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Role of time-normalized laboratory findings in predicting COVID-19 outcome

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Abstract

Objectives: The pandemic COVID-19 currently reached 213 countries worldwide with nearly 9 million infected people and more than 460,000 deaths. Although several Chinese studies, describing the laboratory findings characteristics of this illness have been reported, European data are still scarce. Furthermore, previous studies often analyzed the averaged laboratory findings collected during the entire hospitalization period, whereas monitoring their time-dependent variations should give more reliable prognostic information.

Methods: We analyzed the time-dependent variations of 14 laboratory parameters in two groups of COVID-19 patients with, respectively, a positive (40 patients) or a poor (42 patients) outcome, admitted to the San Raffaele Hospital (Milan, Italy). We focused mainly on laboratory parameters that are routinely tested, thus, prognostic information would be readily available even in low-resource settings.

Results: Statistically significant differences between the two groups were observed for most of the laboratory findings analyzed. We showed that some parameters can be considered as early prognostic indicators whereas others exhibit statistically significant differences only at a later stage of the disease. Among them, earliest indicators were: platelets, lymphocytes, lactate dehydrogenase, creatinine, alanine aminotransferase, C-reactive protein, white blood cells and neutrophils.

Conclusions: This longitudinal study represents, to the best of our knowledge, the first study describing the laboratory characteristics of Italian COVID-19 patients on a normalized time-scale. The time-dependent prognostic value of the laboratory parameters analyzed in this study can be used by clinicians for the effective treatment of the patients and for the proper management of intensive care beds, which becomes a critical issue during the pandemic peaks.

Keywords: aminotransferase; COVID-19; laboratory parameters; lactate dehydrogenase; longitudinal; lymphocytes; neutrophils; time-dependent; white blood cells (WBC).

Introduction

At the end of 2019, a novel severe acute respiratory syndrome (COVID-19) emerged in Wuhan, Hubei, China. The disease is sustained by a novel coronavirus (SARS-CoV-2) [1] which rapidly spread around the globe. As of September 26th, the pandemic reached 213 countries with more than 30 million infected people and almost 1 million deaths [2]. Italy, one of the country most affected by the disease both in term of infected people (over 300,000) and deceased (over 35,000), shows one of the highest mortality rate (approximately 12%) [2]. Severe cases are usually the consequence of clinical complications associated with the disease, like interstitial pneumonia, viremia and viral sepsis, intravascular coagulopathies, targeted or multiple-organ failure, which require hospitalization in intensive care units (ICU) and might lead to patients' death [3, 4].

At present, there is no vaccine or specific treatments for COVID-19 [5]. Thus, identification of potential risk factors which could be monitored promptly to predict disease progression and severity is crucial to improve the treatment/prognosis as well as for the appropriate management

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of cases, progressing into severe and critical condition, requiring the often limited number of ICU beds.

Previous Chinese studies analyzed the laboratory parameters' differences between severe and mild-to-moderate patients and evaluated the risk factors for the development of critical cases [6–8]. Recent systematic literature reviews highlighted the most important laboratory findings that have been observed in Asian COVID-19 patients like lymphocytes, neutrophils, C-reactive protein (CRP), white blood cells (WBC), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer and interleukin-6 (IL6) [6, 9] as well as other laboratory parameters which have been found to predict the severity of the disease progression [6]. However, studies outside the Asian region, and especially in Europe, are currently scarce [10–12], whereas significant differences have been previously reported in the clinical and demographic features of COVID-19 patients in different regions of the world [13].

In this study, by analyzing the blood test results of 82 Italian COVID-19 patients, with either poor (death) or good (recovery) outcome, we aim to determine laboratory parameters differences between the two groups in order to associate them with reliable prognostic values. The early identification of COVID-19 patients likely evolving into critical cases will allow for the efficient treatment of these patients and will support the management of ICU beds which becomes a critical issue during the pandemic peak [14].

Materials and methods

Patients

Individuals included in the study were patients, admitted to the San Raffaele hospital (Milan, Italy) between the 20th of February and the 20th of March, 2020, which were diagnosed with COVID-19 according to current standards (i.e. suggestive findings at chest computed tomography and positive results of real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2) and that were hospitalized for at least one week. Of the 82 COVID-19 patients (25 females, 77 males), 42 of them (30 males and 12 females) had a poor prognosis (death) whereas 40 of them (27 males and 13 females) had a good outcome (recovered).

