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Pace Napoleone C, Aidala E, Cascarano MT, Deorsola L, Iannandrea S, Longobardo A, Bonaveglio E, Zanin M, Peruzzi L

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Brief Report

Hemoadsorption contribution in failing Fontan pediatric heart transplantation

Carlo Pace Napoleone[a], Enrico Aidala[a], Maria Teresa Cascarano[a], Luca Deorsola[a], Stefania Iannandrea[b], Annalisa Longobardo[b], Enrico Bonaveglio[b], Mattia Zanin[b], Licia Peruzzi[c]

[a] Pediatric and Congenital Cardiac Surgery, Regina Margherita Children's Hospital, Torino, Italy

[b] Pediatric Cardiac Anesthesiology and Intensive Care Unit, Regina Margherita Children's Hospital, Torino, Italy

[c] Pediatric Nephrology, Regina Margherita Children's Hospital, Torino, Italy

Short Title: Hemoadsorption in pediatric heart transplantation

Corresponding Author:
Carlo Pace Napoleone
E-mail: cpacenapoleone@cittadellasalute.to.it

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Abstract

Introduction A systemic inflammatory response is triggered in patients undergoing cardiothoracic surgery with cardiopulmonary bypass. This response is particularly evident in pediatric patients, especially if of low weight and after undergoing long cardio-pulmonary by-pass (CPB) and can severely impair surgical result. Adsorptive blood purification techniques have been proposed to limit this systemic inflammatory response. To test its efficacy, we added the hemoadsorption filter Jafron HA 380 to CPB in a very compromised pediatric patient who underwent heart transplantation.

Methods A 10-year-old single ventricle patient previously treated with Fontan operation was listed for heart transplantation due to the evidence of failing Fontan condition. He experienced many episodes of cardiac arrest and underwent heart transplantation in very compromised general and hemodynamic conditions. The hemoadsorption filter Jafron HA 380 was used for all the duration of CPB and the inflammatory biomarker Interleukin 6 (IL-6) was assayed.

Results Post-operative outcome was uneventful and comparable to that of an elective pediatric heart transplantation. The Interleukin 6 (IL-6) levels showed an impressive post-operative reduction and after 2 days the IL-6 level was comparable with a typical uneventful post-transplant course.

Conclusions The use of hemoadsorption filter can contribute to improve pediatric transplant results especially in very high-risk patients.

Introduction

A systemic inflammatory response is triggered in patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB) as a result of the combination of surgical trauma, activation of blood components in the extracorporeal circuit, ischemia/reperfusion injury, and endotoxin release [1]. This response is particularly evident in pediatric patients, in which the unfavorable ratio between their low body weight and the surface of the CPB circuit plays an important role [2]. In these patients, the incidence of the so-called "systemic inflammatory response syndrome" (SIRS) can be 21.9~33.3% or even higher, especially in the presence of low mean age, low body weight, long CPB duration, and large amount of fresh frozen plasma used during operation. This is a common complication after pediatric congenital heart surgery and can significantly prolong the time of mechanical ventilation and length of Intensive Care Unit and in hospital stay [3]. The pathophysiological mechanisms of SIRS involve a cytokine-mediated general capillary leakage followed by intravascular volume depletion, generalized edema, circulatory compromise, and altered microcirculation. The inflammatory process may further impair the function of the lung, myocardium, kidney, liver, intestine, and brain [3]. A variety of approaches have been adopted to limit the incidence of SIRS after CPB. Among these, modifications to CPB equipment, such as filters to remove inflammatory leukocytes or soluble mediators, minimized circuits to reduce surface area, coatings to improve the biocompatibility of extracorporeal surfaces have been proposed. In recent years, adsorptive blood purification techniques (BPTs) have emerged in the control and treatment of systemic hyperinflammatory states, such as refractory septic shock patients. However, the evidence on efficacy and safety of adsorptive BPTs application during CPB surgery to reduce SIRS are still inconclusive [4]. This technique was used in adult heart transplanted patients and was associated with reduced vasopressor demand and less frequent renal replacement therapy with a favorable tendency to the reduction of length of mechanical ventilation and ICU stay [5]. To the best of our knowledge, no reports have been published on the use of this type of filter in pediatric heart transplantation. Single ventricle patients treated with Fontan operation, where the venous blood enter the lungs without the boost of a ventricle and the single systemic ventricle pushes oxygenated blood in the aorta, can experience a so-called failing Fontan condition. In these patients, the Fontan-associated liver disease (FALD), is one of the most important secondary morbidities, resulting in fibrosis and cirrhosis. FALD is a distinctive type of congestive hepatopathy, and its pathogenesis is thought to be a multifactorial process driven by increased nonpulsatile central venous pressure and decreased cardiac output, where a chronic inflammatory status plays an important role [6]. In these patients, heart transplantation is the only opportunity but the results are not comparable to other pediatric heart transplantation essentially for the very bad preoperative conditions and multisystemic involvement. The HA 380 hemoadsorption filter (Jafron Biomedical, Zhuhai City, China), with an adsorption surface of over 54000m^2 able to adsorb molecules from 10 to 60 kDa, was demonstrated to provide an effective removal of inflammatory cytokines in SIRS [7]. We report our experience with the use of Jafron HA 380 hemoadsorption filter in a very compromised failing Fontan pediatric patient who underwent heart transplantation.

