Temporal trends in laboratory parameters in survivors and non-survivors of critical COVID-19 illness and the effect of dexamethasone treatment

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Abstract. Although coronavirus disease 2019 (COVID-19)-induced changes in laboratory parameters in patients upon admission have been well-documented, information on their temporal changes is limited. The present study describes the laboratory trends and the effect of dexamethasone treatment on these parameters, in patients with COVID-19 in the intensive care unit (ICU). Routine laboratory parameters, namely white blood cell (WBC), neutrophil, lymphocyte and platelet (PLT) counts, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH) and albumin concentrations, were recorded upon admission to the ICU and, thereafter, on days 3, 5, 10, 15 and 21; these values were compared between survivors and non-survivors, as well as between those who were treated with dexamethasone and those who were not. Among the 733 patients in the ICU, (mean age, 65±13 years; 68% males; ICU mortality rate 45%; 76% of patients treated with dexamethasone), the WBC and neutrophil counts were persistently high in all patients, without significant differences over the first 15 days. Initially, low lymphocyte counts exhibited increasing trends, but remained higher in survivors compared to non-survivors (P=0.01). The neutrophil-to-lymphocyte ratio (NLR) was persistently elevated in all patients, although it was significantly higher in non-survivors compared to survivors (P<0.001). The PLT count was initially increased in all patients, although it was significantly decreased in non-survivors over time. The fibrinogen and LDH values remained similarly elevated in all patients. However, the increased levels of CRP, which did not differ between patients upon admission, further increased in non-survivors compared to survivors after day 10 (P=0.001). Declining trends in albumin levels over time, overall, with a significant decrease in non-survivors compared to survivors, were observed. Dexamethasone treatment significantly affected the temporal progression of fibrinogen and CRP in survivors and that of NLR in non-survivors. On the whole, the present study demonstrates that patients in the ICU with COVID-19 present persistently abnormal laboratory findings and significant differences in laboratory trends of NLR, CRP, PLT and albumin, but not in WBC and neutrophil count, and fibrinogen and LDH levels, between survivors and non-survivors. The temporal progression of fibrinogen, CRP and NLR is affected by dexamethasone treatment.

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Introduction

In addition to affecting the respiratory system, coronavirus disease 2019 (COVID-19) (1) frequently complicates itself by involving multiple organs (2-5) in its most severe forms, leading to various laboratory abnormalities. Since the early onset of the pandemic, several key laboratory characteristics have been identified in the acute phase, facilitating the evaluation of disease severity (3-5). The importance of certain laboratory abnormalities induced by COVID-19, measured on the day of hospital admission, has been extensively demonstrated in numerous articles (6-19).

However, during the period of hospitalization, patients with severe COVID-19 experience a variety of changes in clinical and laboratory measures. Routine hematological and biochemical monitoring is essential for assessing the disease severity, therapeutic options and treatment response (20). Notwithstanding, despite the increased interest in laboratory abnormalities upon hospital admission, studies exploring the evolution of laboratory parameters over the course of the disease are limited and variable, particularly in the setting of the intensive care unit (ICU). Some of these studies include a small patient population or both critically and non-critically ill patients (6,21-23), whereas the limited number of large studies available (24-28) on patients with COVID-19 admitted to the ICU have demonstrated diverse results. Furthermore, the effects of dexamethasone, recommended for the treatment of COVID-19 (29), on the trajectory of various laboratory values have not been fully investigated.

The aim of the present study was to investigate the temporal trends in routine laboratory parameters characteristic of COVID-19 according to the clinical outcome, as well as the potential effects of dexamethasone treatment on patients admitted to the ICU due to COVID-19, using a large database.

Patients and methods

The present study was a single-center retrospective cohort study of prospectively collected data derived from the COVID-19 dataset (formed in March, 2020) for all critically ill patients admitted to the university ICU at 'Evangelismos' Hospital, a tertiary care center in Athens, Greece, between March, 2020 and December, 2021. All patients suffered from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by a real-time reverse transcriptase-polymerase chain reaction assay of nasopharyngeal swab specimens.

Demographics, comorbidities, the severity of illness upon admission to the ICU, mechanical ventilation, the length of stay in the ICU, dexamethasone treatment and the ICU mortality rates were recorded. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II (30) and Sequential Organ Failure Assessment (SOFA) (31) scoring systems. Routine laboratory tests for COVID-19, namely hematological parameters, including white blood cell (WBC) count, neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), platelet (PLT) count, fibrinogen and D-dimer concentrations, as well as the biochemical parameters, C-reactive protein (CRP), lactate dehydrogenase (LDH) and albumin, were selected on the basis of their routine use, on a daily basis. For analysis, laboratory values upon admission to the ICU, and on days 3, 5, 10, 15 and 21 post-ICU admission were used. The determination of SARS-CoV-2 variants in the patients with ICU over course of the pandemic was not performed routinely. However, the consecutive pandemic waves in Greece followed the global pattern, e.g., prior to the current Omicron wave, the predominant variants were Delta and Alpha. Taking into consideration the study period, which was March, 2020 to December, 2021, the vast majority of the cases in the present study were attributed to the Alpha and Delta variants.

The collection of anonymized data for the study was approved by the 'Evangelismos' Hospital Ethics Committee (Protocol No. 116/2021). Informed was obtained from all included patients.