Clinical data

Measurements of enzyme activities (AST, ALT, GGT, ALP and LDH) were performed on a Roche COBAS 8000 apparatus (Roche Diagnostic, Basel, Switzerland). Pyridoxal phosphate was added when measuring AST and ALT. All of the methods for measurement of enzyme activity are standardized to IFCC reference measurement procedures. Creatinine (CREA), CRP, IL6 and NT-proB-type Natriuretic Peptide (proBNP) were also measured on a Roche COBAS 8,000 instrument, using the following: immunoturbidimetric assay (CRP), enzymatic method (CREA), electrochemiluminescent assay (IL6 and pro-BNP) [15]. D-dimer measurements were performed using a Star Max Instrument (Diagnostica Stago, Inc.) using a Stago reagent, in Latex turbidimetric principle. WBC, platelets, neutrophils and lymphocytes were measured on Sysmex XE 2100 (Sysmex, Japan). Blood samples were collected, daily or every other day, as described elsewhere [16, 17].

The RT-PCR was performed on a Roche Cobas Z480 thermocycler using the Roche provided PCR Kit [18]. Clinical information on comorbidities were from ER medical records.

Individuals signed an informed consent authorizing the use of their anonymous data for retrospective observational studies (article 9.2.j; EU general data protection regulation 2016/679 [GDPR]), in accordance to the San Raffaele Hospital policy (IOG075/2016).

Statistical analysis

All hospitalizations have been normalized, that is, divided by their length in days. Thus, every stay spans from 0 (admission) to 1 (discharge). This normalized time-frame has been further divided in ten portions (deciles). On average, each decile was 1.4 and 2.5 days long for recovered and deceased patients, respectively. Based on the day of withdrawal, laboratory findings have been assigned to the corresponding decile and have been stratified according to the prognosis. Hypothesis testing procedure was applied to the data contained in each decile, for each laboratory findings, in order to detect any significant difference between the strata mentioned above. In particular, we applied the Mann Whitney tests for medians, considering the null hypothesis of no significant difference between recovered and deceased patients, at the 95% confidence level. No overlap between the confidence intervals is consistent with a statistically significant difference. Hypothesis testing (Student's *t*-test) between the cumulative mean of all the values collected during the first 7 days, averaged for all patients, was also performed for the two groups.

Results

The population of COVID-19 patients included approximately 30% women and 70% men, equally distributed between the poor and good outcome groups (Table 1). In contrast, the deceased group was, on average, almost 14 years older than the recovered group (p-value <0.001). The presence of comorbidities showed no statistically significant differences between the two groups except for cardiovascular diseases which were significantly prevalent in the deceased group (p-value <0.001). The length of the hospitalization period was also significantly different between the two groups (p-value <0.001) where the occurrence of death shortens the hospitalization period of approximately 10 days (Table 1).

Table 1: Averaged demographic and clinical characteristics of the 82 patients involved in the study.

Characteristics	Outcome	
	Death	Recovery
Age, years	74.1±11.3	60.4±11.2
Males, n (%)	30 (71.4%)	27 (67.5%)
Females, n (%)	12 (28.6%)	13 (32.5%)
Hospitalization, days	14.42±6.9	24.2±11.3
Mechanical ventilation[a]	39	38
Cancer	4	1
Cardiovascular disease	21	1
Diabetes	8	5
Metabolic disease	2	0

[a]Either invasive or non-invasive.

Hematological parameters

Figure 1 shows the time-dependent variation of the four hematological findings collected in this study. All of the parameters, except WBC, were similar, in the two groups, at hospital admission (first decile) however, already in the second decile, lymphocytes and platelets started to increase significantly in the recovered group while, in the deceased group, they remained relatively stable.

Interestingly, platelets showed a highly significant difference between the two cohorts until the ninth decile, whereas in the 10th the two groups showed similar values (Figure 1). The deceased group showed, compared to the recovered patients, significantly increased values for both WBC and neutrophils starting at the 5th decile and the gap constantly broaden until the end of the hospitalization (Figure 1). It must be noted that WBC values were also significantly different in the first decile but such difference was lost from the second up to the fifth decile (Figure 1).

