JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

*Coronavirus Pandemic*

# Could serum intestinal fatty acid-binding protein and citrulline levels be predictive markers of mortality in critically ill COVID-19 patients?

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## Abstract

Introduction: The global Coronavirus Disease 2019 (COVID-19) pandemic has been demonstrated to cause severe acute respiratory syndrome and is frequently associated with gastrointestinal (GI) manifestations. Intestinal fatty acid binding protein (IFABP) and citrulline have been identified as potential biomarkers of intestinal (dys)function. The present study was undertaken to ascertain the relationship between serum IFABP and citrulline concentrations and mortality in patients with COVID-19.

Methodology: This observational study was conducted in the medical intensive care unit (ICU) and included adult patients diagnosed with PCR-confirmed cases of severe acute respiratory syndrome (SARS-CoV-2). Serum citrulline and IFABp concentrations were quantitatively analyzed using an enzyme-linked immunosorbent assay (ELISA) within the initial 24 hours following ICU admission.

Results: A total of 85 critically ill patients (mean age: 70.0 ± 12.4 years) were recruited for this study. The mean Acute Physiology and Chronic Health Evaluation (APACHE II) score was 20.0 ± 7.1. In comparison with survivors (n = 48 patients), non-survivors (n = 37 patients) exhibited significantly elevated serum IFABp concentrations (median (interquartile range, IQR): 13.27 [6.41-17.87] vs. 7.23 [3.26-12.25] ng/mL, p = 0.007) and diminished citrulline levels (median (IQR): 7.61 [4.37-8.52] vs. [4.67 (3.34-8.90] nmol/L, p = 0.043). Receiver operating characteristic (ROC) analysis revealed that the cut off value of serum IFABp and citrulline concentrations to predict ICU mortality was 8.15 ng/mL (AUC: 0.722, 95% Cl: 0.611-0.833, $p$ = 0.001) and 5.99 nmol/L (AUC: 0.671, 95% Cl: 0.551-0.791, $p$ = 0.009), respectively.

Conclusions: The findings of this study indicate that serum IFABP and citrulline concentrations possess the potential to function as biomarkers for predicting mortality in critically ill patients with confirmed cases of SARS-CoV-2.

**Key words:** Citrulline; COVID-19; intensive care unit; intestinal (dys)function; intestinal fatty acid binding protein.

*J Infect Dev Ctries* 2025; 19(7):1024-1029. doi:10.3855/jidc.20862

(Received 18 September 2024 – Accepted 19 December 2024)



## Introduction

Coronavirus Disease 2019 (COVID-19) has been associated with unfavorable clinical outcomes, including acute respiratory distress syndrome, renal/hepatic dysfunction, and multiple organ dysfunction syndrome [1]. The intestinal host cells are central to the pathophysiological processes triggered by sepsis. Viral spike proteins that bind to the angiotensin-converting enzyme (ACE) receptor have been shown to be capable of infecting the gastrointestinal tract [2]. Previous studies have demonstrated that patients with COVID-19 have experienced gastrointestinal symptoms and/or dysfunction [3-5].

Intestinal fatty acid binding protein (IFABP) is predominantly located in enterocytes and plays a pivotal role in the metabolism of long-chain fatty acids. It is considered a biomarker of intestinal cellular damage [6]. In healthy individuals, enterocyte turnover occurs naturally, resulting in undetectable or low IFABp concentrations [7]. However, IFABp may increase under certain clinical conditions, including sepsis/septic shock [8,9], trauma [10], and critical illness [10-12].

Citrulline is a non-essential amino acid that is synthesized from glutamine in the enterocytes. Citrulline has been identified as a limiting factor in the

de novo synthesis of arginine, a process that plays a crucial role in nitric oxide metabolism [13]. It is posited to be a marker of enterocyte (dys)function in critically ill patients [6]. Several studies have reported that citrulline levels are reduced in critically ill patients and that this reduction is associated with poor clinical outcomes [11,14,15].

