Combined lymphocyte/monocyte count, D-dimer and iron status predict COVID-19 course and outcome in a long-term care facility

Flavia Biamonte
Department of Experimental and Clinical Medicine, Magna Graecia University
Cirino Botta
Annunziata Hospital
Maria Mazzitelli
Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, Magna Graecia University
Salvatore Rotundo
Department of Experimental and Clinical Medicine, Magna Graecia University
Enrico Maria Trecarichi
Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, Magna Graecia University
Daniela Foti
Department of Health Sciences, Magna Græcia University of Catanzaro
Carlo Torti
Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, Magna Graecia University
Giuseppe Viglietto
Department of Experimental and Clinical Medicine, Magna Graecia University
Daniele Torella (dtorella@unicz.it)
Department of Experimental and Clinical Medicine, Magna Graecia University
Francesco Costanzo
Center of Interdepartmental Services (CIS), “Magna Graecia” University of Catanzaro

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Abstract

Background: The Sars-CoV-2 can cause severe pneumonia with multiorgan disease, which created an urgent need for the identification of clinical and laboratory predictors of the progression towards severe and fatal forms of this illness. In the present study, we retrospectively evaluated and integrated laboratory parameters/variables of 45 elderly subjects from a long-term care facility with Sars-CoV-2 outbreak and spread, to identify potential common patterns of systemic response able to better stratify patients' clinical course and outcome.

Methods: Baseline white blood cells, granulocytes', lymphocytes', and platelets' counts, hemoglobin, total iron, ferritin, D-dimer, and interleukin 6 (IL-6) concentration were used to generate a principal component analysis (PCA). Statistical analysis was performed by using R statistical package version 4.0.

Results: Of the 45 patients, 19 were male and 26 were female, with a median age of 81 years. The overall mortality rate was 26.67%. By PCA and clustering approach we identified 3 laboratory patterns of response, renamed as low-risk, intermediate-risk, and high-risk, strongly associated with patients' survival ($p<0.01$). D-dimer, iron status, lymphocyte/monocyte count represented the main markers discriminating high- and low-risk groups. Furthermore, patients belonging to the high-risk group presented a significantly longer time to ferritin decrease (p:0.047). Iron-to-ferritin-ratio (IFR) significantly segregated recovered and dead patients in the intermediate-risk group (p:0.012).

Conclusions: Our data generate the hypothesis that a combination of few laboratory parameters, and in particular iron status, D-dimer and lymphocyte/monocyte count at admission and during the hospital stay, can predict clinical progression in COVID-19.

Background

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2), the viral agent causing the novel coronavirus disease 2019 (COVID-19), has generated a worldwide pandemic after its initial outbreak in Wuhan, China (1). As of July 1, 2020, Sars-CoV-2 has affected more than 200 countries, resulting in more than 10 million identified cases with about 500 000 confirmed deaths (1).

Diagnosis of COVID-19 is typically performed using polymerase chain reaction testing via nasopharyngeal swab. However, because of the false-negative test result rates of Sars-CoV-2 PCR testing by nasopharyngeal swabs, several clinical, laboratory, and imaging findings have been useful to make a presumptive diagnosis (2-4). Sars-CoV-2 infection may be asymptomatic, or it may cause a wide spectrum of symptoms, such as fever, dry cough, and shortness of breath. COVID-19 severity can also progress to severe and eventually critical conditions defined by respiratory failure, septic shock, and/or multiple organ dysfunction (5-9). It is therefore of paramount importance for clinicians to establish reliable predictors of the progression of this illness for timely clinical/therapeutic decision-making.

Common laboratory abnormalities among hospitalized patients include lymphopenia (83%), elevated inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-α, IL-1, IL-6), and abnormal coagulation parameters (eg, prolonged prothrombin time, thrombocytopenia, elevated D-dimer, low fibrinogen). Most of these laboratory characteristics are nonspecific and are common in pneumonia. Aside from the established clinical risk factors, lymphopenia (absolute lymphocyte count $<1.0 \times 10^9$/L) is the sole cardinal laboratory finding with prognostic potential (1,10-12). Furthermore, different acute phase biomarkers, like ferritin, and a hypercoagulability state, indicated by elevated D-dimer, have all been associated with greater illness severity and mortality (13).

In the present study, we retrospectively evaluated and integrated laboratory parameters/variables of 45 COVID-19 patients admitted to our hospital, consisting of a homogenous group of elderly subjects from a long-term care facility with Sars-CoV-2 outbreak and spread, to identify potential common patterns of systemic response able to better stratify patients' clinical course and outcome, independently from clinical co-morbidities.