Biochemical parameters

Ten routinely tested biochemical findings, previously shown to be altered in COVID-19 cases [3, 12, 19], were also followed during the entire hospitalization period of the 82 patients (Figure 2). AST, ALP, GGT and IL6 measurements were statistically very similar in the two cohorts of patients, in all of the ten deciles (Figure 2). It must be noted that no IL6 measurement was available, in the recovered groups, for the last two deciles. In contrast, the time series for CREA, CRP and LDH values became statistically different already after the second (LDH) and third (CREA and CRP) decile and their gaps increased with time (Figure 2). The proBNP values were significantly higher, in the deceased group, between the fourth and the ninth decile whereas in the 10th decile no significant difference was detected (Figure 2). ALT activity was significantly different, between the two groups, only in the central part of the hospital stay (deciles 4 to 7) whereas at the beginning and at the end of the hospitalization, the two cohorts of patients showed similar values (Figure 2). The D-dimer variation was significantly different between the two groups only at the end of the disease progression (decile 9 and 10), whereas during the beginning and central part of the hospitalization no significant differences were detected, with the exception of decile 4, which showed a poor yet significant difference (Figure 2).

First hospitalization week

The laboratory findings of the two patients' cohorts, during the first hospitalization week, were averaged and compared in order to identify statistically significant differences within the first hospitalization period. Table 2 shows that among the 14 parameters analyzed WBC, neutrophils, platelets, CRP, ALP, LDH, D-dimer and CREA were significantly different ($p<0.05$) between the two groups. Among them platelets showed the lowest p-value (<0.001), neutrophils and CRP showed p-values between 0.01 and 0.001 whereas ALP, LDH, D-dimer, CREA and WBC had p-values between 0.01 and 0.05.

Discussion

Saturation of the often limited ICU beds during the COVID-19 infection peak, occurring in several countries, has been one of the main problem caused by the pandemic and probably the source of several loss of lives. Furthermore, severe COVID-19 patients need long hospitalization periods, thus, identification of routine and readily available laboratory findings predicting the severity of the disease, at a stage, becomes crucial in managing healthcare facilities.

In our study, we observed hospitalization stays as long as 51 days. The averaged length was 14 and 24 days for deceased and recovered patients respectively. This was in agreement with previous studies from China, analyzing more than 1,300 patients [20].

In contrast to most of the previous longitudinal studies, which analyzed the averaged laboratory parameters over the entire patients' hospitalization period [11, 21], we followed the time-dependent laboratory parameters changes on a normalized patients' hospitalization stay divided in 10 identical time-slots (deciles). Such analysis

