TRABAJO FIN DE GRADO

Grado de Medicina

ASSOCIATION BETWEEN ORGAN DYSFUNCTION AS MEASURED BY THE SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE (SOFA) AND ADVERSE OUTCOMES IN PATIENTS WITH TOXIC EPIDERMAL NECROLYSIS (TEN) ADMITIED TO THE BURN ICU OF THE HOSPITAL UNIVERSITARIO DE GETAFE.

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I wanted to thank, overall, my dog, and Dr. Lorente. Also those who have been by myside unconditionally, like my parents, family, friends and Raquel. But, overall, my dog, Cinta.

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1. ABSTRACT:

BACKGROUND: Cutaneous adverse reactions range from mild manifestations to severe conditions such as Toxic Epidermal Necrolysis (TEN), with drugs causing up to 94% of the cases. The estimated mortality rate for TEN is approximately 30%, with sepsis associated with multiorgan failure or respiratory compromise being the main causes of death. Despite this, the SCORTEN scale, validated for predicting mortality in these patients, does not incorporate organ failure as a parameter of its evaluation. The hypothesis stated that the presence of organ dysfunction is associated with mortality and unfavorable outcomes in patients with toxic epidermal necrolysis.

MATERIAL AND METHODS: An observational, retrospective study was conducted in patients over 18 years diagnosed with TEN and treated in Hospital Universitario de Getafe. Clinical data was collected through the clinical history in HCIS and/or requested to the archive of the Hospital.

RESULTS: Of the 84 patients included, 16 died (19%), of which 2 were early deaths, and the remaining 14 were late deaths. The median age of the patients was 50 (34.25-65). The median SCORTEN was 3, and the median affected skin surface (%) was 75% [Interquartile Range (IQR) 50-90] with a mean length of stay of 13.85 days [95% Confidence Interval (CI) 6.74-26.49] hospitalized in the Burn ICU. Significant differences were identified between the age, skin surface area affected, APACHE II, SAPS II, SCORTEN II, and SOFA from days 0 to 4 of the survivors and those who exhibited late mortality; in addition to a significantly higher presence of cardiovascular, respiratory, and renal failure in the latter one. A higher incidence of infections was also observed in patients with organ failure. The ratio (fluid input/diuresis) on day +2 in the ICU and arterial pH on day +1 were significantly different between patients who survived and those who experienced late mortality, showing the highest Area Under the Receiver Operating Characteristic (ROC) Curve (AURC) among all variables analyzed. Additionally, arterial pH on day 1 greater than 7.353 was identified as the variable with the highest sensitivity and specificity for discriminating between survivors and patients with late mortality, supported by an Odds Ratio (OR) of 9.646 (95% CI 2.578-34.746).

CONCLUSION: Organ failure frequently complicates the course of TEN, exhibiting an independent correlation with mortality measurable by the SOFA scale. Mortality prediction improves when considering variables like age, affected body surface area, and variables related to resuscitation (ratio fluid input/diuresis and arterial pH during resuscitation). Adjusted predictive models, such as those considering age, affected skin surface area, APACHE II, and

arterial pH on day 1, have been found to discriminate mortality more effectively than the SCORTEN method.

KEYWORDS: Mortality, TEN, Organ failure, SCORTEN, SOFA, predictor, Lyell Syndrome.

2. INTRODUCTION:

Cutaneous manifestations are one of the most frequent Adverse Drug Reactions (ADR). Cutaneous involvement may vary from an appearance limited to a small area of erythema to the most severe (although rare) form corresponding to Toxic Epidermal Necrolysis (TEN), also known as Lyell's Syndrome (1).

The incidence of cutaneous adverse drug reactions ranges from 3-15% of generically reported ADRs (1,2). However, there is a difference between the incidence of these ADRs in hospitalized patients (10-20%) and in outpatients (3-7%) (2,3,4). It should be emphasized that severe involvement represents only between 0.1-0.3% of reported cases (1,3). In these cases, which may not seem alarming in percentage terms, the mortality association increases, reaching up to 30% in TEN, with sepsis associated to multi-organ failure or respiratory compromise being the main causes of death (3,5).

Cutaneous adverse reactions, as previously mentioned, correspond to a wide range of manifestations in which, among the different ways of classifying them, emphasizing the distinction between non-immune and immune reactions. The latter can be subdivided into the most common reactions, such as maculopapular eruptions, pruritus, urticaria... and the rare and severe ones, such as DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome, DHIS (Drug-induced Hypersensitivity Syndrome) and SJS (Steven-Johnson Syndrome) / TEN , on which this study focused (2).

TEN is a type IVc autoimmune reaction *[Image 1* (6)] (mediated by cytotoxic T lymphocytes with release of cytotoxic mediators, characteristically Granulosin, which causes apoptosis of keratinocytes and secondary epidermal necrosis) (2), triggered in 80-90% of the cases by drugs (7) among which the drugs with higher association and risk are allopurinol and cyclooxygenase-2 inhibitors. Other drugs with increased risk but less association include proton pump inhibitors, fluoxetine, mirtazapine, and sulfasalazine, whereas no association has been found between oxycam, benzodiazepines, citalopram, paroxetine, venlafaxine, and 5-phosphodiesterase inhibitors and TEN/SJS (8). In a much smaller percentage of cases, it has not been possible to exclude the possibility that infections of viral origin or Mycoplasma Pneumoniae may have triggered the disease (1).

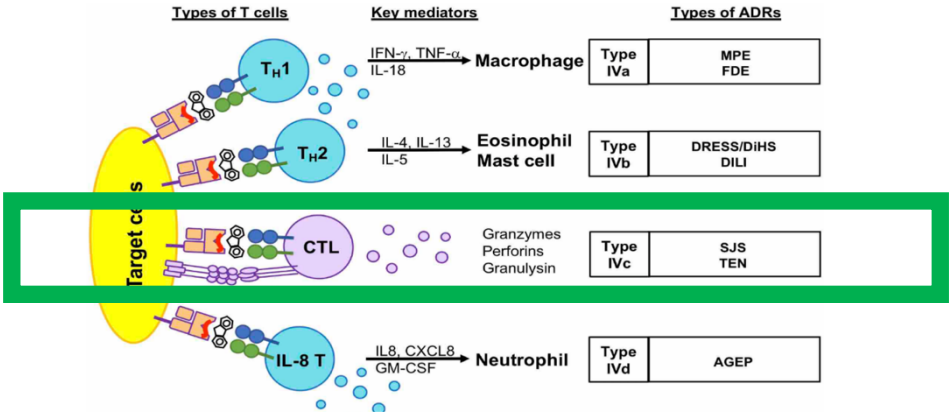


Image1: Types IV of Autoimmune reactions.

The pathophysiology of this phenomenon is based on a drug-specific reaction in which there is a presentation of the drug metabolites through the HLA complex, causing an exacerbated activation of cytotoxic T lymphocytes, Natural Killer and Th17 cells, and the release of inflammatory molecules that exert a direct toxic role on keratinocytes, causing their apoptosis and subsequent epidermal detachment [*Image 2* (9)]. Certain risk factors have been associated, such as some HLA polymorphisms in specific populations (B*1502 and Carbamazepine or B*5802 and allopurinol), HIV infection, active cancer, radiotherapy treatment, ethnicity black or Asian people being at higher risk) (1,10). Clinically, there is an incubation period of up to 4 weeks between ingestion of the drug and appearance of skin lesions. These are preceded, up to 90% of cases, by a nonspecific prodrome, followed 1-3 days by the appearance of atypical lesions and/or purpuric macules, which may coalesce to form a confluent erythema lasting up to 7 days [*Image 3 (*11)]. This phase is continued by the appearance of flaccid vesicles in the affected areas without a specific duration, but which eventually causes the detachment of the epidermis on light digital pressure (Nikolsky's sign). This process can occur on both mucous membranes or skin and can be differentiated according to the percentage of affected area: SJS <10%, SJS-TEN overlap 10-30%, TEN/Lyell Sd. >30%, with mortality increasing directly with the percentage of affected surface (3,8). Mucous involvement [*Image 4* (12)] in various areas is very common, being the oropharynx the most frequently affected (93%), followed by ocular location (78%) and the genital region (63%). However, complications may affect other organs, such as kidneys (glomerulonephritis or acute tubular necrosis), liver (hepatitis and hepatocellular necrosis) and other systemic manifestations (hypoalbuminemia, leukocytosis, leukopenia, hyperamylasemia or normochromic and normocytic anemia).

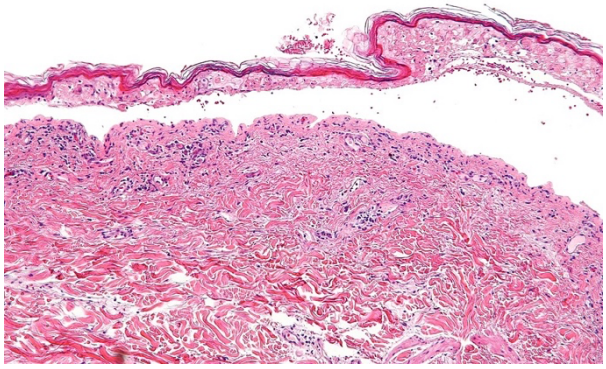


Image2: Microscopic view of epidermal detachment in TEN.

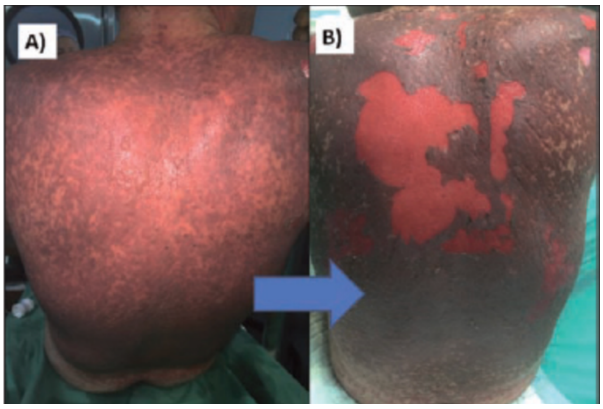


Image3: Evolution of TEN skin lesions into a confluent erythema (Nikolsky's sign (+))

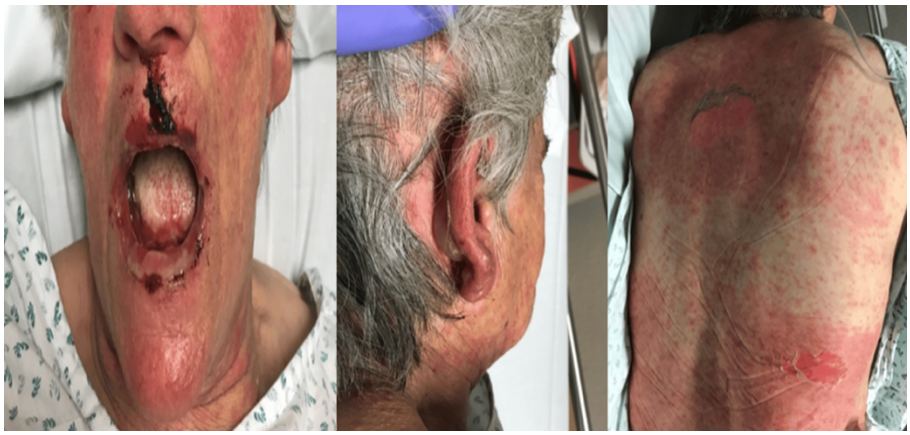


Image4: Mucocutaneous affection in TEN.

