Burns Open 6 (2022) 10–18

Contents lists available at ScienceDirect

Burns Open

journal homepage: www.sciencedirect.com/journal/burns-open

Blood coagulation alterations over the first 10 days after severe burn injury

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ARTICLE INFO

Keywords:
Burn injury
Coagulopathy
Blood products
Fluid resuscitation
Thrombocytopenia

ABSTRACT

Introduction: Coagulation disorders occur during the first 48 h after major burn injury, affecting mainly PT/INR and aPTT. Some authors consider them burn specific. The aim was to assess the magnitude of coagulation disorders during the first 10 days after severe burn injury and its eventual association with fluid intakes.
Methods: Retrospective study of prospectively collected data including patients with burns ≥ 20%BSA (body surface area) who stayed ≥ 24 h at the burn-intensive care unit (ICU). Predetermined data for the analysis of fluid and blood products administration and laboratory values were extracted from the computerized information system. Descriptive statistics, data as median.
Results: 167 patients included. The volumes of fluid resuscitation decreased over the first 10 days (median 6815 ml on day 1 decreasing to 4190 ml by day 10, $p < 0.0001$). During the first 48 h, PT was frequently abnormal and strongly related to fluid volumes ($R^2 = 0.124$, $p < 0.0001$). Perturbations of PT/INR and aPTT improved after 72 h while the thrombocytopenia had a nadir by day 4, persisting in the most severely burned. Overall, only 12 (7.2%) patients presented combined coagulation alterations.
Conclusions: This study shows transient and self-resolutive coagulation disorders related to fluid delivery, apparently without burn specificity. The late thrombocytopenia is a new observation.

1. Introduction

Major burn patients, defined as burned ≥ 20% BSA (body surface area) and requiring intensive care treatment, necessitate a complex acute reanimation including airway protection, stabilization of the hemodynamic situation by fluid resuscitation and pain control [1]. The exact amount of fluid to deliver depends on several physiological factors is still debated [2].

The potential deleterious consequences of excessive fluid resuscitation have been known since the 1990 s, and include pulmonary oedema, compartment syndromes, circulatory failure as well as prolonged mechanical ventilation and hospital length of stay. This eventually led to replacement of Parkland's historical formula (4 ml × kg × %BSA) in favor of the concept of "permissive hypovolemia" in the early 2000′s [3–5]. Moreover, this fluid reanimation even if properly administered, has the side effect of diluting circulating factors, including blood coagulation factors; the only study addressing this specific question dates back to 1981 when liquid resuscitation was performed mainly with colloid infusions [6]. Recently, several studies analysed the importance of coagulopathy in small cohorts of severely burned patient, focusing mainly on the first 48 h after injury and using different definitions of burn coagulopathy (see Table 1) [7–11].

These studies point out a burn-induced coagulopathy, defined as uncontrolled activation of the coagulation mediators in severe thermal injury, that is predictive of 28-day mortality, mechanical ventilation duration and ICU length of stay [12]. It is also associated with higher percentages of total burned area and full-thickness burn as well as the presence of inhalation lesion and clinical consequences on the surgical

Abbreviations: ABSI, abbreviated burn severity index; ALAT/ALT/GPT, alanine aminotransferase; aPTT, activated partial thromboplastin time; ARF, acute renal failure; ASAT/AST/GOT, aspartate transaminase; BSA, burn surface area; BW, bodyweight; CK, creatine kinase; CPR, cardio-pulmonary resuscitation; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; EGL, endothelial glycocalyx; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; ICU, Intensive care unit; INR, international normalized ratio; MW, medical withdrawal; PLT, platelets; PLT100, platelets < 100 G/L; PLT 50, platelets < 50 G/L; PRBC, packed red blood cells; PT, prothrombin time; RBC, red blood cells; ROSC, return of spontaneous circulation; ROTEM, rotational thromboelastometry; SAPS II, simplified acute physiology score II; TT, thrombin time.

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https://doi.org/10.1016/j.burnso.2021.08.075
Received 25 May 2021; Received in revised form 28 July 2021; Accepted 11 August 2021
Available online 19 August 2021

Table 1
Laboratory diagnostic criteria of three blood coagulation disorder entities described in the literature.

Variables	Acute traumatic coagulopathy [11]	Disseminated intravascular coagulopathy [9,10]	Acute burn coagulopathy [7,8]
PT	Not defined	PT < 60%	Not defined
INR	INR ≥ 1.3	Not defined	INR > 1.2–1.5
aPTT	aPTT increased by 1.5x	Not defined	aPTT > 45–60 s
Thrombocytes	150–450 G/L	<100 G/L	Not defined
Fibrinogen	preserved	≤1 g/L	Not defined
Other		Increased D-Dimers	

aPTT = activated partial thromboplastin time, INR = international normalized ratio, PT = prothrombin time.

management of burn patients [13]. These results are comparable to known data for all intensive care patients in whom coagulopathy is recognized as part of a deadly triad [14]. Furthermore, the sum of age and burned area BSA% (i.e. Baux score) seems to be the best predictive factor for the development of deep vein thrombosis and pulmonary embolism [15].

The aim of this retrospective study was to assess the magnitude of coagulation disorders during the first 10 days after severe burn injury, its evolution, and its eventual association with fluid intakes.

