

# Clinical Efficacy of Eucaloric Ketogenic Nutrition in the COVID-19 Cytokine Storm: a Retrospective Analysis of Mortality and ICU Admission

**Samir Giuseppe Sukkar** (✉ [samirsukkar@yahoo.it](mailto:samirsukkar@yahoo.it))

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy  
<https://orcid.org/0000-0003-4194-1547>

**Ludovica Cogorno**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy. Experimental Medicine Department, Medical Pathophysiology, Food Science and Endocrinology Section. Food Science and Human Nutrition Research Unit. Sapienza University, Rome (Italy)

**Andrea Pasta**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Pisciotta Livia**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Antonio Vena**

**Raffaella Gradaschi**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Chiara Dentone**

Infectious Disease Clinic Genoa University, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Erica Guiddo**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Eleonora Martino**

Dietetics and Clinical Nutrition Unit, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Sabrina Beltramini**

Pharmacy, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

**Lorenzo Maria Donini**

Experimental Medicine Department, Medical Pathophysiology, Food Science and Endocrinology Section. Food Science and Human Nutrition Research Unit. Sapienza University, Rome (Italy)

**Luca Carmisciano**

Epidemiology and Biostatistics. University of Genoa, Italy

**Maria Pia Sormani**

Epidemiology and Biostatistics. University of Genoa, Italy

**Matteo Bassetti**

Infectious Disease Clinic Genoa University, IRCCS-Policlinic Hospital San Martino, Genoa, Italy

## Research Article

**Keywords:** Ketogenic diet, Eucaloric ketogenic diet, Cytokine storm syndrome, COVID-19, Macrophage, Disseminated intravascular coagulation, Warburg effect, Aerobic glycolysis, Interferon type I, Hyperglycemia, Alveolar cell type II, Obesity, Diabetes

**Posted Date:** November 30th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-103541/v2>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** Some patients affected by COVID-19 present a life-threatening hyperinflammatory state known as cytokine storm syndrome (CSS) associated with a high mortality rate. Our hypothesis is that a eucaloric ketogenic diet (EKD) may be a safe and efficacious treatment option to reduce CSS and consequently to reduce the need for CPAP, ICU admission and COVID-19 mortality.

**Aim of the study:** The primary objective is to explore the effect of an EKD on mortality, admission to the ICU and the need for NIV in hospitalized patients with COVID-19 in comparison to a eucaloric standard diet (ESD). The secondary objectives are to collect data about the safety and feasibility of an EKD during hospitalization and to evaluate the effect of the diet on biological and inflammatory parameters, particularly interleukin-6 (IL-6).

**Patients and methods:** The study is a retrospective explorative analysis of 34 patients fed with an EKD during hospitalization for COVID-19 in comparison to 68 patients fed an ESD selected and matched using propensity score one-to-two to avoid the confounding effect of interfering variables.

**Results:** A trend of reduced 30-day mortality (HR 0.416, 95% CI 0.122 – 1.413, P = 0.160) and a trend regarding the need for ICU admission (HR 0.357, 95% CI 0.045 – 2.847, P = 0.331) were observed in subjects treated with the EKD compared to patients fed with the standard diet. No significantly different risks in the need for CPAP (HR 0.968, CI 0.289 – 3.242, P = 0.958 for EKD) or the composite endpoint (HR 0.674, CI 0.233 – 1.949, P = 0.446 for EKD) were detectable between the two groups of dietary patterns.

Furthermore, IL-6 concentrations between t 0 and t 7 (seven days after the beginning of the diet) in the ketogenic nutrition group showed a median difference of -26.0  $\mu\text{g/mL}$  and a mean difference of -164  $\mu\text{g/mL}$  (data from 23 of the 34 pairs) compared to controls, with a trend toward significance (P = 0.062). EKD was safe and no adverse events were observed in patients fed an EKD.

**Discussion and conclusions:** These preliminary data on the clinical results for mortality, need for ICU admission and the effect on the IL-6 concentration during EKD feeding, collected in a retrospective way during the most aggressive period of the COVID-19 pandemic, suggest a favorable role of this dietary treatment in COVID-19 clinical management. The EKD was safe and well accepted by patients during hospitalization and seems to be an interesting tool in controlling COVID-19 CSS. The results of the prospective controlled randomized trial, currently underway with a large number of subjects, are necessary to confirm these preliminary data.

## 1. Introduction

COVID-19 is a pandemic disease caused by SARS-CoV-2 virus that is characterized by respiratory and gastrointestinal symptoms<sup>1</sup> and in a subgroup of these patients by cytokine storm syndrome (COVID-19 CSS) characterized by fulminant and fatal hypercytokinemia associated with multiorgan failure and high mortality<sup>2</sup>.

The mortality reported by our recent retrospective GECOVID group for 275 patients affected by SARS-COV-19 was 43.6% <sup>3</sup>.

Currently, there is no proven drug for the treatment of COVID-19 cytokine storm syndrome.

From the beginning of the pandemic, the approaches aimed at the control of hyperinflammation due to CSS are anti-inflammatory therapies such as corticosteroids, interleukin-6 inhibitors, anti-GM-CSF, PD-1 checkpoint inhibitors, hydroxychloroquine (HCQ), cytokine adsorption devices and intravenous immunoglobulin (IVIG) <sup>4-5</sup>.

According to the WHO, systemic steroids are the only proven therapy in critical and severe COVID-19 <sup>6</sup>; therefore, any possible alternative treatment should be investigated.

Recently, we proposed an immunometabolic hypothesis identifying a treatment capable of reducing the state of hyperinflammation associated with SARS-CoV-2 infection<sup>7</sup>.

In COVID-19, interstitial pneumonia causes significant hypoxemia, which significantly reduces the energy input from cellular metabolism in alveolar epithelial cell type II (ATII) and macrophage cells and increases the uptake and utilization of glucose via glycolysis to obtain energy <sup>7</sup>. ATII cells release cytokines and chemokines that activate alveolar resident macrophages (AMs) <sup>7</sup>.