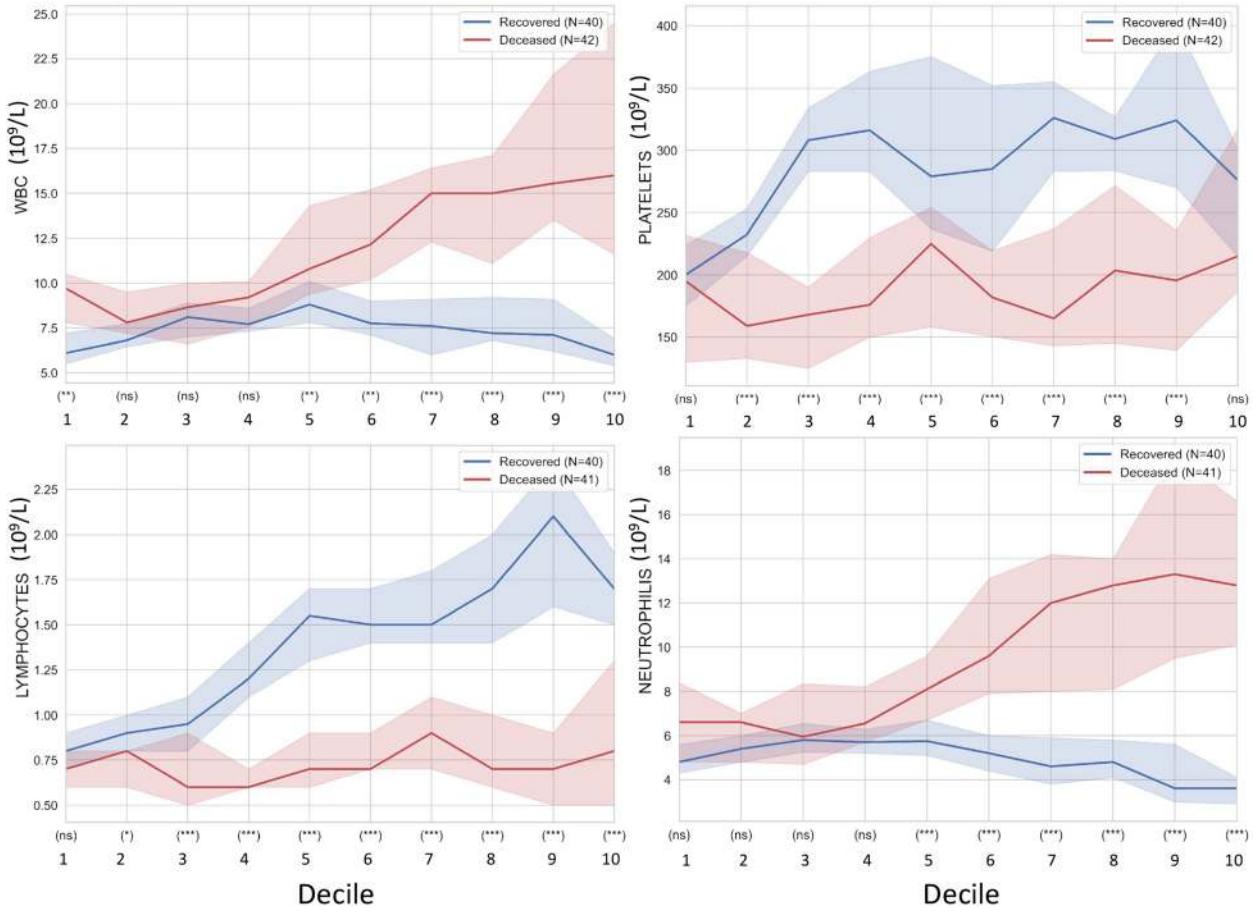

Figure 1: Time series analysis of the hematological parameters collected in this study with 95% confidence intervals.
(*) Refers to p-value between 0.05 and 0.01; (**) refers to p-value between 0.01 and 0.001; (***) refers to p-value <0.001. "n" represents the number of patients with available laboratory parameters' measurements.

shows how the laboratory findings changed during the disease progression and whether they acquired a prognostic value. It must be noted that although the American Statistical Association reported that a p-value, or statistical significance [22], does not measure the size of an effect, we used it as an indication of "good" or "poor" prognostic values.

Our study showed that the earliest prognostic values could be obtained from hematological parameters (platelets and lymphocytes) already after 2–3 days of hospitalization (second decile). This was in contrast with the work of Bonetti et al. [11] which showed a non-significant p-value for platelets. The reason for this discrepancy might be attributed to the time-dependent variation of the platelets levels, which remained low in the deceased group whereas, in the recovered group, increased at the beginning of the hospital stay and then decreased when approaching the outcome (Figure 2). By averaging the entire hospitalization period, as in Bonetti et al. [11], the two groups would show similar platelets averaged values whereas by considering their time-dependent variation, platelets became one the earliest prognostic value.

The severity of the disease could be further predicted by WBC and neutrophils, which started to significantly diverge at decile 5 (7–12 days after hospital admission). It must be noted that WBC showed a poor, yet significant difference already at decile 1, however, because the following 3 deciles showed no significant difference, such result might depend on the relatively low number of patients involved in our study. Thus, further data are needed to verify whether WBC might have a prognostic value already at day 0.

