Clinical Efficacy of Eucaloric Ketogenic Nutrion in Covid-19-cytokine Storm: A Retrospective Analysis on Mortality and ICU Access

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Abstract

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

Aim of the study: Primary objective is to explore the effect of EKD on mortality, access to ICU and the need of NIV in COVID-19 hospitalized patients in comparison to a eucaloric standard dietstandard diet (ESDESD). Secondary objectives are to collect data about safety and feasibility of EKD during hospitalization and to evaluate the effect of the diet on biological and inflammatory parameters and particularly on interleukin -6 (IL-6).

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

Results: A trend of reduction of 30-day mortality (HR 0.416, 95% CI 0.122 – 1.413, P = 0.160) and a trend in need for ICU admission (HR 0.357, 95% CI 0.045 – 2.847, P = 0.331) were observed in subjects treated with EKD respect to patients fed with standard one. No significant different risks in need for CPAP (HR 0.968, CI 0.289 – 3.242, P = 0.958 for EKD) and 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), collected in the ketogenic nutrition group, show a median IL-6 difference of -26.0 μg/mL or a mean IL-6 difference of -164 μg/mL (data from 23 of the 34 pairs) compared to controls, with a trend to (P = 0.062).

Discussion and conclusions: These preliminar data, collected in a retrospective way during the most aggressive period of Covid-19 pandemia, on clinical results on mortality, need for ICU and effect on IL-6 concentration during EKD suggest a favorable role of this dietary treatment in COVID-19 clinical management. EKD resulted 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, actually ongoing, in a largest number of subjects are necessary to confirm these preliminary data.

1. Introduction

COVID-19 is a pandemic disease caused by SARS-Cov-2 virus, characterized by respiratory and gastrointestinal symptoms [1] and in a subgroup of these patients by a cytokine storm syndrome (COVID -19 CS) characterized by a fulminant and fatal hyper-cytokinemia associated with multi-organ failure and a high mortality[2] .

Mortality reported by our recent retrospective GECOVID group for 275 patients affected by SARS- COV 19 was of 43,6% [3].

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

From the beginning of the pandemia, the approaches aimed to 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 Device and Intravenous Immunoglobulin (IVIG) [4-5] .

Anyway, According to WHO, systemic steroid is the only proven therapy sin critical and severe covid-19 [6] and therefore, any possible alternative treatment can be an hypothesis to investigate.

Recently we proposed a immunometabolic hypothesis identifying a treatment capable of reducing the state of hyperinflammation associated with SARS-Cov-2 infection[7].

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 [7]. ATII cells release cytokines and chemokines that activate alveolar resident macrophages (AM) [7].

During the exudative phase of ARDS, AM are activated into M1 phenotype. Pro-inflammatory cytokines (IFN-*γ*, TNF-*α*, and IL-β) are excreted by M1 macrophages into the site of inflammation recruiting monocytes from the blood, by means of monocyte chemoattractant protein (MCP), which shift into M1 phenotype.

In COVID-19-CSS there is an 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 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 development of a pro-coagulant and pro-inflammatory environment [9] .

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

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 [11].

In ATII, excess of lactate decreases type I interferon (IFN) -which play a vital role in the defense of the host against virus - suppressing mitochondrial antiviral signaling (MAVS)[11].

Therefore the possible reduction in lactate production might produce a positive effect on the production of innate immune type I IFNs (type I interferons) [7].

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

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

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

2. Materials And Methods

2.1 Subjects

This study is a retrospective analysis on 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 on March 2020 undergone to ketogenic diet. In this regard in the Infectious Disease Unit ketogenic diet entered in 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 the consent to personal data treatment and informed consent to undergo any type of therapy during their hospitalization.

They were also informed that ketogenic diet entered in the routine protocol of the ward, in absence of contraindications, having the possibility to accept or refuse immediately or after, in case of scarse palatability or taste. The pharmacological protocol wasn’t 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 sulphonylureas, repaglinide, GLP-1 analogues, SGLT2 inhibitors, recent ASCVD (within one month); food allergies to diet components; any metabolic disorder that can affect

gluconeogenesis; clinical history of severe hypertriglyceridemia with or without pancreatitis; pregnancy and lactation.
Meanwhile a RCT, with the purpose to study the EKD in an larger sample of subjects in the whole hospital , randomizing the nutritional treatment , was submitted and approved in June by the ethical committee (KETOCOV-1 **Regist**er number **CER Liguria: 198/2020 - DB id 10517**; *ClinicalTrials.gov identifier (NCT number):* ***NCT04492228***) and actually it has been started at the end of September 2020 with the recrudescence of the infection in Italy.