2. Material and methods

2.1. Study design and participants

Retrospective study in patients admitted to the burn ICU of the "Centre des Brûlés" CHUV (Lausanne, CH) between 1st of January 2006 and 30th of June 2018. The competent ethical board (CER-VD) approved this project (registered under Swissethics N° CER 2018–02268). Patient informed consent was waived. The inclusion criteria were an admission at the burn-ICU between 1st of January 2006 and 30th of June 2018 with a ≥ 24 h ICU length of stay and a burn injury equal or >20% BSA. Exclusion criteria were a burn injury < 20% BSA or an ICU stay < 24 h. Patients were subdivided into three groups according their BSA: 20–40% BSA (group 1), 41 and 60% BSA (group 2) and > 60% BSA (group 3) based on definition (burns < 20% BSA are not major burn and do not require fluid resuscitation) and previous research attesting of increased mortality rates between these BSA intervals groups [16]. Fluid resuscitation was initiated with 2 ml × kg BW (bodyweight) × %BSA for burns 20–50% and with 4 ml × kg BW × %BSA for burns > 50%. According to our protocol, all patients received all unfractionated heparin 10'000 UI/24 h as continuous intravenous (I.V.) infusion since their admission, except in the case of overt bleeding.

2.2. Data collection

Coded data were extracted from the ICU's computerized system (MetaVision®, iMD-soft, Tel Aviv, Israel). Demographic and severity injury scores included: age, gender, %BSA, surgical percentage rate (ratio between burned BSA and requiring surface grafted), inhalation injury, mechanical ventilation duration, length of ICU stay, outcome (dead or alive) and several severity scores [SAPSII (simplified acute physiology score), Ryan, ABSI (abbreviated burn severity index), Baux et revised Baux [14]]. Treatment variables were: fluid types and volumes infused per 24 h [crystalloids (mainly Ringer Lactate), colloids (albumin20%), blood products, such as fibrinogen, fresh frozen plasma (FFP), packed red blood cells (PRBC), and platelet concentrates], infused heparin per 24 h and laboratory variables. The laboratory values included blood coagulation parameters (PT, INR, aPTT, TT [thrombin time], fibrinogen, anti-factor Xa activity, factor V), simple blood count (leucocytes, red blood cells (RBC), platelets, hemoglobin, hematocrit) and chemistry parameters [ionized calcium, albumin, creatine kinase (CK), liver cytolysis enzymes (ASAT, ALAT)].

For each patient and each day, four labs and the 24-hours sum of each type of fluid were extracted.

A second-step analysis selected the most pathological coagulation tests with the lowest (worst) daily platelet values. These worst values were analysed as single variables or as combinations.

Given that a single isolated pathologic parameter may not reflect a clinically relevant alteration, a third-step screening for combinations and/or repetitions ≥ 2 pathological parameters was done.

For clotting tests, the cut-offs selected as being pathological values were based on the previous literature: PT < 60%, INR > 1.5, aPTT > 60 s (Table 1). Two pathological thresholds for platelets were selected: platelets (PLT) < 100 G/l (PLT100), as it represents the minimal value required for extensive surgeries, including skin grafting, while values below 50 G/l (PLT50), represent the minimal threshold for invasive diagnostic investigations, such as pleural or hepatic punctures [17–19].

Of note, PT reagents display variability in their sensitivity to vitamin K-dependent coagulation factors. Conversion between PT values and INR may differ according laboratories, as a function of the local reagent/coagulometer combination. In our study, pathological cut-offs for INR and PT, >1.5 and < 60% respectively, are not the exact conversion of each other in our lab. PT < 60% corresponds to INR values > 1.38 and INR > 1.5 correspond to PT values < 46%.

2.3. Data analysis

Data are expressed as median and 25–75 interquartile ranges.

The continuous variables were compared using the one-way and two-way ANOVA, while the categorical variables were compared using Chi2 tests. For non-parametric variables, Kruskal-Wallis rank sum test was used. The results were presented in medians and interquartile ranges [25; 75] after visual analysis of their non-normal distribution.

The software used were JMP version 14.2 for Windows, SAS Institute and R version 3.5.3, 2019, The R Foundation for Statistical Computing. A p-value < 0.05 was considered as statistically significant.

3. Results

1. Patient characteristics

167 patients were included in the study. The median age and burn surface were 39 years [26; 58] and 35% BSA [24; 50] respectively. The characteristics of the 3 groups of patients is shown in Table 2. Mortality showed difference across groups essentially due to comorbidities and therapy withdrawal. Inhalation injury was present across groups without difference.

2. Fluid and blood product delivery

Crystalloid infusion was required during the first 24 h in all groups and the total amount of fluid infused per 24 h, all patients and groups combined, was highest during the first 48 h. Then, the volume of fluid resuscitation decreased progressively. Fluid requirements were proportional to burn severity. Heparin was used as prophylaxis without difference between groups. PRBC infusion after day 2 were related to surgical procedures and required essentially in larger burns. Early FFP infusion was required only in largest burns. Differences between groups were reduced after day 4 (Fig. 1).

3. Labs and coagulation parameters

A total of 1497 clinical chemistry samples, 3950 arterial gas analyses, 2843 complete blood counts, and 2510 blood coagulation tests (aPTT, INR, PT) were available.

Combining the most pathological coagulation tests with the lowest

Table 2
Patient characteristics by burn category. Data in median [IQR].

