COAGULATION DISORDERS AND MORTALITY IN BURN INJURY: A SYSTEMATIC REVIEW

COAGULOPATHIE ET MORTALITÉ CHEZ LE BRÛLÉ: REVUE DE LA LITTÉRATURE

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SUMMARY. Even though coagulopathy is a familiar entity in trauma, its relationship to burn injury remains unclear. Literature appears inconsistent as to the conclusions of the use of coagulation assays, either routine methods or newer viscoelastic coagulation assays (VCAs), thromboelastography (TEG) and rotational thromboelastometry (ROTEM), for prediction of patients' coagulation status and mortality. The use of diagnostic assays as mortality markers will be of great importance, since they would recognize at early stages patients with great medical demands and objectify burn injury severity. The aim of this study was to review the literature and evaluate burn patients' characteristics and coagulation markers in the early post burn period. The secondary outcome was to investigate the role of different coagulation assays in mortality prognosis. Literature search was performed using PubMed, ScienceDirect, Wiley Online Library, Google Scholar, Proquest Dissertation and Theses Global, Scopus and Cochrane Library databases. All types of articles referring to adults with any type of burn injury admitted in the first 24h assessing coagulation and mortality were included. PRISMA guidelines ensured the evidence-based process. Eleven studies met the eligibility criteria. This review demonstrated the indubitable relationship of coagulopathy with burn injury and its significant impact on mortality. The rapid and dynamic process of coagulation makes standard coagulation assays unable to detect short-lived haemostatic changes. More susceptible markers such as VCAs need to be applied to the routine assessment of burn patients in order to obtain an overview on coagulopathy and standardize the gained knowledge.

Keywords: coagulation, burn, mortality, coagulopathy, systematic review

RÉSUMÉ. Alors que la coagulopathie est bien décrite chez le traumatisé, sa relation avec la brûlure reste floue. La littérature reste élusive en ce qui concerne l'utilité des tests de routine, des tests viscoélastiques (TVE) et des thrombo- élastogrammes « ancien » (TEG) et optimisé (ROTEM) pour évaluer les troubles de coagulation et prédire la mortalité chez les brûlés. Hors, il s'agit d'une donnée importante pour prévoir la charge en soin (et l'éventuelle futilité- NDRLF) à prévoir. Cette étude a pour but de caractériser les patients brûlés et leurs troubles de coagulation, comme décrits dans la littérature, ainsi que d'évaluer la précision pronostique des différents tests de coagulation. La recherche bibliographique a été faite sur PubMed, Science Direct, Wiley Online Library, Google Scholar, Proquest Dissertation and Theses Global, Scopus et Cochrane. Toutes les études, pour peu qu'elles concernent des adultes, quel que soit le type de la brûlure, admis dans les 24 h, se penchant sur la coagulation et la mortalité étaient éligibles (11 au total). Les pré- requis PRISMA ont été utilisés pour juger de la pertinence. Il existe clairement une relation entre brûlure et coagulopathie, comme entre sa survenue et la mortalité. La rapidité des changements rend les tests standard peu utiles, si bien que les TVE ou les thrombo- élastogrammes sont nécessaires, ne serait- ce que pour préciser la coagulopathie des brûlés et, éventuellement, y remédier.

Mots-clés : brûlés, coagulopathie, mortalité, revue de littérature

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Introduction

Burn patients are an incomparable population as their injury initiates inflammatory pathways which disturb the balance between the activity of coagulation factors and fibrinolytic activity.[1,2] Since the first published article by Blonska and Kamienski in 1957, who described "coagulation disorders in burns",[3] lots of studies have been done focusing on the hematological profile of these patients. However, there is still significant research interest in this field.