The management of these patients is of significant importance and complexity, requiring a multidisciplinary approach. The treatment plan is predicated on four fundamental pillars: life support, systemic therapies, surgical debridement, and topical treatment. The patient should be admitted to the burn intensive care unit (BICU). To provide adequate support, it is necessary to initiate fluid resuscitation with lactated Ringer's solution and provide nutritional support, given the intense catabolic and metabolic activity that is taking place. The medication suspected of

causing the condition should be immediately ceased, and analgesia should be initiated. It is imperative to emphasize that the administration of antibiotics is not initiated in the absence of suspicion for sepsis (13). In addition to these measures, the initiation of immunosuppressive therapy is indicated. In such cases, a definitive guide is not available, but several studies have been conducted on the subject. However, these studies have not yielded any evidence to support a decrease in mortality when using corticosteroids or Intravenous Immunoglobulins (IVIG). A recent study has demonstrated that the administration of etanercept, a TNF-alpha inhibitor, at doses ranging from 25 to 50 milligrams twice weekly until the healing of lesions, has been observed to result in a decrease in mortality among patients diagnosed with TEN when compared to patients treated with corticosteroids. No superiority was demonstrated when comparing the use of IVIG and the use of Cyclosporine A (14). Nonetheless, In many specialized medical centers, Cyclosporine has been identified as the preferred treatment option for patients with this particular pathology. Previous studies have demonstrated its efficacy by showing a significant reduction in the time required to arrest disease (24-36 hours) and to achieve re-epithelization when compared to historical controls. Additionally, the use of Cyclosporine has been associated with a reduced mortality rate when compared to the predictive mortality rate. (15). The surgical approach is based on debridement of the necrotic epidermis under general anesthesia. The exposed dermis should be covered with synthetic dressings (Biobrane) and biological dressings (homograft, porcine xenograft skin). This allows for more precise management of analgesia, reduced fluid loss, and enhanced healing. It is important to protect the viable dermis to expedite re-epithelialization through the proliferation of basal keratinocytes from the skin appendages and to prevent infection; to do so topical antimicrobial agents such as sulfadiazine cream, silver nitrate solution, and chlorhexidine gluconate solution are used (14).

Initial fluid resuscitation is a cornerstone in the management of these patients. They undergo massive intravascular fluid loss through the affected skin, which has lost its barrier function; therefore, intravenous fluid administration to maintain volemia and cardiac output is essential to improve survival. However, recent studies in critically ill patients have shown that excessive fluid resuscitation, especially when administered at high rates that may cause adverse effects, is associated with increased mortality. Therefore, careful monitoring of fluid volume is crucial to avoid both overload and deficit, thereby preventing organ hypoperfusion and potential multiorgan dysfunction (16,17,18).

SCORTEN (SCORe of Toxic Epidermal Necrosis), based on 7 parameters measured in the first 24 hours after admission, has been validated to predict mortality in these patients (7). However, organ involvement or failure is not considered in this scale, being this one of the main

factors involved in the death of the patients. The most affected organs are described to be the lungs (19), followed by the kidneys (20). The importance of controlling the function of the various systems is such that treatment is not only based on early withdrawal of the offending drug, wound care and systemic treatment with cyclosporine, but also includes continuous monitoring of organ parameters (such as creatinine, PaO2/FiO2, platelets…) and adjustment of life support according to them (7). These variables, are, at the same time, the different features measured in the SOFA score (respiratory, coagulation, liver, cardiovascular, central nervous, and renal). This clinical tool will let the physician evaluate the degree of the organ dysfunction based on a 0-24 score (21,22). There is scarce literature relating the SOFA score to mortality in patients with TEN, although it is supported in patients who have suffered major trauma, patients admitted to the Burnt Intensive Care Unit (BICU) with major burns (23), and in critically ill (non-burned) patients admitted to the BICU, where the highest and average SOFA scores during admission and first 48h are associated with mortality (24).

Although in other areas of Intensive Care Medicine the utility of describing organ dysfunction and its association with poor outcomes has been demonstrated, this has not yet been confirmed in patients with TEN. Moreover, in this group of patients, the characteristics of fluid resuscitation and their correlation with adverse outcomes have neither been studied nor described. For this reason, the present study was conducted.

3. HYPOTHESIS AND OBJECTIVES:

- **Hypothesis:**

The SOFA score is a reliable prognostic tool in patients with TEN, although it is not a specific scale for this disease (23).

- **Objectives:**
    - **Primary:**
        - To evaluate the association of organ dysfunction during the resuscitation phase with unfavorable outcomes (infection, death).
    - **Secondary:**

1. Characterization of patients:
    - Describe the sociodemographic characteristics of the patients studied (sex, age, affected skin surface,
    - Describe the percentage of skin and mucosal involvement.

2. To analyze the predictive capacity of mortality scales commonly used in critically ill patients.

3. To describe a multivariate model predictive of mortality.

4. To define the relationship between the quality of initial resuscitation and mortality.

4. METHODOLOGY:

- **Study design:**

This was an observational, longitudinal, descriptive-analytic, retrospective study.

- **Environment and population studied:**

Patients affected by SJS/TEN who had been admitted to the burn unit of Hospital Universitario of Getafe between January 1992 and December 2014.

- Inclusion criteria:
    - Patients over 18 years.
    - Diagnosed with SJS/TEN.
    - Drug identified as the trigger of the SJS/TEN.
    - Admitted to the burn unit of Hospital Universitario of Getafe between January 1992 and December 2014.
- Exclusion criteria:

- Missing daily follow-up data charts.
- Latter dismiss of SJS/TEN diagnosis after further complementary tests.

- **Sample size:**

Assuming an alpha error of 0.05 (95% confidence level) and a statistical power of 80%, which allows detection of a high relationship between the SOFA score and mortality (OR of 3) and considering an event rate of 30% (mortality in patients with TEN), a minimum of 52 participants were required for this study. These data were calculated under the assumption of a strong association between the SOFA score and mortality in this specific population.

- **Data collection:**

A pseudonymized database was used. The clinical tutor had the clinical history number in a private database, as well as a number assigned by the order of the patient study. The variables were collected through the clinical history in HCIS and/or requested from the hospital archive to have them on paper. All these anonymous data, together with the number assigned to each patient at the beginning of the order, was the database managed by the student.

- **Variables:**

The main variables studied were the SOFA value in the different systems with an assessment of respiratory function (PaO2/FiO2), coagulation (platelets), liver function (bilirubin), cardiovascular system (mean arterial pressure), nervous system (Glasgow scale), and renal function (creatinine). Organ failure is determined by a value >2 points on the system studied according to the SOFA Scale (annexed at the end). Mortality was also collected as a dichotomous variable (yes/no).

The secondary objectives of the study necessitated the collection of additional data, including the patients' sex (female/male), age, expressed in integer values, and place of origin upon admission to the burn unit. The categories of place of origin included previous hospitalization in Getafe, domicile in Madrid, or hospital or domicile outside Madrid. The affected body surface area was also collected as a discrete quantitative variable, as was the duration in days of admission to the BICU. The study also examined the presence of sepsis as a qualitative dichotomous variable (Yes/No); the administration of corticosteroids prior of after the diagnose of TEN (qualitative dichotomous variable: Yes/No); the scores of SCORTEN, APACHE II, and SAPS II; the necessity for mechanical ventilation (early within the initial 72 hours of admission to the BICU [Yes/No]) and subsequently (after 72 hours of admission); and the absolute values of the aforementioned variables. Resuscitation-related values such as diuresis, hydric intake or hydric balance were also measured daily during the first 4 days, and metabolic

variables such as bicarbonate, pH and base excess, also during the first 4 days of admission. All these values were collected as continuous quantitative variables. Finally, adverse outcomes such as pneumonia, bacteremia, skin and urinary tract infections were recorded as dichotomous qualitative variables (Yes/No) in each patient.

- **Statistical analysis plan:**

Initially, a descriptive analysis of the variables was carried out. Qualitative characteristics were presented in terms of both absolute (n) and relative (%) frequencies, as well as the corresponding CI. Quantitative characteristics were analyzed to determine whether they follow a normal distribution; those following a normal distribution were described using the mean and standard deviation, while those with a non-normal distribution were summarized using median and interquartile range (IQR).

The determination of whether there is a relationship between the SOFA score and mortality in patients with TEN was be carried using the Student's-t test or U-Mann-Whitney according to the distribution the data.

To identify factors independently associated with mortality, a multivariate logistic regression model was performed. Given the limited number of fatal events, a maximum of 2 variables were included (following the rule of 1-2 variables per 10 events). A backward elimination strategy was used, in which variables were removed one by one and the OR [of the main variable of interest] was calculated, alongside with its 95% CI. If its OR variation was over 20% after removing a covariate, that covariate was considered a confounder and kept in the final model. The discriminative ability of the different variables and models was assessed using the area under the receiver operating characteristic (ROC) curve. A difference from the null hypothesis (area = 0.5) was considered statistically significant when $p < 0.05$.

All statistical analyses were carried out using Jamovi 2.2.2.

- **Ethical and legal aspects:**

The present study has been approved by the ethics committee of Hospital Universitario de Getafe, with the reference code CEImTFG81/24 (TFG_CEIM_24/81), whose document is attached at the end of the project. It must be noted that the present study was granted a waiver of the requirement of obtaining informed consent from participants, as it had previously received approval from the relevant ethics committee.

The work was executed in accordance with the established bioethical regulations, as delineated by the Helsinki Declaration, the Belmont Report, and the Oviedo Convention.

Additionally, it was conducted in compliance with the principles outlined in the Declaration of Helsinki, the Belmont Report, the Oviedo Convention on Human Rights and Biomedicine, and the legislation stipulated by Law 14/2007 of July 3, 2007, which pertains to biomedical research.

The management of patients' personal data has been executed in accordance with Organic Law 3/2018 of December 5, 2018, which stipulates the Protection of Personal Data and the Personal Data Protection and Guarantee of Digital Rights. This legislation is further complemented by Law 41/2002 on Patient Autonomy, which pertains to the Patient Autonomy Law 41/2002 regarding the utilization of the clinical history. Additionally, the Biomedical Research Act 14/2007 of November 14, 2007, which governs patient autonomy and the autonomy, rights, and obligations concerning clinical information and documentation, has also been considered.

5. RESULTS:

A total of 87 patients were selected for inclusion in the study. These patients were treated and hospitalized at the University Hospital of Getafe with a diagnosis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) between 1992 and 2014 (inclusive). Of the patients included in the study, a total of 3 were excluded from the analysis. Two of these were excluded due to the absence of follow-up charts during admission or incomplete data collection. The third patient was excluded because the final diagnosis recorded at discharge and after treatment differed from the initial diagnosis of TEN. Subsequent to the exclusion of the aforementioned three patients from the study, the final sample size was determined to be 84.