The objective of this study was to ascertain the serum concentrations of IFABp and citrulline in order to predict the mortality risk of patients diagnosed with COVID-19 in the intensive care unit (ICU).

## Methodology

*Study design and population*

This observational study was conducted in the medical ICU of Kayseri City Training and Research Hospital between July 2021 and September 2021. The study was approved by the local ethics committee, and all procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975 (revised in 2008). Written informed consent was obtained from all participants or legal guardians at the time of admission to the study.

The study inclusion criteria were as follows: age ≥ 18 years, PCR-confirmed diagnosis of COVID-19 infection, and an expected need for ICU treatment for a period exceeding 48 hours. In the context of our clinical practice, patients exhibiting the following conditions were deemed to necessitate the provision of ICU support [16]:

- Dyspnea and respiratory distress
- Respiratory rate ≥ 28 breaths per minute
- Oxygen saturation < 93% or partial oxygen pressure < 60 mmHg despite nasal oxygen support of ≥ 5 liters/min
- PaO2/FiO2 < 300
- Clinical deterioration and bilateral infiltrates on chest X-ray or tomography or multilobar involvement or increased infiltrates compared to previous imaging
- Hypotension (systolic blood pressure < 90 mmHg, > 40 mmHg decreases from usual systolic blood pressure, mean arterial pressure < 65 mmHg) or vasopressor requirements
- Skin perfusion abnormalities, lactate > 4 mmol/L, Sequential Organ Failure Assessment (SOFA) score ≥ 2 units increase
- Elevated cardiac enzymes (troponin) or arrhythmia findings
- Macrophage activation syndrome (MAS) findings

Patients with malignancy, acute or chronic mesenteric ischemia, short bowel syndrome resulting from gastrointestinal surgery, or coeliac disease were excluded from the study.

*Data collection*

Age, gender, body mass index (BMI), clinical symptoms related to COVID-19 infection, and comorbidities of the study participants were recorded. Following admission to the ICU, the severity of illness was evaluated using the following scoring systems: the Acute Physiology and Chronic Health Evaluation (APACHE II) score, the SOFA score, and the Glasgow Coma Scale (GCS). The nutritional status of study participants was assessed using The Nutrition Risk in Critically Ill (NUTRIC) score [17], a specific tool for ICU patients. A NUTRIC score of > 5 was defined as malnutrition. The administration of mechanical ventilation (MV) to the participants was documented throughout their stay in the ICU.

*Blood analysis*

Peripheral blood samples were collected in serum-separating tubes within the first 24 hours following admission to the ICU. Serum samples were separated by centrifugation at 1500 × g with a refrigerated centrifuge for a period of 10 minutes within 60 minutes of sample collection. Subsequently, they were then aliquoted and stored at -80 °C until analysis. Serum IFABp and citrulline concentrations were analyzed using an ELISA method (Cat No: E1541Hu for IFABp and Cat No: E3718Hu for citrulline, Bt-Laboratory, Shanghai, China).

*Statistical analysis*

All data were analyzed using SPSS software (version 26.0). Continuous data are presented as mean ± standard deviation (SD) or median (25th-75th quartile, IQR), in accordance with the normality of the data, as determined by the Shapiro-Wilk test. Categorical data are presented as numbers (percentages). The difference between two sets of continuous data was analyzed using two independent sample T test or Mann-Whitney U tests. The chi-square test was used to assess the differences between the categorical variables. The correlation between serum IFABp and citrulline concentration was analyzed using Spearman's correlation analysis. Spearman's rho was classified as: < 0.2, negligible; 0.2-0.4, weak; 0.4-0.6, moderate; 0.6-0.8, strong; and 0.8-1.0, very strong. A