Coagulopathy is a familiar entity in trauma patients, since 25% of severely injured patients are coagulopathic on admission.[4] It seems that coagulopathy associated with burn injury is divided into two entities: traumatic coagulopathy due to systemic inflammatory response, hypothermia, platelet dysfunction and tissue injury, and iatrogenic coagulopathy due to resuscitation, hemodilution and blood loss after surgical excision.[4-8] Both types may lead to serious venothromboembolic complications.[9,10]

Standard coagulation assays, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are indirect indicators of extrinsic and intrinsic clotting pathway respectively. They are highly used in daily medical routine and direct critical interventions.[11,12] Laboratory signs of hypocoagulation are associated with mortality in critically ill patients.[12] Likewise, a shortened aPTT on admission is associated with an increased risk of in-hospital mortality.[13] On the contrary, recent studies depict the inability of these assays to identify differences in coagulation profile, as they are small snapshots of an enormous and dynamic coagulation pathway.[14,15]

Viscoelastic coagulation assays (VCAs), such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are gaining ground in the diagnosis of coagulopathy by analyzing all stages of hemostasis, including clotting time (CT) and clot structure/strength in whole blood samples.[15,16] Information obtained from VCAs refer to clot formation, clot progress and its lysis, qualitative platelet function and fibrinolysis.[17] Though a signature chart, TEG/ROTEM evaluate the three phases of haemostasis: initiation phase with R or CT value, that depicts the time from start to initial clot formation, depending on clotting factors, amplification phase though K value, which is the necessary time to achieve a certain level of clot strength and finally propagation phase though alpha angle (α-angle) assessing the rate of clot formation. Time to maximum amplitude (TMA – MA) estimates the stability of the clot regarding platelets and fibrin, amplitude at 30 / 60 min (A30, A60 or LY30, L60) refers to the fibrinolysis at 30 and 60 min post-MA, while CLT stands for clot lysis time.[17] In critically ill patients they are considered the best perioperative monitoring tests, since they can detect both transfusion needs and bleeding disorders.[12,18]

Concerning burn injury, the existing literature appears inconsistent as to the conclusions of the use of different coagulation assays, either PT/PTT/INR or TEG/ROTEM, for prediction of patients' coagulation status and their impact on overall survival. The potential use of routine assays as mortality markers will be of great importance, since they would recognize at early stages patients with great medical demands and objectify burn injury severity.

The aim of this study was to review the literature and evaluate burn patients' characteristics and coagulation markers in the early post burn period. The secondary outcome was to investigate the role of different coagulation assays in mortality prognosis. The ultimate goal is to summarize the current state of research and identify future research needs in an effort to contribute in the future to drafting diagnostic and therapeutic guidelines.

Materials and methods

A manual search was conducted by one author in March 2021 in PubMed, ScienceDirect, Wiley Online Library, Google Scholar, Proquest Dissertation and Theses Global, Scopus and Cochrane Library databases. Using the terms: "burn" AND "coagulation" AND "mortality", 360 articles were identified, in the period 1980-2020 (*Table I*). All types of articles in English, referring to adult patients with any type of burn injury, admitted the first 24h post burn, assessing coagulation and clinical outcome, were included. After removal of duplicates, the articles were evaluated. Animal studies, pediatric and trauma patients were not included. Lastly, abstracts of these articles were re-

Table I - Search strategy used for each database with the corresponding results

Electronic databases	Search strategy	Limits	Hits
Pubmed	(burn AND mortality AND coagulation)	Publication date: 01/01/1980 – 31/03/2021 English language	203
ScienceDirect	(burn AND mortality AND coagulation)	Year 1980-2021 Limited to title, abstract or author-specified keywords	20
Wiley Online Library	(burn AND mortality AND coagulation)	Year 01/1980-03/2021 Publication type journals limited to title	2
Google Scholar	(burn AND mortality AND coagulation)	Publication date 1980-2021 Limited to title	2
Proquest Dissertation and Theses Global	(burn AND mortality AND coagulation)	Anywhere except full text Publication date: 01/01/1980 – 31/03/2021 English language	15
Scopus	(burn AND mortality AND coagulation)	Publication date: 1980 – 2021 English language Limited to title, abstract or keywords	98
Cochrane Library	(burn AND mortality AND coagulation)	Publication date: 1980 – 2021	20
			360 total hits

Fig. 1 - Prisma 2009 Flaw Diagram

viewed and evaluated according to inclusion and exclusion criteria. Titles and abstracts were assessed by two independent reviewers. Discussion solved any disagreements. Fifteen full-text articles were assessed, of which eleven studies met all inclusion criteria, and were thus selected for the qualitative synthesis. The procedure is presented in *Fig. 1*.

