admission and the development of respiratory failure.

PATIENTS AND METHODS

This retrospective study was conducted at Sanz Medical Center–Laniado Hospital, Netanya, Israel. All adult patients (≥ 18 years old) with laboratory-confirmed SARS-CoV-2 infection referred to Laniado Hospital and subsequently admitted between 14 March 2020 and 14 May 2020 were included. Patients lacking documented clinical symptoms and laboratory findings at the time of admission with at least three consecutive laboratory tests during hospitalization were excluded. We divided patients into two cohorts based on the development of respiratory failure mandating invasive ventilation during hospitalization: non-invasive ventilation (NIV) vs. invasive ventilation (IV). COVID-19 diagnosis was confirmed by positive real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay from nasal and oropharyngeal swab specimens. Routine blood tests included complete blood count and serum biochemical panel (including CRP and CK) with frequency of test determined by treating physician. We defined poor disease outcome as COVID-19 induced respiratory failure requiring admission to the intensive care unit (ICU) followed by orotracheal intubation and invasive ventilation. Criteria for intubation were defined as tachypnea with a respiratory rate ≥ 30 per minute, desaturation with peripheral oxygen saturation (SpO_2) ≤ 90% with patient on high flow oxygen (18 liter/min). Criteria for discharge included clinical improvement with normalization of blood laboratory results regardless of negative SARS-CoV-2 throat swabs since patients were released to home care or hotels repurposed for COVID-19 shelters until full recovery.

DATA COLLECTION

We reviewed patient electronic records for demographic characteristics including gender, age, ethnicity, underlying co-morbidities (chronic obstructive pulmonary disease, diabetes, hypertension, coronary artery disease, cerebrovascular disease, chronic renal disease), laboratory parameters (complete blood count and biochemical panel), clinical symptoms (fever, dry cough, expectoration, hemoptysis, shortness of breath, myalgia, confusion, headache, dizziness, fatigue, rhinorrhea, pharyngalgia, anorexia, nausea and vomiting, diarrhea, abdominal pain), and invasive ventilation status to track disease severity.

Approval for this study was granted by the Helsinki Committee of Sanz Medical Center–Laniado Hospital. Due to the nature of the retrospective chart review, the need for informed consent from individual patients was waived. All procedures were performed in accordance with the requirements of good clinical practice and the Israeli Ministry of Health regulations for the conduct of clinical studies.

STATISTICAL ANALYSIS

Categorical data are reported as frequency (n) and percent (%) and numerical data as mean and standard deviation (SD). Statistical differences were evaluated by Pearson's Chi-square or Fisher's exact tests as categorical variables. We compared means for continuous variables by using independent group *t* tests when the data were normally distributed; otherwise, we used the Mann-Whitney test. To explore risk factors associated with respiratory failure mandating invasive ventilation we compared laboratory findings on admission between cohorts (NIV vs. IV). Laboratory parameters that were significantly different were used in a multivariant logistic regression model to derive correlation to respiratory failure. The area under the curve (AUC) and the 95% confidence interval (95%CI) of the receiver operator characteristic (ROC) curve were compared to assess the accuracy of these factors in predicting respiratory deterioration (the probability that the predictor's value for a randomly chosen patient requiring intubation would be higher than its value for a randomly chosen patient not requiring intubation). The optimal cut-off points for prediction were determined by Youden's index [9]. A two-sided $P < 0.05$ was considered significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

We collected data from 58 patients with laboratory-confirmed COVID-19 that were admitted to Laniado Hospital between 14 March 2020 and 14 May 2020. Demographic and clinical characteristics are presented in Table 1. The mean ± SD age of our patients was 70.7 ± 16.9 years with 31 males (53%) and 27 (47%) females; 43 (74%) patients had at least one co-morbidity and 52% of patients were from a Jewish Ashkenazi background. The overall case fatality rate (CFR) was 15%. At hospital admission, one patient (1.72%) presented with respiratory distress and was immediately intubated; 57 patients presented with mild to moderate disease according to community-acquired pneumonia guidelines (American Thoracic Society guideline) [10]. Dry cough (30; 55%), fever (24; 44%), fatigue (19; 35%), and dyspnea (18; 33%) were the most common symptoms on admission to the emergency department.