Methods

All methods were carried out in accordance with relevant guidelines and regulations. Patients

This study was carried out at the 'COVID unit' of the Magna Graecia University- "Mater Domini" Hospital in Catanzaro, Italy from March 9th to April 1st, 2020. THE study was approved by the Magna Graecia University institutional ethics committee, and a waiver of informed consent was obtained by the committee.

All patients included in this case series had a Sars-Cov-2 laboratory-confirmed infection diagnosed by quantitative reverse transcriptase- PCR (qRT-PCR) (GeneFinderTM COVID-19 Plus RealAmp Kit, Elitech Group) performed on nasopharyngeal specimens or bronchoalveolar lavage (BAL).

Clinical and laboratory assessment

Basic information such as gender, age, clinical symptoms, and signs was collected from the admission records. Admission testing included in the integrated analysis were hematologic parameters (i.e. white blood count (WBC), granulocyte count, lymphocyte count, monocyte count, platelets count, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) platelet-to-lymphocyte ratio (PLR), hemoglobin (HGB), and iron) and inflammatory markers (i.e. ferritin, IL-6, and D-dimer) which were repeated along with the hospitalization.

Statistical analysis

Statistical analysis was performed by using R statistical package version 4.0. Specifically, laboratory data known to be associated with inflammation and routinely performed in COVID-19 patients (white blood cells, neutrophils, lymphocytes, platelets counts, hemoglobin, ferritin, iron, D- dimer, and IL-6) were scaled to be used for PCA estimation. On these results, patients were clustered into 3 groups according to the K-means algorithm. Next, Student's t-test and ANOVA (according to the number of groups to be tested) were used to evaluate differences in the means of the different variables. Pearson's Chi-Square was used for comparisons between categorical variables. Correlation between variables was assessed by Pearson's correlation test. Kaplan-Meier estimate and logrank tests were used for time to events (ferritin, D-dimer, and IL-6 decrease) calculation. The following packages have been used during the whole analysis: base package to perform Student's t-test, ANOVA and Pearson's tests; ggpubr and ggplot2, for figure preparation; corrplot and corrr for correlation analysis; survminer for Kaplan Meier and logrank tests; cluster and ggfortify for PCA calculation and K-means based clustering, ggradar for radar plot.

Results

Patients' characteristics at baseline

Fifty patients were admitted to our institution following a COVID-19 outbreak that occurred in a long-term care facility. Of them, 45 patients presented all the required laboratory variables at baseline and further presented D-dimer, IL-6, and ferritin during the follow-up; thus, they were included in this retrospective analysis. Patients' characteristics at baseline are reported in Table 1.

Briefly, 19 males and 26 females with a median age of 81 years (range 55-98 years) and a median time from symptoms appearance to admission to hospital of 5 days were included in our analysis. Among them, 33 (73%) were under treatment for hypertension, 23 (51%) presented neurological diseases, 19 (43%) had a chronic kidney failure and 11 (24%) assumed drugs for psychiatric disorders. The overall mortality rate was 26.67%, in line with that reported according to the median age of Italy (14).

Table 1. Demographic and clinical patients' characteristics at baseline. 130

	Patients (n= 45)

Age, years *(median and range)*	81 (55-98)
Sex	
Male	19 (42%)
Female	26 (58%)
Comorbidities	
Hypertension	33 (73%)
Type 2 DM	9 (20%)
Malignancy	7 (16%)
COPD[a]	7 (16%)
CKD[b]	19 (42%)
Obesity	5 (11%)
Neurological dis.	23 (51%)
Psychiatric dis.	11 (24%)
Outcome	
Recovered	33(73%)
Deaths	12(27%)