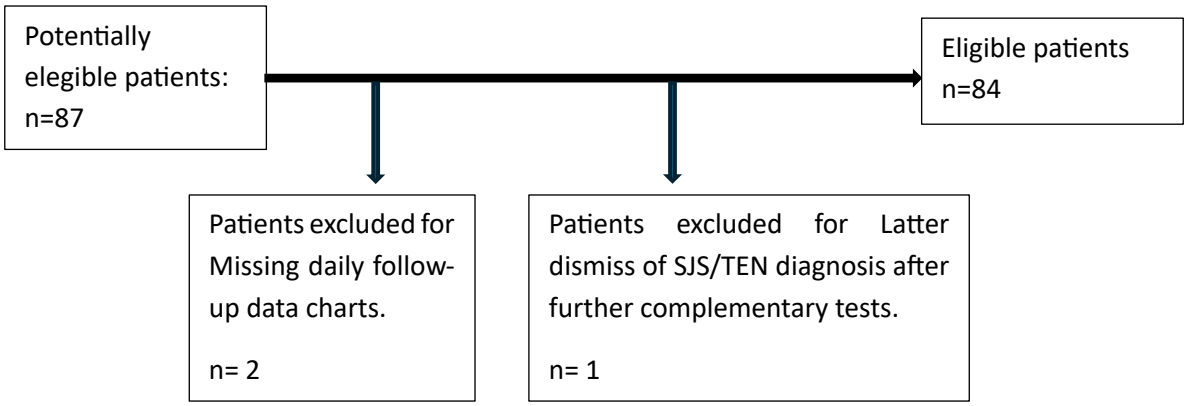


Figure 1: Flow chart of patients under the diagnosis of SJS included in the study.

5.1 DESCRIPTION OF THE CLINICAL-PATHOLOGICAL CHARACTERISCTIS OF PATIENTS DIAGNOSED WITH TEN:

Among the 84 patients included in the study, 57% were women. The body surface area (BSA) affected ranged from 50% to 90%, with a median of 75%, and the mean length of stay in the BICU was 13.85 days (95% CI 6.74–26.49 days).*Chart 1* provides a summary of the main clinical and pathological characteristics of the patients. This includes the incidence of infections during their stay in the BICU, the use of mechanical ventilation, which was required in 47 cases (56%), and various severity measures: Organ dysfunction, defined as present when the SOFA scale score exceeds 2 points; scores on the APACHE II, SAPS II, and SCORTEN scales and the fatal outcome (mortality), which occurred in 19% of cases (16 patients).

Chart 1: ***Sociodemographic characteristics of the sample studied and clinicopathological characteristics related to mortality in NET patients.*** *Values are expressed as median (interquartile range), with parentheses indicating the IQR unless otherwise noted. In the case of absolute frequencies, parentheses indicate the corresponding percentage.*

		Study sample (n=84)
Clinical features	Age (years)	**50.00 (34.25-67.00)**
	Sex (women)	**48 (57%)**
	Percentage of affected skin surface	**75.00 (50.00-90.00)**
	Mean length of stay in BICU (days)*	**13.85 (6.74-26.49)**
Infections	Sepsis of cutaneous origin	**16 (19%)**
	Bacteremia	**26 (31%)**
	Pneumonia	**28 (33%)**
	Urinary tract infection	**14 (17%)**
Need for mechanical ventilation		**47 (56%)**
Early (≤ 72 h)		**35 (42%)**
Late (> 72 h)		**12 (14%)**
Mean duration of ventilation (days) (n=47)*		**15.66 (9.86-27.10)**
Organ dysfunction		
Cardiovascular (SOFA >2)		**24 (28%)**
Respiratory (SOFA >2)		**24 (28%)**
Renal (SOFA >2)		**10 (12%)**
Hepatic (SOFA >2)		**4 (5%)**
Hematologic (SOFA >2)		**8 (10%)**
Arterial pH day 1		**7.420 (7.360-7.450)**
SOFA day 0		**1.00 (0.00-4.00)**
SOFA day 1		**2.00 (0.00-4.00)**

SOFA day 2		**2.00 (0.00-5.00)**
SOFA day 3		**2.00 (0.00-5.00)**
Severity scores	APACHE II	**13.00 (11.00-16.00)**
	SAPS II	**35.00 (28.00-45.75)**
	SCORTEN	**3.00 (2.00-3.00)**
Mortality		**16 (19%)**
Early (≤72 h)		**2 (2,4%)**
Late (>72h)		**14 (17%)**

**Asterisk indicates that the values correspond to the 95% CI instead of the IQR.*

5.2 ASSOCIATION BETWEEN CLINICAL VARIABLES AND ORGAN DISFUNCTION WITH MORTALITY.

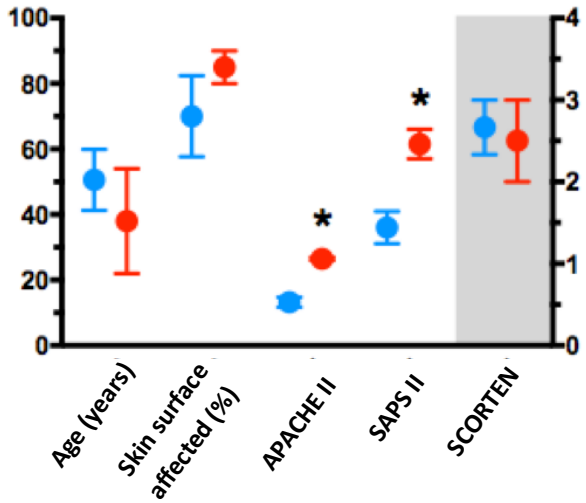
➔ **Early death (<72h):**

These two graphs compare the characteristics of patients with early mortality (<72 hours), represented in red, and survivors, represented in blue.

In *Graph 1*, patients with early mortality showed higher scores in APACHE II, and SAPS II compared to survivors. However, no significant differences were observed in SCORTEN, age, or affected surface area.

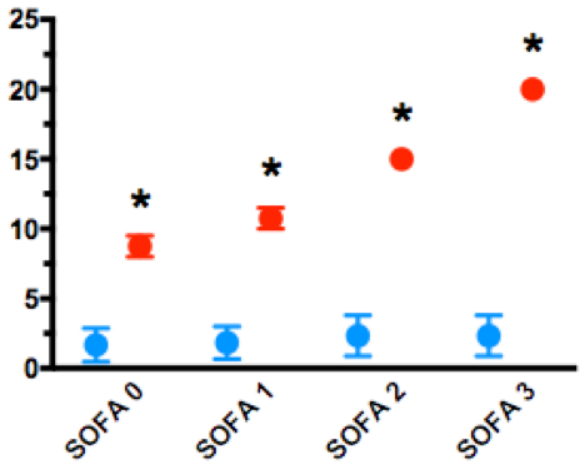
Graph 2 depicts the SOFA scores on days 0, 1, 2, and 3 of admission. Across all four days, the SOFA scores differed significantly between the two groups.

Graph 1: Mortality related variables in early death cases.



Blue represents survivors. Red represents deceased. Asterisks indicate statistically significant differences between groups according to the Mann–Whitney U test ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

***Graph 2*: SOFA scores in days 0 to 3 in early death cases.**



Blue represents survivors. Red represents deceased. Asterisks indicate statistically significant differences between groups according to the Mann–Whitney U test ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

The following chart (*Chart 2*), shows the cases of early deceased versus the remaining patients, stratified according to organ dysfunction; to compare both groups a Fisher test was carried out. Additionally, the OR is provided in each of the stratum as a measure of the strength of association. This, allows the characterization of organ dysfunction in both groups of patients, resulting into significant differences only observed at hematological and renal levels.

***Chart 2:* Organ dysfunction pattern in patients with early deaths (≤72 h) (n=2) versus all other patients (n=82) (univariate analysis).**

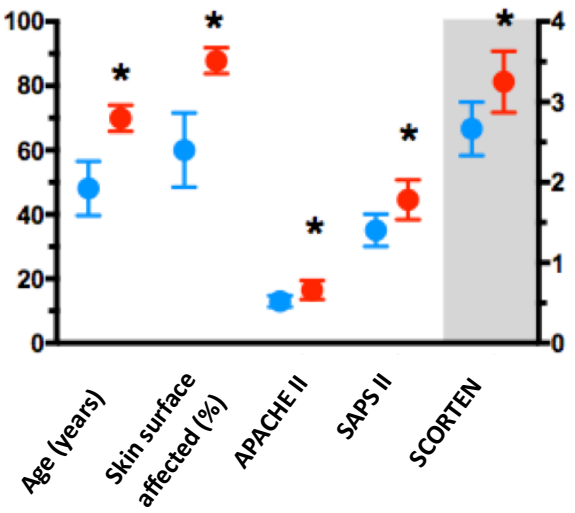
Organ dysfunction	Remaining patients (n=82)	Early deaths (n=2)	P value	OR	CI 95%
Cardiovascular, n (%)	22 (27%)	2 (100%)	0,08	5,364	0,463-62,148
Respiratory, n (%)	22 (27%)	2 (100%)	0,08	5,364	0,463-62,148
Renal, n (%)	8 (10%)	2 (100%)	**0,01**	**18,250**	1,485-224,337
Hepatic, n (%)	3 (4%)	1 (50%)	0,09	26,333	1,308-529,980
Hematological, n (%)	6 (7%)	2 (100%)	**<0,01**	**25,000**	1,971-317,120

➔ **Late mortality (>72h):**

The upcoming 2 graphs compare the characteristics of patients with late mortality (>72 hours), represented in red, and survivors, represented in blue.

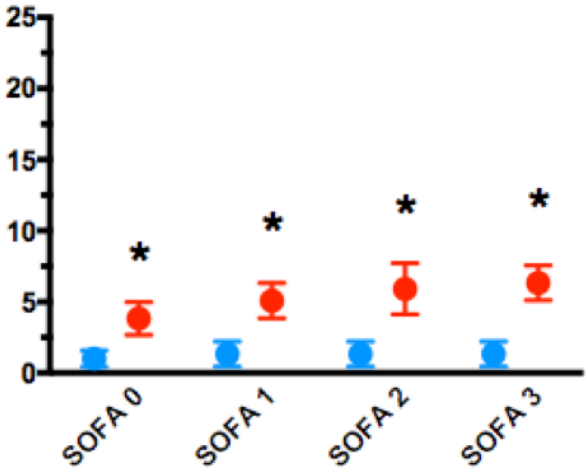
In *Graph 3*, patients with late mortality demonstrated a significant analytical difference in all of the variables studied: age, skin surface affected, APACHE II, SAPS II and SCORTEN. *Graph 4* shows a significant difference between the SOFA score on the first 4 days collected.

***Graph 3*: Mortality related variables in late death cases (>72h).**



Blue represents survivors. Red represents deceased. Asterisks indicate statistically significant differences between groups according to the Mann–Whitney U test ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

***Graph 4*: SOFA scores in days 0 to 3 in late death cases.**



Blue represents survivors. Red represents deceased. Asterisks indicate statistically significant differences between groups according to the Mann–Whitney U test ($p < 0.05$). Error bars represent the standard error of the mean (SEM).