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

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

Inclusion criteria to enter in the analysis of the data were: documented diagnosis of COVID-19 defined by a positive result of an RT-PCR assay of a respiratory sample, Pa O2 < 60 mm hg at rest in ambient-air or P/F <200 (arterial oxygen concentration to the fraction of inspired oxygen),

age older than 18 years.

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

All patients were investigated about 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, hemiplegia.

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

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

Laboratory data required by the ward doctor were the routinary 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 the 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 steps of the analysis.

2.2 Diet administration

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

According to the LARN (Reference Intake of Nutrients and Energy for Italian Population) and to the Italian guidelines for a healthy diet [13-14], The Standard oral diet was based on the Mediterranean style [15] 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 carbohydrates intake of 50-55%.

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

2.3 Endpoints and Outcomes

Primary outcomes were 30-day mortality, ICU access and need for CPAP and they were also considered together in a combined outcome.

Secondary outcomes were the effects of 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). The Kolmogorov-Smirnov analysis was used to test the normality of the variables. The results of continuous variables were expressed as the median and inter quartile interval range. For categorical variables, contingency tables were used indicating the frequency and percentage in the population. For the comparison of continuous variables between different groups of patients non-parametric Kruskal-Wallis or Mann-Whitney tests were used when appropriate. Nominal variables were

examined with Pearson’s chi-squared (X2) test and Spearman's rank correlation index was used for the correlation with continuous variables.

To adjust for baseline differences that are intrinsic in non-randomized studies, patients in the EKD diet (34 patients) were matched 1:2 to patents 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 with ESD and EKD respectively.

The PS was estimated by a logistic regression model including variables statistically different between the two groups: Charlson score, lymphocytes count, AST, albumin as continuous variables and presence of diabetes, chronic pulmonary disease, hematological neoplasia and therapy with corticosteroid, Remdesivir and Tocilizumab as categorical data. The caliper levels of 0.8 has been considered for PS.

The cox regression analysis has been used to estimate the effect of the different dietary regimes on all primary endpoints (i.e. 30-day mortality, the ICU access, need for CPAP and composite endpoint). Because all patients in standard diet group began their diet at hospital admission, but subject in ketogenic group start their diet few days later, the ketogenic diet start was considered as a time-varying covariate in order to avoid immortality bias. The results have been reported as hazard ratio (HR) and 95% confidence interval (95% CI) of HR. The period from hospitalization to the onset of each outcomes has been 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 ESD and 34 fed with EKD, were reported in Table 1.

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

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

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

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

No significant different risks in need for CPAP (HR 0.968, CI 0.289 – 3.242, P = 0.958 for Ketogenic diet) and 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 ρg/mL or a mean IL-6 difference of -169 ρg/mL (data from 22 of the 34 pairs) compared to controls.

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

No adverse event was observed in patients fed with EKD.

4. Discussion

Nutritional status appears a relevant factor influencing the outcome of patients with COVID-19, but not much information has emerged about the impact of early nutritional support in pre-ICU patients on the course of the disease [16].

Surely nutrition has a pivotal role in the prevention of the comorbidities most frequently associated to Covid-19 such as hypertension, cardio and cerebrovascular disease and diabetes and which have been noted as twofolds, threefolds and twofolds, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts[17] .

Nevertheless obesity is associated with a worse prognosis in patients affected by COVID-19, especially among the young [18].

An hyperinflammatory response response of COVID-19 has been recognized as the main cause of morbidity and mortality in these patients [19].

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

Anyway 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 [20].

However, Covid19-CS 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 in ARDS and multisystemic organ failure [21].

Effective treatments for COVID-19 and COVID-19 CS are needed in the immediate. 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.[22]It is well known that the ketogen diet can inhibit inflammation. Studies have shown that KD reduces circulating inflammatory markers in humans.[29] The KD, via hydroxybutyrate (HB), is capable of activating the hydroxycarboxylic acid receptor 2 (HCA2), a protein-coupled receptor G, which inhibits NF-kB in macrophages, dendritic cells and microglia, and reduces neuroinflammation.[23]

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 were observed.[24] In addition, a 20-day ketogenic diet shows a significant decrease in the end-tidal carbon dioxide tension (PETCO2)[25] .

As reported in the introduction the use of corticosteroids is nowadays suggested by the World Health Organisation guidelines and it is actually the first approach in severe disease [6].