Materials and Methods

A right single ventricle patient, whose parents gave their written informed consent to publish this paper, underwent staged extra-cardiac Fontan operation at 4 years of age. For the progressive impairment of tricuspid valve incompetence, the patient developed a reduction of cardiac function with signs of liver and kidney insufficiency. Cardiopulmonary exercise test evidenced a severe reduction of functional ability and hemodynamic evaluation demonstrated a pulmonary pressure of 13mmHg with normal pulmonary vascular resistances. He was listed for heart transplantation at 10 years of age. He then experienced a cardiac arrest at home and was resuscitated and recovered to our ICU where other episodes of cardiac arrest were documented. His conditions were stabilized with mechanical ventilation and high dose inotropes and, after checking the neurological integrity, he was listed in emergency. He underwent heart transplantation 10 days later in very bad clinical conditions, as documented by the pre-operative blood sample analysis (shown in Table 1). The CPB circuit was primed with Fresh Frozen Plasma (FFP) 200 ml, Albumin 20% 50 ml and Ringer Acetate 800 ml. Continuous ultrafiltration was used for all CPB duration. A Jafron HA 380 hemoadsorption filter was added to CPB circuit and was kept in use for all the 218 minutes of pump time. Methylprednisolon 30 mg/Kg was administered at operation start. Concentrated Red Blood Cell (RBC) (500 ml) and FFP (600 ml) were added at the end of CPB. Total ischemic time of the graft was 230 min.

Results

Blood levels of IL6, C Reacting Protein (CRP), Procalcitonin and renal and liver functions markers were analyzed at defined intervals in the first 48 hours after heart transplant (shown in Table 1). An important reduction of inflammatory markers was evident during the procedure, reaching the minimum at the end of CPB for IL6 and CRP while Procalcitonin level after reduction started to rise again at the end of CPB. Renal and liver function markers showed a progressive reduction during CBP and up to ICU transfer followed by an increase much lower than usually observed. Post-operative inotrope stimulation with adrenaline 0.1 mcg/kg/min was progressively tapered and stopped in post-operative day 3 concomitantly with extubation. He was discharged from ICU in 15th post-operative day and discharged from the hospital to home after 20 days of uneventful recovery. Being conscious of the limited value of a comparison with a similar clinical situation, we evaluated the results of another pediatric heart transplanted patient, whose parents gave written informed consent to publish this paper. She is a 5-year-old girl suffering from primitive dilatative cardiomyopathy who was treated with bi-ventricular Berlin Heart VAD implant and underwent heart transplantation 6 months later in very good clinical conditions. We chose her because we considered her hemodynamic and clinical conditions as the best we can obtain in a patient undergoing heart transplantation. The two patients received the same pharmacologic medication during operation and CPB machine was primed in the same manner. The inotropic score of the 2 patients reveals a very low necessity of inotropes without differences between them (shown in Figure 1). The control patient showed a normal pre-operative IL6 level, indicating a negative inflammatory status, that progressively increased during operation to reach the peak at the conclusion of surgery at time of ICU arrival, with an opposite trend compared to the Fontan transplanted patient. Her IL6 level declined in POD 1 and returned to preoperative level in 3 days. We can presume that probably the same level would have been reached also by the Fontan patient in a comparable interval of time (shown in Figure 2). Due to the observation of a completely different curve of increase and decline of IL-6 we can speculate that hemoadsorption filter changed the intra- and post-operative inflammatory response in an extremely compromised patient making it comparable to that obtained in a clinically stable case in perfect hemodynamic compensation. We claim that the downgrading of the inflammatory response positively influenced the postoperative course with a consequent favorable impact on the clinical results.