During the exudative phase of ARDS, AMs are activated into the M1 phenotype. Proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , and IL- $\beta$ ) are excreted by M1 macrophages into the site of inflammation, recruiting monocytes from the blood by means of monocyte chemoattractant protein (MCP), which shifts these monocytes into the M1 phenotype.

In COVID-19 CSS, there is hyperactivation of M1, which produces excessive chemokines (i.e., macrophage inflammatory protein-2 (MIP-2) and interleukin-8 (IL-8)), attracting neutrophils from circulating blood to the alveolar space and causing tissue damage, as described in ARDS.

Moreover, together with neutrophils, pulmonary activated platelets play a crucial thrombo-inflammatory role by forming platelet-neutrophil complexes (PNCs) and monocyte-platelet aggregates, causing the development of a procoagulant and pro-inflammatory environment <sup>9</sup>.

From a metabolic point of view, activation of the M1 phenotype induces a metabolic shift from oxidative phosphorylation (OXPHOS) to aerobic glycolysis (the Warburg effect). The activity of the TCA tricarboxylic acid cycle is reduced while lactate production increases.<sup>10</sup>

ATII cells have a marked tendency to use lactate for the production of mitochondrial oxidative energy under normoxia but, under hypoxia, undergo proteomic changes presumably activating aerobic glycolysis as well <sup>11</sup>.

In ATII cells, excess lactate decreases type I interferon (IFN), which plays a vital role in the defense of the host against virus, suppressing mitochondrial antiviral signaling (MAVS)<sup>11</sup>.

Therefore, the possible reduction in lactate production might produce a positive effect on the production of innate immune type I IFNs (type I interferons)<sup>7</sup>.

From these considerations, we have raised the hypothesis that an EKD, with a low glycemic load, could reduce M1 phenotype metabolism and activity with a consequent reduction in lactate production<sup>7</sup> and instead enhance M2 phenotype metabolism with beneficial consequences on the exacerbated inflammatory process of CSS<sup>7-8,10</sup>.

Ketone bodies are endogenous metabolites that are normally elevated during a period of fasting or when following a ketogenic diet. A “physiological” level of ketosis is an adaptive, regulated response to lowered carbohydrate availability and can be safely sustained over many months. Ketones maintain cellular energy but can also affect immune activity, metabolism, and epigenetics with drug-like signaling activities<sup>7</sup>.

The aim of this retrospective observational study was to evaluate the effect of an EKD on mortality, admission to the ICU and the need for NIV in hospitalized patients with COVID-19 in comparison to a standard diet and to collect data about the safety and feasibility of a ketogenic diet in hospitalized patients during the pandemic period in Italy (March-July 2020).

## 2. Materials And Methods

### 2.1 Subjects

This study is a retrospective analysis of patients suffering from SARS-CoV-2 disease who were admitted to IRCCS San Martino Hospital between February and July 2020, with a peak in hospital admission in March 2020, and who underwent a ketogenic diet. In this regard, in the Infectious Disease Unit, a ketogenic diet entered the routine protocol of the ward in the absence of indications or contraindications for a specific diet in COVID-19, according to its anti-inflammatory role.

All patients signed consent for the use of personal treatment data and informed consent to undergo any type of therapy during their hospitalization.

They were also informed that a ketogenic diet entered the routine protocol of the ward, in the absence of contraindications, and had the possibility of accepting or refusing immediately or thereafter, in case of poor palatability or taste. The pharmacological protocol was not conditioned by the choice of the diet.

The exclusion criteria for EKD were type I diabetes mellitus; insulin-dependent type II diabetes or type II diabetes in treatment with sulfonylureas, repaglinide, GLP-1 analogs, SGLT2 inhibitors, or recent ASCVD (within one month); food allergies to the diet components; any metabolic disorder that can affect

gluconeogenesis; clinical history of severe hypertriglyceridemia with or without pancreatitis; and pregnancy or lactation.

Meanwhile, an RCT, with the purpose of studying the EKD in a larger sample of subjects in the whole hospital, randomizing the nutritional treatment, was submitted and approved in June by the ethics committee (KETOCOV-1 Register number CER Liguria: 198/2020 - DB id 10517; *ClinicalTrials.gov* identifier (NCT number): **NCT04492228**), and it was started at the end of September 2020 with the recrudescence of the infection in Italy.

Considering the approval of the RCT by the Ethics Committee, at the end of the first wave of the pandemic in July, the data of the patients treated in the Infectious Disease Unit who followed the routine diet protocol with the EKD for a minimum period of 2 weeks were analyzed.

To avoid the confounding effect of interfering variables between the two diet groups, a one-to-two propensity score-matching analysis was performed with patients treated in other facilities and made available to a single management software to have adequate controls for a valid statistical analysis (see paragraph 2.4 Statistical Analysis).

Inclusion criteria to enter in the analysis of the data were as follows: documented diagnosis of COVID-19 defined by a positive RT-PCR assay result of a respiratory sample, PaO<sub>2</sub> < 60 mmHg at rest in ambient air or P/F < 200 (arterial oxygen concentration to the fraction of inspired oxygen), and age older than 18 years.

The initial sample of 669 patients was reduced to 479 patients (297 males and 182 females) because 190 patients had missing data (118) or did not meet the inclusion criteria (72). After the propensity score-matching analysis, 34 EKD patients were included in the study and compared with 68 SD patients.

All patients were investigated for demographic data and the presence of the following comorbidities: diabetes, hypertension, ASCVD, heart failure, chronic pulmonary disease, solid and hematological neoplasia, ulcerative disease, moderate/severe liver disease, dementia, collagen diseases, metastatic neoplasia, and hemiplegia.

The Charlson Comorbidity Index (CCI) has been used as a measure of 1-year mortality risk<sup>12</sup> and was calculated for all subjects. The laboratory data and P/F ratio (arterial oxygen concentration to the fraction of inspired oxygen) were taken into account on the day of hospital admittance for the patients considered the control group (fed a standard diet) and the day before the administration of the ketogenic diet for patients in the studied group.