Decreased lymphocyte count were consistent with the recently demonstrated expression of angiotensin-converting enzyme 2 (ACE2), the entrance target of SARS-CoV-2, at lymphocytes' cell surface [23]. Viral infection of these cells induces their gradual decline and, if not recovered, the lymphocytic dysfunction and immunosuppression lead patients to a worse prognosis often caused by bacterial/viral co-infections [24]. The latter was consistent

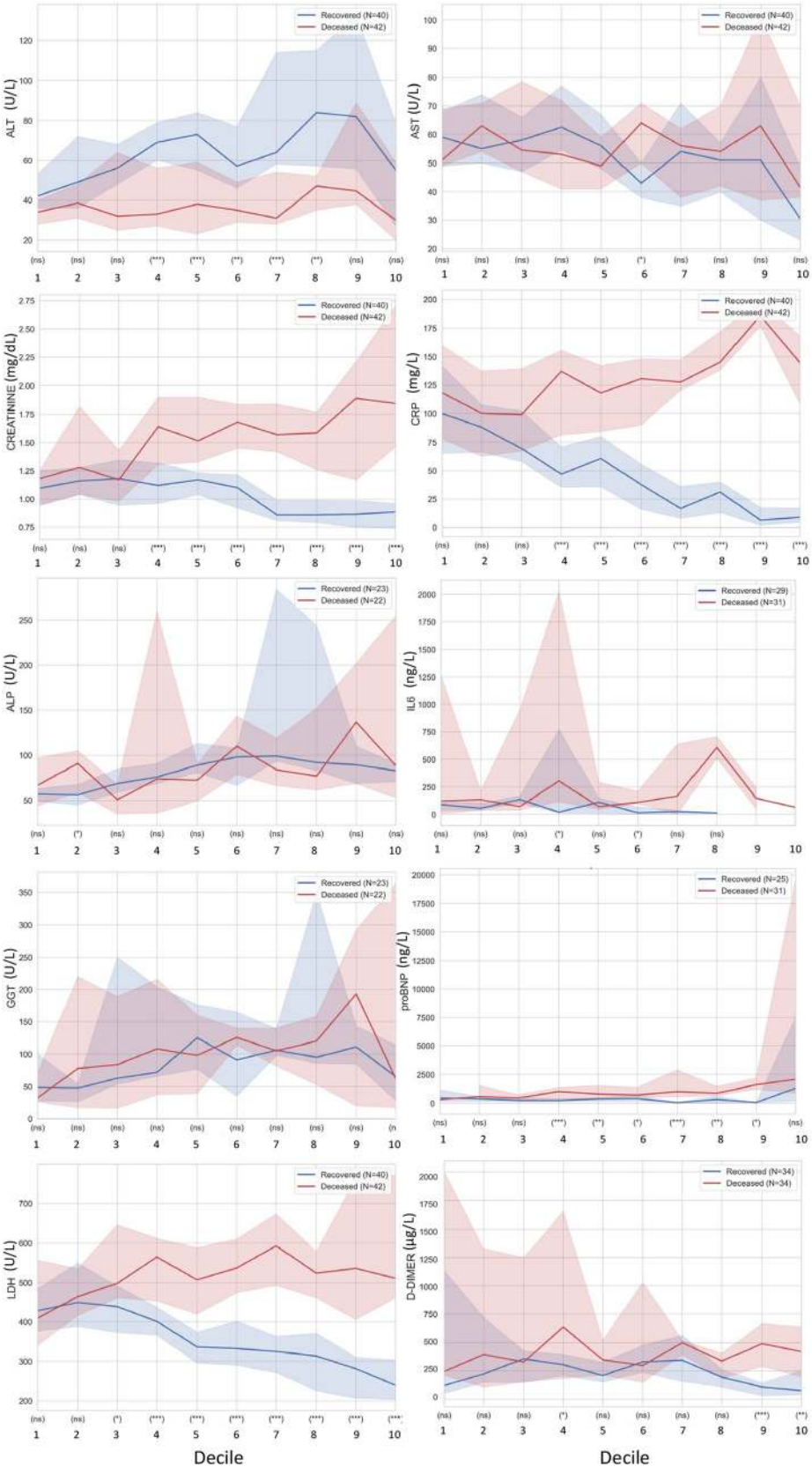

Figure 2: Time series analysis of the biochemical parameters collected in this study with 95% confidence intervals.
(*) Refers to p-value between 0.05 and 0.01; (**) refers to p-value between 0.01 and 0.001; (***) refers to p-value <0.001. "n" represents the number of patients with available laboratory parameters' measurements.