Statistical analysis. All quantitative data are reported as the mean ± SD. The diagrams in all figures represent the mean ± SEM values. Qualitative variables are reported as number and percentage. Comparisons between the two ICU outcome groups (survivors and non-survivors) of quantitative variables were performed by using the independent samples unpaired Student's t-test. Differences between groups of patients of qualitative variables were assessed using the Chi-squared or Fisher's exact tests when appropriate. Repeated measurements were performed by using two-way repeated measures ANOVA. Whenever sphericity assumption was violated, the Greenhouse-Geisser test of within subjects effects was used. The overall mean value of each variable per outcome group, the overall mean differences of values across time, as well as the group x time interaction were estimated. In both groups, post-hoc pairwise within-subjects comparisons across time, as well as post-hoc between-subjects comparisons at each one of the six time points were performed. All P-values were adjusted for multiple comparisons using the Bonferroni correction. The SPSS statistical program (v.24; Dotmatics) was used for data analysis. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 733 patients (mean age, 65±13 years; 68% males) were included in the present study. The mean APACHE II and SOFA scores upon admission to the ICU were 15±6 and 6±3, respectively. The crude ICU mortality rate was 45%. Of these patients, 561 (76%) were treated with dexamethasone at a dose of 6 mg daily for up to 10 days. The characteristics of the patients the whole cohort upon admission in, as well as according to clinical outcomes, are presented in Table I.

Temporal trends of hematological parameters. The overall mean value of WBC per outcome group did not differ significantly. The overall mean differences in WBC values over time were significant: F(3.8, 858)=6.64, P=0.001. The group x time interaction was also significant: F(3.8, 858)=3.6, P=0.008. Post hoc between-subject comparisons at each one of the six time points revealed a significant difference in the mean WBC between the two outcome groups (survival and non-survival) on day 21 ($-3.5 \times 10^3/\mu$l, P=0.001) (Fig. 1A).

The overall mean value of neutrophils per outcome group differed significantly: F(1.226)=5.9, P=0.016. The overall mean differences in neutrophils values across time were significant: F (3.7, 852)=3.86, P=0.005. The group x time interaction was also significant: F(3.7, 873)=3.2, P=0.014. Post-hoc between-subject comparisons at each one of the six time points revealed a significant difference in the mean number of neutrophils between the two outcome groups (survival and non-survival) on day 21 ($-3{,}6 \times 10^3/\mu$l, P=0.001) (Fig. 1B).

The overall mean value of lymphocytes per outcome group did not differ significantly. The overall mean differences in lymphocyte values over time were significant: F(1.7, 389)=12.3, P=0.001. However, the group x time interaction was significant: F(1.7, 389)=3.6, P=0.03. Post-hoc between-subject comparisons at each one of the six time points revealed a significant difference in the mean lymphocyte values between

Table I. Baseline characteristics of the patients in the entire cohort and according to ICU outcomes.

Parameter	All patients (n=733)	Survivors (n=380)	Non-survivors (n=353)	P-value
Sex, male, n (%)	498 (68)	256 (67)	242 (68)	0.75
Age, years	65±13	59±13	71±12	0.001
Severity scores				
Charlson comorbidity index	3±2	2±2	4±2	0.001
APACHE II score	15±6	11±4	19±6	0.001
SOFA score	6±3	4±2	8±3	0.001
Comorbidities				
CKD, n (%)	58 (7)	12 (3)	44 (12)	0.001
Neoplasm, n (%)	68 (8)	17 (4)	45 (12)	0.001
COPD, n (%)	100 (12)	36 (9)	60 (17)	0.003
Coronary disease, n (%)	180 (23)	70 (18)	100 (28)	0.002
Obesity, n (%)	95 (12)	56 (14)	34 (9)	0.04
Diabetes, n (%)	191 (24)	92 (24)	94 (26)	0.5
Hypertension, n (%)	311 (39)	136 (35)	154 (43)	0.05
Other patient characteristics				
ICU LOS, days	21±20	22±21	19±18	0.036
MV duration, days	15±17	13±16	18±16	0.001
Pre-ICU hospital stay, days	4±7	3±5	5±7	0.001
Days before hospital admission	6±3	6±3	6±3	0.03
PaO_2/FiO_2 on admission, mmHg	144±99	144±72	141±12	0.7
MV upon admission, n (%)	549±70	219±57	296±83	0.001
HFNO upon admission, n (%)	154±19	110±28	40±11	0.001
Shock presence upon admission, n (%)	251±32	131±34	109±30	0.2
CRRT need during ICU stay, n (%)	186±23	41±10	136±38	0.001
Hematological parameters				
WBC, $x10^3/\mu l$	11.5±6.4	10.3±5.4	12.8±7.2	0.001
Lymphocyte count, $x10^3/\mu l$	1.1±1.7	1.1±1.7	1.1±1.7	0.65
Neutrophil count, $x10^3/\mu l$	10.5±8.1	9.3±7.8	11.7±8.5	0.001
NLR	14.6±12.1	12.2±8.9	17.4±14.7	0.001
Platelet count, $x10^3/\mu l$	258±110	269±106	242±11	0.002
Hemoglobin, g/dl	12.5±9.5	13.1±13.1	11.8±2.4	0.07
D-dimer, $\mu g/ml$[a]	5.0±31.6	4.9±41.0	5.2±18.8	0.11
Fibrinogen, mg/dl	590±183	601±175	578±189	0.9
Biochemical parameters				
C-reactive protein, mg/dl[b]	13±9	12±8	14±9	0.003
Procalcitonin, ng/ml[c]	2.1±9.6	1.1±7.2	3.3±12.0	0.03
Troponin T, pg/ml[d]	170±752	159±71	190±828	0.6
LDH, IU/l	552±488	477±279	642±646	0.001
ALT, IU/l	67±238	54±78	84±341	0.13
AST, IU/l	91±316	69±271	120±370	0.04
Creatinine, mg/dl	1.2±1.3	1.0±1.0	1.5±1.5	0.001
Na^+, mmol/l	140±6	138±5	141±6	0.001
Ferritin, $\mu g/l$	1,255±2,022	984±1,461	1,589±2,518	0.004
Albumin, g/dl	3.2±0.5	3.3±0.4	3.0±0.5	0.001
Lactate, mmol/l	2.1±2.1	1.6±1.2	2.7±2.7	0.001
Dexamethasone treatment, n (%)	561±76	291±76	270±76	0.977