Laboratory data and the P/F ratio (arterial oxygen concentration to the fraction of inspired oxygen) were taken into account on the day of hospital admittance for the patients considered the control group (fed a standard diet) and the day before the administration of EKD for patients in the studied group.

Laboratory data required by the ward doctor included routine blood tests (blood cell count, azotemia, creatinine, AST/GOT, CPK, LDH, albumin, triglycerides, IL-6, PCR, ferritin, lipid profile, fibrinogen, blood sugar, HbA1c (basal), vitamin D (basal)), urine test (basal) and complete urine analysis.

The study was conducted in accordance with the Declaration of Helsinki.

Figure 1 reports a detailed scheme of the patients included and the analysis steps.

## 2.2 Diet administration

Patients included in the analysis belonged to two different dietary groups: the standard diet group, including subjects fed the ESD, and the ketogenic diet group, including subjects fed the EKD.

According to the LARN (Reference Intake of Nutrients and Energy for Italian Population) and to the Italian guidelines for a healthy diet<sup>13-14</sup>, the standard oral diet was based on the Mediterranean style<sup>15</sup> and was characterized by 30 kcal/kg/day (ranging from 1900 to 2250 kcal), protein intake of 15-20%, lipid intake of 25-30% and carbohydrate intake of 50-55%.

The EKD was characterized by a very low carbohydrate amount (< 30 g, 5-6% of total energy) to induce ketosis, with a polyunsaturated/unsaturated/saturated fat ratio of 3:2:1. The protein content of the ketogenic diet was higher than that of an average Mediterranean diet (27-28% of the total calories).

## 2.3 Endpoints and outcomes

The primary outcomes were 30-day mortality, ICU admission and the need for CPAP, and they were also considered together in a combined outcome.

Secondary outcomes were the effects of the EKD on biological and inflammatory parameters and, in particular, on IL-6.

## 2.4 Statistical analysis

The statistical analysis was assessed using IBM SPSS Statistics, Release Version 25.0 (SPSS, Inc., 2017, Chicago, IL, USA, [www.spss.com](http://www.spss.com)). Kolmogorov-Smirnov analysis was used to test the normality of the variables. The results of continuous variables are expressed as the median and interquartile interval range. For categorical variables, contingency tables were used to indicate the frequency and percentage in the population. For the comparison of continuous variables between different groups of patients, nonparametric Kruskal-Wallis or Mann-Whitney tests were used when appropriate. Nominal variables were examined with Pearson's chi-squared (X<sup>2</sup>) test, and Spearman's rank correlation index was used for the correlation with continuous variables.

To adjust for baseline differences that are intrinsic in nonrandomized studies, patients on the EKD diet (34 patients) were matched 1:2 to patients following a standard diet (68 patients) by a propensity score (PS) (Table 1).

Preliminarily, covariates or factors entered into the model were identified by univariate statistical analysis, and the probability value for inclusion was  $p \leq 0.05$  between 445 and 34 subjects fed the ESD and EKD, respectively.

The PS was estimated by a logistic regression model including variables that were significantly different between the two groups: Charlson score, lymphocyte count, AST, and albumin as continuous variables, and the presence of diabetes, chronic pulmonary disease, hematological neoplasia and therapy with corticosteroid, remdesivir and tocilizumab as categorical data. Caliper levels of 0.8 were considered for PS.

Cox regression analysis was used to estimate the effect of the different dietary regimens on all primary endpoints (i.e., 30-day mortality, ICU admission, need for CPAP and composite endpoint). Because all patients in the standard diet group began their diet at hospital admission but subjects in the ketogenic group started their diet a few days later, the ketogenic diet start was considered a time-varying covariate to avoid immortal bias. The results are reported as hazard ratios (HRs) and 95% confidence intervals (95% CIs) of HRs. The period from hospitalization to the onset of each outcome was considered for survival analysis.

### 3. Results

Demographic and clinical characteristics of patients after PS matched analysis.

The demographic and clinical characteristics of the 102 patients, 68 fed with the ESD and 34 fed with the EKD, are reported in Table 1.

The median age (IQR) was 67 (53-77) years, and no significant differences in demographics, comorbidity history, laboratory measures, concomitant pharmacotherapy or P/F values were detected between the two groups.

A Cox regression analysis, considering the beginning of EKD as a time-dependent covariate, was proposed to estimate the effect of the different dietary regimens on all primary endpoints (Table 2).

The 30-day mortality in the survival analysis showed a trend of lower risk in patients fed a ketogenic diet (HR 0.416, 95% CI 0.122 – 1.413) than in subjects fed a standard diet, although this result did not reach statistical significance ( $P = 0.160$ ) (Figure 2A).

Moreover, the ketogenic diet had a trend of association with lower admission in the ICU (HR 0.357, 95% CI 0.045 – 2.847,  $P = 0.331$ ) in contrast to the standard diet (Figure 2B).

No significantly different risks in the need for CPAP (HR 0.968, CI 0.289 – 3.242,  $P = 0.958$  for ketogenic diet) or composite endpoint (HR 0.674, CI 0.233 – 1.949,  $P = 0.446$  for ketogenic diet) were detectable between the two groups of dietary patterns.

EKD-treated patients had a median IL-6 difference of -51.8 pg/mL or a mean IL-6 difference of -169 pg/mL (data from 22 of the 34 pairs) compared to controls.

After IL-6 imputation into delta “lower than” or “higher than or equal to” 0, the Binning IL-6 trend\* (chi sq = 3.698, df = 1, p-value = 0.05447) (Table 3).

EKD was safe and no adverse events were observed in patients fed an EKD. In particular acidosis was never observed and the arterial pH at baseline is similar in controls and EKD patients ( $p = 0.100$ ). At t7, compared to t0, arterial pH falls to a similar percentage in EKD patients compared to controls (57% vs 42%,  $p = 0.484$ ).

The median variation of arterial pH is about +0.0075 in the controls vs -0.0100 in the EKD patients ( $p = 0.342$ ).

## 4. Discussion

Nutritional status appears to be a relevant factor influencing the outcome of patients with COVID-19, but little information has emerged about the impact of early nutritional support in pre-ICU patients on the course of the disease <sup>16</sup>.