Discussion

SIRS can represent a dangerous effect of open-heart surgery and its consequences can impair the result of a perfect operation. Boehne and coll. demonstrated that this complication following congenital cardiac surgery in children was associated with extended length of stay in the PICU, increased inotropic support and a higher risk of developing organ dysfunction [3]. Many studies have shown a higher incidence of SIRS with younger age or lower body weight [2,8]. In these patients the mismatch between the priming volume , the surface of the cardiopulmonary bypass circuit and the patient's blood volume are particularly evident and induce an excessive activation of the inflammatory response, increasing the risk of SIRS. Moreover, younger children have a higher metabolic rate and immature organ function, possibly exposing them to a greater risk of SIRS [9]. On the other side, several other studies reported the lack of influence of younger age and lower weight on the possibility to develop post-operative SIRS [3]. All the published studies agree to identify as a risk factor for post-operative SIRS the duration of CPB. According to Warren et al. two phases of inflammatory response due to cardiopulmonary bypass can be distinguished [10]. In the early phase, triggered by the contact of blood with the surfaces of the CPB circuit, several humoral (complement system, pro-inflammatory cytokines, coagulation system) and cellular (leukocytes, vascular endothelial cells, platelets) inflammatory cascades are activated. The later phase is the result of the ischemia-reperfusion injury and endotoxemia, leading to endothelial injury, with release of reactive oxygen species and alterations of the microcirculation. Therefore, a longer CPB would steadily increase a more intense inflammatory response, even more aggravated in cases with enhanced ischemia-reperfusion injury as a result of suboptimal perfusion [10]. The amount of fresh frozen plasma (FFP) administered intraoperatively might also represent an additional risk factor for SIRS development [3]. FFP can be used to reduce the risk of hemorrhage at the end of cardiopulmonary bypass, especially in reoperations, longer or particularly invasive surgery. As the coagulation and inflammatory system are closely linked in multiple ways, it can be speculated that an additional supplementation of fresh frozen plasma might contribute to the inflammatory response. Allan et al demonstrated that intraoperative blood product administration was associated with higher post-operative interleukin-6 levels in infants [11]. Intraoperative FFP can also cause a transfusion-related lung injury, which has been shown to be associated with coagulopathy, prolonged mechanical ventilation and higher systemic levels of proinflammatory cytokines such as interleukin-6 [12]. Our patient received FFP in the priming solution of CPB to compensate the protein depletion derived from the Protein Loosing Entheropathy (PLE) secondary to the Fontan