Variable	All	Group 1 20–40 %	Group 2 41–60 %	Group 3 > 60 % BSA	p
Patients number	167	109	34	24	
Age	39 [26; 58]	46 [29; 64]	34.5 [24; 49]	32.5 [25; 48]	0.0071
Sex M/F	111/56	65/44	25/9	21/3	0.0133
% BSA	35 [24; 50]	25 [22; 35]	50 [45; 53.5]	80 [67.75; 89.5]	<0.0001
Surgical %	20 [12; 40]	15 [8; 24]	45 [38; 50]	68.5 [55; 72.75]	<0.0001
Inhalation (%)	91/167 (54.5%)	54/109 (49.5%)	21/34 (61.8%)	16/24 (66.7%)	0.1941
ABSI	8 [7; 10]	8 [7; 9]	9.5 [8; 10]	12 [11; 13]	<0.0001
Ryan score	1 [1 : 2]	1 [0; 1]	2 [1; 2]	2 [1; 2]	<0.0001
Baux score	81 [63; 99]	70 [58; 90]	83.5 [71; 98]	112 [100; 129]	<0.0001
Modified Baux	90 [71; 111]	80 [67; 100]	98.5 [77; 114]	126 [112; 145]	<0.0001
SAPS II	36 [26; 47]	36 [24; 43]	36.5 [32; 56]	42.5 [33; 50]	0.0357
Ventilation (d)	9 [2; 23]	6 [1; 12]	22 [9; 34]	26 [6; 49]	<0.0001
ICU stay (d)	24 [12; 45]	20.5 [115; 30]	50.5 [3; 78]	60 [6; 80]	<0.0001
Mortality (%)	25/167 (15%)	9/109 (8.3%)	5/34 (14.7%)	11/24 (45.8%)	0.0002

ABSI = abbreviated burn severity index, BSA = burn surface area, d = day, F = female, ICU = intensive care unit, M = male, SAPS II = simplified acute physiology score II.

(worst) platelet values on a daily basis reduced the available variables (worst aPTT, INR, PT, platelets) to 1839 hits.

Most variables normalized by day 4, exceptions are: hematocrit and thrombin time (TT) decreased with length of stay; white blood cells (WBC) and platelets increased at the end of the first week; CK, ALT and AST showed no difference according to groups neither time (Figs. 2–4).

Only 165 anti-factor Xa activity measurements values and two factor V values were available.

Among all the variables, PT perturbation appeared with the strongest association with burned surface category ($R^2 = 0.668$, $p < 0.0001$).

4. Changes in blood coagulation parameters across time

Alterations of aPTT, PT/INR were more frequent in the acute phase regardless of their combination (Table 3).

3.1. *Alterations during the first 72 h*

During the first 72 h, the proportion of altered coagulation tests and thrombocytopenia increased with burned surface. Altered coagulation tests were more frequent than thrombocytopenia. PT was the most frequently altered variable with 27.5% of all pathological values ($p < 0.001$).

In total, 17 concomitant and repeated disturbances of PT/INR and aPTT appeared during the first 72 h in 12 patients (7% of the cohort) (Table 4).

These 12 patients were severely burned (median 65% BSA) with a high mortality (5/12). Moreover, ten patients received fluid resuscitation exceeding 20 L within the first 48 h. For half of these patients, thrombocytopenia was also present besides altered coagulation tests and three patients had platelets < 50 G/L. Complications involved in coagulation alteration were screened and we found isolated cases of heparin-associated thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), cardiorespiratory arrest or continuous renal replacement therapy. Note the preexisting conditions in four patients with altered blood coagulation independently from burn injury: chronic hepatitis B, suspected congenital factor XII deficiency and therapeutic anticoagulation. Their details are available in Table 5.