A total of 15 patients (26%) eventually developed respiratory failure and required invasive ventilation with a mean of 4.5 ± 3 days following admission. The mean age of patients in this IV cohort was 78.18 ± 10.35 years with 12 males (80%) and 3 (20%) females; 14 patients (93%) had at least one co-morbidity. Interestingly, Sephardi Jews (11, 73%), compared to Ashkenazi Jews (4, 27%), were significantly more

predominant in the IV cohort. Mean length of hospitalization was 25.8 ± 14.3 days. The mortality rate was 60% (9 patients) with a mean of 10.6 ± 7.5 days following intubation and invasive ventilation.

The mean age of patients in the NIV cohort was 68.14 ± 18 years with 19 males (61%) and 27 (47%) females; 29 patients (67%) had at least one co-morbidity. The mortality rate was 2%. The patient presented with cardiovascular disease and died from sudden cardiac death following acute myocardial infarction after 16 days of hospitalization. Mean length of hospitalization was 14.7 ± 9.1 days.

LABORATORY FINDINGS ON ADMISSION

In our general cohort of patients (n=58), high CRP and CK values (80% and 40%, respectively), lymphopenia (81%), and increased neutrophil-to-lymphocyte ratio (NLR) (68%) were the most common abnormal laboratory results. Despite the role of platelets as an acute phase reactant we did not observe thrombocytosis (> 450 K). Laboratory findings on admission in the NIV and IV cohorts are presented in Table 2. Unlike platelet and hemoglobin values that remained within normal range in both groups, we observed a more dramatic change in NLR and degree of lymphopenia in the IV cohort (5.78 and 0.886 K/µl, respectively). In the biochemistry

Table 1. Demographic and clinical characteristics on admission of laboratory confirmed COVID-19 patients refereed to Laniado Hospital

			Invasive ventilation, n (%)		*P* value*
			Yes	No	
Demographic information					
Total number		**58**			
Gender	Male	31 (53%)	12 (39%)	19,61%)	**< 0.05**
	Female	27 (47%)	3 (11%)	24 (89%)	
Ethnicity	Ashkenazi	30 (52%)	4 (13%)	26 (87%)	**< 0.05**
	Sephardi	25 (43%)	11 (44%)	14 (56%)	
	Mix	3 (5%)	0 (0%)	3 (100%)	
Co-morbidities**	Yes	43 (74%)	14 (33%)	29 (67%)	**< 0.05**
	No	15 (26%)	1 (7%)	14 (93%)	
Clinical characteristics					
Total number		**55**			
	Fever	24 (44%)	8 (33%)	16 (67%)	
	Dry cough	30 (55%)	10 (33%)	20 (67%)	
	Expectoration	3 (5%)	1 (33%)	2 (67%)	
	Dyspnea	**18 (33%)**	**8 (44%)**	**10 (56%)**	**< 0.05**
	Myalgia	1 (2%)	0 (0%)	1 (100%)	
	Confusion	4 (7%)	2 (50%)	2 (50%)	
	Headache	1 (2%)	0 (0%)	1 (100%)	
	Fatigue	19 (35%)	6 (32%)	13 (68%)	
	Rhinorrhea	3 (5%)	0 (0%)	3 (100%)	
	Pharyngalgia	4 (7%)	0 (0%)	4 (100%)	
	Loss of appetite	2 (4%)	0 (0%)	2 (100%)	
	Nausea and vomiting	5 (9%)	0 (0%)	5 (100%)	
	Diarrhea	4 (7%)	0 (0%)	4 (100%)	
	Abdominal pain	4 (7%)	0 (0%)	4 (100%)	

**hypertension, diabetes, coronary heart disease, chronic obstructive lung disease, chronic heart failure, chronic kidney disease
n (%) is the total number of patients with available data
*$P < 0.05$ is significant, bold indicates significance

panel, a compelling increase in CRP and CK were observed in the IV cohort compared to the NIV cohort (163.97 mg/L and 340.87 IU/L vs. 50.01 mg/L and 123.56 IU/L, respectively). In addition, hypocalcemia was the only electrolyte abnormality seen in the IV cohort. Next, we tracked the complete blood count and biochemical panel through disease progression in both cohorts [Figure 1]. Interestingly, laboratory findings that were significantly different between the NIV and IV cohorts on admission (ALC, NLR, CRP, CK) continued to differ with the gap expanding as disease progressed ($P < 0.05$).