Surely nutrition has a pivotal role in the prevention of the comorbidities most frequently associated with COVID-19, such as hypertension, cardiovascular and cerebrovascular disease and diabetes, which have been noted as twofold, threefold and twofold, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts <sup>17</sup>.

Nevertheless, obesity is associated with a worse prognosis in patients affected by COVID-19, especially among the young <sup>18</sup>.

A hyperinflammatory response to COVID-19 has been recognized as the main cause of morbidity and mortality in these patients <sup>19</sup>.

The genetic substrate of CSS has been recently suggested, and alpha-1 antitrypsin deficiency alleles may contribute to national differences in COVID-19 infection.

The association between alpha-1 antitrypsin deficiency and severity and mortality rates has not yet been defined, and the exact pathophysiological mechanism that determines this process is unknown <sup>20</sup>.

However, COVID-19 CSS appears 8-10 days after the onset of symptoms of the disease and is characterized by high fever, dyspnea, bilateral pulmonary infiltrates that can evolve into ARDS and multisystemic organ failure <sup>21</sup>.

Effective treatments for COVID-19 and COVID-19 CSS are needed immediately. Patient timing and selection seem to be particularly crucial in managing the acute phase of COVID-19.

There is a consensus that ketosis protects healthy tissues against oxidative stress by simultaneously decreasing ROS production and increasing endogenous antioxidant capacity.<sup>22</sup> It is well known that the ketogenic diet can inhibit inflammation. Studies have shown that a KD reduces circulating inflammatory markers in humans.<sup>29</sup> The KD, via hydroxybutyrate (HB), is capable of activating hydroxycarboxylic acid receptor 2 (HCA2), a G protein-coupled receptor, which inhibits NF- $\kappa$ B in macrophages, dendritic cells and microglia and reduces neuroinflammation.<sup>23</sup>

Finally, from a clinical point of view, previous experiences show a clinical improvement in respiratory function following a ketogenic diet. After ten days of modified protein-saving fasting (a ketogenic diet with very low calorie content), a statistically significant improvement in functional residual capacity (FRC) and expiratory reserve volume (ERV) was observed.<sup>24</sup> In addition, a 20-day ketogenic diet shows a significant decrease in end-tidal carbon dioxide tension (PETCO<sub>2</sub>)<sup>25</sup>.

As reported in the introduction, the use of corticosteroids is currently suggested by the World Health Organization guidelines, and it is actually the first approach in severe disease<sup>6</sup>.

In our study, corticosteroid treatment was present in 75% of patients treated with the ESD and 85.3% of patients treated with the EKD.

Tocilizumab was present in 54.4% of patients treated with standard diet nutritional therapy and in 67.6% of patients treated with eucaloric ketogenic nutrition.

The anti-inflammatory efficacy of the EKD was almost significant and therefore seems independent from steroid or anticytokine treatment with tocilizumab. In fact, the analysis of the course of interleukin-6 in the first week of therapy highlights the almost significant variation in IL-6 from the beginning to seven days after the start of the EKD.

IL-6 did not increase but rather tended to be slightly reduced in the group treated with an EKD (Figure 3). This trend underlines the fact that patients after one week were, at that time, at increased risk of COVID-19 CSS.

Dietary treatment is, in this regard, a possible immunomodulation mainly aimed at the activity of macrophages without interfering with antiviral clinical efficacy.

During the treatment, the patients did not present any adverse events related to diet.

A limitation of the study is the lack of controlled randomization, and the study was conducted in a single hospital facility where the nutritional protocol was used for clinical monitoring issues. A further limitation is the number of cases included, since the cases were discontinued due to the absence of cases admitted from the end of July; therefore, it is possible that the study was underpowered.

The strength of the study is the usefulness of the propensity score, which, with the large hospital COVID-19 database (of approximately 669 cases), allowed a proper 1:2 matching, overcoming the absence of

controlled randomization.

Another result of this study is that the EKD is safe and oriented toward immunomodulation of the hyperactivation of macrophages and not to nonspecific immunosuppression, as occurs with corticosteroids. Moreover, a possible advantage is that the use of the diet could be used ubiquitously in all degrees of severity of the disease both in inpatients than in patients at home suffering from COVID-19 and demonstrates that it may be a safe therapeutic option to improve patient prognosis.

The current study provides preliminary data for all patients who were on a eucaloric ketogenic diet during the epidemic period that ended at the end of July.

The reported data are therefore an exact picture of the actual state, and the trends of reduced mortality, reduced need for ICU admission and reduced IL-6 between 0 and 7 days, although not statistically significant, suggest a possible alternative treatment to the disease, in the absence of side effects, additional costs or risks for the patient.

Differently from other studies in which nutrition is considered a support to drug therapy, this study is the first to underline the role of clinical nutrition therapy as a pathophysiological support to drug therapy in improving the prognosis of not only COVID-19 but also other infectious diseases in which immunomodulation could have a role in reducing hyperinflammation syndromes.

## **Conclusions**

These preliminary encouraging results suggest the efficacy of an EKD in COVID-19 CSS.

The pilot study was focused on the primary objective of verifying mortality outcomes and reducing hospitalization in intensive care units. Patients were randomized using the propensity score, which allowed, with the selection of patients treated in other facilities and made available to a single management software, adequate controls for a valid statistical analysis.

In conclusion, this retrospective pilot study provides valuable preliminary information regarding the possible role of an EKD in controlling mortality and ICU admission by means of the immunomodulation of COVID-19 CSS.

These data must necessarily be supported by further evidence from a larger sample, and the randomized controlled prospective clinical trial, currently started in September, with the recrudescence of COVID-19 infection in Italy, could be particularly useful.

## **Declarations**

No conflicts of interest exist.