Chart 3 shows the association between organ failure in various systems and late mortality (>72h), evaluating the relationship using the OR and identifying statistical significance at a threshold of p<0.05. The analysis revealed statistically significant differences in the prevalence on cardiovascular, respiratory and renal dysfunction among patients who had a late death, compared to survivors.

***Chart 3*: Organ dysfunction pattern in patients with late death (>72 h) (n=14) versus survivors (n=68) (univariate analysis).**

Organ dysfunction	Remaining patients (n=68)	Late death (n=14)	p-value*	OR	CI 95%
Cardiovascular, n (%)	13 (19%)	9 (64%)	**<0,01**	**7,615**	2,184-26,559
Respiratory, n (%)	12 (18%)	10 (71%)	**<0,01**	**11,667**	3,127-43,522
Renal, n (%)	3 (4%)	5 (36%)	**<0,01**	**12,037**	2,450-59,149
Hepatic, n (%)	3 (4%)	0 (0%)	1,00	1,667	0,161-17,306
Hematological, n (%)	5 (7%)	1 (7%)	1,00	0,969	0,104-9,000

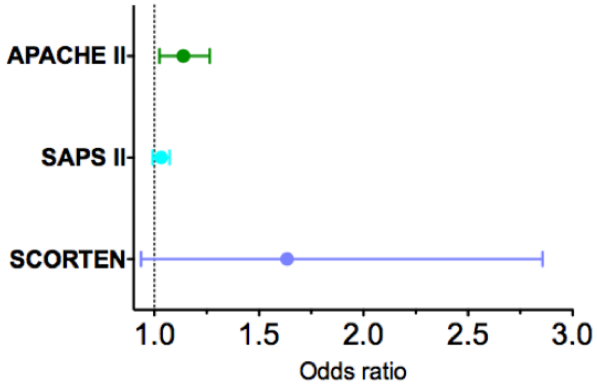
➔ **Predictive models adjusted for APACHE II individually.**

Predictive models adjusted for APACHE II are shown on *Graphs 5,6,7,8*. *Graph 5* and *6* reveals that among the different severity scales studied, only the values of APACHE II were associated with late mortality, in contrast to SAPS II and SCORTEN. SOFA scores (not by domains, but counting all 6 domains) on days 0,1,2,3, in the BICU presented an OR indicating a significant association between this value and patient mortality at a threshold of p<0.05.

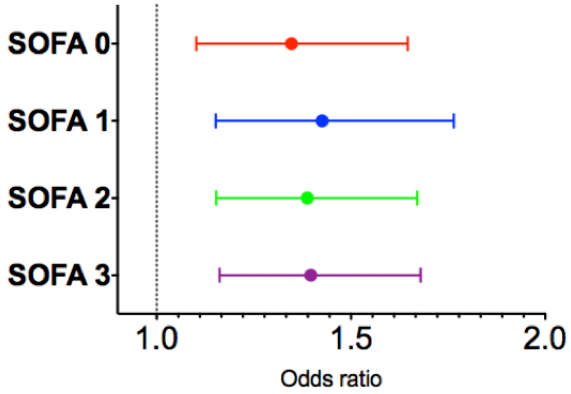
Graph 7 illustrates the association between the age, affected body surface area and arterial pH (individually), to a fatal outcome (late mortality). *Graph 8* examines the relationship between infections acquired during TEN hospitalization and late mortality. This analysis identifies a significant association between the development of pneumonia, bacteriemia and cutaneous septicemia (each individually), and an increased risk of late mortality. However, this strong and

significant association was not found when developing Urinary tract infections. Both studies used the OR to evaluate association, aiming for a p-value <0.05.

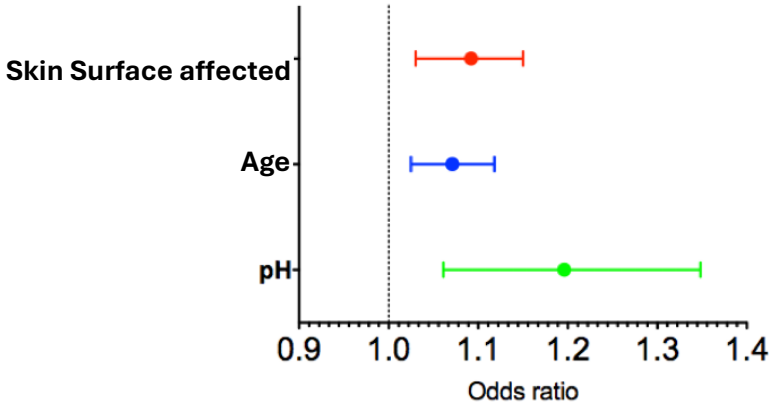
***Graph 5*: Predictive model of severity scales for late mortality in TEN patients, adjusted for APACHE**



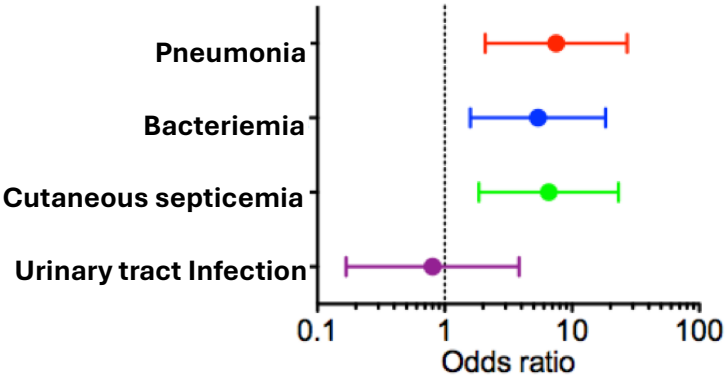
***Graph 6*: Predictive model of SOFA Score for late mortality in TEN patients, adjusted for APACHE II**



***Graph 7*: Predictive model of various variables for late mortality in TEN patients, adjusted for APACHE II**



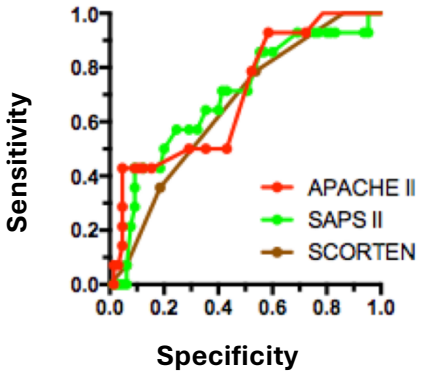
***Graph 8*: Predictive model of infections for late mortality in TEN patients, adjusted for APACHE II**



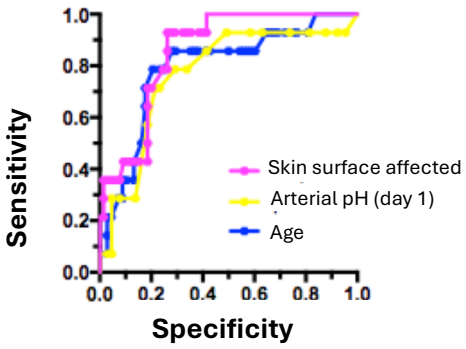
Discriminatory capacity to predict late mortality is represented by the AURC in graphs 9, 10, 11. These figures were elaborated with the data shown in Chart 4.

Chart 4 exposes the variables analyzed as potential predictors of late mortality in patients diagnosed with TEN. Among these variables, the highest AURC corresponds to the percentage of skin surface affected and APACHE II (0,856), and the SOFA score on day 3 (adjusted for APACHE II) (0,823), proving a strong predictive capacity for late mortality. Additionally, p-values measuring the statistical difference from the bisector of the ROC curve (0,5) are shown. Both variables mentioned presented highly significant p-values (p<0.00, and p<0.001, respectively), confirming the statistical relevance of these variables as late mortality predictors.

***Graph 9*: ROC curve**



***Graph 10*: ROC curve**



***Graph 11*: ROC curve**

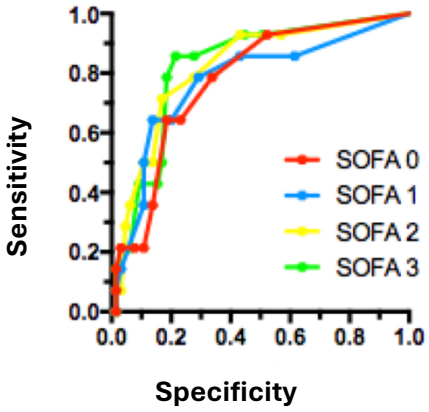


***Chart 4*: Discriminative capacity (area under the ROC curve) of the different predictive models for late mortality (>72 h, n=14) versus survivors (n=68), adjusted for APACHE II (except for APACHE II and SAPS II).**

	AURC	EE	p-value	CI 95%	
Skin Surface affected & APACHE II	**0,856**	0,045	**0,000**	0,768	0,944
Age	0,785	0,069	0,001	0,650	0,921
Arterial pH (day 1)	0,768	0,072	0,002	0,626	0,909
Cardiovascular dysfunction	0,721	0,081	0,010	0,563	0,880
Respiratory dysfunction	0,765	0,076	0,002	0,616	0,914
Renal dysfunction	0,655	0,091	0,069	0,476	0,835
Hepatic dysfunction	0,694	0,076	0,023	0,546	0,842
Hematological dysfunction	0,503	0,085	0,974	0,335	0,670
Pneumonia	0,734	0,077	0,006	0,584	0,885
Bacteriemia	0,698	0,081	0,020	0,539	0,857
Cutaneous septicemia	0,681	0,087	0,035	0,510	0,852
Urinary tract Infection	0,523	0,087	0,792	0,352	0,693
APACHE II	0,698	0,075	0,021	0,550	0,846
SAPS II	0,693	0,079	0,024	0,539	0,848
SCORTEN	0,658	0,074	0,065	0,513	0,802
SOFA day 0	0,776	0,064	0,001	0,651	0,901
SOFA day 1	0,773	0,075	0,001	0,626	0,920
SOFA day 2	**0,819**	0,062	<0,001	0,699	0,940
SOFA day 3	**0,823**	0,059	**<0,001**	0,706	0,939

5.3 TO DEFINE THE ASSOCIATION BETWEEN ORGAN DYSFUNCTION AND INFECTIONS.

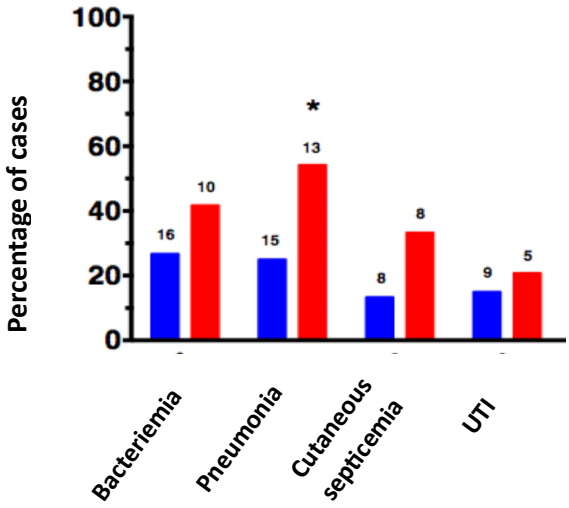
The analysis of this association was conducted on a system-by-system basis, with an individual focus on those who exhibited a significant association with late death, including

cardiovascular dysfunction, respiratory dysfunction, and renal dysfunction. The graphs to follow (12, 13, and 14) are displayed in red columns, representing patients with dysfunction of the system that is analyzed in each section. Conversely, columns in blue represent patients without such dysfunction.