0.807–1) for CRP, 0.784 (95%CI 0.592–0.916) for CK, 0.754 (95%CI 0.592–0.916) for ALC, and 0.913 (95%CI 0.816–1.00) for the integrated parameter [Figure 2A, 2B]. At presentation, the optimal cut-off points for prediction were determined by Youden's index [9]. A CRP level greater than 90.5 mg/L, CK level greater than 92.5 IU/L, and ALC lower than 1.05 K/ul showed high rates of sensitivity to detect patients at risk for respiratory failure (87% for all parameters) with moderate specificity for CK and ALC (67% and 65%, respectively) and high specificity for CRP (94%).

Table 2. Comparison of laboratory parameters obtained on admission between non-invasive ventilation (NIV) and invasive ventilation (IV)

Initial laboratory measures	Total, n mean ± SD	Invasive ventilation, n, mean ± SD		Range	*P* value*
		Yes	No		
White blood cells (K/µl)	52, 7.31 ± 3.61	15, 8.07 ± 3.59	37, 6.99 ± 3.62	3.8–10.5	
Lymphocytes (K/µl)	52, 1.17 ± 0.53	15, 0.886 ± 0.465	37, 1.28 ± 0.52	1.0–3.3	**< 0.05**
Monocytes (K/µl)	52, 0.45 ± 0.32	15, 0.447 ± 0.51	37, 0.449 ± 0.21	1.5–4	
Neutrophils (K/µl)	52, 5.45 ± 3.26	15, 6.47 ± 3.07	37, 5.04 ± 3.28	1.8–7.4	
Neutrophil-to-lymphocyte ratio	52, 5.83 ± 4.59	15, 8.95 ± 5.78	37, 4.56 ± 3.35		**0.001**
Hemoglobin (g/d)	52, 13.1 ± 2.12	15, 13.51 ± 1.99	37, 12.93 ± 2.17	13–18	
Platelets (K/µl)	52, 259.67 ± 125.61	15, 229.73 ± 65.90	37, 271.81 ± 141.91	150–450	
Potassium (mmol/L)	57, 4.46 ± 0.57	15, 4.51 ± 0.74	42, 4.44 ± 0.50	3.5–4.5	
Calcium (mg/dl)	45, 8.82 ± 0.66	15, 8.46 ± 0.71	30, 9.00 ± 0.57	8.8–10.8	**< 0.05**
C-reactive protein (mg/L)	55, 82.21 ± 81.25	15, 163.97 ± 92.88	40, 51.56 ± 50.01	0–5	**< 0.001**
Creatine kinase (IU/L)	49, 188.31 ± 218.79	15, 340.87 ± 303.64	34, 121 ± 123.56	26–170	**< 0.05**