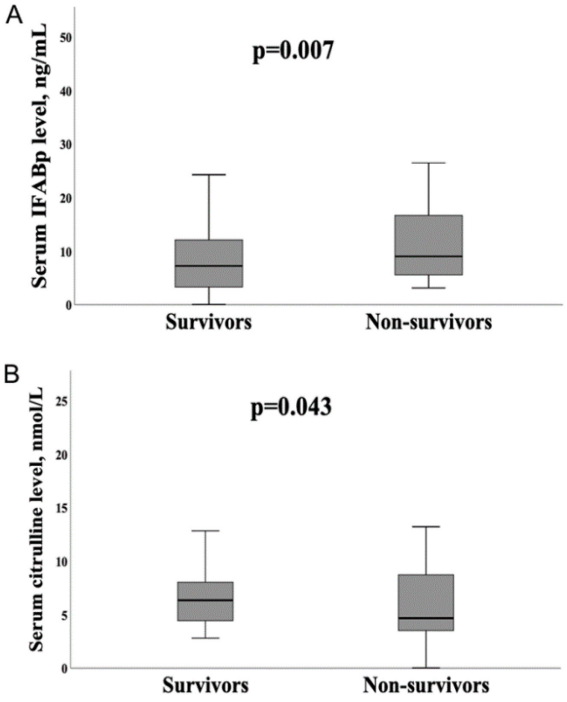
receiver operating characteristic (ROC) analysis was conducted to predict ICU mortality based on serum levels of IFABp and citrulline. The area under the curve (AUC), including 95% confidence intervals (CI), cutoff point, sensitivity, and specificity were established using the Youden Index. Statistical significance was set at a $p$ of 0.05 or less for all tests.

## Results

A total of 85 critically ill patients were enrolled in this study. The mean age of the study participants was 70.0 ± 12.4 years and 55.3% were male. Of the 85 participants, 48 were classified as survivors and 37 as non-survivors. The non-survivor group exhibited a significantly older age compared to the survivor group (73.1 vs 67.7 years, $p$ = 0.034). Non-survivors had significantly elevated APACHE II and SOFA scores in comparison to survivors ($p$ = 0.014 and $p$ = 0.008, respectively). In addition, non-survivor patients had a significantly higher prevalence of malnutrition compared to survivors ($p < 0.05$). Furthermore, 73% of the deceased patients received MV, with a significantly higher rate of MV treatment than that observed in surviving patients ($p < 0.001$) (Table 1).

Non-survivors exhibited significantly elevated D-dimer levels compared to survivors ($p$ = 0.023).

**Figure 1.** The median serum IFABp and serum citrulline concentrations of survivors and non-survivors.




**A.** illustrates the median serum IFABp value and **B.** serum citrulline value of the surviving (n = 48) and non-surviving participants (n = 37). The difference between the two groups was analyzed using the Mann-Whitney U test.