Table 2: Comparison of cumulative 7-days means between recovered and deceased patients during the first hospitalization week.

Parameter	p-Value	Recovered			Deceased		
		n	Mean±STD	CI 95%	n	Mean±SD	CI 95%
WBC, $\times 10^9$/L	**0.045**	40	6.7±2.1	[6.0, 7.4]	41	11.2±13.8	[6.8, 15.5]
Neutrophiles, $\times 10^9$/L	**0.004**	40	5.2±2.2	[4.5, 5.9]	40	7.36±4.00	[6.08, 8.65]
Lymphocytes, $\times 10^9$/L	0.164	40	0.97±0.40	[0.85, 1.08]	40	0.80±0.60	[0.60, 1.01]
Platelets, $\times 10^9$/L	**≤0.001**	40	278.3±115.4	[241.4, 315.2]	41	191.8±103.3	[159.2, 224.4]
CRP, mg/L	**0.008**	40	97.4±63.5	[77.1, 117.7]	41	139.7±76.2	[115.7, 163.8]
AST, U/L	0.926	40	68.1±59.3	[49.1, 87.1]	41	69.2±40.3	[56.4, 81.9]
ALT, U/L	0.147	40	66.9±77.7	[42.0, 91.7]	41	47.3±35.7	[36.0, 58.6]
ALP, U/L	**0.033**	22	65.0±18.9	[56.6, 73.4]	21	85.8±39.7	[67.7, 103.9]
GGT, U/L	0.617	23	97.2±122.7	[44.1, 150.2]	20	80.9±81.4	[42.8, 119.0]
LDH, U/L	**0.039**	40	428.1±167.6	[374.5, 481.7]	41	514.9±202.4	[451.0, 578.8]
D-dimer, µg/L; FEU[a]	**0.024**	26	346±560	[121, 570]	26	780±780	[468, 1101]
IL6, ng/L	0.744	26	316.5±996.7	[0, 719.1]	27	393.5±688.0	[121.3, 665.7]
proBNP, ng/L	0.133	23	690.2±1075.4	[225.1, 1155.2]	27	6295.8±17527.6	[0, 13229.5]
CREA, mg/dL	**0.032**	40	1.26±0.9	[0.96, 1.56]	41	1.91±1.60	[1.39, 2.42]

Detailed results of hypothesis testing (Student's t-test), p-value (p), number of patients (n), mean and standard deviation (mean±SD), and the 95% confidence interval (CI 95%). Bold numbers correspond to statistically significant differences. [a]FEU, fibrinogen equivalent units.

with the statistically significant increased neutrophils count (a marker of viremia and/or bacterial infection) observed in the deceases group.

Among the biochemical parameters chose for this study and shown to be altered in COVID-19 patients [12, 25, 26], ALP, AST and GGT had essentially no prognostic value, meaning that their levels were altered in COVID-19 patients regardless of disease severity. In contrast, CREA, CRP and LDH, showed a relatively early prognostic value by significantly diverging already between the 5th and the 10th hospitalization day (third decile). As for neutrophils count, CRP is a marker of infection, thus, a higher level in the deceased group was expected. Similarly, the higher values of LDH and CREA, found in the poor prognosis group, were consistent with the extent injuries caused by the virus to lung and kidney respectively [27, 28]. High levels of proBNP, a marker of heart failure, were also early signs of a poor prognosis. Statistically significant differences were observed already at the fourth decile confirming that the disease has a direct or indirect impact on the heart functionality [26] and that COVID-19 patients with cardiovascular diseases are more likely associated to a worse prognosis [29]. The proBNP values dramatically increase in the last decile of the deceased group. Several patients showed proBNP levels often exceeding the 70,000 ng/L instrumental limit, probably as a consequence of heart damages associated with patients' death. The absence of a statistically significant difference in the last decile, due to a proBNP increase also in the recovered group, was the consequence of the low number of measurements in this group (proBNP was measured mainly in critical patients and rarely on patients on their way to recovery). Among them, a patient had a single high proBNP measurement (approximately 10,000 ng/L), at the very last hospitalization day, which abnormally increased the average proBNP level of the recovered groups' 10th decile.