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

Tocilizumab was present in 54.4% of patients treated on a standard diet nutritional therapy and in 67,6% of patients with eucaloric ketogenic nutrition.

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

IL-6 does not increase but rather tends to a slight reduction in the group treated with EKD (figure 3). This trend underlines the fact that patients after one week were, in that moment, at increased risk of COVID-CS.

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

During the treatment the patients didn’t present any adverse events related to diet.

Limits of the study are the lack of controlled randomization, the study was conducted in a single hospital facility where the nutritional protocol was used for clinical monitoring issues. A further limit was given by 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 strenghtness of the study is the usefulness of propensity score which, with the big hospital COVID-19 database (of about 669 cases) allowed a proper matching 1:2 ,overcoming the absence of controlled randomization.

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 the exact picture of the state of fact, and , the trend in reduced mortality, reduced need to ICU and reduced Il-6 between 0 and 7 days , although not statistically significant, suggests 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, firstly, underlines the role of clinical nutrition therapy as a pathophysiological support to drug therapy in improving the prognosis not only of COVID-19 but also in infectious diseases in which an immunomodulation could have a role in reducing hyperinflammation syndromes.

Conclusions

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

The pilot study was oriented on the primary objective of verification of mortality outcome and reduction of hospitalization in intensive care. Patients were randomized using Propensity Score, which allowed, with the selection of patients treated in other facilities and made available to a single management software, to have adequate controls for a validable statistical analysis.

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

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

Declarations

No conflict of interest

The paper was approved by the Ligurian Ethical committee on November, 11 2020

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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
Demographics				
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
Comorbidities, (n %)				
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
Clinical features				
PaO2/Fi02	281 (205-323)	312 (166-384)	286 (188-348)	0.312
Laboratory values				
WBC [mil/m³]	7.26 (5-10.58)	6.78 (5.3-8.96)	7.02 (5.09-10.06)	0.531
Limph [x100/m³]	0.9 (0.6-1.3)	1.05 (0.74-1.32)	1.00 (0.69-1.32)	0.514
PLT [x100/m³]	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
Concomitant Pharmacotherapy (n, %)				
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

