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Immune system effectors as biomarkers of prognosis after acute burns in a case-control study

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Highlights

*Severe burns are a global health problem, and the initial stages after the burn are crucial.

*Biomarkers of prognosis in acute burns are needed to allow proper management.

*This work demonstrates that serum total protein, albumin, complement C4 protein, and transferrin allow an adequate assessment of the initial stages of burn patients. These parameters have a significant correlation with the total burned surface area.

*In this case-control study, it was found that total immunoglobulin G, cholesterol, and pseudocholinesterase activity are independent parameters that correlate well with patient prognosis, arising as suitable easy-to-measure laboratory biomarkers.

Abstract

Burns are a global health problem due to frequent complications, which lead to systemic inflammation, acute respiratory distress syndrome, multiorgan dysfunction, and death. Following the initial injury, it has been demonstrated that the immune system plays a key role in early inflammation, tissue regeneration, and the response against pathogens. In this study, the performance of laboratory determinations as biomarkers of prognosis in acute burned patients was evaluated in a retrospective case-control protocol. Laboratory determinations were immunoglobulin G (IgG), immunoglobulin M (IgM), C-reactive protein (CRP), complement C4 protein (C4), total serum protein (TP), albumin, prealbumin, cholesterol (CHOL), pseudocholinesterase activity (CHE), and transferrin. Patients in the deceased group (DG) showed lower initial IgG levels ($p < 0.05$) than patients in the survivor group (SG), with a negative predictive value (NPV) of 0.86, and this difference persisted during the hospitalization period. Furthermore, DG patients showed a decrease in CHOL and CHE during the hospitalization period (NPV of 0.86), a tendency that was not observed for the SG. Albumin, TP, C4, and transferrin showed lower initial values in DG than the SG, with a strong correlation with the total burned surface area (TBSA). These results indicate that IgG, CHOL, and CHE measurement might provide useful information for medical intervention independently of the TBSA and suggest that the measurement of TBSA-linked parameters might help to estimate the severity of burns more objectively. In this paper, the causes and implications of the alteration of effector molecules of the immune system are discussed.

Keywords: *severe burns, biomarkers, immune system, IgG*

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1. Introduction

According to the numbers published by the World Health Organization, burns are a global health problem, which leads to about 180,000 deaths worldwide, mainly in low-to-middle-income countries, with almost two-thirds occurring in Africa and South East Asia [1]. Previous studies indicate that each year, almost 8 million people in the world get burned, and about 1,000,000 of them have severe burns, which cover more than 30% of their body surface [2]. In Argentina, the Asociación Argentina de Quemaduras (Argentinian Burn Association) estimated in 2011 that burns—as a result of exposure to fire, hot liquids or objects, caustic agents, chemical substances, radiation, electricity, or biological agents—have an incidence of 5/1,000 inhabitants per year, which implies that approximately 190,000 individuals get burned each year in the country, being 10% classified as severe (G III) or critical (G IV). Within the group of burned individuals, and according to the same source, the mortality rate ranges from 18% to 20% [3].

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Severe and critical burns are a cause of high morbidity and mortality because they frequently become complicated as a consequence of inhalation wounds, local infections, and generalized sepsis, which lead to systemic inflammation, acute respiratory distress syndrome, multiorgan dysfunction, and death [2]. Despite the advances in the field of critical care, infections are still a prevalent complication and lead to generalized sepsis in almost 60% of burned patients. Furthermore, burns have deep consequences on long-term life quality and are one of the most expensive traumatic injuries for the health system because patients often require long-term hospitalization periods, sophisticated rehabilitation procedures, and expensive wound and scar treatments [4].

Early stages after burn are crucial because during the first hours after injury, a critical condition might occur, known as "burn shock". The main features of burn shock are the edema of burned tissue and the edema of surrounding (not burned) tissue [5, 6]. After these initial events, the release of inflammatory mediators, such as histamine, bradykinin, prostaglandins, leukotrienes, complement, and others, reinforces the endothelial damage of small blood vessels. Osmotic pressure gets reduced, allowing fluid to escape carrying water, electrolytes, and proteins, leading to hypovolemia, hemoconcentration, generalized edema, reduced urine output, and cardiovascular dysfunction [5–8]. In this scenario, the role of the immune system is critical for many reasons. First of all, it has been extensively described that burn injuries induce an inflammatory response, both locally and systemically. This inflammation activates innate immune system mechanisms, which allow early and proper defense against pathogens, and also participates in tissue regeneration. However, prolonged inflammation and immune system activation have also been associated with negative processes, such as tissue fibrosis and scarring of the skin and damage to the heart, lungs, blood vessels, kidneys, and other organs, making the immune system evaluation an important aspect of medical care and patient follow-up [9, 10]. Moreover, some researchers have demonstrated that burn shock may lead to an immunosuppression characterized by lymphopenia, decreased interleukin 2 (IL-2) secretion, neutrophil activity, and impaired phagocytosis, among other findings [11]. Altogether, these alterations might be the cause of the increased susceptibility to infections.