➔ **Cardiovascular dysfunction:**

The prevalence of cardiovascular dysfunction was determined to be 24 out of 84 patients in the study sample. As illustrated in Graph 12, the four infections studied (bacteremia, pneumonia, cutaneous septicemia, and urinary tract infection) demonstrate a higher incidence in patients with cardiovascular failure. However, this discrepancy in incidence is only statistically significant in the case of pneumonia, where 15 cases were observed in patients without dysfunction, constituting 25% of the total cases in this group. In contrast, 13 cases were recorded in the 24 patients with cardiovascular failure, representing 54.17%.

Graph 12: Risk of infection in cardiovascular dysfunction



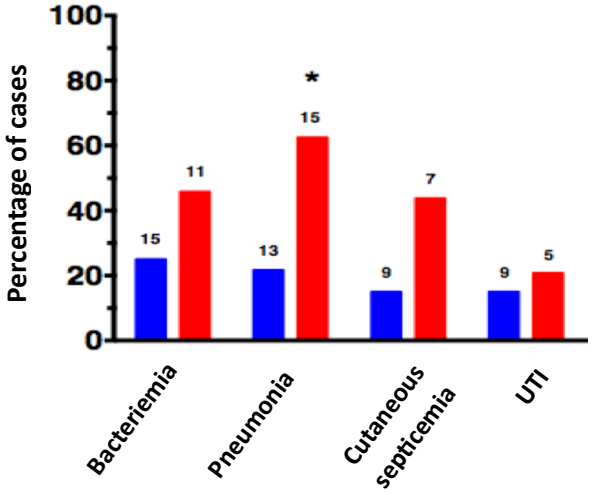
Blue represents patients without cardiovascular dysfunction. Red represents patients with cardiovascular dysfunction. Asterisk represents statistical difference assessed by Chi2 test.

➔ **Respiratory dysfunction:**

The study revealed that 24 out of the 84 patients were diagnosed with respiratory dysfunction. As illustrated in Graph 13, the 4 infections studied demonstrate a higher incidence in patients with respiratory failure. However, as in the case of cardiovascular dysfunction, this discrepancy in the development of infections is only statistically significant in cases of pneumonia. Pneumonia was observed in 13 of the 60 patients who did not exhibit respiratory dysfunction, constituting 21.67% of the group. In contrast, among the patients with dysfunction,

the prevalence of pneumonia was recorded in 15 of the 24 cases, representing 62.5% of the patients.

***Graph 13*: Risk of infection in respiratory dysfunction**

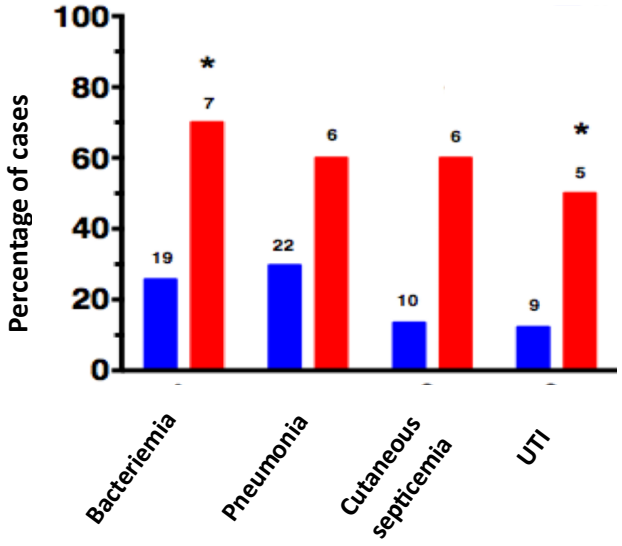


Blue represents patients without respiratory dysfunction. Red represents patients with respiratory dysfunction. Asterisk represents statistical difference assessed by Chi2 test.

➔ **Renal dysfunction:**

Renal dysfunction was detected in 10 of the 84 patients included in the study. As illustrated in Graph 14, the incidence of the four infections is elevated in individuals with renal dysfunction compared to those without. In this case, statistical significance is observed in three of the four infections bacteriemia, cutaneous septicemia and Urinary tract infection (UTI). Bacteriemia was diagnosed in 70% of the cases among patients with renal failure, compared to 27.14% of those without renal function impairment. Cutaneous septicemia was detected in 60% of the patients with renal dysfunction, compared to 13.51% of those without it. UTI was present in 50% of the patients renally affected, while the group without renal failure demonstrated a rate of 12.16% (9 cases).

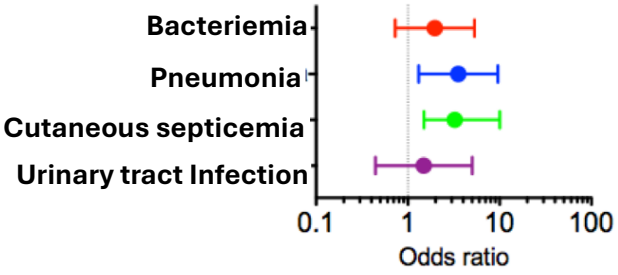
***Graph 14*: Risk of infection in renal dysfunction.**



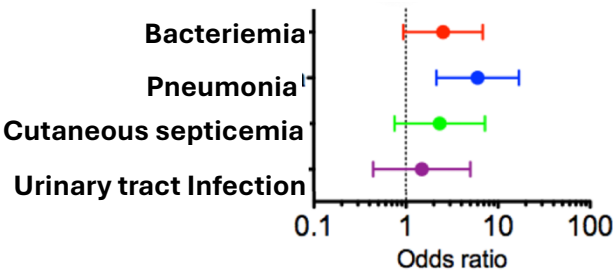
Blue represents patients without cardiovascular dysfunction. Red represents patients with cardiovascular dysfunction. Asterisk represents statistical difference assessed by Chi2 test.

These data were analyzed with OR. *Graph 15* shows a positive correlation between cardiovascular failure and an elevated risk of pneumonia and cutaneous septicemia, with an OR >1 in both cases. As illustrated in Graph 16, the presence of respiratory failure is associated with an elevated risk (OR>1) of pneumonia in patients with NET. In Graph 17 demonstrates a strong association (OR>1) between having renal failure and an elevated risk of bacteremia, cutaneous septicemia, and urinary tract infection.

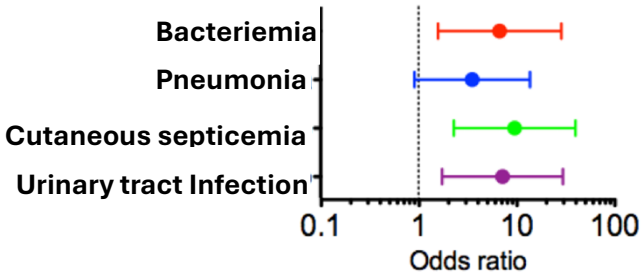
***Graph 15:* Cardiovascular dysfunction.**



***Graph 16*: Respiratory dysfunction.**



***Graph 17*: Renal dysfunction.**



5.4 TO DEEFINE THE ASSOCIATION BETWEEN INITIAL RESUCITATION AND LATE MORTALITY:

➔ **Fluid Resuscitation variables:**

Chart 5 displays the median values of each variable associated with fluid resuscitation, accompanied by the interquartile range observed in patients who presented late mortality versus the survivors. A p value of less than 0.05 has been accepted as statistically significant. Statistically significant differences were identified in the following parameters: admission day 2, diuresis day 2 and 3, hourly balance day 2 and 3, and ratio from day 0 to 4, being the day 2 ratio exhibited the greatest statistical significance.

***Chart 5:* Fluid resuscitation parameters of late mortality patients (n=14) and surviving (n=68) patients**

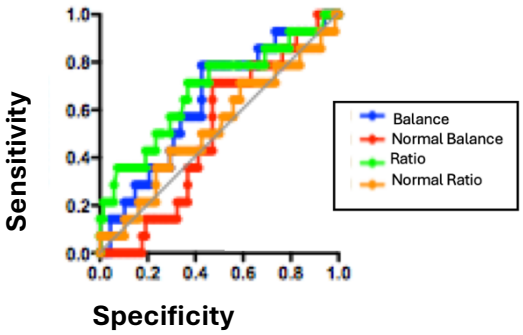
		Survivors (n=68)				Late mortality cases (n=14)				
Variable	**Day**	**n**	**median**	**p25**	**p75**	**n**	**median**	**p25**	**p75**	**p**
Fluid input (ml/kg/h)	0	68	3,510	2,496	5,275	14	4,700	3,672	7,085	0,057
	1	67	2,885	2,083	4,583	14	4,617	2,018	6,323	0,226
	2	66	2,594	1,798	3,889	14	4,917	2,081	6,731	**0,023**
	3	63	2,418	1,667	3,571	14	4,754	1,903	5,958	0,029
Diuresis (ml/kg/h)	0	68	1,242	0,898	1,775	14	0,883	0,652	1,380	0,130
	1	67	1,198	0,833	1,667	14	1,068	0,503	1,615	0,230

	2	66	1,266	0,924	1,667	14	0,897	0,470	1,392	**0,031**
	3	63	1,389	0,926	1,731	14	0,865	0,447	1,228	**0,015**
Fluid input (ml/kg/h/Surface*)	0	68	7,203	4,199	11,647	14	5,628	4,509	7,564	0,306
	1	67	5,270	3,493	8,889	14	5,285	3,065	6,502	0,454
	2	66	4,305	2,813	9,071	14	5,392	3,433	7,198	0,909
	3	63	4,040	2,778	8,201	14	5,362	3,102	6,450	0,979
Balance* (ml/kg/h)	0	68	2,229	0,801	4,532	14	3,688	2,384	5,857	0,112
	1	67	1,607	0,556	3,264	14	2,489	1,178	4,997	0,108
	2	66	1,174	0,538	2,700	14	3,001	1,336	5,569	**0,014**
	3	63	1,154	0,343	2,014	14	3,601	0,897	5,413	**0,020**
Balance* (ml/kg/h/Surface*)	0	68	0,041	0,017	0,077	14	0,044	0,026	0,063	0,902
	1	67	0,026	0,011	0,054	14	0,030	0,016	0,053	0,591
	2	66	0,020	0,008	0,043	14	0,035	0,020	0,065	0,083
	3	63	0,018	0,008	0,036	14	0,039	0,011	0,057	0,184
Ratio* (ml/kg/h)	0	68	2,701	1,694	5,198	14	5,185	2,731	9,683	0,033
	1	67	2,450	1,417	4,200	14	3,497	2,143	6,595	**0,047**
	2	66	1,929	1,410	3,284	14	4,809	2,411	7,786	**0,001**
	3	63	1,828	1,259	2,682	13	3,294	1,976	8,312	**0,009**

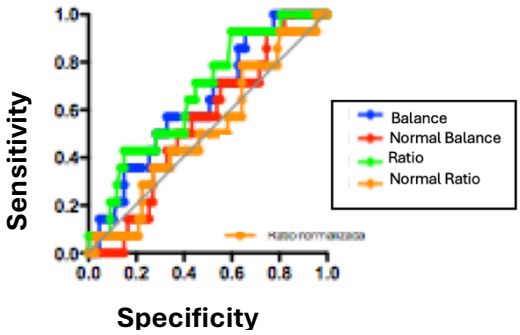
**Fluid input refers to the amount of fluid the patient receives daily via parenteral or orally. When referring to surface, it indicates the percentage of body surface area affected. Balance was calculated as Fluid input – diuresis. The ratio is calculated as: daily fluid input / diuresis."*

When displaying these data as a ROC curve, as shown in *Graphs 18,19,20,21,* Ratio in day 2 corresponds to the variable with a higher AURC, becoming the reference point for calculating Youden's Index.