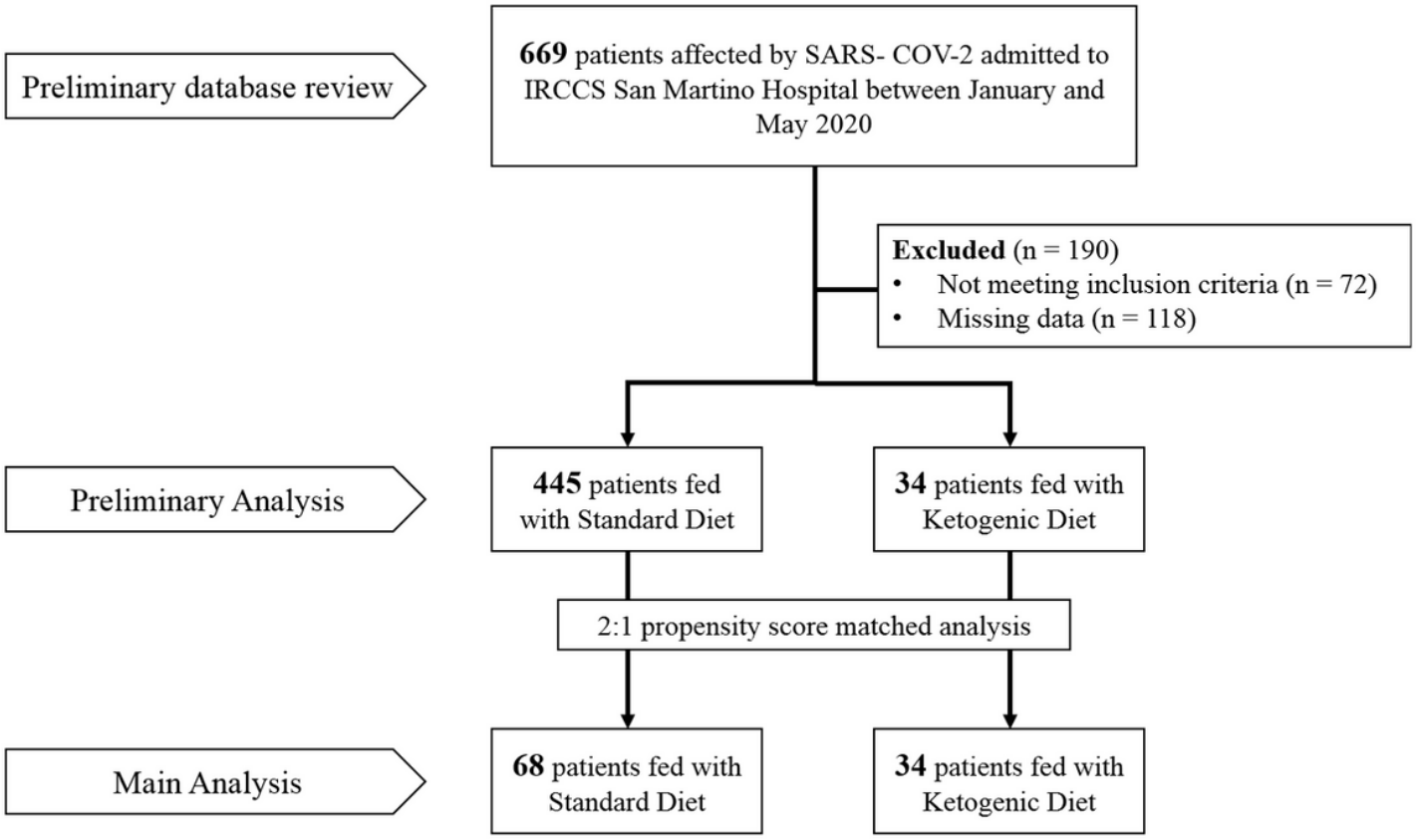

Figure 1

Plan of the study

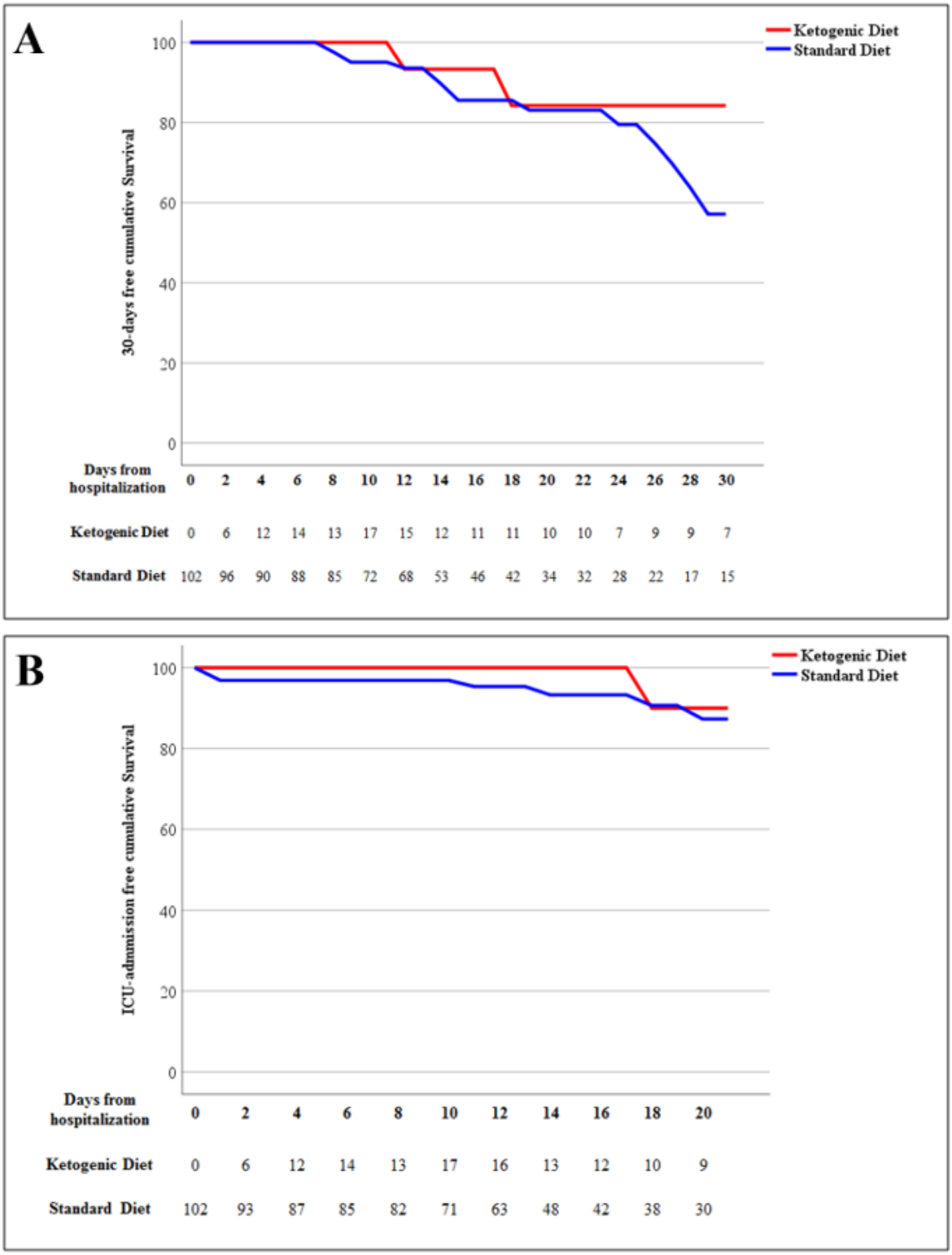

Figure 2