[a]COPD: Chronic Obstructive Pulmonary Disease

[b]CKD: Chronic Kidney Disease

Laboratory pattern of response to Sars-CoV-2 infection

We used baseline values of blood cell count and several biochemical and coagulation-related parameters, widely used for COVID-19 patient assessment to investigate the occurrence of a specific pattern of response. Specifically, white blood cells, granulocytes, lymphocytes, and platelets count, hemoglobin, total iron, ferritin, D-dimer, and interleukin 6 concentration were used to automatically generate a PCA and to cluster patients into 3 different and well-separated groups (Figure 1A). The 3 clusters were found to be strongly associated with patients' survival (Chi-squared test $p<0.001$) and were thus renamed as low risk (1 death over 17 patients), intermediate-risk (4 deaths over 21 patients) and high risk (7 deaths over 7 patients) (patients distribution according to age and sex are reported in Figure 1B). As shown in Figure 1C, 6 out of 9 variables significantly discriminated the 3 groups, with D-dimer, lymphocytes/monocytes count, and iron status representing the main markers of the high- and low-risk group, respectively. The clustering approach was not able to fully discriminate the 21 patients belonging to the intermediate-risk group. We hypothesize that in this group the presence of a "smoldering" systemic inflammation could have been hidden by other confounding factors. To this end, we evaluated the difference in iron to ferritin ratio (IFR) as a surrogate marker of inflammation. Indeed, the increase of ferritin uncoupled from an iron increase (or in the presence of low iron values) leads to low IFR values and is usually associated with chronic inflammation (15,16). Of note, we observed that the difference in IFR significantly segregates recovered and dead patients (high IFR better prognosis) in the intermediate-risk group (p:0.012) (Figure 1D).

Time to ferritin decrease correlates with patients' survival

In the attempt to identify informative markers useful for monitoring illness severity and mortality, we observed that ferritin concentration rose during hospitalization before starting a *decalage* phase almost exclusively in recovering patients, which indeed presented a significantly short time to ferritin decrease (intended as the time from hospital admission to first and stable decrease during hospitalization) (Figure 2A) but not of D-dimer or IL-6 decrease (Figure 2B-2C). Accordingly, patients belonging to the high-risk group presented a significantly longer time to ferritin decrease (Figure 2D, p: 0.047).

Correlation analyses identify lympho/monocytes count, D-dimer, and iron status as "litmus paper" of the systemic response to SARS-CoV-2 infection

Lastly, we performed a correlation analysis, including derivative variables known to be associated with systemic inflammation, such as neutrophils, monocytes, and platelets to lymphocytes ratio (NLR, MLR, and PLR respectively). Interestingly, as shown in Figure 3A, we observed the presence of three different clusters of correlated variables, which have been grouped accordingly to the main systemic function/role they are involved in.

Among the different correlations observed, lymphocytes and monocytes experienced a similar modulation, possibly dependent on the mechanism of action of the virus. This strong relationship has been observed independently of the risk group (Figure 3B).

Moreover, we observed a direct correlation between IFR and IL-6 only in the intermediate risk group, further underscoring the role of IFR in discriminating "hidden" inflammatory responses (Figure 3C).

Other potential associations between laboratory variables and Sex, Age, risk groups, and recovery/death have been explored and reported in Supplementary Figures 1-4.

Altogether, these results further underscore the relevant role of these markers in identifying critical patients who potentially could benefit from increased monitoring and early intervention.

Comorbidities are associated with the presence of markers of the high-risk group at baseline

To investigate if the presence of previous comorbidities is associated with changes in baseline levels of inflammatory variables (thus potentially affecting patients' outcome), we performed a multiple t-test, evaluating every single variable for the association to each condition (results are reported in Figure 4A and 4B, with the last reporting variables with no significant associations). Interestingly, the presence of a

concomitant malignancy is associated with high levels of ferritin and low levels of IFR, and correlates with a worse survival (Figure 4C, p: 0.045).

Discussion

COVID-19 is associated with a high disease burden with nearly 20% of confirmed cases progressing towards critical illness (1). Hospital mortality ranges from less than 5% among patients younger than 40 years to 35% for patients aged 70 to 79 years and greater than 60% for patients aged 80 to 89 years (17). Among the latter, the elderly in long-term care facilities (LTCFs) have been reported as vulnerable to infections and at high risk for mortality (18). Nonetheless, patients with severe illness are likely to suffer substantial sequelae associated with a new physical disability, new cognitive impairment, and increased vulnerability to recurrent infection (1,18).

Currently, effective treatment for COVID-19 is still missing. Treatment for individuals with COVID-19 includes best practices for supportive management of acute hypoxic respiratory failure. Emerging data indicate that dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen (19-21) and that remdesivir improves time to recovery (19,20,22). It is therefore of paramount importance to properly identify patients who are likely to develop critical illness in order to may aid in promptly managing and optimizing the use of limited resources.