The paper has been submitted to the Ligurian Ethical committee for the approval on November, 11 2020

## References

- [1] Ly J, Huang DQ, Biyao Z et al. Epidemiology of COVID-19: A Systematic Review and Meta-analysis of Clinical Characteristics, Risk factors and Outcomes. *J Med Virol*; 2020 Aug 13.
- [2] Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. ,[The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system](#). *Cytokine Growth Factor Rev*. 2020 Jun; 53:25-32.
- [3] Vena A, Giacobbe DR, Di Biagio A, Mikulska M, Taramasso L, De Maria A, Ball L, Brunetti I, Loconte M, Patroniti NA, Robba C, Delfino E, Dentone C, Magnasco L, Nicolini L, Toscanini F, Bavastro M, Cerchiaro M, Barisione E, Giacomini M, Mora S, Baldi F, Balletto E, Berruti M, Briano F, Sepulcri C, Dettori S, Labate L, Mirabella M, Portunato F, Pincino R, Russo C, Tutino S, Pelosi P, Bassetti M; GECOVID study group. Clinical characteristics, management and in-hospital mortality of patients with coronavirus disease 2019 in Genoa, Italy. *Clin Microbiol Infect*. 2020 Aug 15:S1198-743X(20)30484-5. doi: 10.1016/j.cmi.2020.07.049. Epub ahead of print. PMID: 32810610; PMCID: PMC7428680.
- [4] Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, Gurram PR, Stevens RW, Razonable RR et al, [Treatment Considerations for COVID-19: A Critical Review of the Evidence \(or Lack Thereof\)](#), *Mayo Clin Proc*. 2020 Jul;95(7):1454-1466.
- [5] [Yujun Tang, Jiajia Liu, Dingyi Zhang, Zhenghao Xu, Jinjun Ji, Chengping Wen](#), Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies *Front Immunol*. 2020 Jul 10; 11:1708
- [6] <https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1>
- [7] Sukkar SG and Bassetti M. Induction of ketosis as a potential therapeutic option to limit hyperglycemia and prevent cytokine storm in COVID-19. *Nutrition*, 2020  
<https://doi.org/10.1016/j.nut.2020.110967>.
- [8] Huang X, Xiu H, Zhang S, Zhang G. The Role of Macrophages in the Pathogenesis of ALI/ARDS. *Mediators of Inflammation* 2018; 1-8. DOI: 10.1155/2018/1264913 prec 10
- [9] Morris G, Bortolasci CC, Puri BK, Olive L, Marx W, O'Neil A, Athan E, Carvalho AF, Maes M, Walder K, Berk M. The pathophysiology of SARS-CoV-2: A suggested model and therapeutic approach. *Life Sci*. 2020 Oct 1;258:118166. doi: 10.1016/j.lfs.2020.118166. Epub 2020 Jul 31. PMID: 32739471; PMCID: PMC7392886.
- [10] Kelly B., O'Neill L. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res*. 2015;25:771–784.
- [11] Qian Z, Travanty EA, Oko L, Edeen K, Berglund A, Wang J, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome–coronavirus. *Am J Respir Cell Mol Biol* 2013;48:742–8.

- [12] Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47:1245–1251.
- [13] LARN. Nutrients and energy reference intake for Italian population. 4th revision. SINU (Italian Society of Human Nutrition), Linee guida per una sana alimentazione 2018, (n.d.).
- [14] file:///C:/Users/043509a/Downloads/LINEE-GUIDA%20DEFINITIVO%20(1)%20(1).pdf
- [15] V. Vitiello, A. Germani, E. Capuzzo Dolcetta, L.M. Donini, V. Del Balzo, The New Modern Mediterranean Diet Italian Pyramid, *Ann Ig.* 28 (2016) 179–186.
- [16] Laviano A, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2 (COVID-19) *Nutrition* 2020; 74:110834
- [17] Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; 10. DOI: 10.1007/s00392-020-01626-9
- [18] Watanabe, M., Risi, R., Tuccinardi, D., Baquero, C.J., Manfrini, S. and Gnessi, L. (2020), Obesity and SARS-CoV-2: a population to safeguard. *Diabetes Metab Res Rev.* 2020;e3325 doi:10.1002/dmrr.3325
- [19] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395 (10229):1033–4, doi:http://dx.doi.org/10.1016/S0140-6736(20)30628-0.
- [20] Shapira G, Shomron N, Gurwitz D. Ethnic differences in alpha-1 antitrypsin deficiency allele frequencies may partially explain national differences in COVID-19 fatality rates. *FASEB J.* 2020 Sep 22. doi: 10.1096/fj.202002097. Epub ahead of print. PMID: 32960480.
- [21] Langer-Gould A, Smith JB, Gonzales EG, Castillo RD, Figueroa JG, Ramanathan A, Li BH, Gould MK. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. *Int J Infect Dis.* 2020 Aug 6;99:291-297. doi: 10.1016/j.ijid.2020.07.081. Epub ahead of print. PMID: 32768693; PMCID: PMC7406519.
- [22] Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins Leukot Essent Fatty Acids* 2004; 70: 309–319.
- [23] Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Müller-Fielitz H, Pokorná B, Vollbrandt T, Stölting I, Nadrowitz R, Okun JG, Offermanns S, Schwaninger M. The  $\beta$ -hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. *Nat Commun.* 2014 May 21;5:3944. doi: 10.1038/ncomms4944. PMID: 24845831.
- [24] Sukkar SG, Signori A, Borrini C, Barisione G, Ivaldi C, Romeo C, Gradaschi R, Machello N, Nanetti E, Vaccaro AL. Feasibility of protein-sparing modified fast by tube (ProMoFasT) in obesity treatment: a

phase II pilot trial on clinical safety and efficacy (appetite control, body composition, muscular strength, metabolic pattern, pulmonary function test). *Med J Nutrition Metab.* 2013;6(2):165-176. doi: 10.1007/s12349-013-0126-2. Epub 2013 May 30. PMID: 24027606; PMCID: PMC3764321.

[25] Alessandro, R., Gerardo, B., Alessandra, L. et al. Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects. *Lung* 2015; 193: 939–945.

## Tables

Table 1. Demographic and clinical characteristics of the patients after propensity score matched main analysis.