*$P < 0.05$ is significant, bold indicates significance

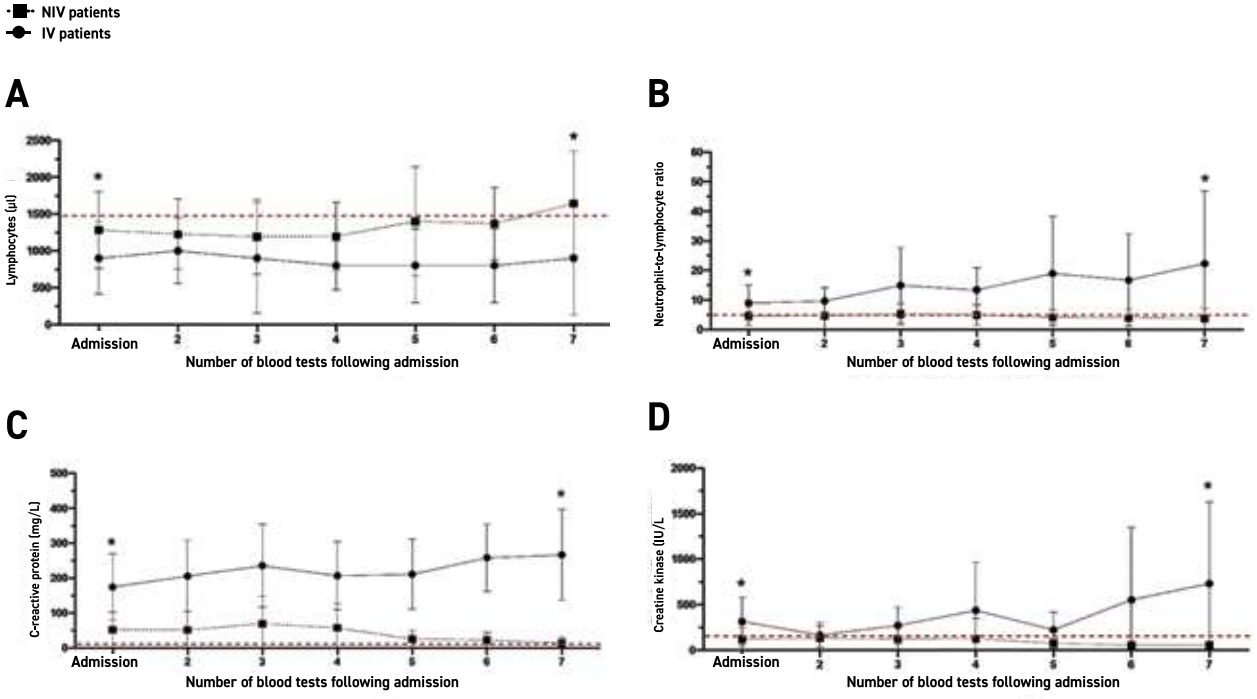
ASSOCIATION BETWEEN LABORATORY FINDINGS ON ADMISSION AND THE DEVELOPMENT OF RESPIRATORY FAILURE

We were interested to further study laboratory findings that were significantly different on admission between the NIV and IV cohorts and could be used to predict respiratory failure without additional processing. CRP, CK, and ALC were used in multivariate logistic regression. This analysis revealed that while individual parameters did not correlate well with the development of respiratory failure, integration of factors revealed a clear correlation (Nagelkerke $r^2 = 0.65$). If age and gender are also integrated with the laboratory findings in the multivariate logistic regression, the correlation was even stronger (Nagelkerke $r^2 = 0.799$). Next, ROC curve analysis was conducted to evaluate these parameters (individually and integrated) in predicting respiratory failure and future need of invasive ventilation [Figure 2]. The AUC was 0.910 (95%CI

DISSCUSION

The ongoing COVID-19 pandemic has forced many countries to deal with an overwhelming shortage of ventilators and has left many others dreading a similar outcome [11]. Israel has imposed a wide range of measures to flatten the curve of cases to avoid overwhelming the nations' healthcare infrastructure as people seek medical care. In this article, we reported a cohort of 58 patients with laboratory-confirmed COVID-19 in Israel and describe their demographic and clinical characteristics. Furthermore, we compared the laboratory findings on admission between patients who advanced to respiratory failure mandating invasive ventilation (IV cohort) to patients who did not (NIV cohort) and tracked their complete blood counts and serum biochemical panels as the disease progressed. We reported the association between CRP, CK, and ALC to respi-

Figure 1. Longitudinal characteristics of white blood cell counts and biochemical panel in SARS-CoV-2 infected patients.
[A] absolute lymphocyte count (ALC), **[B]** neutrophil-to-lymphocyte ratio (NLR), **[C]** C-reactive protein (CRP), and **[D]** creatine kinase (CK) levels in the peripheral blood of non-invasive ventilation (dashed line) and invasive ventilation (bold line) COVID-19 patients analyzed during hospitalization. Dotted red line show the normal limit of each parameter (ALC 4000–1500 µl, NLR 1–3, CRP 0–5 µg/ml, and CK 39–198 IU/L). Statistical significance was determined only for admission and final blood test.
Error bars, mean ± SD, **P* < 0.05, IV = invasive ventilation, NIV = non-invasive ventilation