In this study, we retrospectively evaluated and integrated laboratory parameters/variables of a homogeneous cohort of 45 elderly subjects from a long-term care facility with COVID-19, to identify potential prognostic factors able to better stratify patients' clinical course and outcome. Radiographic and laboratory abnormalities, such as lymphopenia and elevated lactate dehydrogenase, are known to be common, but on their own are not specific for the diagnosis or the prognosis (1. In line with previous findings, we observed that low lymphocytes/monocytes count as well as the high level of D-dimer in the peripheral blood significantly define a group of patients with a shattering outcome (practically 100% mortality rate). The integration of these three laboratory abnormalities well describes the known course and relative pathophysiology of COVID-19 (1,10-12). Indeed, profound lymphopenia occurs in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. The viral inflammatory response, consisting of both the innate and the adaptive immune response, impairs lymphopoiesis, and increases lymphocyte apoptosis. In the progression of the viral infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised, exacerbating the inflammatory response. Finally, in severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur (1,23).

Importantly, our results show that the systemic iron metabolism associated parameters, i.e. iron status, ferritin, and IFR, can help to better predict unfavorable outcomes and to monitor illness progression/regression in COVID-19 patients. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. Previous laboratory findings highlighted that a consistent percentage

of patients with elevated serum ferritin levels faced a higher probability to experience serious complications from COVID-19 (24-27).

In this study, we found that the increase of ferritin accompanied by low iron values, which result in elevated IFR, significantly segregates recovered and dead patients and correlates with a better prognosis in COVID-19 patients belonging to the so-called intermediate-risk group (4 deaths over 21 patients). Our hypothesis is that in this group, the early evaluation of IFR may function as a surrogate marker able to highlight the presence of a “smoldering” systemic inflammation, which could have been hidden by other confounding factors. In agreement, we observed a direct correlation between IFR and IL-6 only in the intermediate risk group. Furthermore, we found that the kinetic changes of ferritin levels, but not those of D-dimer and IL-6, correlate with COVID-19 progression. Indeed, we observed that almost exclusively in the recovering patients, the ferritin concentration peak at the time of hospital admission is followed by a gradual decrease during the second and the third week of the disease course. Accordingly, patients belonging to the high-risk group presented a significantly longer time to ferritin decrease.

This study has several limitations. First, the main weakness of the present study is the small sample size, which makes the reported findings hypothesis-generating. Second, this study included elderly patients from a long-term care facility, which represents an isolated outbreak in a rather homogenous population at risk that may not be representative of the overall heterogeneous general COVID-19 population. Yet, it worth noting here that the study of such a ‘population isolate’ may have helped in generating robust evidence avoiding the confounding effects of multiple co- morbidities as in the general population.

Conclusions

The main findings of this study generate the hypothesis that a combination of few laboratory parameters, and in particular iron status, D-Dimer and lymphocyte count at admission and during a hospital stay can predict clinical progression in COVID-19. Of interest, these data were retrospectively observed in a long-term care facility, which represents a significant issue for COVID- 19 spread and management. Despite the inherent value of the present data for this population, its wide applicability to all COVID-19 patients requires validations in a larger study cohort.

Abbreviations

Sars-CoV-2: Severe acute respiratory syndrome coronavirus 2 COVID-19: coronavirus disease 2019

IL-6: interleukin 6

qRT-PCR: quantitative reverse transcriptase- PCR BAL: bronchoalveolar lavage

WBC: white blood count (WBC) NLR: neutrophil-to-lymphocyte ratio PLR: platelet-to-lymphocyte ratio HGB: hemoglobin

PCA: Principal Component Analysis

COPD: Chronic Obstructive Pulmonary Disease CKD: Chronic Kidney Disease

IFR: iron-to-ferritin ratio LTCFs: long-term care facilities

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the local institutional ethics committee, and a waiver of informed consent was obtained by the committee.

Consent for publication Not applicable

Availability of data

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests

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Not applicable

Author contributions

FC, GV, and DT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. FB and CB contributed equally to the authorship of this article.

Concept and design: DT, GV, FC

Acquisition, analysis, or interpretation of data: FB, CB, MM, SR, GV, FC, DT. Drafting of the manuscript: FB, CB, DT.

Critical revision of the manuscript for important intellectual content: EMT, DF, CT, FC, GV, DT. Statistical analysis: CB.

Supervision: DT, GV, FC.