**Table 1.** Patient demographics and clinical characteristics.

| Variable | Total (n = 85) | Survivors (n = 48) | Non-survivors (n = 37) | *p* |
|---|---|---|---|---|
| **Age (years), mean ± SD** | 70.0 ± 12.4 | 67.7 ± 14.4 | 73.1 ± 8.6 | **0.034** |
| **Gender, n (%)** | | | | |
| Male | 47 (55.3) | 27 (56.3) | 20 (54.1) | 0.84 |
| Female | 38 (44.7) | 21 (43.8) | 17 (45.9) | |
| **Body mass index (kg/m$^2$), mean ± SD** | 27.0 ± 3.9 | 26.6 ± 3.8 | 27.5 ± 4.1 | 0.331 |
| **Clinical symptoms, n (%)** | | | | |
| Nausea/vomiting | 13 (15.3) | 7 (14.6) | 6 (16.2) | |
| Fever | 8 (9.4) | 6 (12.5) | 2 (5.4) | |
| Cough | 7 (8.2) | 5 (10.4) | 2 (5.4) | |
| Digestive symptoms | 2 (2.4) | 2 (4.2) | - | |
| Abdominal pain | 1 (1.2) | 1 (2.1) | - | |
| **Severity illness scores at ICU admission, mean ± SD** | | | | |
| APACHE II | 20.0 ± 7.1 | 18.3 ± 6.2 | 22.1 ± 7.7 | **0.014** |
| SOFA score | 5.8 ± 2.6 | 5.1 ± 2.2 | 6.6 ± 2.9 | **0.008** |
| GCS | 12.5 ± 3.9 | 13.2 ± 3.1 | 11.6 ± 4.7 | 0.072 |
| **Comorbidity, n (%)** | | | | |
| Hypertension | 43 (50.6) | 20 (41.7) | 23 (62.2) | |
| Diabetes mellitus | 34 (40.0) | 17 (35.4) | 17 (45.9) | |
| Cerebrovascular disease | 23 (27.1) | 12 (25.0) | 11 (29.7) | |
| Chronic obstructive pulmonary disease | 21 (24.7) | 14 (29.2) | 7 (18.9) | |
| Coronary artery disease | 11 (12.9) | 7 (14.6) | 4 (10.8) | |
| Chronic kidney disease | 10 (11.8) | 4 (8.3) | 6 (16.2) | |
| Congestive heart failure | 9 (10.6) | 6 (12.5) | 3 (8.1) | |
| Malignancy | 3 (3.5) | 1 (2.1) | 2 (5.4) | |
| **NUTRIC score, median (IQR)** | 5.0 (4.0-6.0) | 5.0 (4.0-5.8) | 6.0 (4.0-7.0) | **0.004** |
| **Malnutrition risk, n (%)** | 54 (63.5) | 27 (56.3) | 27 (73.0) | **0.046** |
| **Patients treated with IMV, n (%)** | 29 (34.1) | 2 (4.2) | 27 (73.0) | **< 0.001** |
| **Duration of IMV (hour), mean (min-max)** | 54.1 (0-785.0) | 3.4 (0-91.0) | 120.0 (0-785.0) | **< 0.001** |
| **Length of hospital stay (day), median (IQR)** | 12.0 (8.0-20.0) | 14.0 (10.3-25.0) | 9.0 (5.5-12.0) | 0.288 |
| **Length of ICU stay (day), median (IQR)** | 8.0 (5.0-12.0) | 8.0 (5.0-12.5) | 9.0 (5.5-12.0) | **< 0.001** |

GCS: Glasgow Coma Scale, ICU: Intensive care unit, IMV: Invasive Mechanical Ventilation; NUTRIC: The Nutrition Risk in Critically ill score, SOFA: Sequential Organ Failure Assessment.

The deceased participants exhibited significantly elevated creatinine and blood urea nitrogen (BUN) levels compared to the surviving participants ($p = 0.020$ and $p = 0.004$, respectively). The median lactate level was observed to be significantly higher in non-survivors ($p = 0.018$) (Supplementary Table 1).

Survivors had significantly lower serum IFABp values than non-survivors (median (IQR): 7.23 [3.26-12.25] ng/mL vs. 13.27 [6.41-17.87] ng/mL, $p = 0.007$). The median serum citrulline value of survivors was significantly higher than that observed in non-survivors (7.61 [4.37-8.52] µmol/L vs. 4.67 [3.34-8.90] µmol/L, $p = 0.043$) (Figure 1).

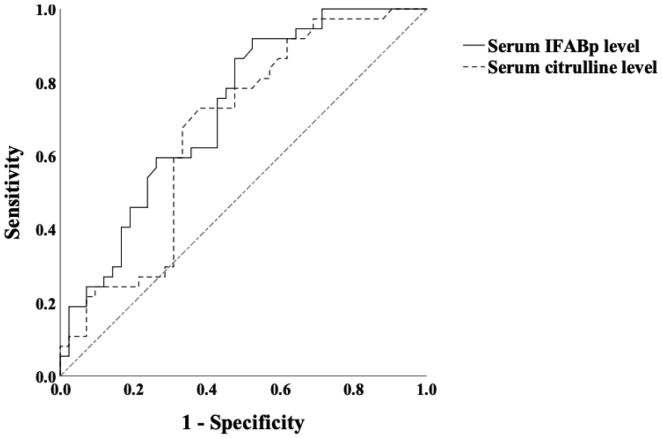
ROC analysis demonstrated that the cut-off values of serum IFABp and citrulline concentrations for the prediction of ICU mortality were 8.15 ng/mL (AUC: 0.722, 95% Cl: 0.611-0.833, sensitivity: 72%, specificity: 76%, $p = 0.001$) and 5.99 nmol/L (AUC: 0.671, 95% Cl: 0.551-0.791, sensitivity: 68%, specificity: 67%, $p = 0.009$) (Figure 2).