In this context, one of the priorities for researchers working on acute burned patients is the identification of prognosis biomarkers, which enable a close, permanent, and reliable follow up of patient evolution. It is expected that adequate prognosis biomarkers would allow effective organ monitoring, as well as proper infection management, through early intervention, which would, in turn, decrease the cost of clinical care. The term "biomarker" implies any measurement or parameter that reflects the interaction of a given biological system with an environmental agent, as are patients and burns [4]. The ideal biomarker should be easily measured in a sensitive, specific, and reproducible manner. It should also be versatile and sensitive to therapeutic interventions.

Several research groups have studied the use of single proteins (e.g., procalcitonin, which is found in higher concentrations in septic versus non-septic patients, after burn injury) and combinations of different parameters (e.g., urinary and clinical parameters) as biomarkers during the first 72 hours post-injury [12]. Within the proposed biomarkers, lactate should be mentioned because some researchers have suggested that chances of survival increase if lactate levels return to normal values within the first 24 hours [13, 14]. Other authors have postulated different candidates, such as age, total burned surface area (TBSA), gender, serum creatinine levels, and cystatin C levels [15]. A review conducted by Carlton et al. [16] proposed a series of biomarkers for pediatric burned patients, which includes inflammatory mediators (chemokines), tissue repair mediators (structural proteins, growth factors), growth and development mediators (hormones and energetic/metabolism mediators, such as albumin, prealbumin, transferrin, apolipoprotein A1 (ApoA1)/high-density lipoprotein (HDL), and apolipoprotein B (ApoB)/low-density lipoprotein (LDL)), and stress markers [16]. The authors conclude that in order to translate these findings into diagnostic or prognostic tools, further research is needed, mainly because most of the studies failed to keep a daily register of laboratory parameters and because of the marked heterogeneity in the time in which samples were taken and the circadian variation of some of the mentioned parameters.

Concerning soluble mediators of the immune system, Tan et al. [17] described an immunoglobulin G (IgG) decrease in nine individuals sampled at days 1, 3, 7, 14, and 28 after burn injury. This study shows that IgG levels are diminished at the beginning of the register, have a minimum at day 3, and then recover to normal values after two weeks (day 14). Although this study provides substantial information, the severity of burn injuries of the volunteers is moderate (only three volunteers had a TBSA higher than 30%). According to the authors, all patients survived, impairing any analysis concerning a search for biomarkers of survival. Regarding IgG, Tan and collaborators cited the papers of Arturson et al. [18] and Munster et al. [19], and both studies were based on the IDR technique, a radial immunodiffusion procedure known to have low precision. Arturson and collaborators showed the results of only two patients explaining neither their TBSA nor the severity of their burns. Furthermore, therapy included the administration of gamma globulin between days 3 and 8 after burn injury, thus making it complex to conclude. However, Munster and collaborators described the decrease in IgG values but no statistical methods were described nor applied in their paper. Furthermore, patients were included in a "deceased group" (DG) for the analysis, but deaths were registered after day 60 post-burn injury, making it difficult to establish a correlation with initial biochemical parameters.

Although there are many reports concerning this matter, there is still an urgent need for new biomarkers in burned patients, in particular laboratory prognosis biomarkers, which would allow a close follow up of patient evolution in a fast, routine, non-invasive, and low-cost manner. In our laboratory, preliminary results indicate that some standard laboratory determinations might help to predict patients' prognosis, such as pseudocholinesterase [20], cholesterol (CHOL) [21], prothrombin, and V factor [22] serum levels. In this context, this study aimed to evaluate the usefulness of a set of laboratory determinations during the first ten days post-injury in acute burned patients, attempting to diminish the variability attributed by Carlton to the time of sampling, performing determinations on a daily basis and registering the extent of burn injuries. Laboratory determinations were chosen to reflect the immunological, metabolic, and nutritional status of the patients. The hypothesis was that an adequate comparison of daily laboratory results from patients with a positive outcome (survival and discharge) and patients with a negative outcome (death) would enable us to identify

determinations that might be used as biomarkers of prognosis in acute burned patients.