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Figures

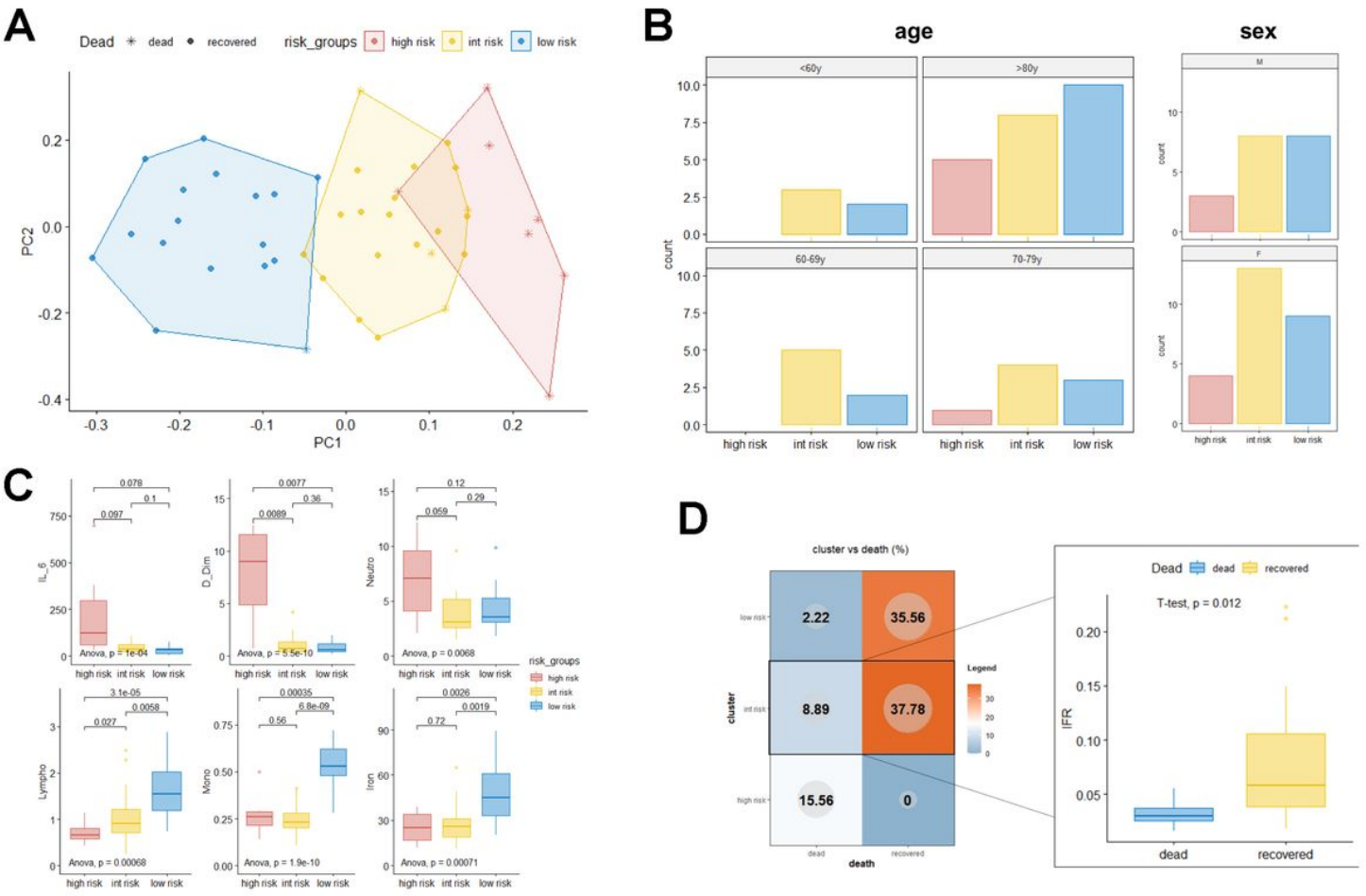

Figure 1

Baseline laboratory parameters define different patterns of response to Sars-CoV-2 infection. A, clustering analysis by a principal component analysis (PCA) scatter plot. Colors and shapes respectively represent the 3 risk groups and the status of the patient (recovered or dead). B, distribution of patients according to risk group and age or sex. C, ANOVA and T-test results of the 6 parameters which mainly influenced patients' clustering, according to their distribution across risk groups. Within each sub-panel, p values for ANOVA comparison (bottom) and for each pairwise comparison (top) are reported. D, patient distribution according to risk groups and dead/recovered status; on the right side, the histogram shows the comparison of iron to ferritin ratio (IFR) between recovered and dead patients within the intermediate-risk.