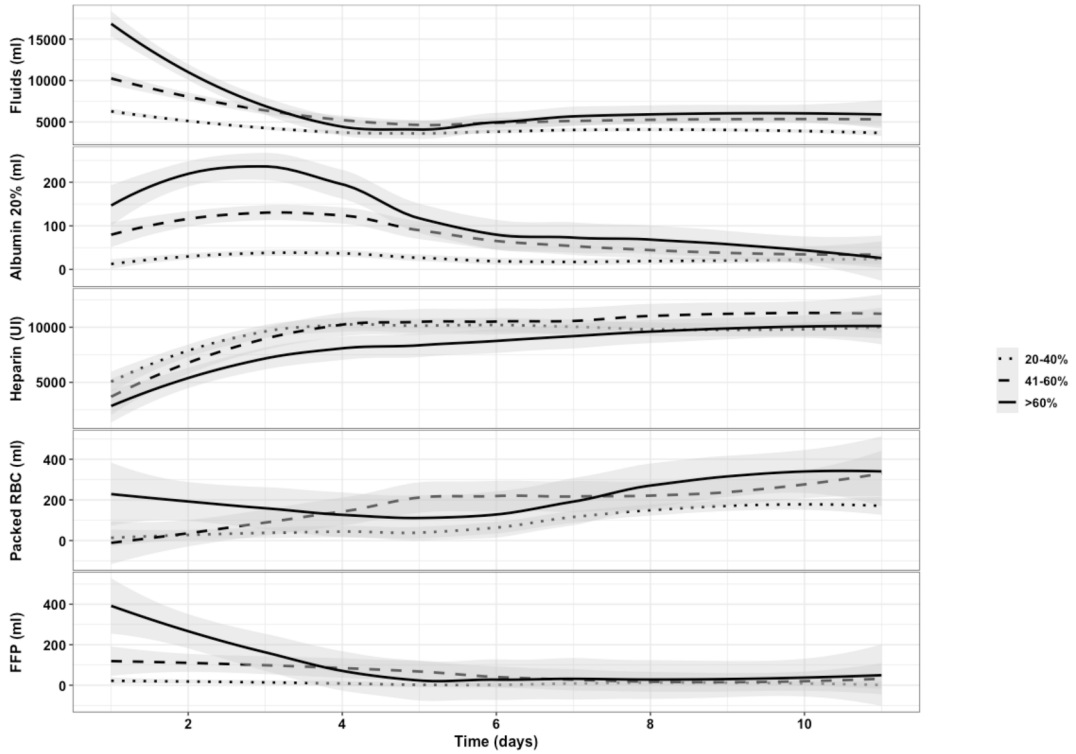

Fig. 1. Fluid (crystalloids), albumin 20%, heparin and blood product infusion by burn category.

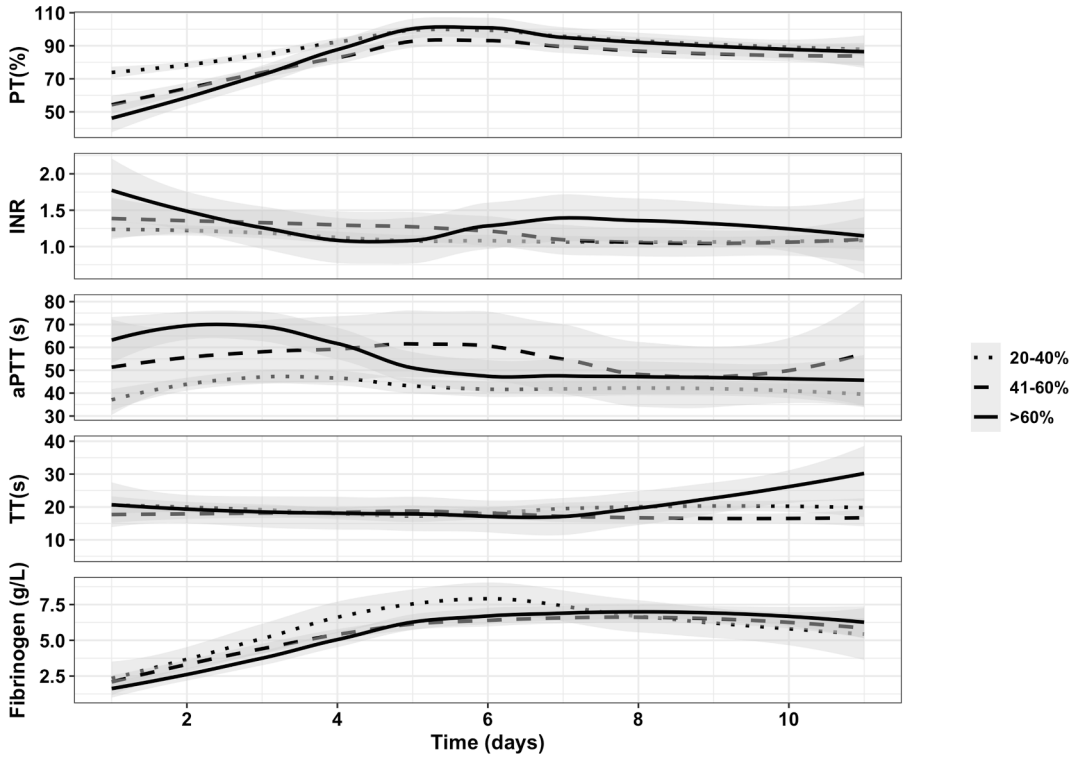

Fig. 2. Blood coagulation parameters by burn category.