Variables	Standard Diet (N = 68)	Ketogenic Diet (N = 34)	All Patients (N = 102)	P-value
<b>Demographics</b>				
Age [years: median; IQ range]	67 (54-77)	67 (52-76)	67 (53-77)	0.943
Sex [M/F: n; %]	40 (58.8%) / 28 (41.2%)	23 (67.6%) / 11 (32.4%)	63 (61.8%) / 39 (38.2%)	0.387
<b>Comorbidities, (n %)</b>				
Diabetes mellitus	7/68 (10.3%)	1/34 (2.9%)	8/102 (7.8%)	0.193
Hypertension	32/68 (47.1%)	15/34 (44.1%)	47/102 (46.1%)	0.779
ASCVD	27/68 (39.7%)	13/34 (38.2%)	40/102 (39.2%)	0.886
Heart failure	3/68 (4.4%)	2/34 (5.9%)	5/102 (4.9%)	0.746
Pulmonary disease	4/68 (5.9%)	0/34 (0.0%)	4/102 (3.9%)	0.149
Solid neoplasia	7/68 (10.3%)	1/34 (2.9%)	8/102 (7.8%)	0.193
Hematological neoplasia	4/68 (5.9%)	5/34 (14.7%)	9/102 (8.8%)	0.139
Ulcerative disease	3/68 (4.4%)	0/34 (0.0%)	3/102 (2.9%)	0.214
Moderate-severe liver disease	2/68 (2.9%)	1/34 (2.9%)	3/102 (2.9%)	1.000
Dementia	3/68 (4.4%)	1/34 (2.9%)	4/102 (3.9%)	0.718
Collagenopathy	1/68 (1.5%)	0/34 (0.0%)	1/102 (1.0%)	0.477
Metastatic Neoplasia	0/68 (0.0%)	0/34 (0.0%)	0/102 (0.0%)	1.000
Hemiplegia	1/68 (1.5%)	1/34 (2.9%)	2/102 (2.0%)	0.614
Charlson score [point: mean±SD; median; IQ range]	3 (1-5)	3 (2-5)	3 (1-5)	0.838
<b>Clinical features</b>				
PaO <sub>2</sub> /FiO <sub>2</sub>	281 (205-323)	312 (166-384)	286 (188-348)	0.312
<b>Laboratory values</b>				
WBC [mil/m <sup>3</sup> ]	7.26 (5-10.58)	6.78 (5.3-8.96)	7.02 (5.09-10.06)	0.531
Limph [x100/m <sup>3</sup> ]	0.9 (0.6-1.3)	1.05 (0.74-1.32)	1.00 (0.69-1.32)	0.514
PLT [x100/m <sup>3</sup> ]	213 (151-274)	233 (144-305)	221 (149-293)	0.616
AST [UI/L]	31 (23-58)	47 (24-73)	36 (23-66)	0.118
ALT [UI/L]	38 (23-47)	34 (24-46.5)	34 (23-47)	0.650
Ferritin [µg/L]	737 (329-1204.5)	773 (326-1257)	771 (326-1207)	0.646
IL-6 [pg/mL]	46.2 (27.85-94.35)	36.2 (18.3-108)	45.4 (21.5-101)	0.647
Albumin [g/L]	27.05 (23.5-30)	30.75 (28.9-34.1)	28.95 (24.85-34.05)	0.065
<b>Concomitant Pharmacotherapy (n, %)</b>				
Corticosteroid	51/68 (75,0%)	29/34 (85,3%)	80/102 (78,4%)	0.233
Antibiotic	37/68 (54,4%)	22/34 (64,7%)	59/102 (57,8%)	0.321
Hydroxychloroquine	42/68 (61,8%)	19/34 (55,9%)	61/102 (59,8%)	0.568

Remdesivir	2/68 (2,9%)	3/34 (8,8%)	5/102 (4,9%)	0.195
Tocilizumab	37/68 (54,4%)	23/34 (67,6%)	60/102 (58,8%)	0.200

Table 2. Cox regression with time-dependent covariate of primary outcomes in patients with treated with EKD vs ESD.

Outcomes	Significance (p value)	HR	95.0% CI for HR	
			Lower	Upper
Death	0.160	0.416	0.122	1.413
Intensive Care Unit	0.331	0.357	0.0045	2.847
CPAP	0.958	0.968	0.289	3.242
Composite Endpoint	0.446	0.674	0.233	1.949