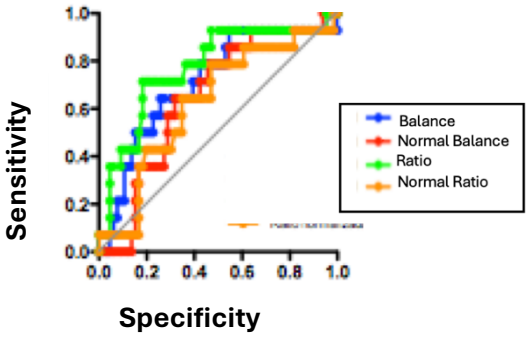
***Graph 18:* ROC Curve day 0.**



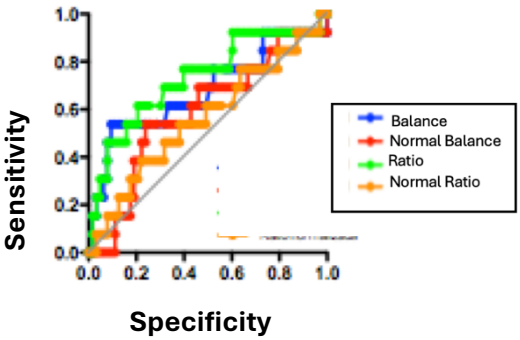
***Graph 19:* ROC Curve day 1.**



***Graph 20:* ROC Curve day 2.**



***Graph 21:* ROC Curve day 3.**



➔ **Metabolic related variables:**

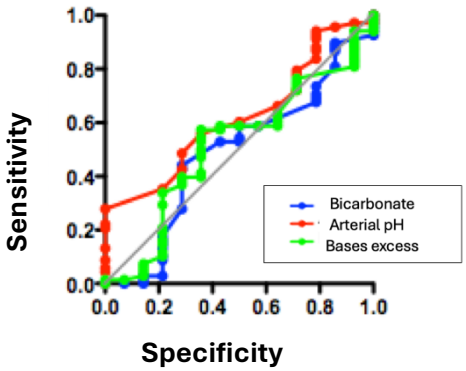
Chart 6 displays the Youden Index values for each metabolic variable, calculated to assess their discriminative ability between patients with late mortality and survivors. Statistical significance was determined by comparing each area under the ROC curve against the null hypothesis (AURC = 0.5), considering p-values < 0.05 as significant. Significant differences were observed for the following variables: arterial bicarbonate on day 3, arterial pH on days 1, 2, and 3, and base excess on day 3. Among them, arterial pH on day 1 yielded the lowest p-value, indicating the highest discriminative capacity, with a corresponding Youden Index of 7.375.

Chart 6: ***Youden Index for each metabolic parameter related to resuscitation in patients without early mortality.***

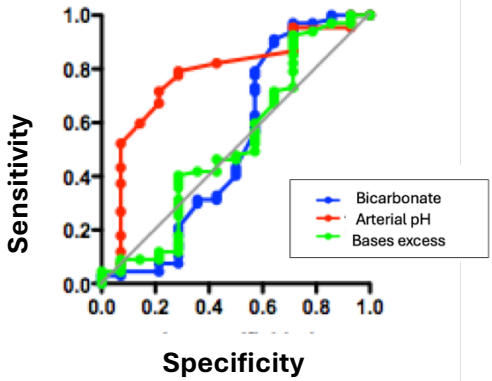
Variable	Day	Value	Sensitivity	Specificity	p
Arterial bicarbonate (mEq/L)	**0**	24,350	0,441	0,714	0,892
	1	21,400	0,910	0,357	0,805
	2	22,200	0,833	0,429	0,212
	3	21,450	0,875	0,571	**0,038**
Arterial pH	**0**	7,475	0,279	1,000	0,160
	1	7,375	0,791	0,714	**0,001**
	2	7,395	0,712	0,786	**0,007**
	3	7,395	0,781	0,714	**0,002**
Arteria bases excess (mEq/L)	**0**	-3,850	0,925	0,286	0,873
	1	-3,850	0,925	0,286	0,810
	2	-3,450	0,940	0,357	0,192
	3	-3,750	0,953	0,429	**0,016**

When displaying these data as a ROC curve, as shown in *Graphs 22, 23, 24, 25*, the value of the arterial pH in day 1 corresponds to the variable with a higher AURC.

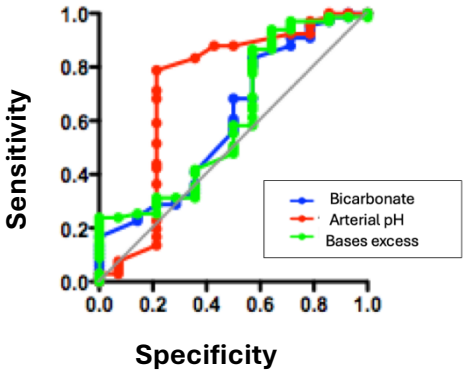
***Graph 22*: ROC Curve day 0**



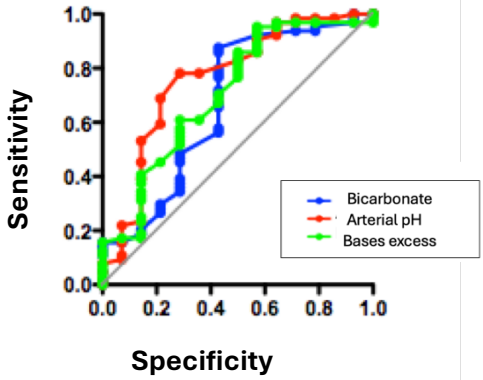
***Grave 23*: ROC Curve day 1**



***Graph 24*: ROC Curve day 2**



***Graph 24:* ROC Curve day 3**



➔ **ASSOCIATION BETWEEN RESUCITATIOIN AND LATE MORTALITY:**

Chart 7 illustrates the association between late mortality and the variables with the highest statistical significance, as determined by Youden's Index. According to the chart, an arterial pH of 7.375 on day 1 serves as a critical threshold. Patients with a pH on day 1 below this value showed a significantly higher risk of late mortality (41.7%) compared to those with a pH above 7.375, where the risk of late mortality was 7%. This finding highlights the strong association found between lower pH values on day 1 and an increased risk of late mortality in patients with TEN, with an OR> 9 for pH values below the threshold. Youden's value for the variable Ratio Day 2 was calculated to be 3.751. A higher value on this variable has been associated with a late-mortality risk of 42.9%, with an OR value of 5.991.

***Chart 7*: Key Variables Analyzed with Youden's Index, Association to late-mortality, and OR.**

			OR*	CI 95%	p
Arterial pH (day 1)	**≥7.375 (n=57)**	**<7.375 (n=24)**			
Mortality	**4 (7.0%)**	**10 (41.7%)**	**9.646**	2.578-34.746	0.001
Ratio (day 2)	<3.751 (n=59)	≥3.751 (n=21)			
Mortality	**5 (8.5%)**	**9 (42.9%)**	**5.991**	1.593-22.563	0.001

6. DISCUSSION AND CONCLUSION:

The present retrospective observational study focuses on evaluating the relevant relationship between organ dysfunction -and the different scales used to measure it- and the clinical evolution of patients with NET admitted to the BICU of the Hospital Universitario de Getafe. The results highlight the usefulness of the classic scales for assessing organ dysfunction, not only as a predictive tool for late mortality - in a similar way to other critical patients - but also their capacity to complement or even surpass classic models specific to this pathology, such as the SCORTEN.

Interpretation of Main Results

First, it is important to highlight the significance of characterizing not only patients who survive but also those who experience late mortality, as this group is directly associated with, or at least impacted by, the management provided in the Critical Care Unit. In this regard, we observed that patients who died late (>72 hours) exhibited statistically significant differences in various aspects compared to survivors. Notably, this includes scores on classic organ dysfunction assessment scales (APACHE II, SAPS II) and the SOFA scale's ability to distinguish between late mortality and survival. This last value is particularly notable on day 3 of admission, where, according to the analyzed data, it has demonstrated a discrimination capacity with an AURC of 0.823 (p-value <0,01). Additionally, the AURC achieved by body surface area adjusted to APACHE II stands out at 0.856 (p-value <0.01), surpassing the AURC of 0.658 observed with ESCORTEN, which has a p-value that does not reach statistical significance.

These findings challenge the reliability of SCORTEN—previously validated and specific for NET—in predicting mortality compared to classical tools that include organ damage stratification, as the ones previously mentioned. Hypotheses emphasizing the importance of organ or system failure in the prognosis of NET have already begun to be studied and proposed. For example, it had already been identified liver disease as a high-risk factor associated with mortality in patients with epidermal necrolysis (including TEN) (25). Similarly, the influence of renal function on the prognosis of patients with Stevens-Johnson Syndrome (SJS) and TEN was investigated, demonstrating that acute renal failure is an early event associated with poor outcomes (26). This hypothesis is further supported by the meta-analysis (27), which underscores the importance of renal function as a prognostic factor in this disease. Predictive models, such as CRISTEN, KDIGO, and ABCD-10, have been developed based on hepatic and renal parameters to stratify mortality risk and patient prognosis in TEN (28-30).

Multiple studies have demonstrated the importance of fluid resuscitation management in critically ill patients and its role in mortality, particularly in those with sepsis, septic shock, and heart failure. Both fluid overload and deficit in ICU patients have been associated with increased mortality in sepsis (16). Moreover, a positive fluid balance has been shown to be independently associated not only with higher mortality in patients undergoing sepsis or septic shock, but also in those with heart failure (18). These findings reinforce the notion that fluid-related variables, especially those measured during early resuscitation, may serve as key prognostic indicators in critical illness. Within this context, this is the first study to stablish an association between fluid resuscitation-related variables and mortality in patients with TEN.