Data are expressed as the mean ± SD, unless otherwise indicated. ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LOS, length of stay; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; HFNO, high flow nasal oxygen; CRRT, continuous renal replacement therapy; WBC, white blood cell count; NLR, neutrophil to lymphocyte count ratio; LDH, lactate dehydrogenase. [a]Upper limit of normal 0.3 $\mu g/ml$; [b]upper limit of normal 0.5 mg/dl; [c]upper limit of normal 0.1 ng/ml; [d]upper limit of normal 12 pg/ml.

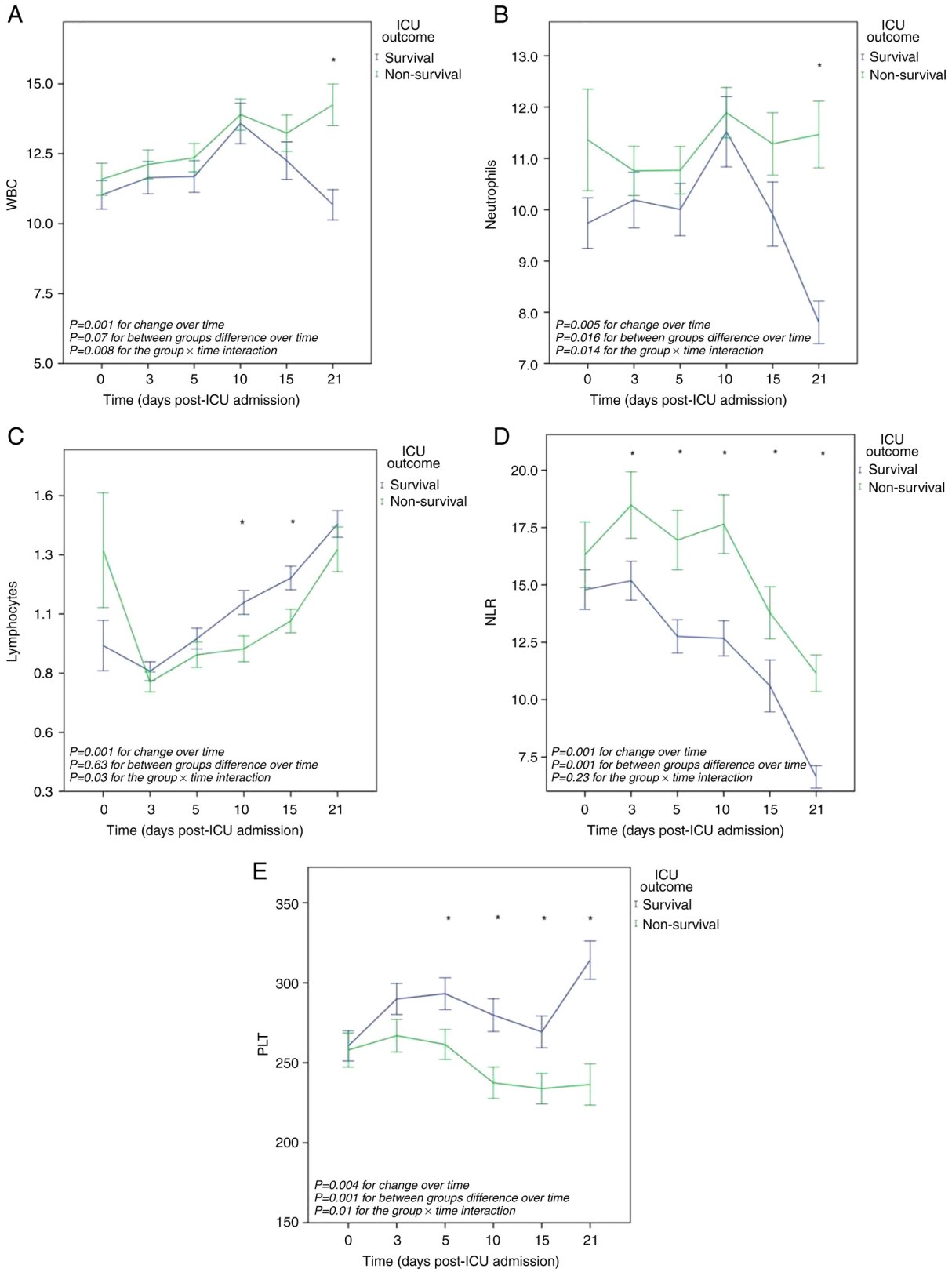

Figure 1. Changes in counts of various hematological parameters over time in the two outcome groups (survivors and non-survivors). The diagrams represent the mean ± SEM values. Concentrations in the y-axes must be multiplied by $10^3/\mu$l, apart from those in panel D. (A) WBC, (B) neutrophils, (C) lymphocytes, (D) NLR, (E) PLT. *P<0.05 for survivors vs. non-survivors. WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; ICU, intensive care unit.

the two outcome groups (survival and non-survival) on day 10 (0.19, P=0.01) and on day 15 (-0.18x$10^3/\mu$l, P=0.01) (Fig. 1C).