Table 3.: variation of IL-6 before and after EKD

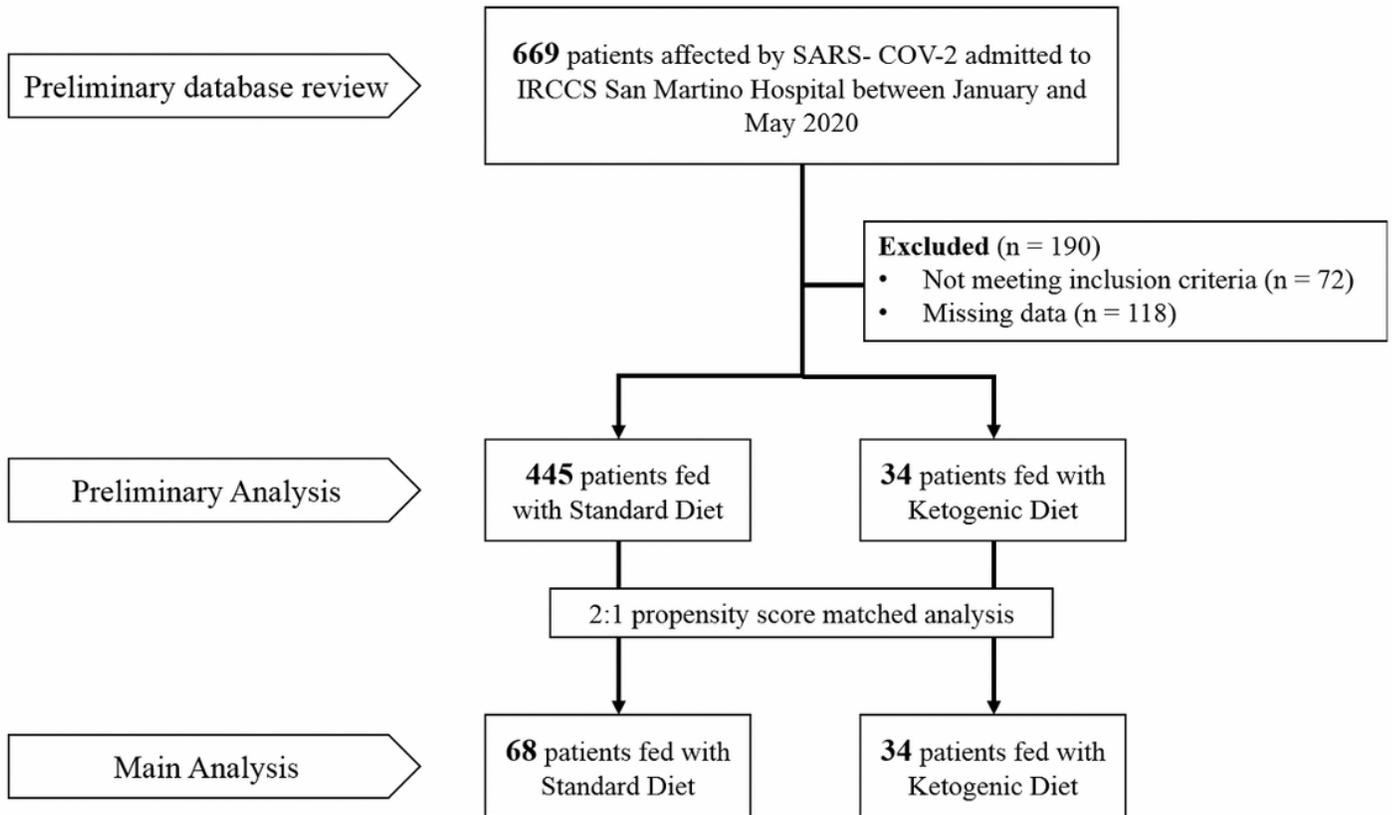
Delta IL-6 between t0 and t7	Controls, N (%)	Treated, N (%)
Increase	14 (58.3)	7 (30.4)
Decrease	10 (41.7)	16 (69.6)

Chisq = 3.698, df = 1, p-value = 0.05447

Data are median and IQR.

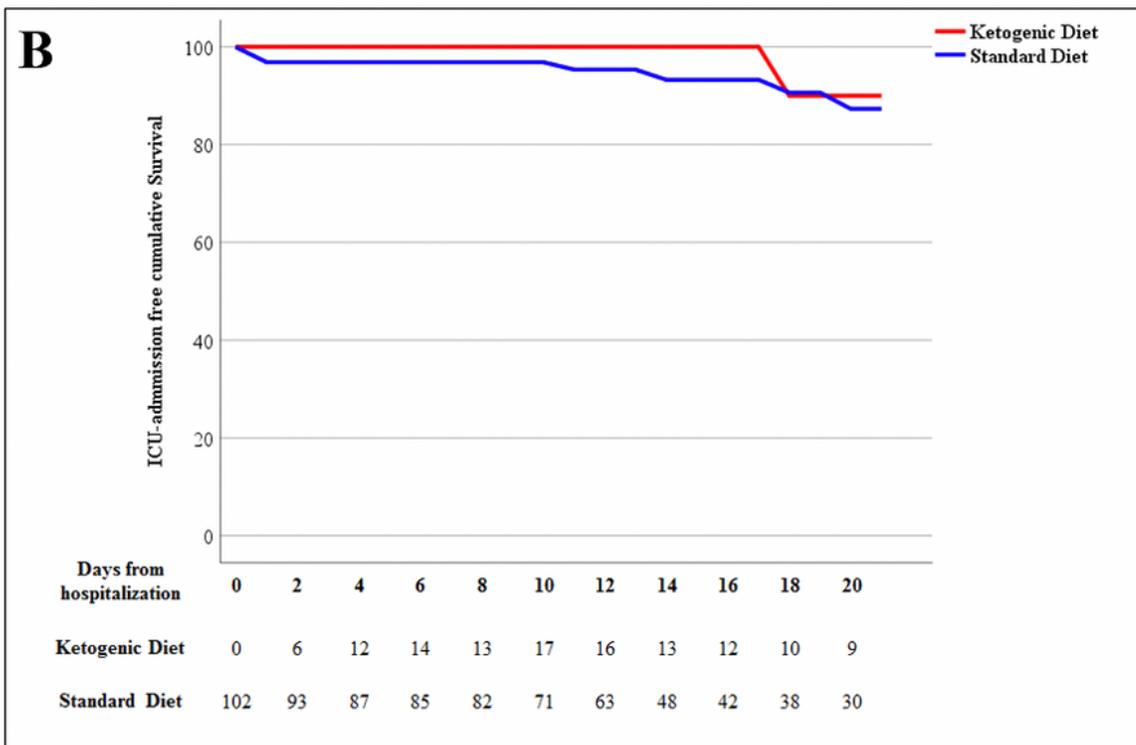
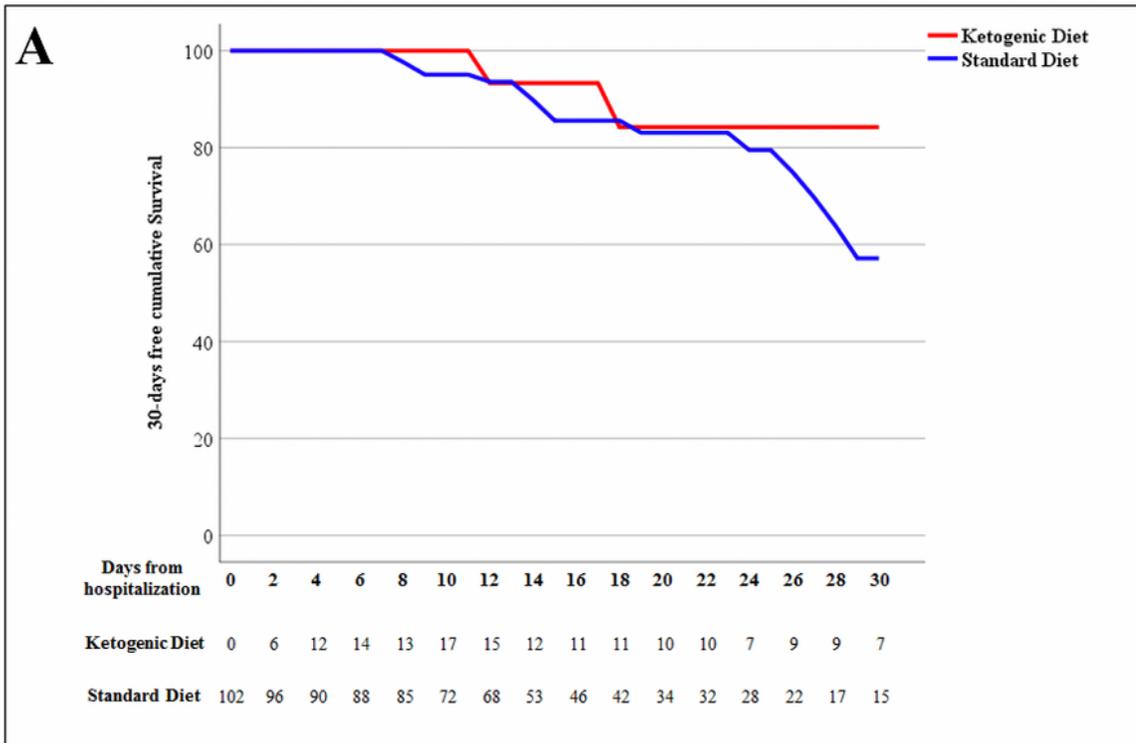
\*p-value at Mann-Whitney U-Test