## Discussion

To the best of our knowledge, this is the most comprehensive study investigating both IFABp and citrulline levels in the largest sample of critically ill COVID-19 patients. In the present study, we evaluated the clinical performance and prognostic value of serum IFABp and citrulline concentrations in a cohort of 85 critically ill patients with COVID-19. Non-survivors exhibited markedly elevated serum IFABp levels and significantly reduced citrulline concentrations relative to survivors. Moreover, serum IFABp (cut-off point: 8.15 ng/mL) and citrulline concentrations (cut-off point: 5.99 nmol/L) were capable of significantly predicting ICU mortality in study participants.

COVID-19 primarily manifests via the respiratory route, with the lungs being the primary organ affected. However, in cases of COVID-19 infection, respiratory symptoms are frequently accompanied by gastrointestinal signs. Clinical evidence indicates that the intestine may serve as an additional viral target organ in patients with COVID-19, exhibiting elevated levels of the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) [18-20]. In the present study, the concentration of IFABp, a biomarker of enterocyte apoptosis, was found to be significantly higher in non-survivors than in survivors. Furthermore, our findings indicate that a serum IFABp concentration exceeding 8.15 ng/mL can be utilized to predict ICU mortality. Similarly, Tyszko *et al.* [21] conducted a prospective study examining the correlation between consecutive plasma IFABp and citrulline levels and

**Figure 2.** The ROC analysis of serum IFABp and serum citrulline value to predict mortality.




The figure illustrates the receiver operating characteristic (ROC) curve of serum IFABp and citrulline concentrations in predicting intensive care unit (ICU) mortality among the 85 study participants.

mortality in 40 critically ill patients diagnosed with COVID-19. The plasma IFABp values were significantly higher in the non-survivor study participants than in the survivor patients and were a reliable predictor of 28-day mortality. A multicenter study conducted by Saia *et al.* [22] reported that critically ill patients with confirmed COVID-19 infection and subsequent mortality had higher urinary IFABp levels than patients with less severe illness. Moreover, elevated IFABp levels were significantly correlated with unfavorable outcomes and severe illness. Another study demonstrated that serum IFABp concentrations were markedly lower in hospitalized patients with COVID-19 infection than in those with non-COVID-19 [4]. Nevertheless, the present study comprised a small number of non-ICU patients.

Citrulline is considered to be a marker of enterocyte mass and function. In our cohort, the low serum citrulline concentrations were observed to be lower in non-survivors than in survivors and were found to be associated with ICU mortality. Uzzan *et al.* [23] conducted a prospective study to investigate the relationship between plasma citrulline concentrations and systemic inflammation, as well as gastrointestinal symptoms in 26 hospitalized COVID-19 patients. Their findings indicated that patients with COVID-19 exhibited decreased plasma citrulline concentrations, which correlated with adverse clinical outcomes, including digestive symptoms (e.g., nausea, vomiting, abdominal pain, and diarrhea) and systemic inflammation. However, that study reported no significant association between low plasma citrulline

levels and mortality. Another study [21] found no significant association between plasma citrulline concentration and mortality in critically ill patients with COVID-19. This discrepancy may be attributable to the fact that the latter study had a smaller sample size than our own and included patients with varying degrees of illness severity. Piton *et al* [15] conducted a prospective observational study comprising 103 critically ill patients to assess the relationship between plasma citrulline and 28-day mortality. Their findings demonstrated that plasma citrulline levels were significantly lower in non-survivors than in survivors and served as a significant predictor of 28-day mortality.