2. Materials and methods

2.1. Experimental design, patient cohorts

The study had a case-control design. Admission information from patients hospitalized in Hospital de Quemados Dr. Arturo Umberto Illia (HQAUI, Buenos Aires, Argentina) from 2016 to 2019 was collected, as well as the laboratory results of a standard set of parameters measured when the first blood sample was taken during patient admission at the hospital. The working dataset for this paper was completed by retrieving the results of a set of daily laboratory determinations during the following ten days of hospitalization.

The initial dataset was then refined by (the) inclusion and exclusion criteria. Inclusion criteria were men and women, above 18 years old, and hospitalized at the hospital's intensive care unit, from November 2016 to July 2019. Exclusion criteria were individuals with more than two days of evolution since the burn date when admitted to the hospital, below 18 years old, and patients with incomplete admission information or laboratory results (more than one laboratory result missing).

For this study, information concerning all deceased patients during the period 2016–2019 was included (DG), as well as information regarding all discharged patients during the same period, who met the inclusion criteria and were hospitalized for at least two days (survivors group, SG).

2.2. Admission information and laboratory measurements

Data concerning admission information included days of evolution since the burn date, age, gender, TBSA, the presence of inhalatory trauma, and the need for mechanical respiratory assistance (MRA). Laboratory determinations included total IgG, total immunoglobulin M (IgM), C-reactive protein (CRP), complement C4 protein (C4), total serum protein (TP), albumin, prealbumin, total CHOL, pseudocholinesterase activity (CHE), and transferrin. Measurements were conducted on fresh serum or plasma, using a Cobas 311 Analyzer (Roche Diagnostics, Basel, Switzerland) on a daily basis, at the same time (from 8 to 9 a.m.) during the complete hospitalization period.

2.3. Statistical analyses

All statistical analyses and comparisons were conducted using R (The R Foundation for Statistical Computing, Vienna, Austria) and Graph Pad Prism 9.0 (Graph Pad Software Inc, Boston, MA, USA). Statistical tests were chosen depending on the distribution of experimental data and the purpose of each comparison, which are described in the following paragraphs. In all cases, differences were considered significant with $p < 0.05$.

In order to analyze the usefulness of the selected parameters as potential prognosis biomarkers of acute burned patients, initial values of each parameter were compared between individuals with positive and negative outcomes (SG and DG, respectively). A corresponding statistical test was chosen first to evaluate the normality of distributions (using the D'Agostino-Pearson normality test and double-checking results with the Shapiro–Wilk test) and the homogeneity of variances (using Bartlett's test). In the cases in which distribution resulted to be normal, comparison between groups was conducted using a Student's *t*-test (with or without Welch's correction, depending on the homoscedasticity evaluation). Whereas, in the cases in which the distribution resulted to be non-normal, a comparison between groups was conducted using the two-tailed Mann–Whitney test.

Additionally, the correlation of initial values and the TBSA was studied for those parameters, which showed significant differences between groups at the beginning of the hospitalization period. In those analyses, correlation was studied using a Pearson correlation analysis (for parameters with normal distribution) or a Spearman correlation analysis (for parameters with non-normal distribution). When correlation was suspected, a linear regression analysis was conducted, adjusting data to a straight line and testing the significance of the slope and Y-intercept with an *F*-test.

When parameters showed promising results, a cut-off value was chosen and a confusion matrix was built to calculate the positive and negative predictive values (PPV and NPV, respectively).

The evolution of each parameter was studied to compare the two groups of patients. For each parameter and each patient group, measurements during the follow-up period were normalized according to an average value calculated from the initial measurements of that parameter. This strategy allows to express the progress curve of each parameter and each patient, as a ratio of the average initial value. Although this strategy underestimates initial differences among patients from the same group, it enables the understanding of the general behavior of each parameter during the follow-up period, diminishing the high interindividual variability that was detected at the beginning of the record. Then, statistical comparison between groups was performed by calculating the area under curve (AUC) for each patient and then conducting a Student's *t*-test with Welch's correction.