## Figures



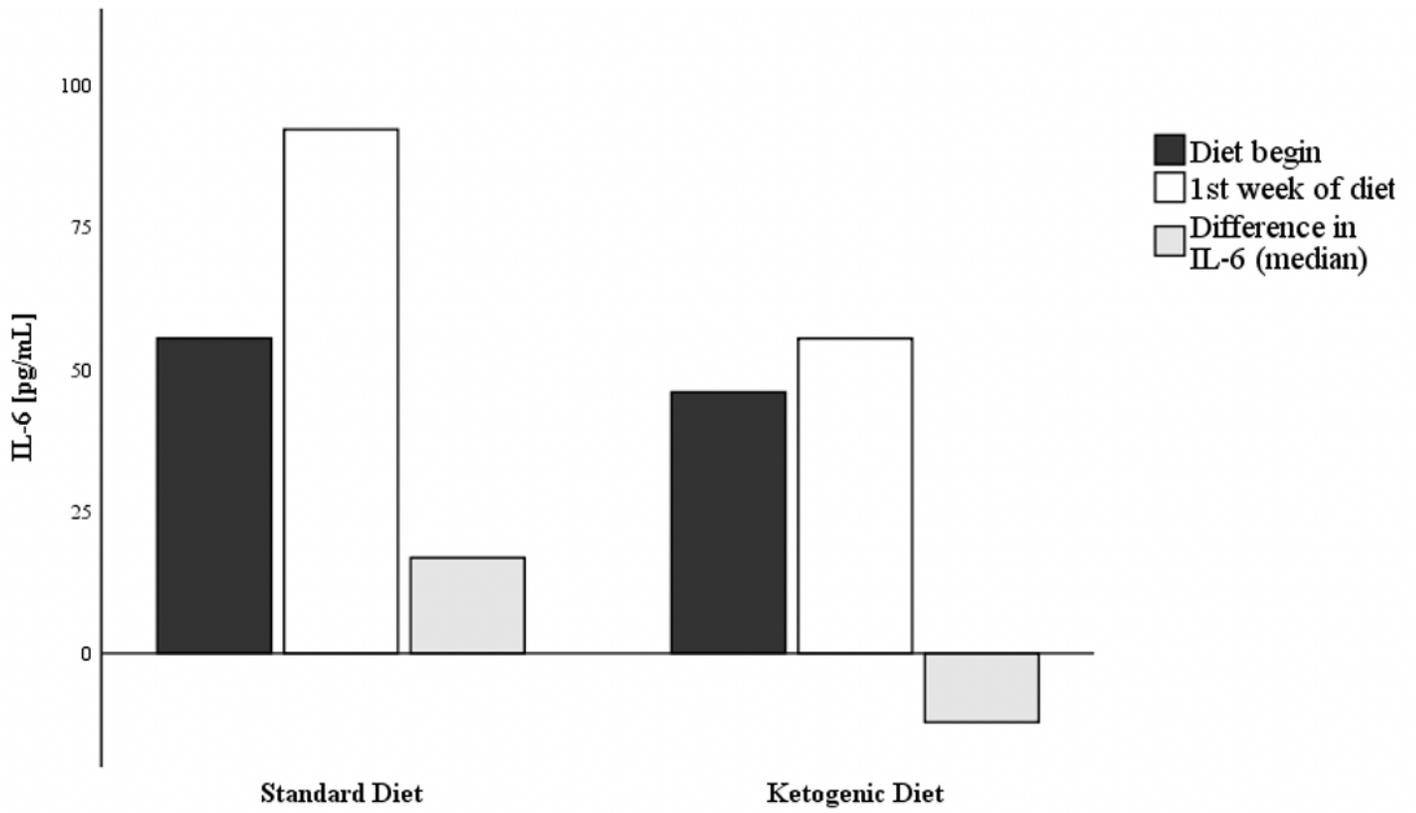
**Figure 1**

Plan of the study



**Figure 2**

Kaplan-Meier estimates stratified by time-varying start of Ketogenic diet for (A) 30-day mortality and (B) need for ICU between Ketogenic and Standard diet groups.



**Figure 3**

Variation of IL-6 during EKD versus ESD.