The overall mean value of NLR per outcome group differed significantly: F(1,226)=15, P=0.001. The overall mean differences in NLR values over time were significant: F(4.2, 952)=21.8, P=0.001. However, the group x time interaction did not differ significantly. Both groups exhibited distinct trends in the NLR over time, with a significant increase observed in

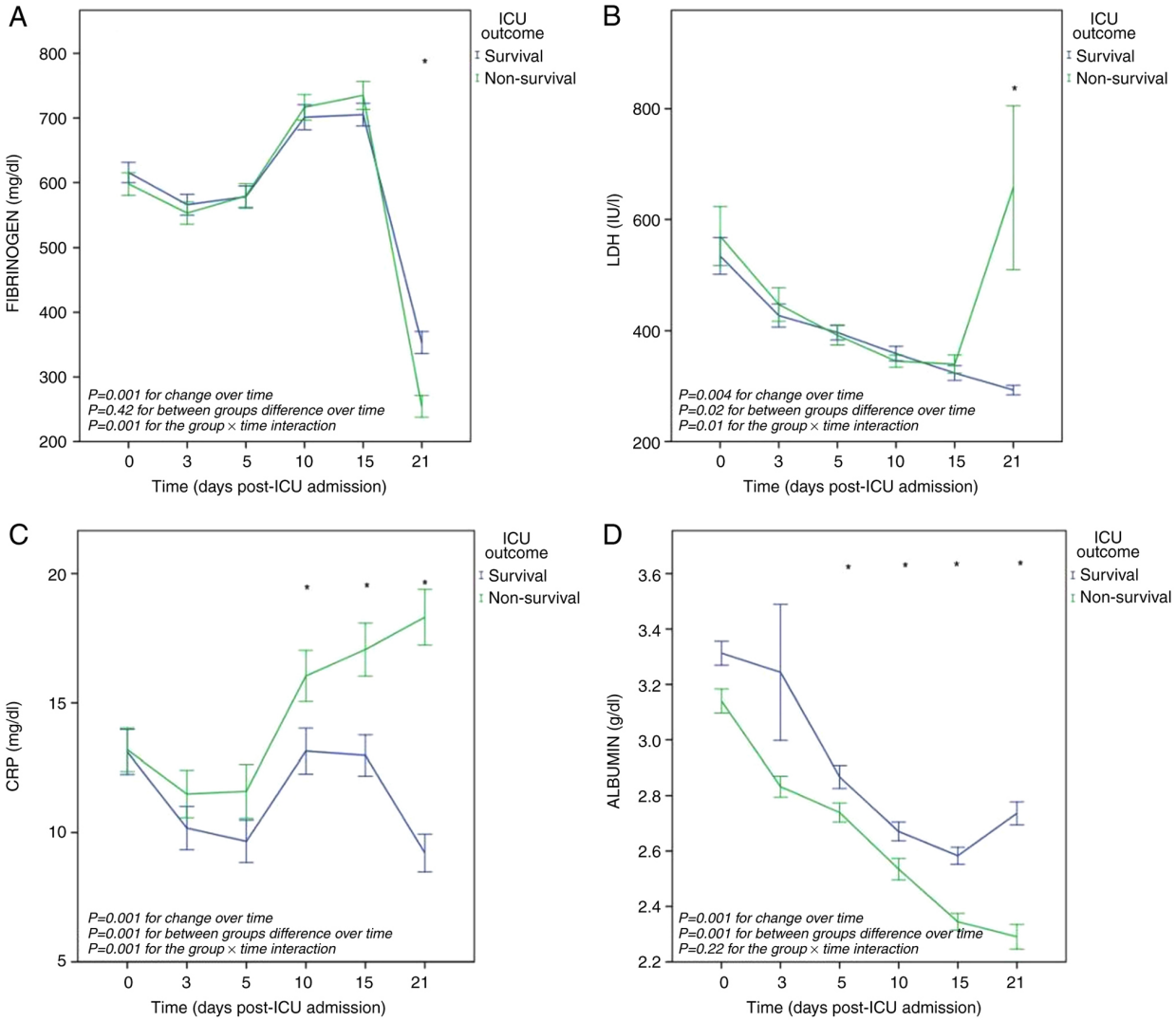

Figure 2. Changes in the concentrations of various biochemical parameters over time in the two outcome groups (survivors and non-survivors). The diagrams represent the mean ± SEM values. (A) Fibrinogen, (B) LDH, (C) CRP, (D) albumin. *P<0.05 for survivors vs. non-survivors. LDH, lactate dehydrogenase; CRP, C-reactive protein; ICU, intensive care unit.

non-survivors compared to survivors. Post hoc between-subject comparisons at each one of the six time points revealed significant differences in the mean NLR between the two outcome groups (survival and non-survival) on day 3 (-3.3, P=0.05), day 5 (-4.2, P=0.004), day 10 (-4.9, P=0.001), day 15 (-3.1, P=0.05) and day 21 (-4.5, P=0.001) (Fig. 1D).

The overall mean value of PLT per outcome group differed significantly F(1.228)=11.6, P=0.001). The overall mean differences in PLT values over time were significant: F(3.4, 779)=4.12, P=0.004. The group x time interaction was also significant: F(3.5, 779)=4.7, P=0.001. Both groups exhibited distinct trends in PLT levels over time, with a significant decrease in non-survivors compared to survivors. Post-hoc between-subject comparisons at each one of the six time points revealed significant mean PLT differences between the two outcome groups (survival and non-survival) on day 5 ($31x10^3/\mu l$, P=0.02), day 10 ($42x10^3/\mu l$, P=0.004), day 15 ($35x10^3/\mu l$, P=0.01) and day 21 ($77x10^3/\mu l$, P=0.001) (Fig. 1E).

Temporal trends of biochemical parameters. The overall mean value of fibrinogen per outcome group did not differ significantly. The overall mean differences in fibrinogen values over time was significant: F(3.9, 879)=218, P<0.001. The group x time interaction was also significant: F(3.9, 879)=4.9, P=0.001. Both groups exhibited parallel trends in fibrinogen levels over time, apart from the values on day 21. Post-hoc between-subject comparisons at each one of the six time points revealed significant mean fibrinogen difference between the two outcome groups (survival and non-survival) on day 21 (98 mg/dl, P=0.001) (Fig. 2A).

The overall mean value of LDH per outcome group differed significantly: F(1,227)=5.3, P=0.02. The overall mean differences in LDH values across time were significant: F(1.4, 323)=6.9, P=0.004. The group x time interaction was also significant: F(1.4, 323)=5.4, P=0.01. Both groups exhibited parallel trends in LDH levels across time, apart from the values on day 21. Post hoc between-subject comparisons at each one of the six time points revealed significant difference in the mean LDH values between the two outcome groups (survival and non-survival) on day 21 (-364 IU/l, P=0.008) (Fig. 2B).

The overall mean value of CRP per outcome group differed significantly: F(1,228)=18.9, P=0.001. The overall

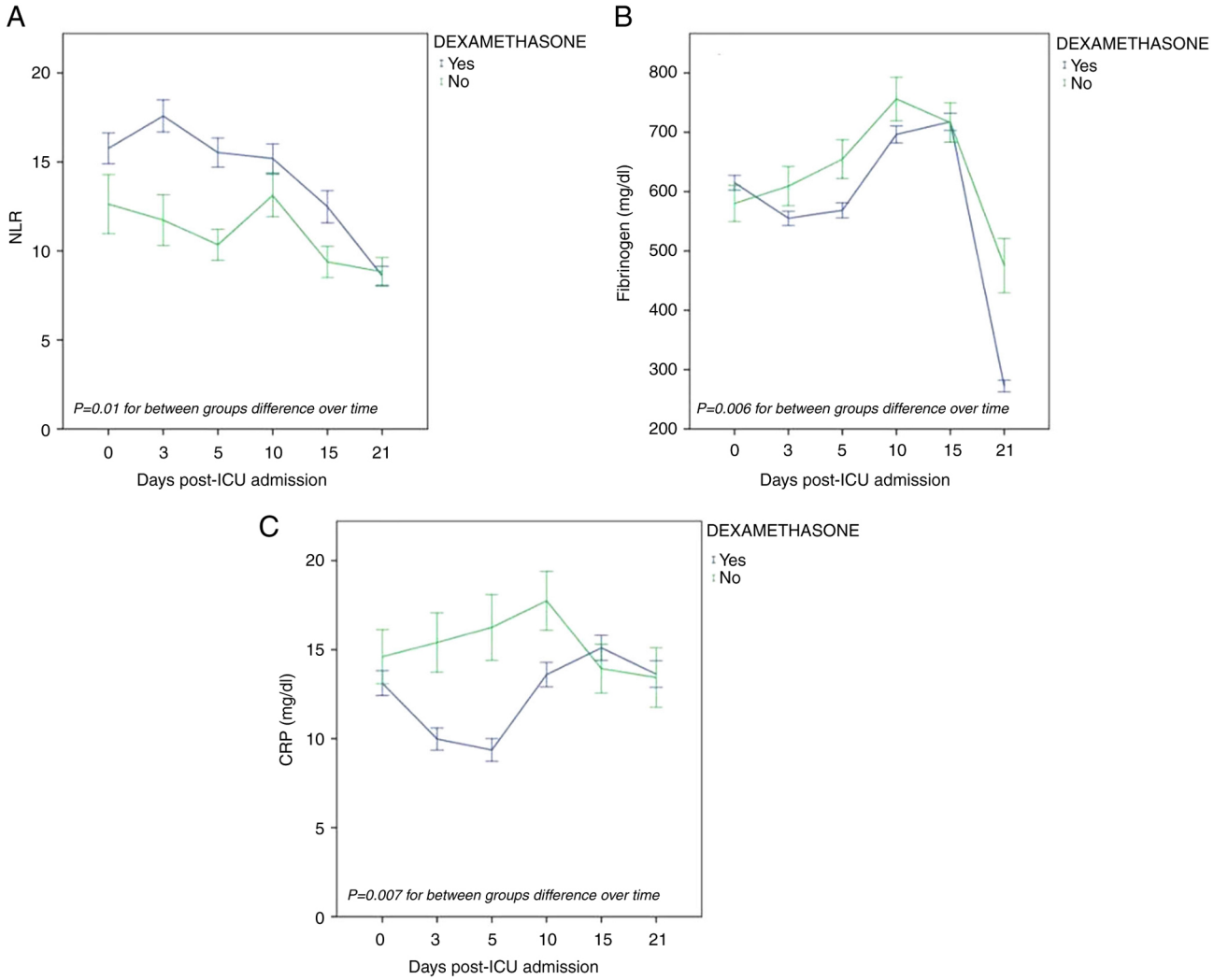

Figure 3. Effects of dexamethasone on temporal trends of various laboratory parameters in the whole study population. The diagrams represent the mean ± SEM values. (A) NLR, (B) fibrinogen, (C) CRP. NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

mean differences in CRP values over time were significant: F(4,936)=10.9, P=0.001. The group x time interaction was also significant: F(4,936)=7.9, P=0.001. Both groups exhibited distinct trends in CRP levels over time, with a significant increase in non-survivors compared to survivors. Post hoc between-subject comparisons at each one of the six time points revealed significant mean CRP differences between the two outcome groups (survival and non-survival) on day 10 (-2.9 mg/dl, P=0.03), day 15 (-4 mg/dl, P=0.002) and day 21 (-9 mg/dl, P=0.001) (Fig. 2C).

The overall mean value of albumin per outcome group differed significantly: F(1,272=20, P=0.001. The overall mean differences in albumin values across time were significant: F(1.2,287)=28.8, P=0.001. The group x time interaction was not significant. Both groups exhibited parallel, declining, though distinct trends in albumin levels over time, with a significant decrease in non-survivors compared to survivors. Post-hoc between-subject comparisons at each one of the six time points revealed significant mean albumin differences between the two outcome groups (survival and non-survival) on day 5 (0.12 g/dl, P=0.02), day 10 (0.13 g/dl, P=0.008), day 15 (0.23 g/dl, P=0.001) and day 21 (0.44 g/dl, P=0.001) (Fig. 2D).

Sensitivity analysis

Effects of dexamethasone on temporal trends of laboratory parameters in the whole population. To determine the effects dexamethasone on the laboratory data, two-way repeated measures analyses for the same parameters that were analyzed above were performed. The patients were categorized into two treatment groups, according to the administration of dexamethasone or not. Only the overall mean values of NLR, fibrinogen and CRP per treatment group differed significantly: [F(1,237)=6.81, P=0.01], [F(1,234)=7.38, P=0.006] and [F(1, 240)=7.37, P=0.007], respectively. More specifically, both fibrinogen and CRP exhibited declining trends over time in the dexamethasone group as compared to the group of patients who did not receive dexamethasone. On the contrary, NLR exhibited an increasing trend (Fig. 3).

Effects of dexamethasone on the temporal trends of laboratory parameters in non-survivors. Only the overall mean value of NLR per treatment group differed significantly [F(1, 104)=6.17, P=0.015], exhibiting an increasing trend over time in the dexamethasone group as compared to the group of patients who did not receive dexamethasone (Fig. 4A). No significant difference was observed in the fibrinogen and

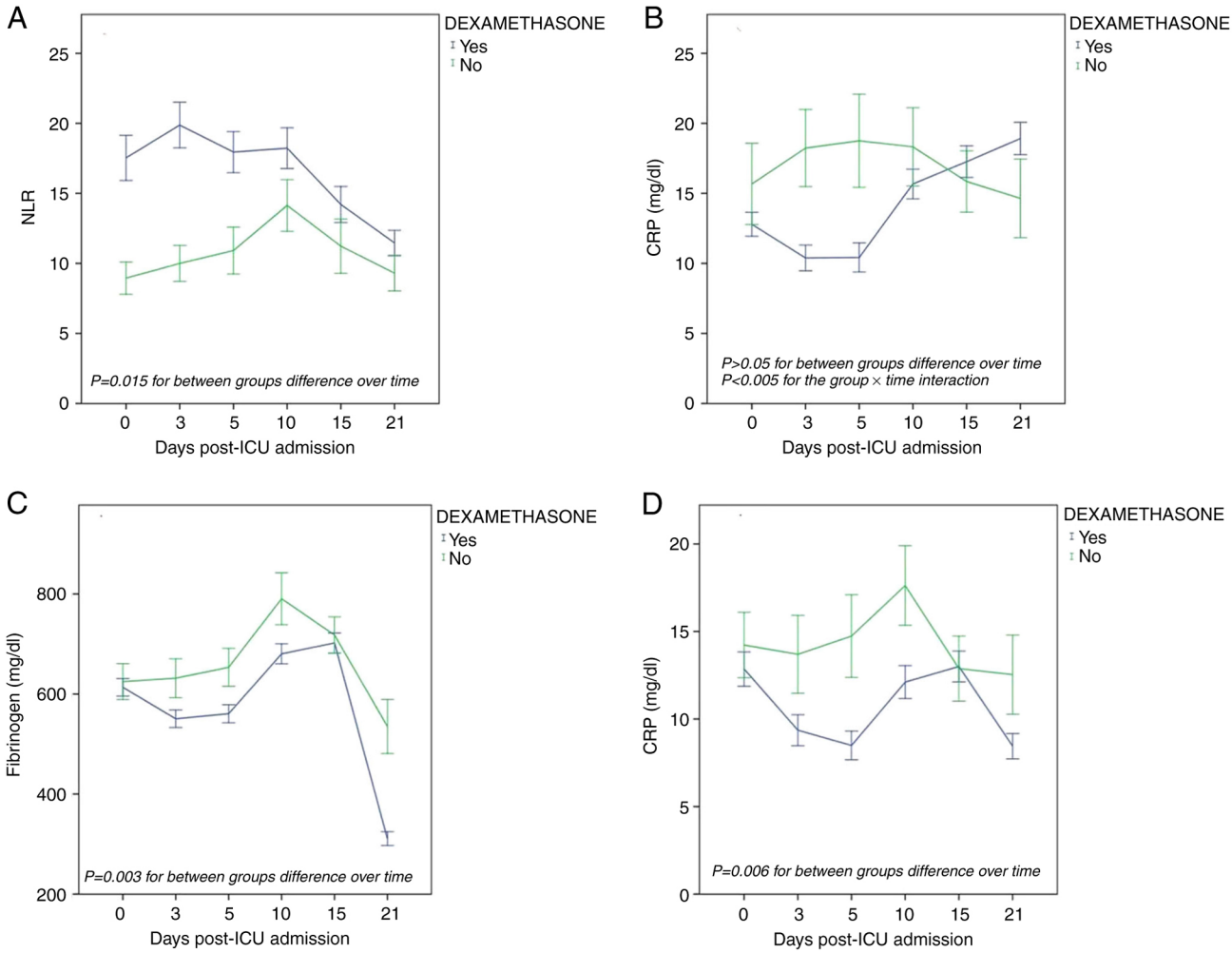

Figure 4. Effects of dexamethasone on temporal trends of various laboratory parameters in the two outcome groups (survivors vs. non-survivors). The diagrams represent the mean ± SEM values. (A) NLR in non-survivors, (B) CRP in non-survivors, (C) fibrinogen in survivors, (D) CRP in survivors. NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

CRP levels between the two treatment groups. However, CRP x dexamethasone interaction was significant [F(4,429)=3.75, P=0.005]. More specifically, CRP exhibited an initially decreasing trend during the first 10 days in the dexamethasone group and thereafter, an increasing trajectory (Fig. 4B).

Effects of dexamethasone on temporal trends of laboratory parameters in survivors. Only the overall mean values of fibrinogen and CRP per treatment group differed significantly: [F(1,120)=9.32, P=0.003] and [F(1,121)=7.73, P=0.006)], respectively. They both exhibited a decreasing trajectory over time in the dexamethasone group as compared to the group of patients who did not receive dexamethasone (Fig. 4C and D). There was no significant difference in NLR between the two treatment groups.

Discussion

The present study describes the temporal progression of routine laboratory markers, characteristic of COVID-19, in a cohort of 733 patients critically ill with COVID-19. The main findings were as follows: i) Persistently abnormal laboratory values in both survivors and non-survivors; ii) significant differences between survivors and non-survivors concerning the dynamic changes of NLR, CRP, PLT and albumin, but not of WBC and neutrophil count, fibrinogen and LDH over time; iii) significant effects of dexamethasone treatment on the temporal progression of fibrinogen and CRP values in survivors and that of NLR in non-survivors.

Similar to previous studies (28,32,33), WBC and neutrophil counts upon admission to the ICU, as well as within the first 15 days post-admission were steadily elevated, indicating persistent inflammatory activation; however, they did not differ significantly between survivors and non-survivors. Therefore, though a notable decrease in both counts was observed in survivors on day 21 after admission, the temporal changes of these variables cannot be used in prognostication. By contrast, previously (17), WBC and neutrophil counts were elevated over time only in non-survivors; however, all hospitalized, and not exclusively patients with COVID-19 in the ICU, were included in that study.

Both survivors and non-survivors had profound lymphopenia upon admission, probably reflecting the severity of COVID-19 in this critically ill population. Notably, during the stay in the ICU, both groups had persistent lymphopenia, with a nadir on day 3. Despite the gradual recovery observed thereafter, consistent with that previously reported (26), the

mean lymphocyte count did not reach normal values within the 3 weeks of observation (remaining <1,500/μl). Although significantly different mean lymphocyte counts between survivors and non-survivors were observed only at two time points (days 10 and 15), lower values in non-survivors were steadily observed.

Even more impressive than the evolution of lymphocyte values was the association between the temporal trends of NLR values and survival. Highly elevated upon admission to the ICU, NLR values did not differ significantly between survivors and not survivors, in contrast to those previously reported by Zanella *et al* (23) and Ye *et al* (34). Subsequently, the slopes of NLR were distinctly different between survivors and non-survivors, with steadily higher values in non-survivors at each time point. It should be noted that in survivors, although the mean NLR values were gradually decreasing, apart from day 21, they remained elevated, namely >10, indicating, along with the non-resolving lymphopenia, a persistent inflammation. These temporal changes in NLR are consistent with those of previous studies (27,28,35), confirming the superior role of NLR, as compared to the WBC count, concerning risk stratification in the clinical context of COVID-19.

Whereas the PLT count upon admission did not differ between the two outcome groups, contrary to that reported elsewhere (23,28), their temporal trend exhibited significant differences between the two groups, with ICU survivors presenting consistently higher counts. This is in accordance with previous findings (23,28,36). It should be noted that PLT counts in the patients in the present study were maintained mostly within or higher than the normal range, indicating a hypercoagulation state that persisted over time. This finding is in accordance with that by Wendel Garcia *et al* (24), although they are in contrast to findings reported elsewhere showing thrombocytopenia in patients critically ill with COVID-19 (27,31). The lower counts of PLT in non-survivors relative to survivors may be attributed to their more severe inflammatory status, leading to increased PLT destruction, either mechanically through disseminated intravascular coagulation, or immunologically.

Notable differences in temporal changes were also found for CRP values. The high CRP values upon admission to the ICU gradually decreased over the first 5 days in all patients. Such a decrease has not been described in studies conducted during the first wave of the pandemic (36). This could be explained by the dexamethasone treatment which has been recommended for severe COVID-19 after the first wave (29). Accordingly, Zacharias *et al* (37) recently evaluated the effects of dexamethasone on the trajectory of CRP values among critically ill patients with COVID-19, demonstrating, similarly to the findings of the present study, a significant reduction in CRP in the first 3 days of treatment. Of note, in the present study, following an initial decrease, a second increase in CRP values was observed on days 10 and 15. A plausible explanation for this increase may be the onset of nosocomial infections, usually complicating the clinical course (38,39). Indeed, in patients critically ill with COVID-19, ICU-acquired bacteremia developed after a median time of 11 days after ICU admission, as shown in a previous study from the ICU (40). Both survivors and non-survivors exhibited similar trends up to and including day 10. After that day, CRP values in non-survivors continued to increase, signaling a more intense inflammatory response, whereas a tendency towards normalization was observed in survivors.

A downward trend in LDH in both survivors and non-survivors was observed in the present study. Although overall significantly different over time, LDH values did not differ between survivors and non-survivors, except for day 21. By contrast, significant differences in temporal changes of LDH between survivors and non-survivors were reported by Xie *et al* (22) and by Wendel Garcia *et al* (24), as well as by two additional studies (23,41), with LDH levels remaining elevated in patients with unfavorable outcomes. Of note, the sharp increase of LDH on day 21 in non-survivors in the present study is in accordance with a similar increase of LDH on the day of or a day prior to death, in the study by Chen *et al* (28). This, combined with the sharp decrease in fibrinogen occurring on the same day, could possibly indicate widespread tissue damage due to ischemia, in the context of disseminated intravascular coagulation secondary to late bacterial sepsis.

Finally, albumin kinetics exhibited a rapid decrease following ICU admission, regardless of outcomes. Although initially not different, serum albumin levels were persistently lower in non-survivors compared to survivors. These findings are consistent with those of previous studies (23,28,36). Notably, following an initial deterioration phase, the albumin levels improved after the 15th day in survivors, highlighting a recovery phase. Notably, such a recovery time point occurred earlier, at ~7 days after ICU admission, in the study by Su *et al* (42). Thus far, additional data reporting albumin kinetics in the context of COVID-19 are lacking.

Information regarding the effects of dexamethasone on the temporal progression of laboratory values in patients with COVID-19 is limited (37). Since dexamethasone is known to suppress the pro-inflammatory response, the finding that, among survivors, both fibrinogen and CRP exhibited decreasing values over time in patients treated with dexamethasone as compared to those who did not, appears plausible. On the other hand, the finding of an increasing NLR in non-survivors who received dexamethasone, compared to those who did not, could reflect their enhanced vulnerability caused be dexamethasone to secondary bacterial infections and the subsequent neutrophilia.

The present study had certain limitations, which should be mentioned. First, some laboratory tests characteristic of COVID-19, such as ferritin, D-dimer and various cytokines, were not included in the present study as the selection of parameters was based on their routine daily measurement; thus, the full laboratory spectrum of COVID-19 was not analyzed. Second, age-related differences in laboratory features, which may have played a role (43) in the interpretation of the results, were not considered. Third, as in almost all relevant studies, comparisons with non-COVID-19 ICU patients were not included. Therefore, it remains unclear whether laboratory trends in COVID-19 differ from those in other causes of infection. Nevertheless, the present large cohort study, based on prospectively collected data, reveals the importance of longitudinal data compared to a sole measurement on admission and provides further information regarding the temporal trends in laboratory parameters according to clinical outcomes, as well

as the effects of dexamethasone treatment on the laboratory values, useful for prognostic models and risk stratification in this critically ill subpopulation.

In conclusion, the present study demonstrates the association between the temporal progression of routine laboratory variables and clinical outcomes in patients admitted to the ICU due to COVID-19. There were significant differences between survivors and non-survivors concerning the dynamic changes over time of NLR, CRP, PLT and albumin, but not of WBC and neutrophil count, fibrinogen or LDH. The aforementioned differences may represent distinct sub-phenotypes or endotypes of COVID-19, the further elucidation of which may potentially have a profound effect on treatment. Finally, dexamethasone treatment significantly affected the temporal progression of fibrinogen and CRP values in survivors and that of NLR and CRP in non-survivors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AKa, SKo and CR conceptualized the study. AKa, SKa, CR, VEG, AG, DAS, DK, SKo, PK, TN, CG, MAK, GD, ET, SO and AKo made a substantial contribution to data collection, interpretation and analysis, and wrote and prepared the draft of the manuscript. SKo and AKa analyzed the data and provided critical revisions. SK, AKo and CR confirm the authenticity of all the data. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in line with the Declaration of Helsinki and obtained approval from the 'Evangelismos' Hospital Ethics Committee (protocol No. 116/2021). Informed was obtained from all included patients.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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