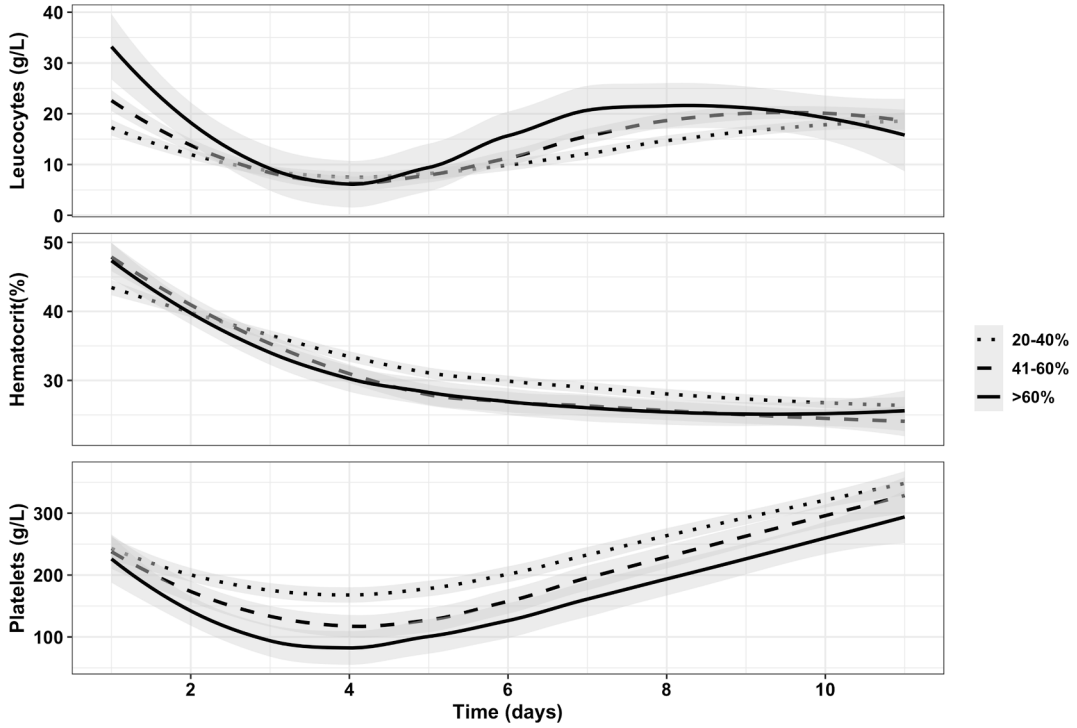

Fig. 3. Leucocytes, hematocrit and platelets (thrombocytes) values. by burn category.

3.2. Alterations after the first 72 h

Thrombocytopenia < 100 G/l was the most frequent alteration after the acute phase of 72 h, for all patients and within each burn category. PT alteration was more frequent than thrombocytopenia < 50 G/l for all patients combined and in group 1 (20–40% BSA). However, in the two other groups, the proportion of severe thrombocytopenia < 50 G/l increased. As for the acute phase, all combinations were significantly more frequent with increased burn surface (Table 3).

5. Relation with fluid administration

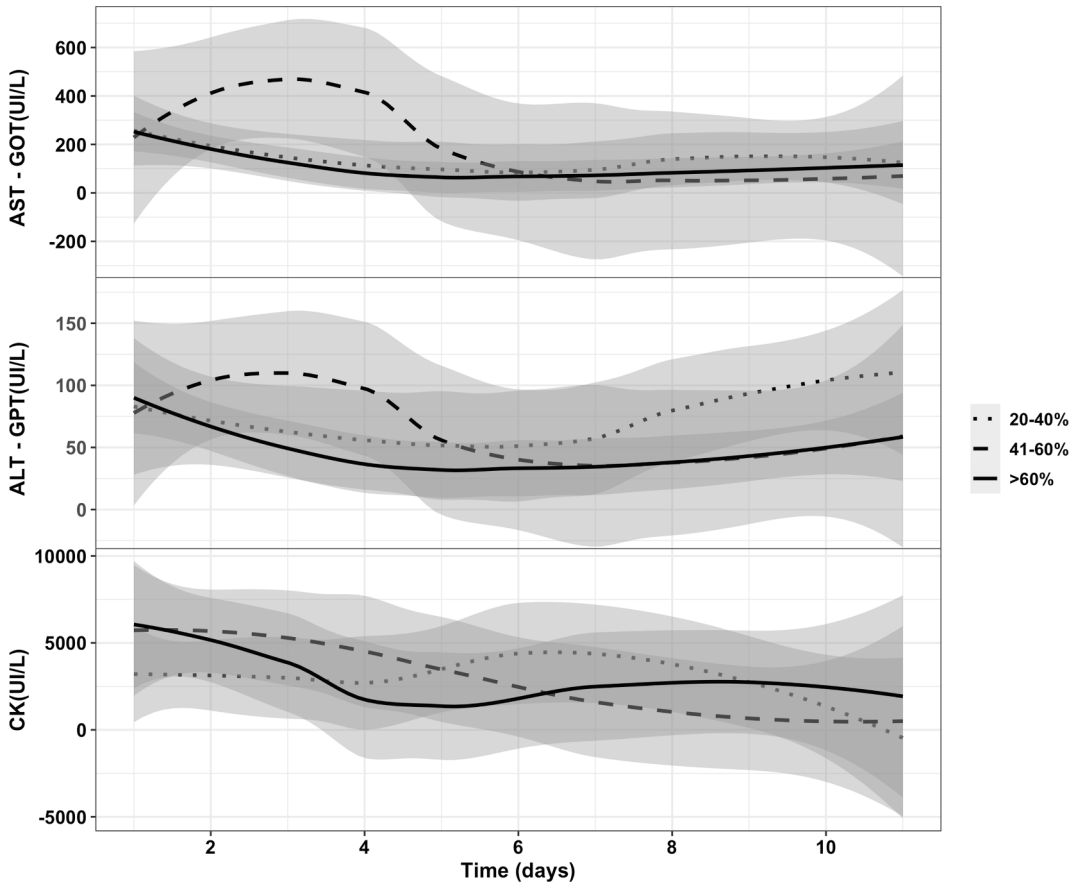

Fig. 4. ASAT (AST), ALAT (ALT) and CK values by burn category.

Table 3
Number of measurements (N) with alterations of the 4 variables (PT*,INR*, aPTT, PLT) alone or combined during the first 72 h or later, in all patients. The number in brackets stands for the percentage of all alterations due to the variable or combination of the line.