It is worth highlighting the identification of two variables related to the primary resuscitation of patients, whose significance in the prognosis of TEN had not been previously described. Data analysis revealed a strong association between arterial pH (a metabolic variable) on the first day of admission and late mortality, with an OR >9. Specifically, a pH value <7.375 on day 1 was associated with a 41.7% probability of late mortality, and is also indicative of unsuccessful fluid resuscitation, correlating with a poorer clinical prognosis. Similarly, within this category, the importance of the Ratio on day 2 was observed. Supported by an OR of 5.991, a Ratio value >3.751 was linked to a 42.9% risk of late mortality in these patients. Monitoring this variable, could allow early identification of high-risk patients, especially when fluid input exceeds the diuresis by more than threefold. In such cases, early intervention aimed at reducing the ratio, may contribute to lowering the mortality risk. This approach is consistent with the previously mentioned evidence, in which positive fluid balance worked as a n independent predictor of poor outcomes in critically ill patients.

Study Limitations

Despite exceeding the minimum sample size initially calculated to detect a strong association between SOFA score and mortality (assuming an OR of 3 and an event rate of 30%), the study still faces a limited sample size (n=84) due to the low prevalence of Lyell's syndrome/TEN. This limitation underscores the relevance—and potential necessity—of conducting meta-analyses to further explore and validate these findings.

Additionally, another limitation of this study could be the potential for diagnostic errors in TEN. Both overdiagnosis and underdiagnosis are concerns. Studies have shown that in databases with more than 200 patients initially diagnosed with NET, only 28.4% had a final diagnosis of the disease (31). Similarly, underdiagnosis may occur due to confusion with other similar clinical conditions, such as severe erythema multiforme, among others (32). To minimize

these potential biases, it is recommended that cases suspected of TEN undergo histopathological confirmation.

Clinical Implications and Future Research

This study highlights the importance of including organ dysfunction as an important parameter in predicting mortality in NET. Integrating preexisting scales or even updating validated ones could provide relevant and relatively early insights into patient prognosis, enabling timely and effective interventions to address late mortality cases and improve disease outcomes.

Moreover, our study opens the door for conducting meta-analyses and developing new protocols to delve deeper into the significance of organ dysfunction compared to other disease-specific variables. It also encourages expanding the database and comparing mortality rates, disease progression, and organ failure in patients treated over the past 10 years with those presented in this study.

Conclusions

In accordance with the objectives proposed, the following conclusions were drawn from the findings of this study:

- Multiorgan dysfunction is a frequent and significant complication in patients with TEN admitted to the BICU. Its presence is independently associated with increased late mortality. Moreover, organ dysfunction was also correlated to a higher risk of infection, particularly cutaneous septicemia, pneumonia and bacteriemia, reinforcing the prognostic value of early organ dysfunction.
- The population studied was predominately female, with a median age of 50 years. The median affected skin surface was 75% and cutaneous involvement was frequent among the studied patients.
- The SOFA score (specially on day 3), while not specific for this condition, exhibits a strong predictive capability (AURC 0.823) and proves to be a valuable tool for identifying patients at elevated risk of adverse outcomes, such us late mortality. APACHE II also demonstrated a high discriminatory power for mortality prediction in TEN patients. These findings suggest that the incorporation of organ dysfunction parameters, enhances the prognostic performance of traditional TEN-specific models.

- Arterial pH on day 1 (adjusted for APACHE II), significantly improved the late-mortality prediction.
- This is the first study to demonstrate that variables related to early fluid resuscitation, particularly the fluid input/diuresis ratio on day 2, and arterial pH on day 1, are significantly associated with late mortality in TEN. An arterial pH <7.375 and a fluid input/diuresis ratio greater than 3.75 were both significant independent predictors of mortality. These results emphasize the importance of customized and closely monitored resuscitation protocols in these patients.

These findings support the integration of dynamic organ function assessment and resuscitation quality into current TEN management algorithms. Further prospective and multicentric studies are needed to validate these predictors and to inform the development of updated, more comprehensive mortality prediction models in TEN.

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8. ANEXES:

I. POSITIVE RESOLUTION OF THE ETHICAL COMMITTEE.

Hospital Universitario de Getafe

SaludMadrid

INFORME DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS (CEIm) DEL HOSPITAL UNIVERSITARIO DE GETAFE

D. Óscar Peñuelas Rodríguez, Presidente del Comité de Ética de la Investigación con Medicamentos del Hospital Universitario de Getafe

CERTIFICA:

Que este Comité en su reunión del día jueves, 19 de diciembre de 2024 (A12/24) ha evaluado la documentación presentada por Dña. Isabel Lucila Ramos del Moral, correspondiente al Trabajo fin de Grado titulado: **"Organ dysfunction as measured by the sequential organ failure assessment score (SOFA) and adverse outcomes in patients with toxic epidermal necrolysis (TEN) admitied to the Burn Unit of the Hospital Universitario de Getafe".**

- **Protocolo:** *Sin versión*

y considera que:

- Se cumplen los requisitos necesarios de idoneidad del Protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- La capacidad del investigador y los medios disponibles son adecuados para llevar a cabo el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto de los postulados éticos.

Por ello, este Comité emite **Informe Favorable** sobre la realización de dicho Trabajo fin de Grado a, Dña. Isabel Lucila Ramos del Moral, alumna del Grado de Medicina de la Universidad Europea de Madrid, como Investigadora principal y cuyo tutor es el Dr. José Ángel Lorente Balanza, del Servicio de Medicina Intensiva de nuestro centro.

Lo que firmo en Getafe, a 19 de diciembre 2024.

Fdo.: D. Óscar Peñuelas Rodríguez
Presidente del CEIm
Hospital Universitario de Getafe

Hospital Universitario de Getafe

SaludMadrid

D. Óscar Peñuelas Rodríguez, Presidente del Comité de Ética de la Investigación con Medicamentos del Hospital Universitario de Getafe.

HACE CONSTAR QUE:

Que la composición del CEIm, en la reunión en la que ha sido evaluado el Trabajo fin de Grado titulado: **"Organ dysfunction as measured by the sequential organ failure assessment score (SOFA) and adverse outcomes in patients with toxic epidermal necrolysis (TEN) admitied to the Burn Unit of the Hospital Universitario de Getafe".** *Sin versión*

Es la siguiente:

Presidente	D. Óscar Peñuelas Rodríguez
Vicepresidenta	Dña. Mª Teresa Ramírez López
Secretaria Técnica	Dña. Isabel Sánchez Muñoz
Vocales	Dña. Rocío Álvarez Nido Dña. Mercedes M. Cavanagh Dña. Marina Carbonero García Dña. Ana Isabel Castillo Varón Dña. Patricia Cuenca Gómez Dña. Irene Cuadrado Pérez Dña. Mª Concepción García Escudero Dña. Marta González Bocanegra Dña. Olga Laosa Zafra Dña. Teresa Molina García D. Alfonso Monereo Alonso Dña. Rocío Queipo Matas D. Javier Sánchez-Rubio Ferrández Dña. Ana Rosa Solórzano Martín

II. VARIABLES CHART.

Variable	Classification	Units	Clarifications
Key variables			
Organ dysfunction	Discreet quantitative	0 to 24	**SOFA score,** which will measure: - Respiration (PaO2/FiO2). - Coagulation (platelets). - Liver function (bilirubin). - Cardiovascular system (MAP: Mean Arterial Pressure). - Nervous system (Glasgow Scale). - Renal function (Creatinine). And according to the patient's values, a score (0-24) will be assigned.
Mortality	Dichotomic Qualitative	- Yes - No	
Secondary variables			
Sex	**Dichotomic Qualitative**	- **Woman.** - **Man**	
Age	Discreet Quantitative		Integer values.
Drug suspected	Nominal Qualitative		
Other prescribed drugs consumed	Nominal Qualitative		As reflected in the clinical History.

Previous diagnosed illnesses	Nominal Qualitative		As reflected in the clinical History.
Place of origin at the time of admission in the Burn unit.	Nominal Qualitative	- Hospitalization floor of Hospital Universitario of Getafe. - Home in Madrid. - Different Hospital in Madrid. - Home town outside Madrid. - Hospital outside Madrid. - Unknown.	As reflected in the clinical History.
Days between drug-intake and the appearance of the rash	Discreet Quantitative		
Days between drug-intake and hospitalization.	Discreet Quantitative.		
Days between drug-intake and admission to burn unit.	Discreet Quantitative.		
Days between hospital admission and admission in burn unit.	Discreet Quantitative.		

Days between the appearance of the rash and the admission in the burn unit.	Discreet Quantitative.		
Days between the admission in the burn unit and the stop of the breakthrough.	Discreet Quantitative.		
Days between the appearance of the rash and the stop of the breakthrough.	Discreet Quantitative.		
Days between the admission in the burn unit and the reepithelization.	Discreet Quantitative.		
Days between the appearance of the rash and the reepithelization.	Discreet Quantitative.		
Previous Corticoids intake	Dichotomic Qualitative	- Yes. - No.	As reflected in the Clinical History.
Corticoids administered due to TEN	Dichotomic Qualitative	- Yes. - No.	
Previous Cyclosporine intake	Dichotomic Qualitative	- Yes. - No	As reflected in the Clinical History.
Cyclosporine administered due to TEN	Dichotomic Qualitative	- Yes. - No.	

Date of first administration of Cyclosporine during admission in burn Unit.	Discreet Quantitative		
Mucosa affected	Nominal Qualitative.	- No. - One mucosa affected. - More than one mucosa affected.	
Mucosae type affected	Nominal Qualitative	- Oral. - Genital. - Ocular.	This could be more than one option.
Surface of skin affected	Discreet Quantitative	%	
Sepsis	Dichotomic Qualitative	- Yes - No	
APACHE II	Discreet Quantitative		
SAPS II	Discreet Quantitative		
Temperature when admitted.	Continuous Qualitative		Up to 2 decimals.
Discharge of burn unit.	Nominal Qualitative		
Fluids administered	Continuous Quantitative	liters	Up to 2 decimals. This variable must be collected on days 0,1,2,3,4, individually, each of which accounts as a different variable.
Diuresis	Continuous Quantitative	liters	Up to 2 decimals.