Also, as well as with the initial values, a cut-off value was chosen for promising parameters, and a confusion matrix was built to calculate the PPV and NPV, respectively. Furthermore, a "single-point" comparison between SG and DG was performed for promising parameters using *t*-tests for the results of each day.

This follow-up statistical analysis was not conducted with non-variable parameters (age, gender, TBSA, and days of evolution since the burn date).

3. Results

3.1. Patient cohorts: descriptive parameters

Initially, information corresponding to 53 patients was gathered, from which 12 had to be discarded as a consequence of incomplete data (admission information or more than one laboratory result missing), and 4 due to the evolution time since the burn date was longer than two days. Of the remaining 37 patients, 8 (21.6%) belong to the DG and 29 (78.4%) belong to the SG. The definitive patient cohort constituted of 11 women (29.7%) and 26 men (70.3%), ranging from 17 to 72 years old, with a median of 33 years. The percentage of TBSA ranged from 2% to 80%, and an initial analysis showed that patients with a TBSA lower than 30% did not die within the study period. For this reason, the 30% TBSA was further indicated in the figures, when needed. **Table 1** shows information about gender, age, TBSA, inhalatory trauma, MRA, the incidence of infection, and concomitant diseases of the cohort of patients.

Table 1 • Cohort of patients: descriptive parameters

	SG	DG	Total
Number of patients (%)	29 (78.4)	8 (21.6)	37 (100)
Age mean (and median)	38 (32)	37.12 (36)	36.56 (33)
Gender distribution (%, M/F)	69/31	75/25	70/30
TBSA (%) <10% 10–20% 20–50% >50%	21.7 24.1 31.0 41.4 3.4	55.5 0 0 50 50	28.1 18.9 24.3 43.2 13.5
Inhalatory trauma (%)	3.4	37.5	13.5
MRA (%)	37.9	75	48.6
Infection (%)	41.4	75	48.6
Concomitant diseases and conditions (number of cases)	Drug abuse (2) Alcohol and tobacco abuse (1)	Obesity and hypertension (1) Alcoholism (1) Morbid obesity and dyslipidemia (1)	

SG stands for the survivors group, and DG for the deceased patients group. The table includes information concerning the number of patients in each group, their gender, TBSA, the occurrence of inhalatory trauma, the use of MRA (patients were monitored by pulse oximetry), the incidence of infections during the hospitalization period, and the incidence of concomitant diseases on admission (the number of patients with each condition is indicated in parentheses).

3.2. Analysis of laboratory initial values

Analysis of admission information and initial laboratory values showed significant differences in the case of the following variables: TBSA, total proteins, albumin, C4, total IgG, and transferrin (see **Figure 1**).

When considering the incidence of infections during the hospitalization period, there is a significant difference between SG and DG ($p < 0.05$, one-tailed chi-square test). Given this difference, an attempt was made to establish the existence of a correlation between IgG levels and the incidence of infections by means of a contingency table, showing a significant association between IgG values under the normal lower limit informed by Roche, and the incidence of infection during the hospitalization period (one-tailed chi-square test, $p < 0.05$). The procedure was also conducted exploring the C4 parameter, and no correlation was found but a subtle tendency (lower values of C4 seem to be associated with the occurrence of infections).

In **Figure 2**, the correlation between the TBSA and each of the significant parameters included in **Figure 1** is shown. It can be clearly seen that—besides C4 complement protein—all individuals with laboratory parameters within normal ranges have good prognosis. Total IgG is the only study parameter, which has no dependence on the TBSA.

A cut-off value for IgG was calculated as the mean value of IgG from the DG, plus twice its standard deviation. The result (8.005 mg/dL), slightly higher than the lower normal limit reported by Roche (7 mg/dL), was used to classify all samples from both groups (SG and DG) into positive (higher than 8.005 mg/dL) and negative (lower than 8.005 mg/dL). A confusion matrix was built to calculate the PPV (0.55) and the NPV (0.88), suggesting that burned patients with an IgG value lower than 8.005 mg/dL have an 88% probability of mortality.

3.3. Results of progress analysis

The results of the AUC analysis of the regular register of laboratory parameters during the first ten days after injury are shown in **Table 2**, distinguishing each parameter and each group of patients (SG and DG). **Figure 3** shows the progression curves of each parameter having a significant behavior—in terms of differences among groups—during the first ten days after injury.