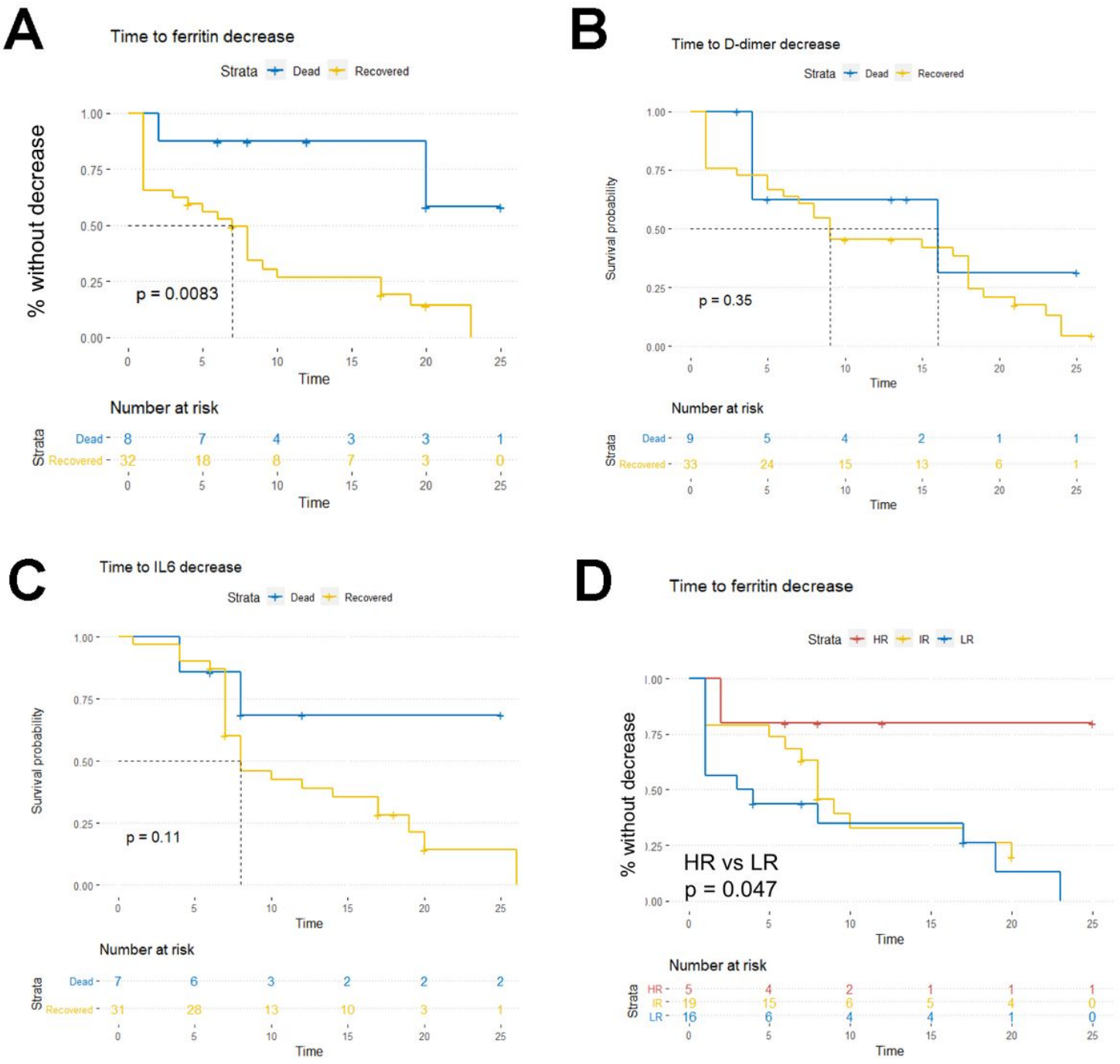

Figure 2

Patients with a worse outcome present a significantly longer time to ferritin decrease. A, B, C: Kaplan Meier curves reporting the time to ferritin, D-dimer, and IL-6 decrease (intended as the time from hospital admission to first and stable decrease during hospitalization) respectively, stratified on dead/recovered status (p value calculated through LogRank test). D, Kaplan Meier curves reporting the time to ferritin decrease stratified on risk groups (p value calculated through LogRank test comparing High-Risk vs Low-Risk patients).