ALT activity was significantly different, between the two groups, only in the central part of the hospitalization making this laboratory finding a less prompt prognostic marker. This was in agreement with other studies which showed no significant difference between the averaged values of deceased and recovered patients [11, 21]. Furthermore, the ALT activities were mostly within the normal clinical range (males 6–59 U/L, females 6–41 U/L), consistent with previous studies showing that liver is not extensively affected by COVID-19 [30]. As expected, the D-dimer levels were higher in the deceased group confirming that abnormal coagulation parameters are associated with poor prognosis [4]. However, a significant statistical difference between the two groups was observed only at decile 9, which makes the D-dimer a late and not very useful prognostic indicator.

IL6, another marker of infection, have been shown to be associated to a poor prognosis in COVID-19 Chinese patients [3]. Our data showed that differences in IL6 levels between the two groups was scarcely or not at all significant. Data from the last two deciles were missing for the recovered patients, however, even if a significant difference had to be observed in the last hospitalization period,

IL6 would be classified as a late and not particularly useful prognostic marker.

A further analysis obtained by averaging the above-mentioned parameters collected in the first hospitalization week only (Table 2), represented a second strategy for identifying prognostic factors for COVID-19 severe cases. Platelets, neutrophils, CREA, CRP, LDH and D-dimer confirmed their prognostic values observed in the time-series analysis. In contrast, lymphocytes, ALT, AST, IL6 and pro-BNP lose their prognostic value, when considered in the first week only, whereas ALP acquired a poor, yet significant, prognostic value.

Several recent studies showed that a greater number of comorbidities were correlated with poorer clinical outcomes in COVID-19 patients [31]. Although, the poor prognosis group showed a higher prevalence of cardiovascular diseases, the laboratory findings analyzed in this study should not be altered by the presence of this comorbidity unless a myocardial infarction was occurring which would increase the level of proBNP, LDH and AST [32]. However, the fact that AST was very similar in the two groups for the whole hospitalization period and that proBNP dramatically increased only in the last decile of the deceased group, likely means that severe damage to the heart only occurred at the very end of the poor prognosis patients.

Therefore, comorbidities can be considered as independent predictors of mortality which do not affect the prognostic values of the laboratory findings. In other words, our study shows that, regardless of the patients' characteristics like a diagnosed (or yet to be diagnosed) comorbidity, changes in laboratory findings can be exploit to predict COVID-19 clinical outcomes.

Limitations

Our study suffers from a few limitations like the relatively low number of patients and the absence of details about: clinical interventions, pharmacological therapy and severity of comorbidities. However, since patients were from the same hospital and units, homogeneous treatment has likely to be occurred. Furthermore, the difference in hospital stay between the recovered and deceased patients affects the length of the decile, hence the number of data encompassed by each time frame. Lastly, since inter-decile statistical testing was not corrected for multiple comparisons, differences associated with p-values higher than 0.01 should be taken with caution and their plausibility be assessed in light of available clinical signs.

Conclusions

Our study represents one of the few longitudinal studies on the laboratory characteristics of Italian COVID-19 patients with poor and good outcomes and, to the best of our knowledge, was the first study representing normalized hospitalization stays. Thanks to the time-series analysis we could assign to laboratory findings a prognostic value as well as a time frame. This information can be used by clinicians for a timely interpretation of the blood tests aimed at the effective treatment of the patients and at the proper management of ICU beds, which becomes a critical issue during the pandemic peaks.

According to the time series, the earliest prognostic indicators were, respectively: platelets, lymphocytes, LDH, CREA, ALT, CRP, WBC and neutrophils. Later indicators of poor prognosis were higher levels of D-dimer and proBNP. Furthermore, by focusing mainly on those parameters that are routinely tested, prognostic information could be readily available even in low-resource settings.

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Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: Individuals signed an informed consent authorizing the use of their anonymous data for retrospective observational studies (article 9.2.j; EU general data protection regulation 2016/679 [GDPR]), according to the San Raffaele Hospital policy (IOG075/2016).

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