This study has some limitations. The study design did not incorporate consecutive sampling of serum IFABp and citrulline concentrations. Furthermore, there are potential limitations in the interpretation of IFABP and citrulline levels, including the reliance on laboratory assays, the absence of standardized measurement methodologies, and the lack of population-specific reference intervals. Future research should aim to validate these findings through studies employing larger sample sizes and longitudinal data collection.

Our data indicated that non-survivors exhibited markedly elevated serum IFABp concentrations and diminished serum citrulline levels in comparison to survivors. Furthermore, serum IFABp and citrulline levels demonstrated a significant capacity to predict ICU mortality in critically ill patients with COVID-19.

## Authors' contributions

Sevda Onuk, Aynur Karayol Akin and Kursat Gundogan contributed to the conception and design of the research; Esma Eryilmaz Eren and Hilal Sipahioglu contributed to the design of the research; Cigdem Karakukcu, Nurhayat T. Ozer, Serap Sahin Ergul contributed to the acquisition and analysis of the data; Sevda Onuk and Nurhayat T. Ozer contributed to the interpretation of the data; and Sevda Onuk and Nurhayat T. Ozer drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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## Conflict of interests

No conflict of interests is declared.

## References

1. Xie J, Tong Z, Guan X, Du B, Qiu H (2020) Clinical characteristics of patients who died of coronavirus disease 2019 in China. JAMA Netw Open 33: e205619. doi: 10.1001/JAMANETWORKOPEN.2020.5619.
2. Wan Y, Shang J, Graham R, Baric RS, Li F (2020) Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 94: 127–147. doi: 10.1128/JVI.00127-20.
3. Parasa S, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, Spadaccini M, Colombo M, Gabbiadini R, Artifon ELA, Repici A, Sharma P (2020) Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. JAMA Netw Open 3: e2011335. doi: 10.1001/JAMANETWORKOPEN.2020.11335.
4. Guedjid K, Uzzan M, Soudan D, Trichet C, Nicoletti A, Weiss E, Manceauid H, Nuzzo A, Corcos O, Treton X, Peoc'h K (2021) I-FABP is decreased in COVID-19 patients, independently of the prognosis. PLoS One 16: e0249799. doi: 10.1371/journal.pone.0249799.
5. Ramachandran P, Onukogu I, Ghanta S, Gajendran M, Perisetti A, Goyal H, Aggarwal A (2020) Stomach and duodenum: research article gastrointestinal symptoms and outcomes in hospitalized coronavirus disease 2019 Patients. Dig Dis 38: 373-379 doi: 10.1159/000509774.
6. Blaser R, Padar M, Tang J, Dutton J, Forbes A (2019) Citrulline and intestinal fatty acid-binding protein as biomarkers for gastrointestinal dysfunction in the critically ill. Anaesthesiol Intensive Ther 51: 230–239. doi: 10.5114/AIT.2019.86049.
7. Edinburgh RM, Hengist A, Smith HA, Travers RL, Koumanov F, Betts JA, Thompson D, Walhin JP, Wallis GA, Hamilton DL, Stevenson EJ, Tipton KD, Gonzalez JT (2018) Preexercise breakfast ingestion versus extended overnight fasting increases postprandial glucose flux after exercise in healthy men. Am J Physiol Endocrinol Metab 315: E1062. doi: 10.1152/AJPENDO.00163.2018.
8. Derikx JPM, Bijker EM, Vos GD, Van Bijnen AA, Heineman E, Buurman WA, Van Waardenburg DA (2010) Gut mucosal cell damage in meningococcal sepsis in children: relation with clinical outcome. Crit Care Med 38: 133–137. doi: 10.1097/CCM.0B013E3181B4A5ED.
9. Sekino M, Funaoka H, Sato S, Okada K, Inoue H, Yano R, Matsumoto S, Ichinomiya T, Higashijima U, Matsumoto S, Hara T (2017) Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: a preliminary study. J Crit Care 42: 92–100. doi: 10.1016/J.JCRC.2017.07.012.
10. Donmez-Altuntas H, Sahin Ergul S, Altin-Celik P, Bulut K, Eciroglu H, Uzen R, Sahin GG, Ozer NT, Temel S, Arikan TB, Esmaoglu A, Yuksel RC, Sungur M, Gundogan K (2023) Gut barrier protein levels in serial blood samples from critically ill trauma patients during and after intensive care unit stay. Eur J Trauma Emerg Surg 49: 2203–2213. doi: 10.1007/S00068-023-02298-6.
11. Onuk S, Ozer NT, Ozel M, Sipahioglu H, Kahriman G, Baskol G, Temel S, Gundogan K, Akin A (2023) Gastric ultrasound, citrulline, and intestinal fatty acid-binding protein as markers