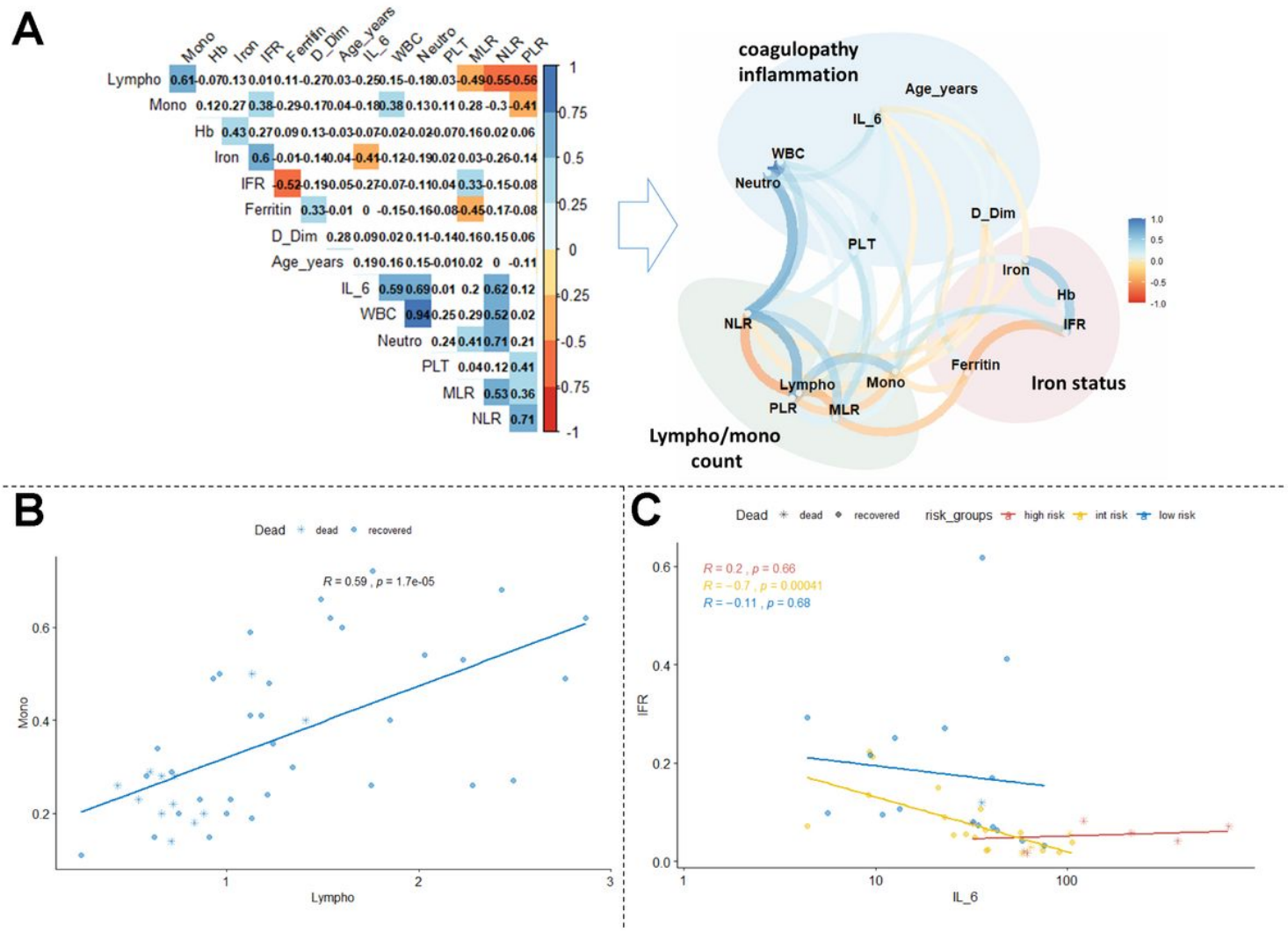

Figure 3

Correlations among lymph/monocytes count, D-dimer, and iron status significantly affect the systemic response to SARS-CoV-2 infection. A, left: correlation plot of all variables (including derivative variables such as iron to ferritin ratio (IFR), neutrophils to lymphocytes ratio (NLR), platelets to lymphocytes ratio (PLR), monocytes to lymphocytes ratio (MLR)) to identify potential inter-variables correlations. The color represents the direction of the correlation. Only boxes showing a significant correlation have been colored; right, network plot showing direction and distribution of correlations between variables. Clusters of variables belonging to similar functions have been grouped. B, scatter plot representing the correlation between lymphocytes and monocytes. Remarkably, almost all the deaths are localized within the lower left quadrant of the plot. C, scatter plot showing the association between IL-6 and IFR. This correlation reaches statistical significance within the intermediate group only, further supporting the discriminating role of IFR within this subgroup.