failure, to avoid further reduction of plasmatic proteins level due to the dilutional effect of the extracorporeal circuit. Another FFP infusion was necessary at the end of CPB to provide fresh coagulation factors and limit the high post-operative bleeding risk due to the 4th median sternotomy. For this reason, it was crucial to perform an accurate surgical hemostasis but also to optimize blood coagulation. FFP was transfused according to the results of thromboelastography test. This strategy, recommended in many guidelines, allows for the administration of blood products targeted on observed abnormalities and reduces useless supplementation of coagulation factors, as FFP, with a positive impact on post-operative inflammatory state [13]. Reducing inflammation is expected to decrease postoperative morbidity and mortality but clear evidence of this result has yet to be demonstrated [14]. A randomized controlled study has failed to demonstrate that hemoadsorption by CytoSorb® (CytoSorbents Europe GmbH, Berlin, Germany), another filter very commonly used in cardiac surgery, was beneficial in the vast majority of elective cardiac procedures [16]. This result was confirmed by a recently published meta-analysis that concluded that there is no evidence for a positive effect of the CytoSorb® adsorber on mortality across a variety of diagnoses that justifies its widespread use in intensive care medicine [17]. On the contrary, a controlled, randomized pilot study demonstrated a significant reduction in pro-inflammatory cytokine levels (IL-8 and TNFα) in a group of 21 patients treated with hemadsorption (CytoSorb®) during CPB compared to control group. Furthermore, in these patients a significantly increased cardiac index after weaning from CPB was demonstrated [17]. To explain these inconstant results it was suggested that the clinical positive impact of hemoadsorption to post-operative outcomes was more evident in high-risk patients (aortic arch surgery with hypothermia arrest and selective cerebral perfusion, infective endocarditis surgery, higher EuroSCORE II, emergency surgery or implanted mechanical circulation support, and heart transplantation patients) [18]. This phenomenon can be rationally explained considering that hemadsorption is concentration-dependent, therefore a higher therapeutic effect can be obtained in conditions with strong pre-operative systemic hyperinflammation. However, at present the conclusions of currently available studies in endocarditis, heart transplantation and aortic surgery are contradictory [19]. Hemoadsorption is a physical process that in clinical use can have the drawback of reducing also plasmatic levels of pharmacological molecules like antibiotics. Lorenzin and coll. in an in vitro experiment demonstrated that HA380 adsorbs significant amounts of vancomycin [20]. This must be considered when an hemoadsorption strategy is conducted during post-operative course, adding the HA380 to an ECMO or a Continuous Renal Replacement Therapy (CRRT) circuit. Our patient was treated intraoperatively during CPB, a period during which only anesthetic drugs are administered. This therapy is titrated according to the Bispectral Index (BIS) monitor that collects raw EEG data through its sensors and uses an algorithm to analyze and interpret the data. Any adsorption of anesthetic drugs by the cartridge would have been evident at BIS monitor and treated with an increase of anesthetic administration. With these premises, we described the case of a patient that can be included among the most complex patients undergoing heart transplantation. As a matter of fact, he suffered from a failing Fontan status, with severe impairment of cardiac function due to progressive severe tricuspid valve incompetence. This condition is strictly linked to a chronic hyperinflammatory preoperative state that was further exacerbated by the recent multiple episodes of cardiac arrest. The necessity to treat the patient with mechanical ventilation and high dosages of inotropes posed him among the most complex and difficult candidates to heart transplantation. However post-operative course was substantially comparable to other pediatric transplanted patients. We cannot attribute this result only to the use of HA 380 hemoadsorption filter, but it can be clearly appreciated that we started the intervention with very high level of inflammatory markers that were effectively reduced during CPB, displaying a lower and slow increase in the early post-operative period (shown in Table 1). The same reduction was demonstrated for all the markers of kidney and liver function. It is reasonable to think that hemoadsorption treatment can be useful also in younger patient, especially neonates, that are most sensitive to CPB and in which cardiac surgery is often very aggressive. In our center we are conducting a prospective study regarding the use of the pediatric version of this hemoadsorption filter, the HA60 (Jafron Biomedical, Zhuhai City, China), with only 60ml of priming volume, during major neonatal surgery, and we are confident that this experience will open new opportunities to reduce the impact of CPB and hopefully to improve surgical outcomes.

Conclusion

We reported our favorable clinical experience with HA 380 hemoadsorption filter during CPB in an extremely difficult child suffering from Fontan failure treated with heart transplantation. The highly chronic inflammatory status present before transplant was efficiently blunted by hemoadsorption favoring a better hemodynamic state and post operative course. To confirm the positive impression of a relevant contribution of hemoadsorption in

improving the outcome and post operative course of this extremely complex pediatric cases, prospectively and properly designed multicenter studies are required. To the best of our knowledge, this is the first reported case of successful pediatric heart transplantation treated with HA 380 hemoadsorption filter.