	D1 to D11	≤72 h after admission	>72 h after admission	p
N	1839	502	1337	
INR (%)	66 (4.3)	43 (9.1)	23 (2.1)	<0.001
aPTT (%)	94 (10.8)	49 (17.8)	45 (7.6)	<0.001
PT (%)	177 (11.4)	130 (27.5)	47 (4.3)	<0.001
PLT < 100 (%)	216 (13.4)	69 (14.2)	147 (13.0)	0.581
PLT < 50 (%)	63 (3.9)	17 (3.5)	46 (4.1)	0.68
INR + aPTT (%)	24 (1.6)	17 (3.7)	7 (0.7)	<0.001
INR + PT (%)	24 (1.6)	17 (3.7)	7 (0.7)	<0.001
aPTT + PT (%)	47 (3.2)	36 (8.5)	11 (1.0)	<0.001
INR + PT + aPTT (%)	24 (1.6)	17 (3.7)	7 (0.7)	<0.001
INR + PLT < 100 (%)	37 (2.3)	15 (3.1)	22 (2.0)	0.221
PT + PLT < 100 (%)	41 (2.7)	20 (4.4)	21 (2.0)	0.012
aPTT + PLT < 100 (%)	41 (2.7)	20 (4.4)	21 (2.0)	0.012
INR + PT + aPTT + PLT < 100 (%)	14 (0.9)	8 (1.7)	6 (0.5)	0.054
INR + PLT50 (%)	22 (1.4)	7 (1.4)	15 (1.3)	1
PT + PLT50 (%)	21 (1.3)	7 (1.5)	14 (1.3)	0.932
aPTT + PLT50 (%)	21 (1.3)	7 (1.5)	14 (1.3)	0.932

*: the authors are aware that PT and INR are different expressions of the very same raw laboratory results (same test): see text for discussion of this fact.

Table 4
Number of measurements (N) with perturbations of the four variables PT*, INR*, aPTT, PLT) alone or combined by burn category in the first 72 h. The number in brackets stands for the percentage of all alterations due to the variable or combination of the line.

	All	Group 1 20–40 %	Group 2 41–60 %	Group 3 > 60 % BSA	p
N	502	327	102	73	–
INR (%)	43 (9.1)	16 (5.2)	12 (12.1)	15 (23.1)	<0.001
aPTT (%)	49 (17.8)	14 (8.0)	8 (15.7)	27 (54.0)	<0.001
PT (%)	130 (27.5)	46 (14.9)	45 (45.9)	39 (59.1)	<0.001
PLT < 100 (%)	69 (14.2)	18 (5.7)	22 (22.0)	29 (42.0)	<0.001
PLT < 50 (%)	17 (3.5)	4 (1.3)	5 (5.0)	8 (11.6)	<0.001
INR + aPTT (%)	17 (3.7)	4 (1.3)	3 (3.1)	10 (15.9)	<0.001
INR + PT (%)	17 (3.7)	4 (1.3)	3 (3.1)	10 (15.9)	<0.001
aPTT + PT (%)	36 (8.5)	6 (2.1)	6 (8.0)	24 (38.7)	<0.001
INR + PT + aPTT (%)	17 (3.7)	4 (1.3)	3 (3.1)	10 (15.9)	<0.001
INR + PLT100 (%)	15 (3.1)	3 (0.9)	4 (4.0)	8 (11.9)	<0.001
PT + PLT100 (%)	20 (4.4)	2 (0.7)	4 (4.6)	14 (22.2)	<0.001
aPTT + PLT100 (%)	20 (4.4)	2 (0.7)	4 (4.6)	14 (22.2)	<0.001
INR + PT + aPTT + PLT100 (%)	8 (1.7)	1 (0.3)	2 (2.0)	5 (7.7)	<0.001
INR + PLT50 (%)	7 (1.4)	1 (0.3)	3 (3.0)	3 (4.3)	0,013
PT + PLT50 (%)	7 (1.5)	1 (0.3)	2 (2.1)	4 (6.1)	0,002
aPTT + PLT50 (%)	7 (1.5)	1 (0.3)	2 (2.1)	4 (6.1)	0,002
INR + PT + aPTT + PLT50 (%)	4 (0.8)	0 (0.0)	2 (2.0)	2 (2.9)	0,018

*: the authors are aware that PT and INR are different expressions of the very same raw laboratory results (same test): see text for discussion of this fact.

Table 5
Analysis of 12 patients with concomitant and repeated altered coagulation tests in the first 72 h after admission.

ID/year	Age	BSA	Fluid48h	Etiology	Comorbidities/non-hematologic complications (D01-D11)	Hematologic complications (D01-D11)	Transfusion needs (D01-D11)	Outcome
076/ 2011	59	90	40.4	Electrification, suicide attempt	AKI KDIGO III with CRRT Chronic hepatitis B	HIT on day 5	29 packs RBC, 5 g fibrinogen 4500 ml FFP (18 packs) 6 plt concentrates	D
081/ 2011	70	80	23.5	Gaz explosion	Suspected congenital Factor XII deficiency	Thrombocytopenia < 100 G/l	366 ml FFP	MW
092/ 2012	38	70	22.7	Fuel canister explosion	AKI KDIGO III with CRRT	Thrombocytopenia < 50 G/l Diffuse left arm bleeding Extended mesenteric infarction	8 PRBC 5000 ml FFP 2 plt concentrates	MW
099/ 2012	42	40	23.1	Scalding on epileptic seizure during the shower			6 PRBC	S
104/ 2012	33	92	43.8	Gaz explosion	AKI KDIGO III with CRRT	Thrombocytopenia < 50 G/l Duodenal ulcer with upper gastrointestinal bleeding	16 PRBC 1750 ml FFP 2 plt concentrates	S
110/ 2013	22	35	16.6	Flashback flame (fuel)			4 PRBC	S
118/ 2013	19	41	19.2	Accidental electrification and CPR with ROSC 45 min	AKI KDIGO III with CRRT	Thrombocytopenia < 100 G/l	27 PRBC 7 g fibrinogen 4500 ml FFP 7 plt concentrates	S
121/ 2014	86	42	17.7	Flashback flame (methylated spirits)	AKI KDIGO III with CRRT Anticoagulated mechanical mitral valve	Mesenteric infarction with perforation		MW
122/ 2014	40	66	23.8	Gaz explosion	Chronic hepatitis B	Thrombocytopenia < 100 G/l	4 PRBC 500 ml FFP	S
133/ 2015	49	45	19.9	Fire	Polydrug addiction	DIC Thrombocytopenia < 50 G/l Extended mesenteric ischemia	7 PRBC 6 g fibrinogen 5000 ml FFP 1/2 plt concentrate	MW
139/ 2016	17	64	26.7	Flashback flame (fuel)	1.2x Parkland	Mesenteric infarction with perforation	9 PRBC	S
164/ 2018	26	90	34.3	Car accident	30 L in the first 24 h		5 PRBC 1 g fibrinogen 1500 ml FFP	S