of gastrointestinal dysfunction in critically ill patients: a pilot prospective cohort study. JPEN J Parenter Enteral Nutr 47: 429–436. doi: 10.1002/JPEN.2473.
12. Fagoni N, Piva S, Marino R, Chiarini G, Ferrari D, Grespi E, Bertuetti R, Barbieri S, Latronico N, Rasulo F (2020) The IN-PANCIA Study: clinical evaluation of gastrointestinal dysfunction and failure, multiple organ failure, and levels of citrulline in critically ill patients. J Intensive Care Med 35: 279–283. doi: 10.1177/0885066617742594.
13. Luiking YC, Poeze M, Ramsay G, Deutz NEP (2009) Reduced citrulline production in sepsis is related to diminished de novo arginine and nitric oxide production. Am J Clin Nutr 89: 142–152. doi: 10.3945/AJCN.2007.25765.
14. Piton G, Manzon C, Monnet E, Cypriani B, Barbot O, Navellou JC, Carbonnel F, Capellier G (2010) Plasma citrulline kinetics and prognostic value in critically ill patients. Intensive Care Med 36: 702–706. doi: 10.1007/S00134-010-1751-6.
15. Piton G, Belon F, Cypriani B, Regnard J, Puyraveau M, Manzon C, Navellou J, Capellier G (2013) Enterocyte damage in critically ill patients is associated with shock condition and 28-day mortality. Crit Care Med 41: 2169–2176. doi: 10.1097/CCM.0B013E31828C26B.5
16. Republic of Turkey Ministry of Health Scientific Committee Study (2020) COVID-19 (SARS-CoV-2 infection) guide. Available: https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html. [Article in Turkish]
17. Heyland DK, Dhaliwal R, Jiang X, Day AG (2011) Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 15: R268. doi: 10.1186/cc10546.
18. Lamers MM, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem TI, G Ravelli RB, Paul van Schayck J, Mykytyn AZ, Duimel HQ, van Donselaar E, Riesebosch S, H Kuijpers HJ, Schipper D, van de Wetering WJ, de Graaf M, Koopmans M, Cuppen E, Peters PJ, Haagmans BL, Clevers H (2020) SARS-CoV-2 productively infects human gut enterocytes. Science 3: 50-54. doi: 10.1126/science.abc1669.
19. Qi F, Qian S, Zhang S, Zhang Z (2020) Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun 526: 135-140. doi: 10.1016/j.bbrc.2020.03.044.
20. Kariyawasam JC, Jayarajah U, Riza R, Abeysuriya V, Seneviratne SL (2021) Gastrointestinal manifestations in COVID-19. Trans R Soc Trop Med Hyg 115: 1362–1388. doi: 10.1093/TRSTMH/TRAB042.
21. Tyszko M, Lipińska-Gediga M, Lemańska-Perek A, Kobylińska K, Gozdzik W, Adamik B (2022) Intestinal fatty acid binding protein (I-FABP) as a prognostic marker in critically ill COVID-19 patients. Pathogens 11: 1526. doi: 10.3390/pathogens11121526.
22. Saia RS, Giusti H, Luis-Silva F, Pedroso K de JB, Auxiliadora-Martins M, Morejón KML, Degiovani AM, Cadelca MR, Basile-Filho A (2021) Clinical investigation of intestinal fatty acid-binding protein (I-FABP) as a biomarker of SARS-CoV-2 infection. Int J Infect Dis 113: 82–86. doi: 10.1016/J.IJID.2021.09.051.
23. Uzzan M, Soudan D, Peoc'h K, Weiss E, Corcos O, Treton X (2020) Patients with COVID-19 present with low plasma citrulline concentrations that associate with systemic inflammation and gastrointestinal symptoms. Dig Liver Dis 52: 1104–1105. doi: 10.1016/J.DLD.2020.06.042.