Statements

Study approval statement

Ethics approval was not required

Consent to participate statement

Written informed consent was obtained from the parent/legal guardian of the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare

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Author Contributions

Substantial contributions to conception and design: Carlo Pace Napoleone, Enrico Aidala; Licia Peruzzi
Acquisition of data: Enrico Aidala, Luca Deorsola, Maria Teresa Cascarano;
Analysis and interpretation of data: Carlo Pace Napoleone, Licia Peruzzi;
Drafting the article: Carlo Pace Napoleone;
Revising it critically for important intellectual content: all authors;
Final approval of the version to be published: all authors.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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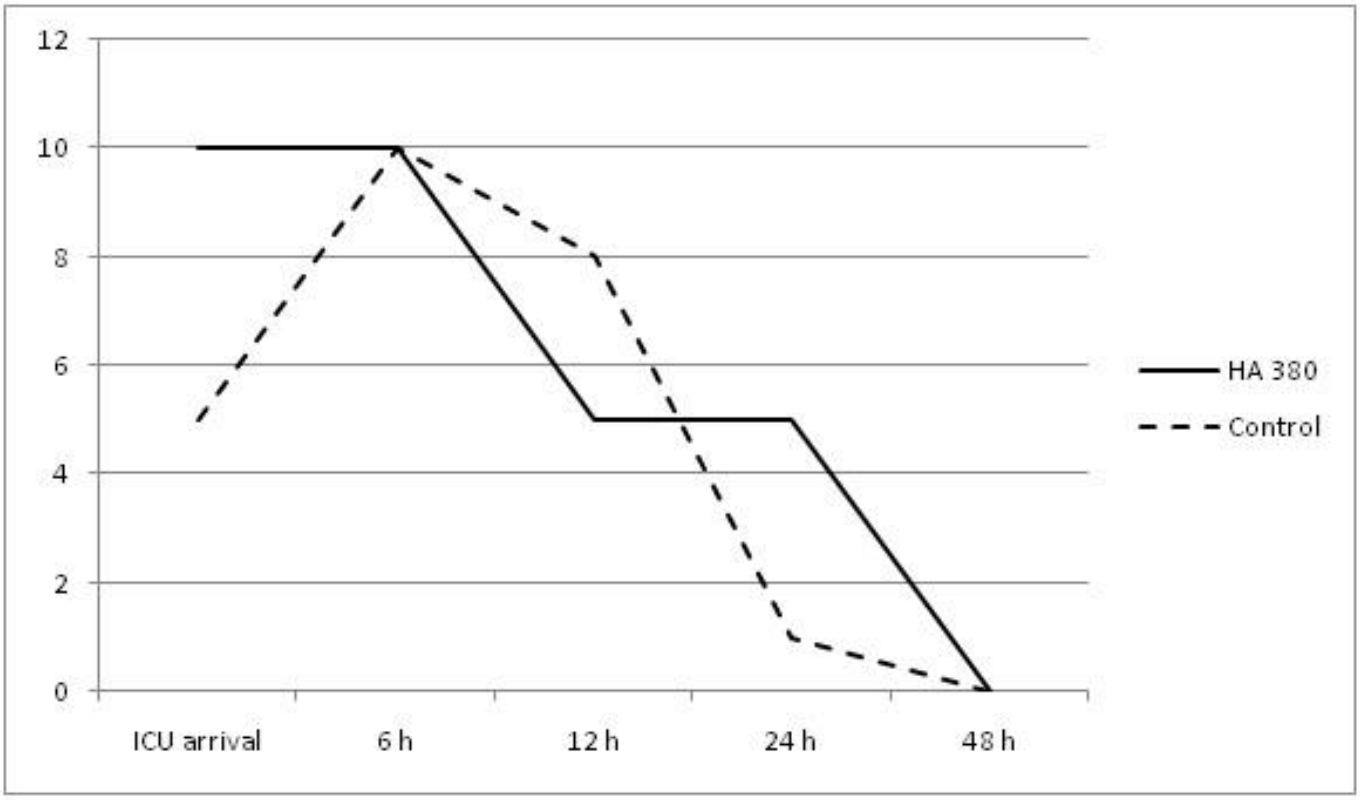
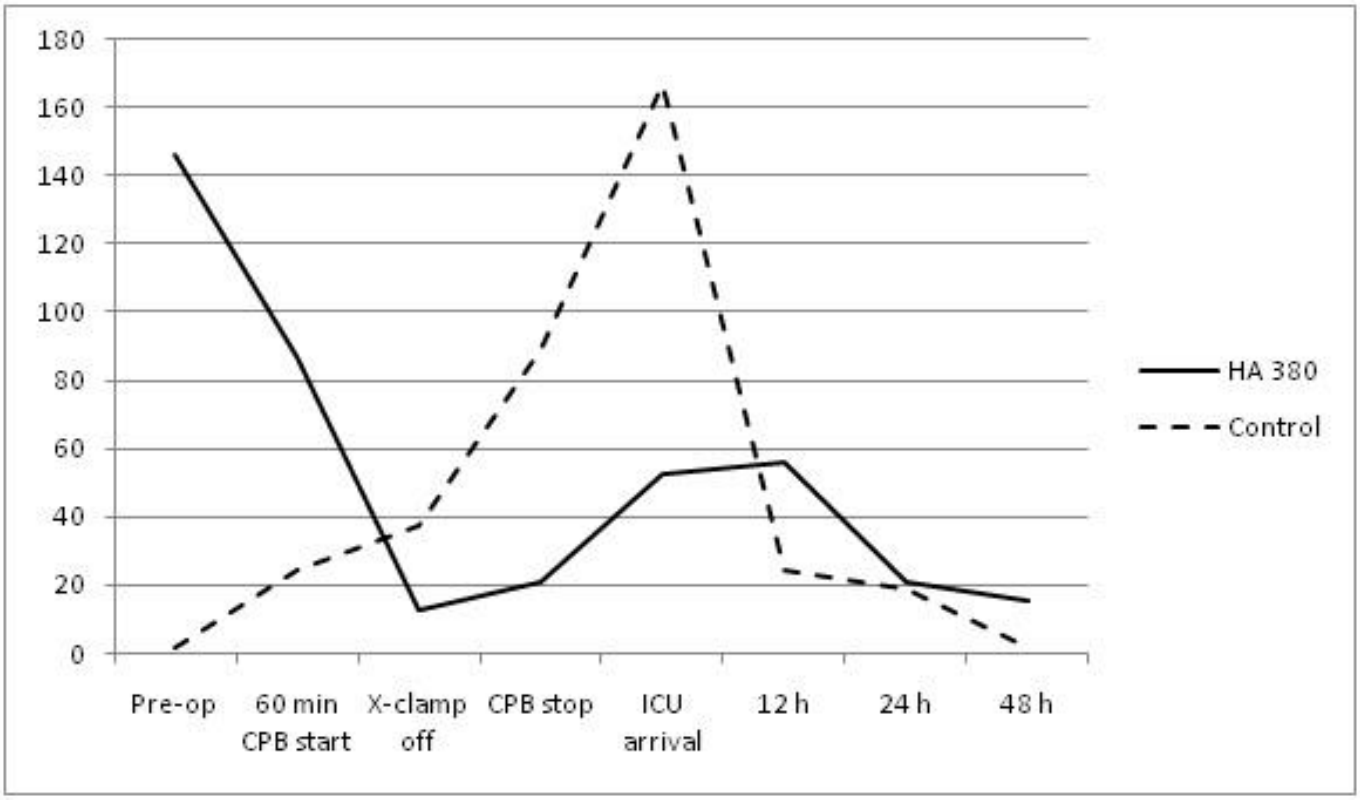
Figure legends

Fig. 1. Inotropic score of filtered patient (HA380) and control patient (Control).

Fig. 2. Interleukin 6 serum level (pg/ml) of filtered patient (HA380) and control patient (Control).





	IL6 pg/ml	CRP mg/l	Procalcitonin mcg/l	Creatinine mg/dl	AST UI/l	ALT UI/l	GGT UI/l	LDH UI/l
Pre-operation	146	169	10,88	1,7	425	219	27	1312
60 min after CPB start	87	173	8,02	1,27	675	273	28	1279
X-clamp off (filter 166 min)	13	114	2,49	0,98	565	192	19	1218
CPB stop (filter 218 min)	21	95,5	6,16	1,09	528	171	18	1241
ICU arrival	53	102	6,27	0,98	619	186	18	1633
h 12	56	112	8,49	1,05	667	200	21	1915
h 24	21	109	7,91	1,16	394	180	24	1066
h 48	16	79,6	6,73	1,26	203	154	32	677

Table 1: Evolution over time of serum levels of markers of inflammation and kidney and liver function. (Il6: Interleukine 6, CRP-C Reactive Protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: Gamma-Glutamyl Transferase, LDH: Lactate DeHydrogenase).