D = died, S = survived AKI: acute kidney injury, CPR: cardio-pulmonary resuscitation, CRRT: continuous renal replacement therapy, D: death, FFP: fresh frozen plasma, Fluid48h: fluid resuscitation volumes in the first 48 h in lite, HIT: heparin-induced thrombocytopenia, ID: patient code, MW: medical withdrawal, plt concentrates: platelet concentrate [250 ml], PRBC: packed red blood cells [300 ml], ROSC: return of spontaneous circulation, S: survival, year: year of admission.

In the first 48 h after admission, PT showed the strongest association with infused fluid volumes (inverse correlation) for all patients combined ($R^2 = 0.124$, $p < 0.0001$). This association strength was negligible beyond 48 h for PT ($R^2 = 0.040$, $p < 0.0106$) and other variables. We also explored the fluid intake during the first 24 h and the worst PT values during the first 72 h. Patients were separated into two groups: standard resuscitation group (≤4 m/kg/%) and overresuscitation group (>4 ml/kg/%). Only patients with a length of stay ≥ 72 h were included (160 patients, Table 6). The overresuscitation group received significantly more fluid (5.4 ml/kg/% vs 3.2 ml/kg/%, $p < 0.001$) and had significantly lower PT values (55% versus 65%, p 0.039). Interestingly, the ABSI score was not significantly different, suggesting that coagulopathy is more closely linked to the infused fluid volume than the severity of the burns. It was not possible to perform a multiple regression due to collinearity between the ABSI score and infused fluid volume, which is logical, since both depend on the percentage of burned area. The proportion of patients requiring transfusion during the first 24 or 72 h was very low and similar in both groups. Repeating the analysis by excluding these patients did not modify the results.

4. Discussion

In this cohort of severely burned patients, major hemostasis disturbances, according to selected pathological cut-off (PT < 60%, INR > 1.5, aPTT > 60 s) were rare. Combined and repeated disturbances of PT/INR and aPTT were observed in only 12 of 167 patients (7.2%) within the first 72 h. Among them, only six patients had concomitant thrombocytopenia. These observations suggest that severe coagulopathy is rare is severely burn patients.

As expected, more alterations were seen in patients who required higher volumes during initial fluid resuscitation, especially in case of overresuscitation. Moreover, as described in the 1990ies when the Parkland formula was widely applied [20], normalization of blood coagulation alterations (PT/INR, aPTT, TT) after 4–5 days was the rule.

PT showed the strongest association with fluid resuscitation, which contrasts with the results of Sherren et al's retrospective study in 117 patients based on admission values [11], which showed no correlation between PT and fluids; this discrepancy could be explained by two main arguments: 1) massive fluid resuscitation does not take place "on site" right after injury but occurs during the first 48 h after admission; 2) we chose to extend the definition of early phase to 72 h, thus allowing a potential dilution effect on the coagulation parameters to progress, as seen in Mitra et al study [8] including 163 patients: those with coagulopathy, according to acute traumatic coagulopathy criteria (Table 1), received more intensive fluid resuscitation during the first 24 h than patients without coagulopathy (5.7 vs 4.6 ml × kg BW × %BSA, p = 0.01). However, prospective studies focusing on the type, quantity and kinetics of fluid infusion, as well as the effect of fluid resuscitation on hemostasis disturbances, are lacking [21].

The originality of this study is an extended analysis over 10 days, which allowed the description of hemostatic disturbances exceeding the traditional early-phase used in the so called "burn-induced coagulopathy". Another strength is the size of the cohort with 167 individuals fulfilling burns ≥ 20% BSA and an ICU stay ≥ 24 h, without any other exclusion criteria, which allows an easy comparison with patients treated in most burn centers.

Beyond 72 h, an increasing rate of late severe thrombocytopenia was observed. To the best of our knowledge, this has not been described yet and is not included in the existing definitions of burn coagulopathy. Absence of thrombocytopenia in previous studies as additional variable to burn coagulopathy definitions (Table 1) reflects the study of a pure coagulation disorder, even if hemostatic alterations contraindicating surgery (debridement/grafting) include thrombocytopenia [13], and possibly the shorter observation span of previous study. However, prospective studies are required to determine if late thrombocytopenia could be a better predictor factor for clinically relevant hemostatic disturbances than PT/INR and aPTT alterations.