The selection of a cut-off value for the ten-day-AUC of total CHOL and for CHE (mean value of parameter results from the DG, plus 1 standard deviation) enabled the construction of a confusion matrix and the calculation of the predictive values. For total CHOL, PPV was 0.5 and NPV was 0.86, indicating that an AUC under the cuff-off during the first ten days implies an 86% probability of mortality. For CHE, PPV and NPV were 0.48 and 0.86, respectively, and the analysis is similar to that of total CHOL.

Additionally, the results of total CHOL and CHE were compared between the SG and the DG each of the first ten days of hospitalization to explore whether data from a "single point" might provide sensitive information. The comparison was performed using multiple *t*-tests, but the results were not significant.

The implications of both AUC analyses and single-point comparisons are further analyzed in the next section.

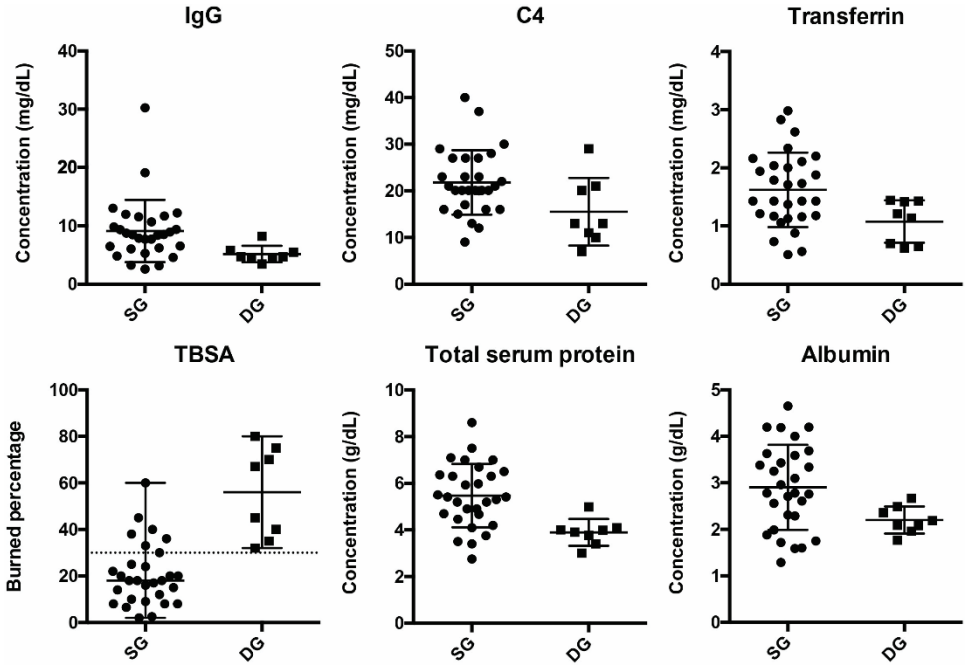

Figure 1 • Analysis of initial laboratory values. Panels correspond to variables, which show statistically significant differences ($p < 0.05$) among groups. Results are expressed as median and range. In the TBSA panel, the dotted line indicates a critical value (30%) with a high association with survival, as it was described in the "Patient cohorts" section. DG stands for the deceased group ("filled black squares"), SG for the survivors group ("filled black dots"), and C4 for the C4 complement protein. Variables that had no significant difference are not shown (prealbumin, total immunoglobulin M, C-reactive protein, and pseudocholinesterase).