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.

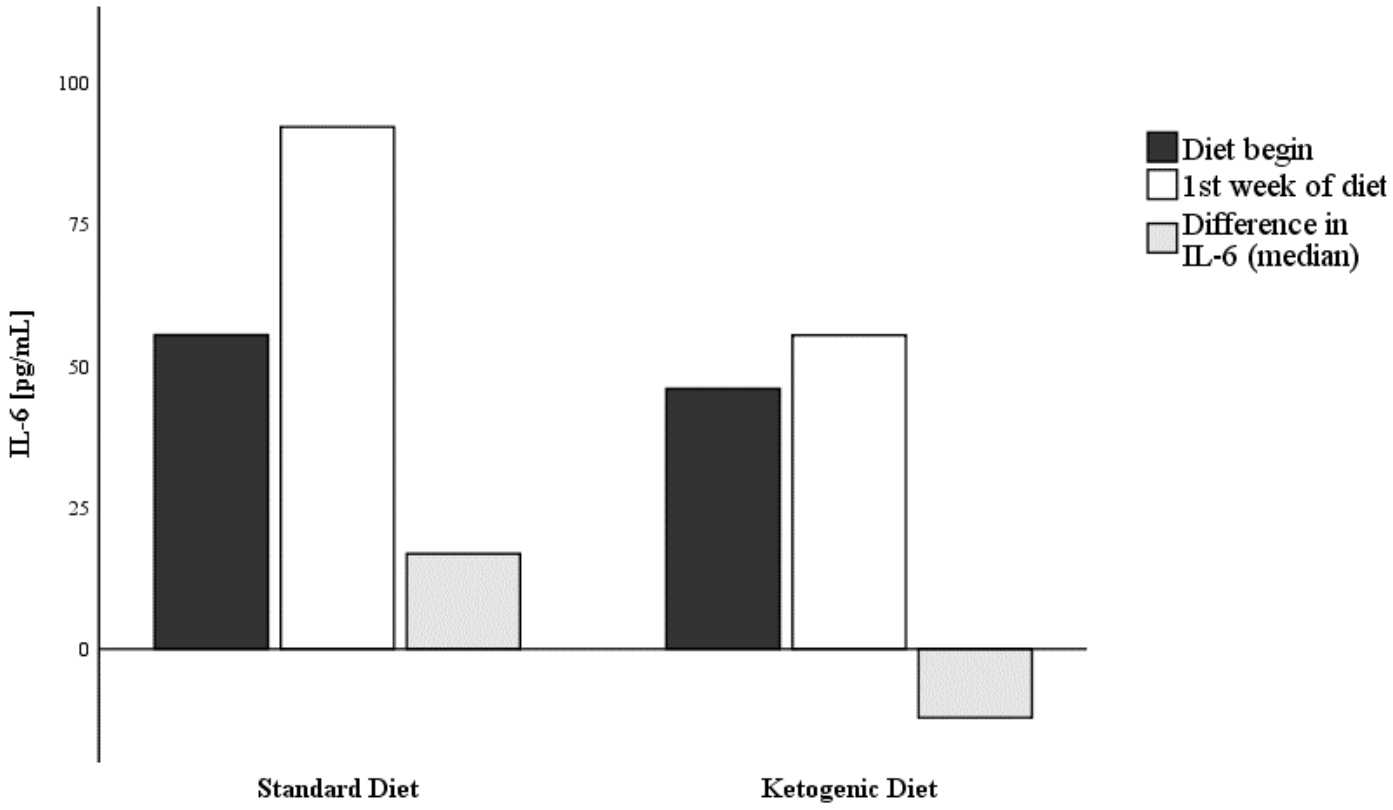

Figure 3

Variation of IL-6 during EKD versus ESD