This late thrombocytopenia may be a peculiar finding in burns. However, thrombocytopenia is known as consumption coagulopathy in other critically ill patients [22]. This model could apply to major burn patients with a deficiency of coagulation factors II, VII and X [13] and an activation of coagulation that could be largely driven by the contact pathway of coagulation and not by tissue factor as typically seen after endothelial damage and systemic inflammation [23]. This suggests an alternative model for pathophysiology of the so-called burn induced coagulopathy [24].

Thrombocytopenia has a high impact on clinical practice in major burn patients especially because they mostly require numerous grafting procedures with increased bleeding risk [25]. Unfortunately for surgical procedures, the platelets' nadir level was observed on day 4, which in our institution corresponds to the time where grafting procedures start (day 4–7) [26]. This explains the increase in the number of transfused PRBC after day 4. As grafting procedures are an independent predictive factor for PRBC transfusions [27,28] and because of recent knowledge about the benefit of a restrictive transfusion therapy [29], any factor favoring bleeding, inclusive thrombocytopenia, should be minimized.

In summary, the coagulation disorders observed in this cohort of severely burned patients seems to be largely a consequence of hemodilution caused by the large amounts of resuscitation fluids that are usually infused [30]. Our findings question the relevance of defining a specific coagulopathy entity for burn victims based on variables PT/INR

Table 6
Initial fluid resuscitation and worst PT values during the first 72 h: Comparison between standard resuscitation and overresuscitation groups.

	Total patients	Standard resuscitation (≤4ml/kg/%)	Overresuscitation (>4ml/kg/%)	p-value
	(n = 160)	(n = 78)	(n = 82)	
Administered volume during the first 24 h (ml/kg/%TBSA)	4.14 (3.21–5.39)	3.18 (2.46–3.70)	5.38 (4.67–6.41)	<0.001
Minimal PT during the first 72 h (%)	60 (48–80)	65 (50–80)	55 (47–70)	0.039
Number of patients with at least 1 abnormal PT (<60%) value during the first 72 h	74 (47.3%)	29 (37.2%)	45 (54.9%)	0.025
Number of patients which received at least one blood transfusion during first 24 h	5 (3.1%)	1 (1.3%)	4 (4.9%)	0.200
Number of patients which received at least one blood transfusion during first 72 h	17 (10.6%)	8 (10.3%)	9 (11%)	0.544
ABSI score	8 (7–10)	8 (7–10)	9 (7–10)	0.987

Only patients with a length of stay of ≥ 72 h were included.
Quantitative data is presented in median (IQR) by default; Qualitative data is presented in n (%) by default.
TBSA = total body surface area burned; ABSI = abbreviated burn severity index.

and aPTT, in agreement with other authors [30].

4.1. Limitations

As for any retrospective study, some data are missing. In particular, although this study demonstrates an inverse association between fluid intake and coagulopathy, it was impossible to retrieve enough factor plasma concentrations to corroborate or refute the hypothesis that their dilution is a key driver of these changes in coagulation function. Nevertheless, the curves of platelets, hematocrit and leucocytes are perfectly parallel from day 1 to day 4 (Figure C), which supports this hypothesis. Moreover, factor plasma concentrations reflect not only their quantity in blood but also their activity; they decrease in case of active consumption and are not a marker of pure hemodilution/concentration in opposite to hematocrit.

During the period 2006–2018, crystalloids (Ringer Lactate) were the basis of the fluid resuscitation. But recent studies propose early plasma resuscitation instead of traditional crystalloid infusion to protect the endothelial glycocalyx (EGL) from shedding [31]. Indeed, recognition of the importance of EGL shedding, and potential protective effect of early plasma resuscitation might modify future resuscitation recommendations. EGL is destroyed in hemorrhagic shock and interventions for preserving an intact glycocalyx might improve survival of trauma patients [32], but not only: sepsis [33] and burn injury induce EGL shedding similar to that in non-burn patients and result in similar higher rate of mortality. The hypothesis that early plasma resuscitation reduces coagulopathy was not examined in this study and should be investigated prospectively.

Furthermore, the correlation between coagulopathy and worse outcomes is well established [11,13,21] and therefore not analyzed in this study. The high mortality rate of 41.7% (5/12) observed in patients with coagulopathy seems to confirm it as severity marker even if the correlation with BSA may be indirect: fluid infusion volumes are related to magnitude of burn injury and influence coagulation parameters. However, the relationship between pathological PT and the administration of blood products is a new finding and will require further analysis.

This study included only clinical routine variables. Specific laboratory variables, such as parameters of in vivo thrombin generation, natural anticoagulants, and fibrinolysis, would allow a more precise investigation of severe burn-induced alteration of the hemostatic balance. Finally, the promising technology of rotational thromboelastometry (ROTEM) was not available, and shows a hypercoagulable state during the first two weeks, while conventional coagulation tests remain normal [34].

5. Conclusion

Hemostasis disorders affect the most severely burned patients but are not frequent. Low PT/INR and aPTT normalize within 72 h while thrombocytopenia appears at the end of the first week. These findings do not support a specific coagulopathy entity for burn victims. The correlation between these disorders and surgery or blood product transfusion also remains to be determined prospectively, including further laboratory analysis of thrombin generation parameters and ROTEM technology.

Funding

This study was not supported by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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