			This variable must be collected on days 0,1,2,3,4 individually, each of which accounts as a different variable
Fluids Balance	Continuous Quantitative	liters	Up to 2 decimals. This variable must be collected on days 0,1,2,3,4, individually, each of which accounts as a different variable
Mechanical Ventilation needed during admission in burn unit.	Dichotomic Qualitative	- Yes. - No	
Mechanical Ventilation (MV) needed during admission in burn unit within the first 72h	Dichotomic Qualitative	- Yes. - No	
Mechanical Ventilation needed during admission in burn unit after 72h since admission	Dichotomic Qualitative	- Yes - No	
Bicarbonate	Continuous Quantitative	mmol/L	Up to 2 decimals. This variable must be collected on days 0,1,2,3,4,7,21,28, death individually, each of

			which accounts as a different variable
pH	Continuous Quantitative		Up to 2 decimals. This variable must be collected on days 0,1,2,3,4,7,14,21,28, death, individually, each of which accounts as a different variable
Base Excess	Continuous Quantitative	mmol/L	Up to 2 decimals. This variable must be collected on days 0,1,2,3,4,7,14,21,28, death, individually, each of which accounts as a different variable.
SCORTEN	Discreet Quantitative.		
Noradrenaline needed during admission in burn unit.	Dichotomic Qualitative	- Yes. - No	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable
PaO2	Continuous Quantitative	mmHg	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable
FiO2	Continuous Quantitative	*0,01	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each

			of which accounts as a different variable
Bilirubin	Continuous Quantitative	mg/dL	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
Creatinine	Continuous Quantitative	mg/dL	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
Platelets	Discreet Quantitative	Platelets /µL	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
INR	Continuous Quantitative	IU	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
Parenteral Nutrition	Dichotomic Qualitative	- Yes. - No.	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable
PCR	Continuous Quantitative	mg/L	This variable must be collected on days

			0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
Leucocytes	Discreet Quantitative	leu/µL	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable.
Procalcitonin	Continuous Quantitative	ng/mL	This variable must be collected on days 0,1,2,3,7,14,21,28 death, individually, each of which accounts as a different variable
Pneumonia	Dichotomic Qualitative	- Yes. - No	
Date of pneumonia	Nominal Qualitative		Date of the confirmation test performed, or beginning of the symptoms if written in the clinical history.
Causative microorganism of the pneumonia.	Nominal Qualitative		
Bacteriemia	Dichotomic Qualitative	- Yes. No	
Date of the Bacteriemia.	Nominal Qualitative		Date of the confirmation test performed, or beginning of the

			symptoms if written in the clinical history.
Causative microorganism of the bacteriemia.	Nominal Qualitative		
Skin infection.	Dichotomic Qualitative	- Yes. No	
Date of the Skin infection.	Nominal Qualitative		Date of the confirmation test performed, or beginning of the symptoms if written in the clinical history.
Causative microorganism of the skin infection.	Nominal Qualitative		
UTI.	Dichotomic Qualitative	- Yes. No	
Date of the UTI.	Nominal Qualitative		
Causative microorganism of the UTI.	Nominal Qualitative		Date of the confirmation test performed, or beginning of the symptoms if written in the clinical history.

III. SCALES:

➔ SOFA Score:

BIOMARKER	SOFA SCORE				
	0	1	2	3	4
Respiratory system- PaO_2/FiO_2 (mmHg)	> 400	<400	<300	<200 with respiratory support	<100 with respiratory support
Nervous system- Glasgow Coma Scale	15	13-15	10-12	6-9	<6
Cardiovascular system- Mean arterial pressure (MAP)	MAP > 70 mmHg	MAP <70 mmHg	Dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	Dopamine > 5 µg/kg/min	Dopamine > 15 µh/kg/min
Liver- Bilirubin (mg/dl) [µmol/L]	< 1.2 (< 20)	1.2–1.9 [20–32]	2.0–5.9 [33–101]	6.0–11.9 [102–204]	>12.0 [> 204]
Coagulation- Platelets $\times 10^3$/ml	> 150	< 150	< 100	< 50	< 20
Kidneys- Creatinine (mg/dl) [µmol/L]; urine output	< 1.2 [< 110]	1.2–1.9 [110–170]	2.0–3.4 [171–299]	3.5–4.9 [300–440] (or urine output < 500 ml/day)	> 5.0 [> 440]; urine output < 200 ml/day

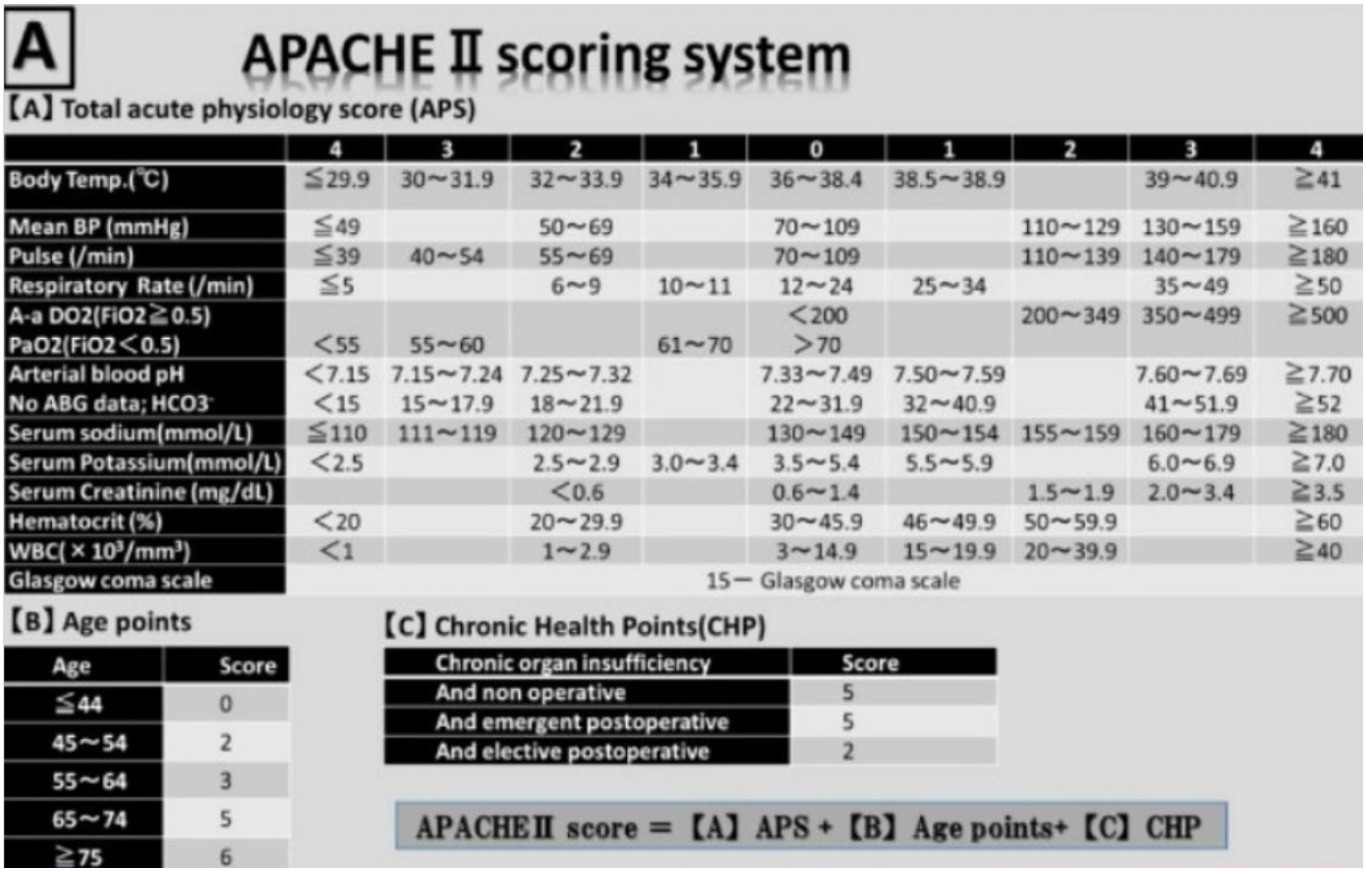
Maximum SOFA score	Mortality (%)
0-6	<2
7-9	0-10
10-12	10-30
13-14	40-60
15	75-90
>15	>90

➔ **SCORTEN**:

Prognostic Factors	Points
Age >40 years	+1
Tachycardia (>120 bpm)	+1
Neoplasia	+1
Initial detachment >10%	+1
Serum urea >10mmol/L	+1
Serum bicarbonate <20mmol/L	+1
Blood Glucose >14mmol/L	+1

SCORTEN value	Mortality (%)
0-1	3
2	12
3	35
4	58
>/=5	90

➔ **APACHE II:**



A APACHE Ⅱ scoring system

【A】Total acute physiology score (APS)

	4	3	2	1	0	1	2	3	4
Body Temp.(℃)	≦29.9	30～31.9	32～33.9	34～35.9	36～38.4	38.5～38.9		39～40.9	≧41
Mean BP (mmHg)	≦49		50～69		70～109		110～129	130～159	≧160
Pulse (/min)	≦39	40～54	55～69		70～109		110～139	140～179	≧180
Respiratory Rate (/min)	≦5		6～9	10～11	12～24	25～34		35～49	≧50
A-a DO2(FiO2≧0.5)					＜200		200～349	350～499	≧500
PaO2(FiO2＜0.5)	＜55	55～60		61～70	＞70				
Arterial blood pH	＜7.15	7.15～7.24	7.25～7.32		7.33～7.49	7.50～7.59		7.60～7.69	≧7.70
No ABG data; HCO_3^-	＜15	15～17.9	18～21.9		22～31.9	32～40.9		41～51.9	≧52
Serum sodium(mmol/L)	≦110	111～119	120～129		130～149	150～154	155～159	160～179	≧180
Serum Potassium(mmol/L)	＜2.5		2.5～2.9	3.0～3.4	3.5～5.4	5.5～5.9		6.0～6.9	≧7.0
Serum Creatinine (mg/dL)			＜0.6		0.6～1.4		1.5～1.9	2.0～3.4	≧3.5
Hematocrit (%)	＜20		20～29.9		30～45.9	46～49.9	50～59.9		≧60
WBC(× 10^3/mm^3)	＜1		1～2.9		3～14.9	15～19.9	20～39.9		≧40
Glasgow coma scale	15－ Glasgow coma scale								

【B】Age points

Age	Score
≦44	0
45～54	2
55～64	3
65～74	5
≧75	6

【C】Chronic Health Points(CHP)

Chronic organ insufficiency	Score
And non operative	5
And emergent postoperative	5
And elective postoperative	2

APACHEⅡ score = 【A】APS + 【B】Age points+ 【C】CHP

APACHE II Score	Mortality (%)
0-4	4
5-9	8
10-14	15
15-19	24
20-24	40
25-29	55
30-34	73
35-100	85

➔ **SAPS II:**

Variables:
Admission mode
Chronic illnesses
Glasgow Scales
Age
MAP
Heart rate
Temperature (ºC)
pO2/FiO2 (if MV or CPAP)
Daily diuresis (L)
Seric urea
Leucocytes
Seric Potassium
Seric sodium
Seric bicarbonate
Bilirubin (if jaundice)

SAPS II Score	Mortality (%)
29	10
40	25
52	50
64	75
77	90

IV. ANNEX 3: Glossary:

Acronyms	Meaning
ADR	Adverse Drug Reactions.
AURC	Area under the ROC Curve
BPM	Beats Per Minute
CI	Confidence interval
DHIS	Drug Induced Hypersensitivity Syndrome.
DRESS Syndrome	Drug Reaction with Eosinophilia and Systemic Symptoms.
FiO2	Fraction of inspired oxygen.
GSC	Glasgow Scale
ICU	Intensive Care Unit.
IQR	Interquartile Range
MAP	Mean Arterial Pressure
MV	Mechanical Ventilation
OR	Odds Ratio
PaO2	Partial pressure of oxygen.
ROC Curve	Receiver Operating Characteristic Curve
SCORTEN	SCORE of Toxic Epidermal Necrosis.
SJS	Stevens-Johnson syndrome.
SOFA Score	Sequential Organ Failure Assessment Score
TEN	Toxic Epidermal Necrolysis.
UTI	Urinary Tract Infection.