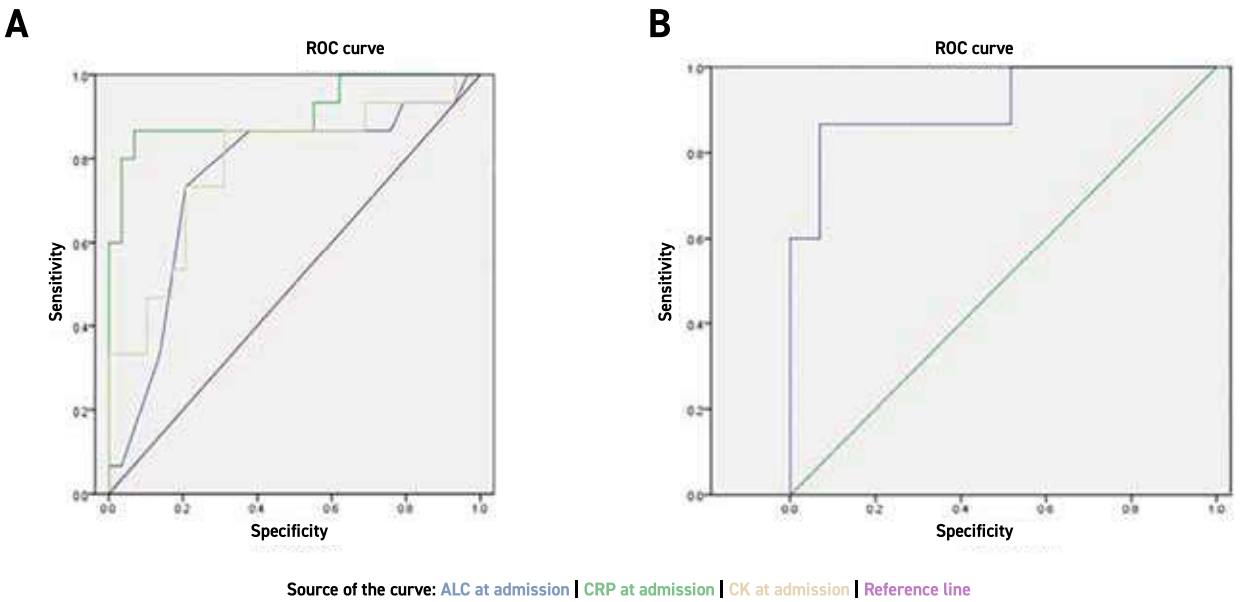


ratory failure leading to invasive ventilation. These laboratory parameters are often part of routine serum panels and are fast and cost effective.

Similar to other recent studies, the most common clinical symptoms in our cohort of patients included dry cough, fever, fatigue, and dyspnea [7,12]. Unlike previous reports, myalgia was not common in our patients. High mortality rates among patients on mechanical ventilators (60%) and an overall CFR of 15% (when corrected to age group) support our current knowledge on COVID-19 [13]. In the IV cohort we observed older age (78.2 ± 10.3 years vs. 68.1 ± 18.18 years, $P < 0.05$), male sex (80% vs. 44%, $P < 0.05$), and higher incidence of co-morbidities (93% vs. 67% $P < 0.05$) compared with the NIV cohort .Our study confirmed higher rates of developing lymphopenia in the IV cohort than in the NIV cohort (86.6% vs. 70%). A predominate degree of lymphopenia and increased NLR, CRP, and CK on admission were also observed in the IV cohort. This finding is indicative of elevated physiological stress and an extent of immunological impairment by SARS-CoV-2. Longitudinal analyses of these laboratory values further demonstrated a continuous worsening in the IV patient's physiological state.

Recent studies have found that lymphopenia is due to decreased absolute counts of T cells, especially CD8+ T cells, but not to the absolute counts of B cells and natural killer cells [14]. Since T cells are important for taming an overactive innate immune response to infection [15], a decrease in T cells during SARS-CoV-2 infection may result in an exaggerated inflammatory response leading to a cytokine storm and its subsequent complications including respiratory distress. Similarly, an exaggerated inflammatory response may result in collateral muscle damage and release of CK, as has been previously described for other viruses such as influenza A H1N1 [16]. Therefore, elevated CK levels may be an early sign of pending immunological dysregulation. This situation could explain the correlation between elevated CK levels in COVID-19 patients and progression to critical illness as described in our study and in other recent reports [17]. In addition, CRP was also observed to be markedly elevated in the IV cohort compared to the NIV cohort. This acute phase reactant is part of the innate immune response and is an important biomarker for the diagnosis and assessment of severe pulmonary infectious diseases [18]. As such, elevated serum CRP is consistent with COVID-19 mediated pulmonary diseases and massive release of inflammatory