## Annex – Supplementary Items

**Supplementary Table 1.** The clinical data of study participants.

| Variable | Total (n = 85) | Survivors (n = 48) | Non-survivors (n = 37) | *p* |
|---|---|---|---|---|
| WBC | 11.7 (6.7-14.6) | 11.7 (6.7-14.1) | 11.6 (6.9-17.6) | 0.620 |
| Lymphocyte | 0.8 (0.5-1.3) | 0.8 (0.5-1.3) | 0.7 (0.4-1.1) | 0.400 |
| neutrophil | 10.0 (5.4-12.8) | 10.0 (5.6-12.8) | 9.9 (5.4-15.3) | 0.749 |
| Hemoglobin | 12.7 (11.3-14.4) | 12.7 (11.2-14.4) | 13.1 (11.3-14.5) | 0.821 |
| Platelet | 218.0 (160.0-299.5) | 216.5 (145.0-313.0) | 224.0 (162.5-294.5) | 0.996 |
| INR | 1.11 (1.05-1.21) | 1.10 (1.04-1.19) | 1.13 (1.08-1.28) | 0.122 |
| D-dimer | 1656 (1005-3416) | 1245 (878-2564) | 2054 (1342-4050) | **0.023** |
| fibrinogen | 5935 (5052-7232) | 5630 (4525-7510) | 6210 (5485-7140) | 0.488 |
| Ferritin | 711 (384-1414) | 661 (385-1121) | 920 (374-1746) | 0.337 |
| Glucose | 157.0 (117.0-232.0) | 139.0 (109.3-210.3) | 165.0 (137.5-251.0) | 0.161 |
| BUN | 30.0 (21.0-49.5) | 25.0 (18.0-35.3) | 38.0 (27.0-53.0) | **0.004** |
| Creatinine | 1.15 (0.90-1.69) | 1.08 (0.84-1.36) | 1.43 (1.01-2.25) | **0.014** |
| Troponin | 25.0 (14.8-58.5) | 20.8 (10.4-40.8) | 47.5 (16.8-192.3) | **0.020** |
| Total bilirubin | 0.50 (0.32-0.70) | 0.50 (0.40-0.70) | 0.50 (0.30-0.70) | 0.886 |
| AST | 36.0 (26.0-55.0) | 29.5 (22.3-39.0) | 44.0 (34.5-67.0) | **<0.001** |
| ALT | 26.0 (18.0-37.5) | 25.0 (15.8-39.8) | 28.0 (22.0-37.0) | 0.206 |
| LDH | 469.0 (360.5-631.5) | 424.0 (339.0-558.5) | 561.0 (440.0-812.8) | **0.002** |
| CRP | 114.0 (61.5-176.5) | 110.0 (62.0-174.5) | 122.0 (60.0-178.0) | 0.982 |
| Procalcitonin | 0.33 (0.15-0.99) | 0.30 (0.12-1.10) | 0.35 (0.17-0.96) | 0.563 |
| Albumin | 3.2 (2.9-3.5) | 3.2 (3.0-3.5) | 3.1 (2.8-3.4) | 0.073 |
| Lactate | 1.9 (1.4-2.9) | 1.6 (1.1-2.6) | 2.4 (1.5-3.2) | **0.018** |

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, INR: International normalized ratio, LDH: Lactate dehydrogenase, WBC: White blood cell.