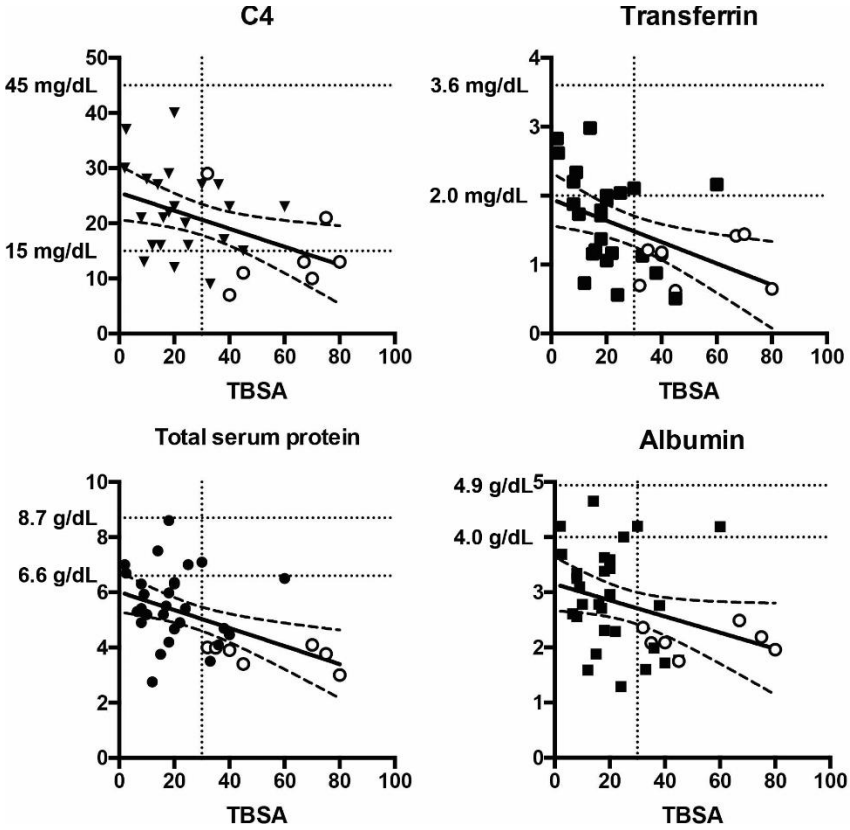

Figure 2 • Correlation of TBSA and laboratory initial values. Panels correspond to the variables, which have statistical dependence on the TBSA. In all panels, the vertical dotted line indicates a 30% TBSA, which arises as a critical value, as it was described in the "Patient cohorts" section. The horizontal dotted lines show the upper and lower limits of the normal range for the given parameter. Black symbols correspond to patients from the SG, and white dots correspond to patients from the DG. Some laboratory results are missing due to incomplete records, depending on the measurement, but no patient had more than one value missing, according to the exclusion criteria. Panels also show the adjusted regression line (continuous lines) and its 95% confidence intervals (slashed lines). DG stands for the deceased group, SG for the survivors group, and C4 for complement C4 protein. Variables with no correlation with the TBSA are not shown (total immunoglobulin G, prealbumin, total immunoglobulin M, C-reactive protein, cholesterol, and pseudocholinesterase activity).

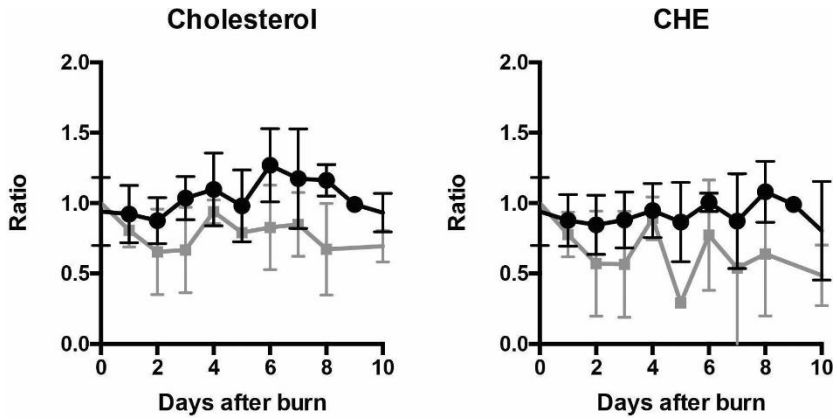

Figure 3 • Progression curves of parameters with significant variation during the first ten days after injury. The figure shows the progression curves for the parameters that had significant differences during the first ten days after injury. The round black dots indicate patients with a positive prognosis (SG); the square gray dots indicate patients with a negative prognosis (DG). All the other parameters maintained the ratio observed at the beginning of the register (data not shown).

Table 2 • Progress analysis during the first ten days after injury

	SG			DG			*p*
Parameter	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	
Total immunoglobulin G	3.23	2.30	29	2.57	2.39	8	0.50
Total immunoglobulin M	3.53	2.05	29	4.20	5.31	8	0.74
Complement C4 protein	1.49	1.12	29	1.79	1.43	8	0.59
Total proteins	0.92	0.78	29	1.01	1.00	8	0.82
C-reactive protein	15.90	34.75	29	18.29	17.45	8	0.79
Albumin	1.21	0.92	29	0.85	0.47	8	0.14
Prealbumin	4.04	4.17	29	3.18	3.24	8	0.55
Transferrin	1.74	1.21	29	1.45	1.26	8	0.56
Cholesterol	2.05	1.37	29	1.17	0.48	8	0.01
Pseudocholines-terase activity	3.27	1.38	29	2.07	1.23	8	0.03