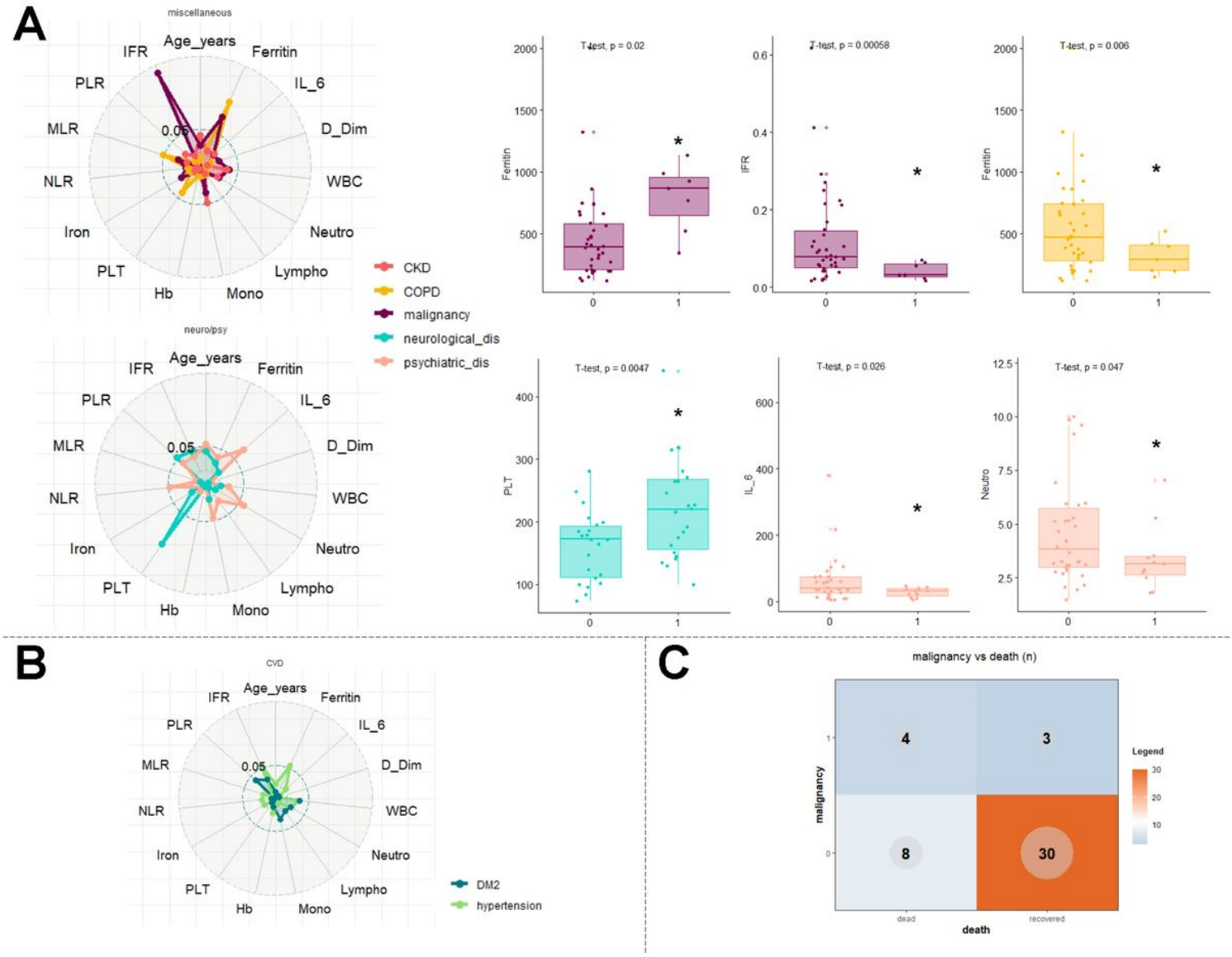

Figure 4

Association between comorbidities and baseline levels of laboratory variables. A, Distribution of different laboratory values according to baseline comorbidities: left, radar-plot showing the p values of the t-test comparing each laboratory variable with each comorbidity. The distance from the center correlates with the significance of the test (the more is far the more is significant); right, box plot representing the distribution of the significant variables only. B, radar-plot reporting CVD (cardiovascular disease) associated variables: none of them presents a significantly different distribution of laboratory variables. C, Distribution of COVID-19- associated deaths according to the presence or absence of malignancies at baseline.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx