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ORIGINAL ARTICLE

Markers of the outcome of COVID-19

Short title: Jolanta Smykiewicz et al., Covid-19 markers

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ABSTRACT

Introduction: Over the last four years, COVID-19 has caused more than 3 million deaths around the world. This phenomenon led to the search for diagnostic markers for COVID-19. Considering that the clinical applicability of specific biomarkers for the prediction of the severity of COVID-19 is still debatable, this study analyses the clinical applicability of NT-proCNP, presepsin, SuPAR, Crp, procalcitonin, interleukin-6 and D-dimers in patients who died and survived COVID-19 to establish cross-relevance between the outcome of COVID-19 and markers level.

Materials and methods: The study sample comprised 84 deceased patients (62 men, 21 women) and 72 survivors (40 men, 32 women). Various immunological techniques were employed to analyse the concentration of specific biomarkers. Statistical analysis was performed using the Student's t-test or the Mann-Whitney test according to the distribution of the sample studied.

Results: This study revealed that the levels of NT-proCNP, presepsin, SuPAR, procalcitonin, and IL-6 increase due to COVID-19. Thus, nonsurvivors are defined by the higher levels of those markers than the survivors.
Conclusions: The study revealed the potential application of NT-proCNP, presepsin, SuPAR, CRP, procalcitonin, IL-6, and D-dimers as markers of progression of the COVID-19 - D. However, considering the physiological mechanism of a dimension of a response of the studied markers as a function of disease progress, it may not be concluded that they are singularly unique for the progress of the COVID-19 - D.
Keywords: COVID-19, markers, outcome

Introduction

During 2019/2020, Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to the deaths of more than 3 million people worldwide [1] According to many studies, chronological age is the strongest predictor of outcome and disease of COVID-19 patients [2–5]. COVID-19 is diagnosed by laboratory tests in patients with an epidemiological history, clinical symptoms, and radiological examinations [6]. Recent research revealed that many biochemical markers are altered in patients with COVID-19 [7]. Furthermore, changes in the levels of specific markers correlate with the severity [8]. Among the markers studied are markers of inflammatory response such as Lactate dehydrogenase[9], C-reactive protein [10], procalcitonin [11], interleukin-1B [12], Interleukin-6 [13], and interleukin-10 [14].

Lactate dehydrogenase is a marker of lung tissue damage, and its increase is observed in patients with COVID-19 admitted to the hospital [15].

C-reactive protein, a plasma protein synthesized by the liver and induced by mediators such as IL-6, is a nonspecific biomarker of inflammatory disorders. It has been shown that its levels increase along with the severity of the disease [16].

Procalcitonin (PCT), a blood biomarker to assess bacterial infection, can be elevated due to inflammatory processes in patients with COVID-19 [17].

Although both the interleukins IL-1b and IL-10 change in patients with COVID-19, changes in the ratio between interleukin-1 and interleukin-10 in severe COVID-19 were shown not to correlate with the severity of COVID-19. However, IL-10 is a potential marker of progression of COVID-19 [18].

Among the other parameters that can be considered predictors of the severity of COVID-19 are troponin I [19], creatine kinase-MB [19], myoglobin [20], natriuretic peptide (NT-proBNP) and alanine aminotransferase [20]. Furthermore, elevated plasma levels of presepsin can be used as COVID-19 progression markers [21].

An increase in the soluble urokinase plasminogen activator receptor (SuPAR) has also been shown to be a marker in patients with the severity of COVID-19 [22].

Considering that the clinical applicability of specific biomarkers for the prediction of the severity of COVID-19 is still debatable, this study analyses the clinical applicability of N-Terminal pro-c-type Natriuretic Peptide (NT-proCNP), presepsin, soluble urokinase Plasminogen Activator Receptor (SuPAR), C-reactive proteins (Crp), procalcitonin, interleukin-6, and D-dimers in patients who died or survived COVID-19.

Materials and methods

The study was carried out according to the Declaration of Helsinki of the World Medical Association (WMA). Data were collected on the date of death or discharge from the hospital. Institutional Ethics Clearance (IEC) granted by the Regional Ethic Committee of the Medical Chamber of Gdansk, Poland, was obtained for this study: KB-29/21. Additionally, each person provided a signed informed consent form.

The study sample comprised 84 deceased patients (62 men, 21 women) and 72 survivors (40 men, 32 women). The characteristics of the study group are shown in Table 1.

Samples were collected at two points: (1) the admission to the hospital and (2) before discharge from the hospital (for patients who survived the disease) and the last blood measurement before death for patients who died from COVID-19.

The concentration of D-dimers was measured using the photometric Dia-D-DIMER method. Dia-D-DIMER is an immunoturbidimetric test reinforced with latex particles. The technique uses the binding of the sample to antibodies directed at D-dimers and the coating of latex particles. An antigen-antibody photometric reaction determined the concentration of D-dimers.

Presepsin levels were measured using an automated chemiluminescent enzyme immunoassay (PATHFAST system, LSI Medience Corporation, Tokyo, Japan). The sample was incubated with ALP-labeled antipresepsin polyclonal antibodies and magnetic particles coated with antipresepsin monoclonal antibodies, allowing the assembling of an immunocomplex with the ALP-labeled antibodies and magnetic particles coated with mouse monoclonal antibodies.

Procalcitonin (PCT) levels were measured using the Elecsys BRAHMS automated electrochemiluminescence assay (BRAHMS, Henningsdorf, Germany, Cat No. 825.050) on the Roche Cobas e-System (Roche Diagnostics, Basel, Switzerland).

Soluble urokinase-type plasminogen activator receptor (SuPAR) levels were measured using the suPARnostic® Turbilatex assay (ViroGates A/S, Birkerd, Denmark, Cat. Nr. T030) on a Cobas c501 clinical chemistry analyser (Roche Diagnostics Ltd.) according to the manufacturer's instructions.

Plasma C-reactive protein levels (CRP) were measured using the Cobas c501 analyser and the same blood sampling tube used for plasma suPAR. Human C-reactive protein (CRP) was a double polyclonal antibody sandwich enzyme immunoassay (EIA) from Merc Life Science (Catalog Number CYT298).

Interleukin-6 levels were evaluated using the Invitrogen IL-6 Human Matched Antibody Pair (Catalog Nr. CHC1263). All assays were performed according to the manufacturer's instructions.

According to the manufacturer's instructions, the serum level of the aminoterminal propeptide of CNP (NT-proCNP) was measured using the BIOMEDICA ELISA kit (CAT.NO. BI-20812). Venous blood samples collected in standardized blood collection tubes using EDTA were allowed to clot for 30 minutes at room temperature. Separation was performed by centrifugation according to the tube manufacturer's instructions. The acquired samples were stored at –25°C. Before the essay was completed, all reagents were brought to room temperature, and manufacturer instructions were followed.

Statistical analysis

Distribution normality was tested using the Shapiro-Wilk test. Based on the results obtained, data analysis was performed using the Student's t-test for paired samples or the Mann-Whitney test. The probability of rejection of the null hypothesis was chosen at a = 0.05.

Results

The analysis of Figures 1A-D shows an increase in NT-proCNP in both groups of patients, that is, those who died from (Fig. 1A) and those who recovered from COVID-19 (Fig. 1B). An increase in NT-proCNP levels in patients who died of the disease is significantly higher than that observed for patients who survived the disease. Furthermore, Fig. 1C-D reveals a greater variance in NT-proCNP levels in terminally ill patients than observed in patients who recovered from the disease.

Figure 2A–D shows the changes in presepsin levels in patients who died from the disease and those who recovered. Analysis of Fig. 2 A–B reveals a more significant variance and higher levels of presepsin in patients who died of the disease. Furthermore, presepsin levels in patients (Fig. 2C) and during the last measurement before death (Fig. 2D) are significantly higher than those observed in patients who survived the illness.

Figure 3A–D reveals changes in SuPAR as a function of the outcome of hospitalization (Fig. 3A–D). There is no significant increase in SuPAR levels at admission and the last measurement in dead and recovered patients (Fig. 3A–B). However, SuPAR levels are significantly higher in patients who died of the disease at admission and the last measurement (Fig. 3C–D) than the levels observed in patients who recovered from the disease (Fig. 3C–D).

Analysis of changes in CRP levels in both groups of patients, that is, those who died and recovered from the disease (Fig. 4A–B), shows statistically equal levels of CRP at admission and the last measurement in both groups of patients. However, there is a significant increase in CRP levels in patients who died from the disease recorded at both measurements, that is, at admission and the last measurement (Fig. 4C–D).

Measurements of procalcitonin levels in both groups of patients at admission to the hospital and in the last measurement show a lack of statistically significant differences between both measurements (Fig. 5A–B). However, procalcitonin levels in patients who died of the disease are significantly higher than those observed in patients who recovered from the disease (Fig. 5C–D).

Analysis of changes in IL-6 (Fig. 6A–D) exhibits statistically significant increases between the first and last measurements in patients who recovered from the disease (Fig. 6a vs Fig 6B). IL-6 levels are significantly higher at admission and at the last measurement in patients who died from the disease (Fig. 6C–D).

Analysis of Figs. 7A–D reveals similar levels of D-dimers at admission and during the last measurement in both groups of patients. However, in patients who died from the disease, the levels of D dimers at the last measurements are significantly higher than the levels observed for survivors (Fig. 7B vs Fig. 7D).

Discussion

The clinical features of COVID-19 are of a wide range, from asymptomatic conditions to fatal lung injury. Furthermore, recent studies revealed several risk factors for COVID-19, such as obesity, gender, and age [23–25].

Although remarkable progress has been made, it is still evident that the status of a patient may worsen for no apparent reason. Thus, identifying critical markers of progress is essential for clinicians. Therefore, this study has been devoted to researching a pool of current and novel biomarkers that may predict the outcome of COVID-19.

Aminoterminal pro-C-type natriuretic peptide (NT-proCNP) is an inflammatory marker of prognostic value in Parkinson's disease [26] in septic patients [27] and meningitis [28]. So far, its role has not been confirmed in COVID-infected patients. However, another member of the natriuretic peptides, namely NT-proBNP, is strongly associated with the survivability of COVID-19 [29]. The results obtained in this study show an increase in NT-proCNP levels in both studied groups, i.e., "dead" and "alive" during the progression of the disease. Thus, this study did not confirm the results of the research reported by Bojti et al. [30], who reported a decrease in Nt-proCNP levels as a function of COVID-19 severity. However, a statistically significant increase in NT-proCNP is observed only in patients who died of COVID-19. This observation confirms the hypothesis that NT-proCNP should be further studied as a potential marker of inflammatory processes accompanying various diseases, including COVID-19.

Plasmatic presepsin is a soluble N-terminal fragment of the differentiation marker protein 14 (CD14) and has been reported to increase sepsis [31]. Since sepsis and SARS-COV-2 share many pathophysiological similarities, such as, among others, coronary heart disease, it has been postulated that it can help assess the severity of COVID-19 disease (COVID-19 - D) [21]. This study confirmed that presepsin levels increase as a function of the severity of COVID-19, and their levels are significantly higher in patients who died of COVID-19 than in those who survived the infection.

Enoccson et al. [32] and Maruszewski et al. [33] independently showed that the soluble urokinase plasminogen activator receptor (SuPAR) predicts the severity of the COVID-19 illness. The results of this study confirm previous observations and reveal significantly higher levels of SupAR in patients with terminally ill COVID-19 during admission and at death from the disease.

In 2020, Ali [34] indicated the potential role of CRP in predicting the severity of COVID-19 infection. In 2022, Bouayed et al. [35] reported that CRP is a poor prognostic biomarker in COVID-19. The results of this study do not confirm the latter and show a statistically significant increase in CRP levels associated with the severity of COVID-19.

Tong-Ming et al. [36], Hui et al. [37] and Ahmed et al. [38] showed that high levels of procalcitonin are associated with mortality in patients with COVID-19. These observations are confirmed by the results of the present study, which reveal a statistically significant increase in procalcitonin levels in patients who died of COVID-19 infection between admission to the hospital and death.

IL-6 is a cytokine with pleiotropic activity and functional redundancy used in host defence mechanisms [39]. During infection, IL-6 is produced by immune-mediated cells, mesenchymal cells, endothelial cells, fibroblasts, and cancer cells [40]. The recent report by Kumar et al. [41] shows that serum IL-6 was a poor survival marker. The conclusion of the present study does not confirm this observation. Indicates significantly higher levels in patients who died from COVID-19 compared to patients who survived COVID and were released from the hospital.

The pooled analysis of the relationship between D-dimer and the outcome of COVID-19 - D showed that its levels are higher in nonsurvivors than in survivors [42]. The results presented in this report reveal that it is true but only applies to the final stages of the disease, before death or release from the hospital. There is no indication that the D-dimer may serve as a potent marker of disease progress or a marker of prognostic value.

Conclusion

The presented study reviewed the potential application of NT-proCNP, presepsin, SuPAR, CRP, procalcitonin, IL-6 and D-dimers as markers of progress of COVID-19 - D. The results confirm the potential applicability of NT-proCNP, presepsin, SuPAR, procalcitonin, and IL-6 [43]. However, considering the physiological mechanism of a dimension of a response of the studied markers as a function of disease progress, it may not be concluded that they are singularly unique for the progress of COVID-19 - D.

The study sample size reported here is 84 (dead patients) and 72 (live patients). In the authors' opinion, it is not enough to indisputably confirm the clinical applicability of the reported

markers. However, simultaneous analysis of changes in NT-proCNP, presepsin, SuPAR, procalcitonin, and IL-6 may strongly indicate the outcome of disease progression.

Article information

Data availability statement: *Data reported in this study are available upon request from authors.*

Ethics statement: *The Regional Ethic Committee of the Medical Chamber of Gdansk, Poland, approved the study.*

Author contributions: *Both authors contributed equally to this report.*

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Conflict of interest: *The authors declare that they have no competing interests.*

Supplementary material: *None.*

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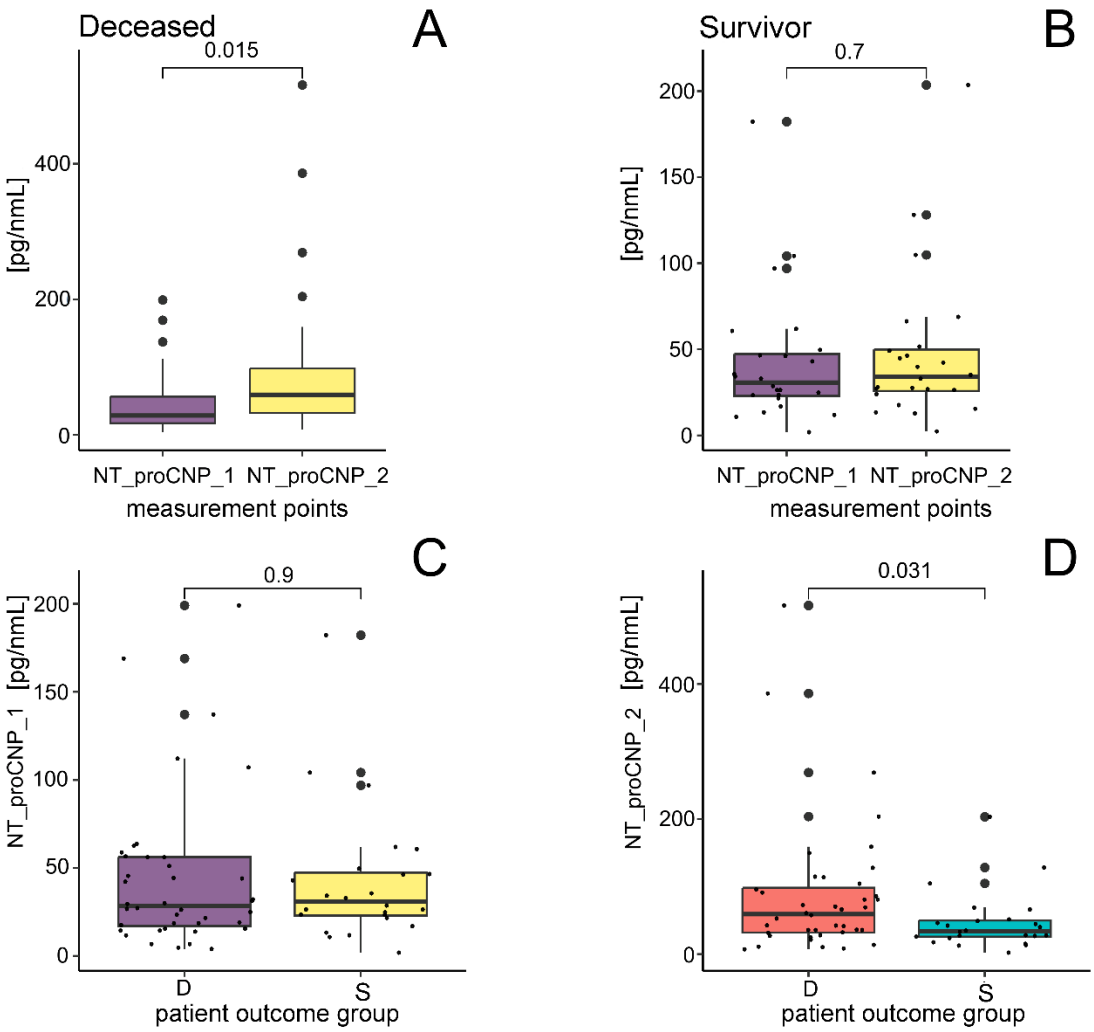

Figure 1. Changes in NT-proCNP levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

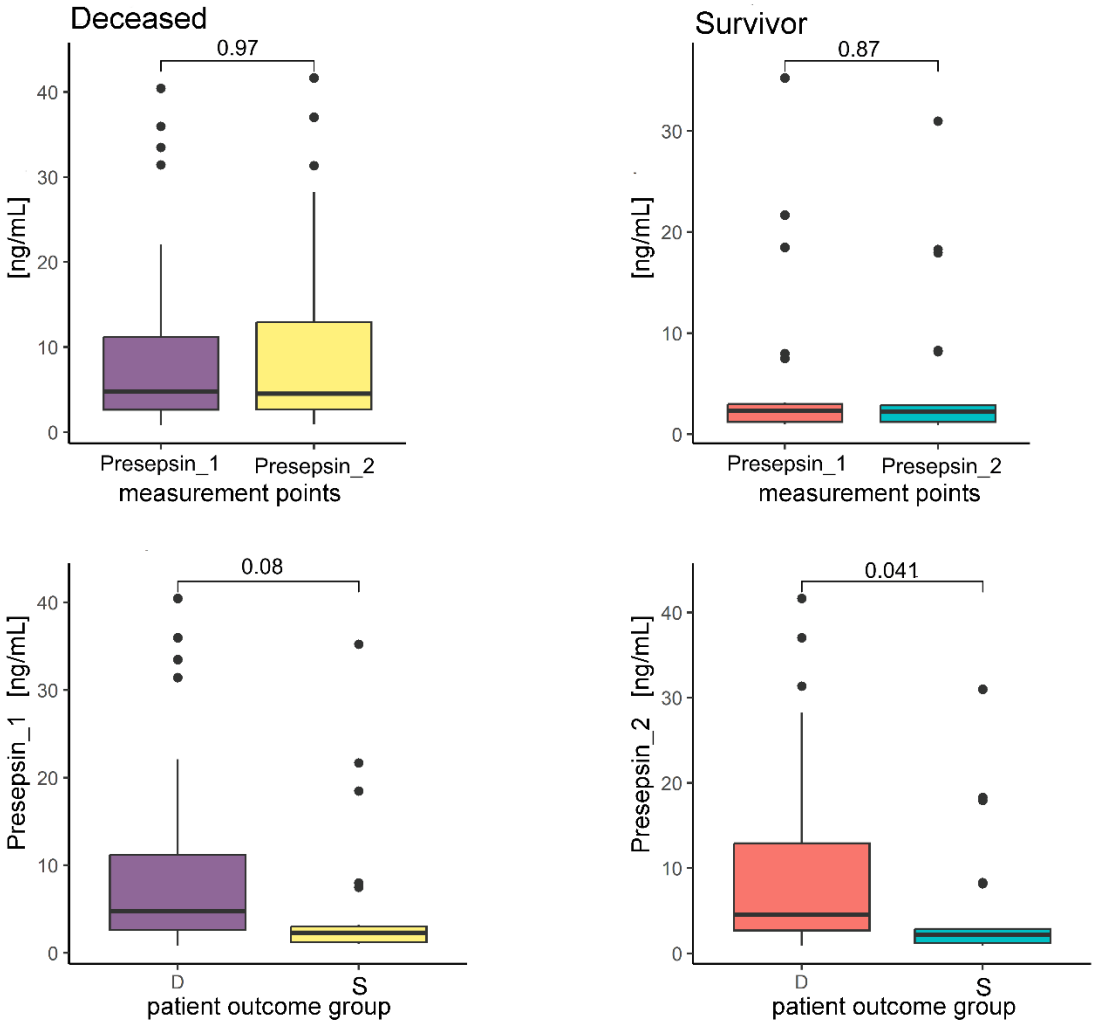

Figure 2. Changes in presepsin levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

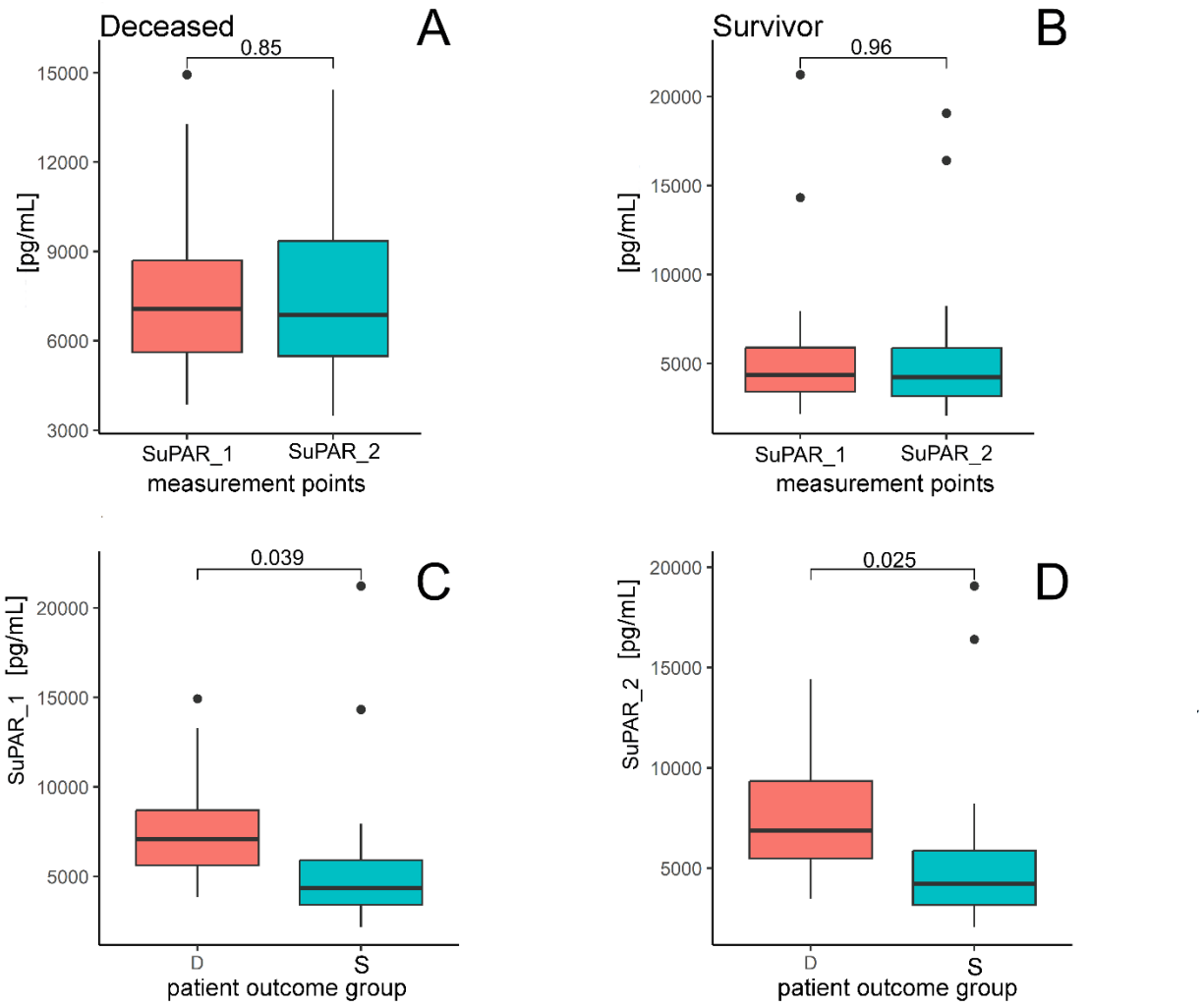

Figure 3. Changes in SuPAR levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

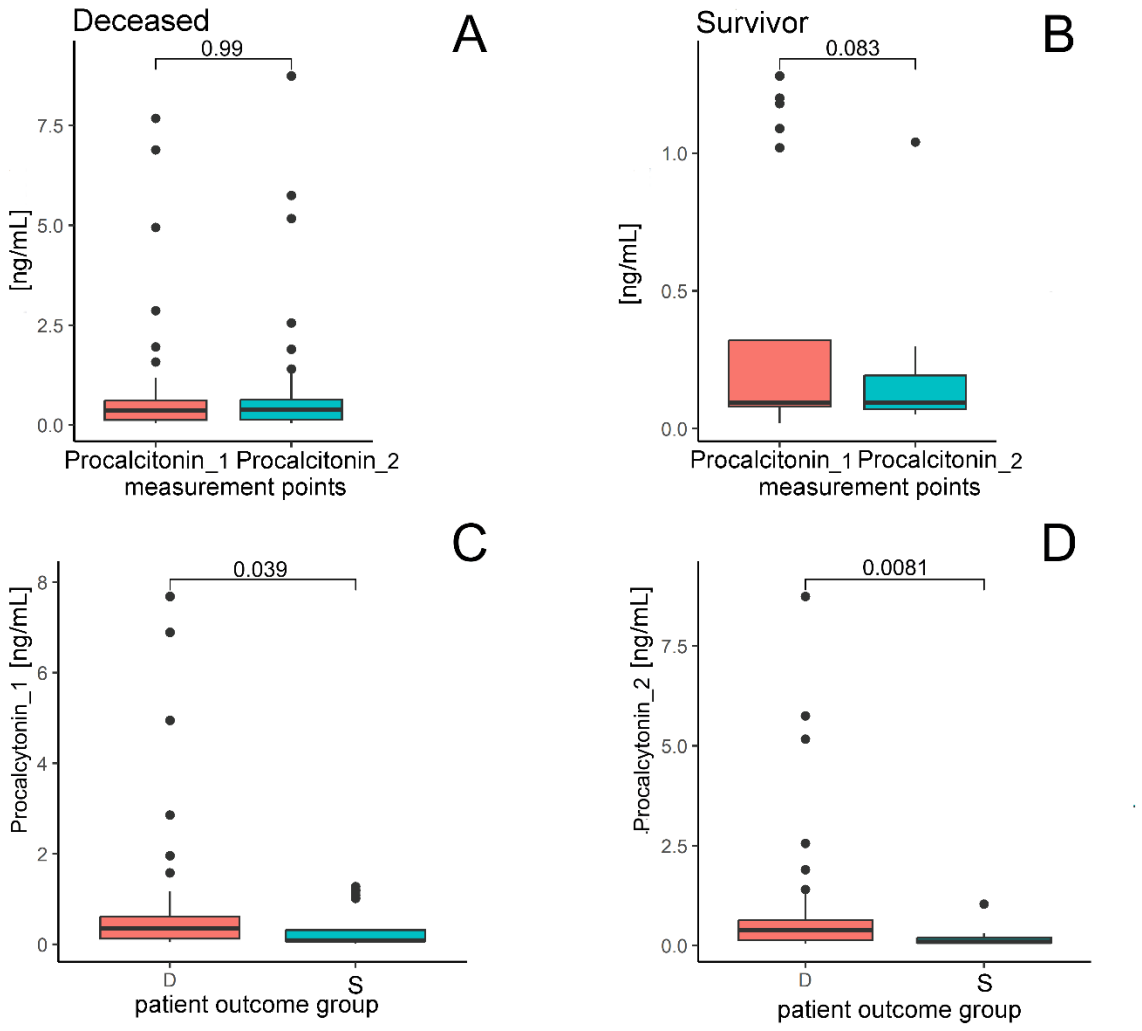

Figure 4. Changes in CRP levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

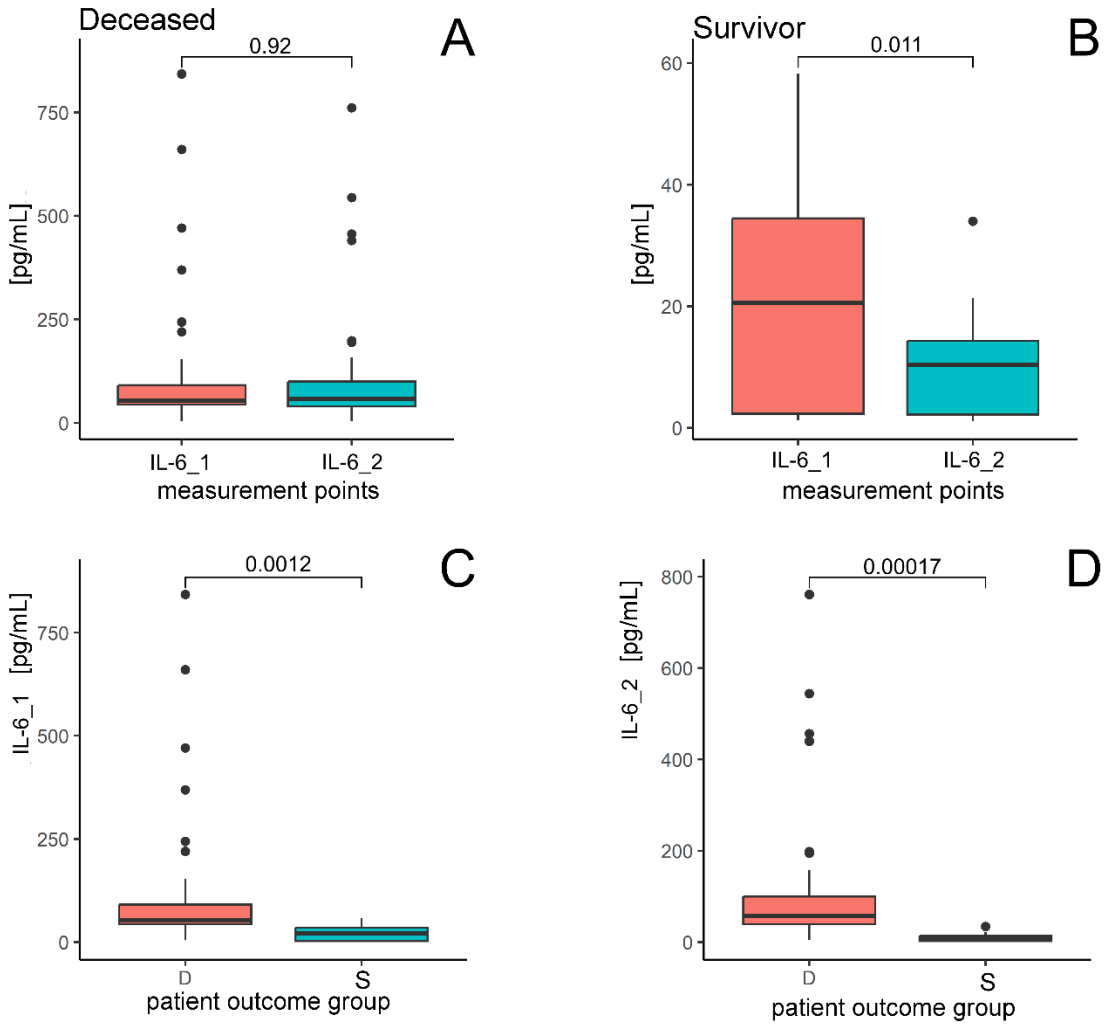

Figure 5. Changes in procalcitonin levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors: **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

Figure 6. Changes in IL-6 levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S) **(brak ryciny)**

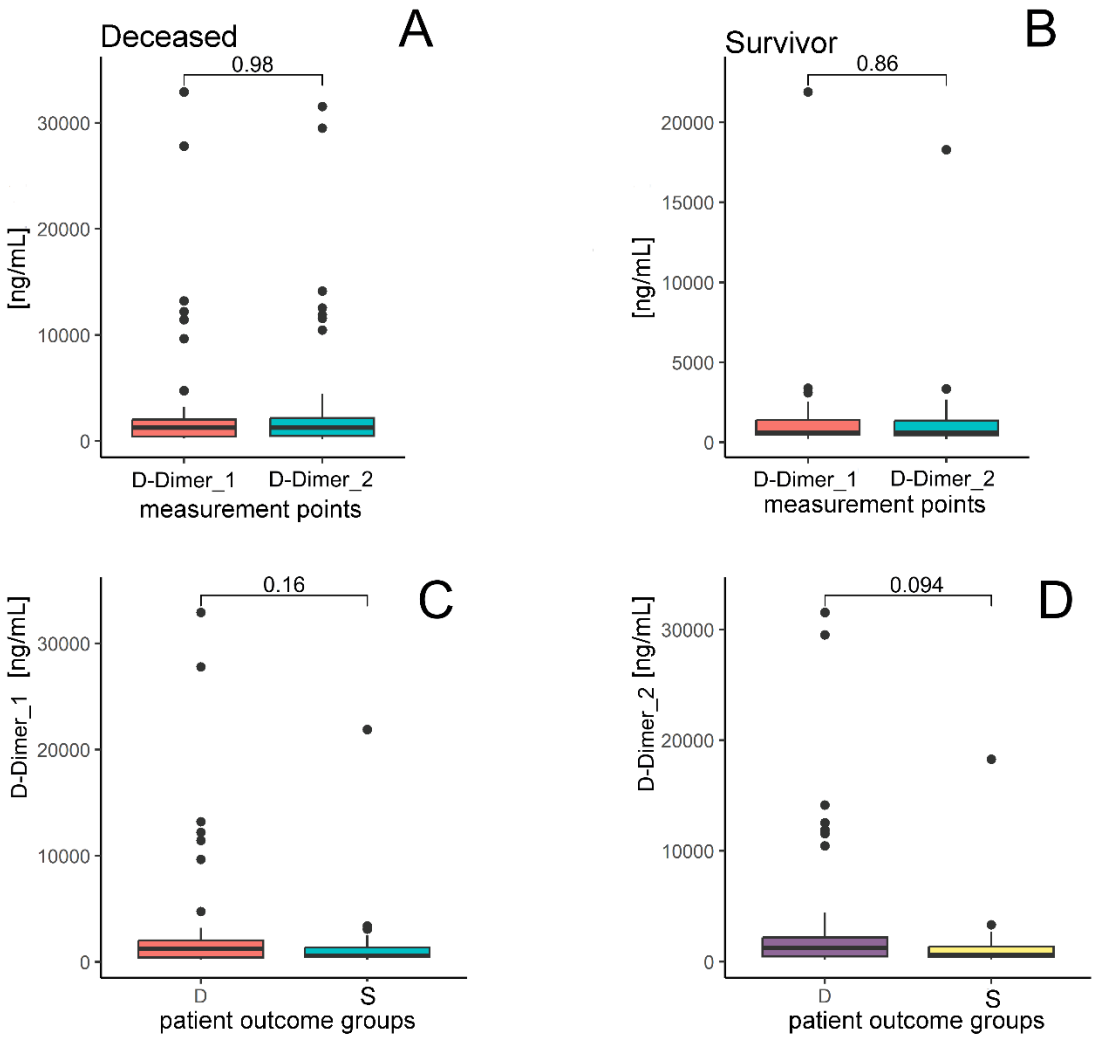

Figure 7. Changes in D-Dimer levels as a function of measurement time and recovery: **A)** between the first and last measurement in nonsurvivors; **B)** between the first (_1) and last (_2) measurement in survivors; **C)** in the first measurement between nonsurvivors (D) and survivors (S); **D)** in the last measurement between nonsurvivors (D) and survivors (S)

Table 1. Characteristics of the study group

	Gender (%)	**Age range**	**cause of death**	**Associated diseases (%)**	**Hospitalization time (range)**	**Drug administered**	**Invasive ventilation (%)**	**Active smoking (%)**
Deceased patients	Male (73.8)	68–80	Cardiorespiratory failure	Diabetes (5); chronic renal failure (10); chronic heart failure (15); pneumonia (2); hypertension (30)	3–34	Molnupiravir, Remdesvir, Paxlovid, RoActemra	52	10
	Female (26.2)	70–84		Diabetes (7); chronic renal failure (6); chronic heart failure (20); pneumonia (2); hypertension (40)			70	15
Survivors	Male (55.5)	70–79		Diabetes (2); chronic renal failure (2); chronic heart failure (17); pneumonia (0); hypertension (40)	8–30		35	5
	Female (44.5)	69–81		Diabetes (1); chronic renal failure (0); chronic heart failure (14); pneumonia (1); hypertension (20)			38	10