The exact *p* corresponds to a Student's *t*-test with Welch's correction performed with the AUC indicated in the table. The results indicate that the only parameters that display a differential behavior among SG and DG patients—during the first ten days after injury—are the total CHOL and CHE (which tend to decrease in the patients with a negative prognosis, the DG). SG stands for the survivors group, and DG for the deceased group. The other parameters showed no difference among groups either by preserving the initial differences (total proteins, albumin, C4, IgG, and transferrin) or displaying similar changes among groups during the first ten days (prealbumin, IgM, and RCP).

4. Discussion and conclusions

The present study was conducted at the HQAUI, a specialized medical center with a low-to-moderate flux of patients and a very low death rate. Furthermore, data recording starts when patients are received at the hospital for allowance but not all of them arrive with the same evolution time since the burn day. Thus, this is a heterogeneity, which cannot be controlled in a study like the present one, leading to an increased dispersion of the initial values, possibly underestimating some of the real differences among groups. Also, the severity of burns combined with the variable TBSA value among patients, as well as the medical background of each individual, constitutes an additional source of variability, thus making it hard to analyze the progression curves. For all these reasons, inclusion/exclusion criteria had to meet reasonable possibilities, the progression curves were analyzed only for the first ten days of hospitalization, and data treatment had to be implemented to overcome the intrinsic heterogeneity of experimental data.

Burns are complex processes, and the behavior of different serum proteins within the first days of evolution depends on several factors, like their increased rate of synthesis, the catabolic state induced by the injury, and the alteration of vascular permeability that characterizes the first hours after burn. Clear consequences of these phenomena are the decrease in albumin levels [23] and the concentration of blood cells (leukocytes and RBC), with the concomitant increase in hematocrit and hemoglobin in blood samples. During the following days, the alteration of laboratory parameters is a consequence of these initial events and a combination of other factors that gain relevance, such as nutritional, metabolic, and septic mechanisms.

As it was stated at the beginning, the objective of this paper was to analyze the ability of some parameters within a set of laboratory determinations to behave as early biomarkers of patient prognosis, which would allow an opportune therapeutic intervention. The results of this study indicate that, within the selected set of determinations, some measurements display significant differences among groups at the beginning of hospitalization but most of them depend on or are closely related to the TBSA. Although the measurement of these TBSA-linked laboratory parameters does not add substantial information regarding patient prognosis, they should not be neglected because some authors indicate that TBSA might be imprecise when the burned surface is

small [24]; thus, these parameters could be used for a less subjective estimation of the initial severity of burns and include albumin, C4, and transferrin. All of these are predominant serum proteins, which together sum up to more than 80% of total proteins, a parameter that can also be included in this group.

The outstanding exception to this apparent link was the measurement of total IgG, which shows a diminished value at the beginning of the record for patients within the DG. As total IgG behaves independently of the TBSA value, it seems to be a valuable and complementary parameter. Using a cut-off value (8.005 mg/dL) slightly higher than the lower normal reported by Roche Diagnostics (7 mg/dL), the PPV and NPV were calculated, showing that burned patients with an IgG value lower than 8.005 mg/dL have an 88% probability of mortality. Furthermore, progress curves show that the difference in the total IgG value among groups remains constant during at least the first ten days after injury.

Although a large-scale study would be needed to clarify the underlying mechanism, the initial alteration of total IgG levels could be due to gross vascular permeability alteration, and the sustained low levels during the following ten days could be due to nutritional factors. It is well known that total IgG concentration is sensitive to nutrient alterations, such as oligo-element deficiencies [25], and it has also been stated that burned patients have increased requirements of these, possibly due to the large tissular loss and the elevated catabolism, thus needing a special requirement of vitamin A, vitamin C, and zinc [26]. The IgG and C4 deficit might lead to a state of immune compromise that increases the odds of sepsis; in fact, our study demonstrated that the incidence of initial low levels of IgG has a statistical correlation with the incidence of infection and the inclusion of patients within the DG. In turn, this evidence suggests that those immune deficiencies might be controlled by adequate supplementation with gammaglobulin, vitamins, and oligo-elements.