Figure 2. Receiver operating characteristic curve analysis of laboratory values taken on admission in predicting respiratory failure requiring invasive ventilation of COVID-19 patients. **[A]** Prediction value of individual variables (absolute lymphocyte count, C-reactive protein, creatine kinase) and of the **[B]** joint variable
ALC = absolute lymphocyte count, CRP = C-reactive protein, CK = creatine kinase, ROC = receiver operating characteristic



cytokines. Interestingly Herold and colleagues [19] recently validated that CRP levels serve as a strong predictor of ventilator support in a cohort of 84 COVID-19 patients. In our study, CRP levels on admission highly correlated with the future need of invasive ventilation thereby strengthen their findings [Figure 2A]. Furthermore, the cutoff point of CRP on admission that would accurately predict ventilation risk (Yoden's Index) was comparable to the previous report and could serve as a promising start for risk-modified monitoring and treatment. Regardless, additional large-scale studies are needed to fully address the optimal CRP threshold level.

Ethnicity and race have been recently shown to be associated with poor outcome of COVID-19 in Brazil and the United States [20,21]. In our study, Sephardi descent was observed to be the most common ethnic background in the IV cohort. Unlike these reports, this ethnicity effect cannot be attributed to differences in availability to healthcare (including intensive care) or socioeconomic impact since the Israeli healthcare system ensures universal coverage for citizens and permanent residents allowing easy access to the general public. One possible hypothesis to explain the association between Sephardi descent and COVID-19 clinical deterioration is based on vitamin D deficiency. Vitamin D mediates cytokine response and strong circumstantial evidence has accumulated to suggest a role in COVID-19 severity [22]. Vitamin D deficiency is more common in populations with darker skin because pigmentation reduces skin synthesis [23]. Indeed, Oren and colleagues [24] reported that in comparison to Jews of Ashkenazi descent, Sephardi Jews displayed significantly lower levels of vitamin D [24]. Overall, it appears that ethnicity plays a complex role in COVID-19 severity and in part may be mediated by vitamin D levels.

The Israeli healthcare system is currently experiencing a significant surge in COVID-19 infection rates. During previous months, hospitalization of all at-risk populations was possible; however, this is not applicable with the current infection characteristics. Clinicians in the emergency departments need to assess which patients may be discharged to recover at home, which will benefit from hospitalization in a designated coronavirus ward, and which are at high risk for clinical deterioration and need to be hospitalized in an intensive care unit. Such guidelines and recommendations are available and are constantly evolving as they are based on current evidence and our accumulating experience [25]. Early identification of patients prone to deteriorate can improve patient care by ensuring close monitoring, facilitating logistic preparedness of the healthcare infrastructure, and strengthening efficient allocation of limited medical resources.

LIMITATIONS OF THE STUDY

Our study has several limitations. First, the sample size was relatively small, which may have an impact on the statistical results. Second, since this was a retrospective study, not all patients were continuously monitored for all laboratory tests and missing data might have led to bias. Last, the data collected for each patient on admission may have been from different disease stages.

CONCLUSIONS

It is critical to identify COVID-19 patients who might become severely ill in a quick and timely manner. This would greatly improve the prognosis of patients in light of limited medical resources.

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Capsule

Cerebrospinal fluid snapshot

The central nervous system features mechanisms to protect against untoward inflammation while allowing immune surveillance for pathogens. **Pappalardo** and colleagues profiled T cells in the cerebrospinal fluid (CSF) of healthy individuals and in patients with multiple sclerosis (MS) using single-cell RNA and T cell receptor sequences to define central nervous system immune homeostasis. In healthy individuals, clonally expanded CSF T cells were largely distinct from those found in the blood, with effector, interferon-γ, and tissue adaptation signatures, whereas CSF T cells from patients with MS differed from healthy controls, with a gene expression signature consistent with increased activation and cytotoxicity. These findings provide insight into the distinct immune environment in the CSF under normal and disease-associated conditions.

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