Progression curves of laboratory parameters during the first ten days indicate that the total CHOL concentration and CHE are good prognosis markers, given that both parameters show a significant decrease during the registry in the DG. The results concerning CHOL and pseudocholinesterase are in accordance with the literature and our own preliminary findings, published in short communications during specific congresses [20–22]. Lipid alterations after injuries have been known for more than 40 years, as it has been reported in 1979 by Coombes et al. [27]. In that case report, the authors hypothesize that lipid alteration might be due to an impaired metabolism, mainly of very low-density lipoprotein (VLDL) to LDL, an impairment that has been also indicated by other authors, such as Clayton et al. [28] and Clark et al. [29]. However, Miquet et al. [30] described an inflammatory cytokine-dependent decrease in CHOL as an adaptive response to trauma, but nevertheless they state that when CHOL falls below certain levels it could cause undesirable effects on the evolution of the patient. This latter phenomenon—the linkage between CHOL levels and patient outcome—is what Vanni et al. [31] also indicated when showing that lower values of CHOL have a strong correlation with longer hospitalization periods.

Pseudocholinesterase is a serine hydrolase primarily produced in the liver, known to catalyze the hydrolysis of choline esters, although its complete role in metabolism is still not understood. The reports concerning its decrease after acute burn are abundant, like the ones of Viby-Mogensen et al. [32] (who proved an 80-fold decrease about four to five days after the burn date), Frolich [33] (who noticed the relevance of CHE decrease for proper degradation of some muscle relaxants such as suxamethonium, commonly used during surgical interventions of burned patients), and Kamolz et al. [34] (who showed that patients with inhalation trauma have lower levels of CHE than patients without lung injury). This difference also reflects the course of illness after a burn injury. These authors stated that the possible mechanisms for this decrease are augmented catabolism and hepatocellular damage and also indicated that CHE decrease is worsened when inhalation trauma occurs.

Both total CHOL and CHE showed normal average values at the beginning of the hospitalization period similar in both the SG and DG (SG: CHOL 123.3 mg/dL, CHE 5481 IU/L; DG: CHOL 123.2 mg/mL, CHE 5281 IU/L), but patients in the DG showed a progressive decrease during the next ten days. This decrease could be quantified using the AUC of the ten-day period, but could not be proved significant by comparing day-to-day results, possibly due to insufficient data. No statistical correlation was found between the incidence of inhalatory trauma and the CHE decrease.

We consider the results presented here to be substantial findings and propose the measurement of total IgG as a prognostic biomarker, as well as CHO levels and CHE activity, which in combination might provide useful information for proper medical intervention. Initial measurement of other serum preponderant proteins (TP, albumin, C4, and transferrin) might also help during the initial evaluation of the severity of burns. Concerning CHO and CHE, larger studies should be carried out to explore their daily variation.

Abbreviations

AUC: area under curve

C4: Complement C4 protein

CHE: pseudocholinesterase activity

CHOL: cholesterol

DG: deceased group

IgG: Immunoglobulin G

IgM: Immunoglobulin M

MRA: mechanical respiratory assistance

NPV: negative predictive value

PPV: positive predictive value

CRP: C-reactive protein

SG: survivors group

TBSA: Total burned surface area

TP: total serum proteins

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Author contributions

Conceptualization, A.F., L.D.C., S.S., M.H., O.P. and M.A.G.; methodology, A.F., L.D.C., S.S. and M.A.G.; formal analysis, A.F., L.D.C., S.S. and M.A.G.; technical procedures, A.F., L.D.C., S.S., M.H., O.P. and M.A.G.; resources, M.A.G.; data curation, A.F.; writing—original draft preparation, A.F.; writing—review and editing, A.F., L.D.C., S.S. and M.A.G.; supervision, M.A.G. and A.F.; project administration, M.A.G. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data supporting these findings are available within the article, at https://doi.org/10.20935/AcadBiol6243, or upon request.

Institutional review board statement

All procedures on patients were conducted under the standard protocols of the HQAUI, and all the analyses in this work were approved by the Ethics Committee of the HQAUI in 2020. Once approved, the project implied the retrieval of all the information from physical files—information that had not been digitalized yet—and the search for a significant set of records matching the inclusion criteria stated in the corresponding section of this paper. The COVID-19 pandemic of 2021 prevented the progress of the project until late 2022.

Informed consent statement

A written consent is always signed at HQAUI by all patients (or guardians) allowing the use of personal and medical information for scientific purposes.

Sample availability

The authors declare no physical samples were used in the study.

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