Due to the novelty of the topic, no randomized controlled studies were reported. Since systematic reviews of cohort studies are acceptable,[19] these types of studies which met the inclusion criteria were included.

PRISMA guidelines were applied in order to ensure the evidence-based process.[20] Critical Appraisal Skills Programme (CASP) checklists evaluated studies for
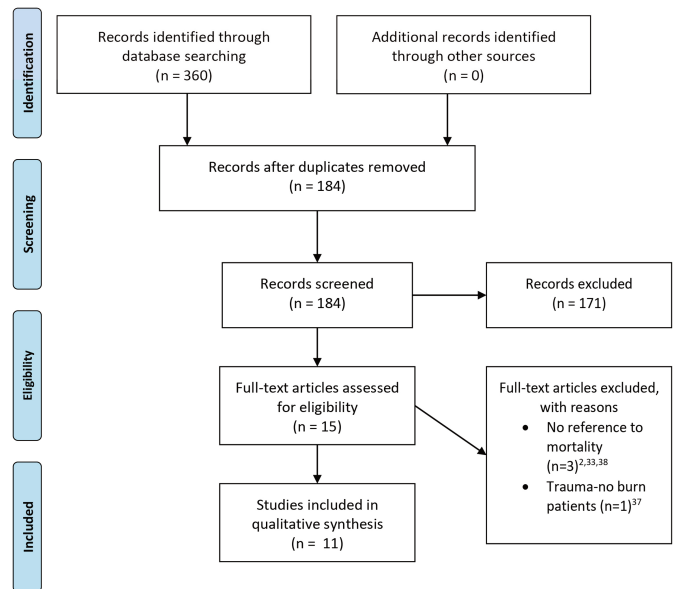
their validity and results.[21] *Table II* summarizes the articles that met the inclusion criteria. Assessment of risk of bias relied on the New Castle-Ottawa.[22] "High quality" studies were assigned 7–8 stars scale for cohorts, "moderate quality" 5–6 stars and "low quality" any number of stars below these, which were excluded by protocol.

Regarding synthesis results, data were summarized and considered suitable for pooling if similar groups were reported. Log Odds Ratios with 95% confidence intervals would be computed for dichotomous outcomes. A random–effects model was chosen, as proposed by DerSimonian and Laird. Between–study heterogeneity is calculated by the I^2 statistic.

Results

Search results

The type of each study, date of publication, aim, conclusion endpoints, and level of evidence were data extracted and presented. A total of 360 related citations were found. Duplicates were removed. Title and abstract evaluation according to inclusion and exclusion criteria was conducted by two independent reviewers. Eleven full-text articles comprising 928 patients were included according to the eligibility criteria.

Study characteristics

From the critical appraisal of the 11 studies[1,5,23-30,31] (*Table II*), we report four level 2b (282 patients)[5,23,28,30] and seven level 3b (636 patients)[1,24-27,29,31] studies.

There were no randomized controlled trials identified (*Table II*). Four studies were conducted in the USA,[22,23,27,28] three in Europe,[5,26,27] one in Australia[25], one in India[30], one in China[1] and one in Japan.[31] All

Table II - Summary of article characteristics, aim and main conclusion

Author & year of publication	Level of evidence	Type of study	Aim	Conclusion
Lavrentieva et al. (2008)[5]	2b	Prospective cohort study, single-center, civilian, Apr 2004 – Dec 2005	Evaluation of coagulation markers in early post-burn period and its role in organ failure and in mortality prognosis	Severe thermal injury is associated with early activation of coagulation cascade, DIC, organ failure, increased mortality
Park et al. (2008)[23]	2b	Prospective, single-center, military, Apr 2004 – May 2005, USA	Combining markers of inflammation and coagulation for early prediction of in hospital mortality in burned and non-burned patients	Six independent risk factors for death: age, 3rd degree, inhalation injury, TNF, MA, MODS
Lu et al. (2013)[24]	3b	Retrospective, single-center, USA	1st: the existence of ATC in burn patients immediately or soon after injury & association with blood utilization and 7 day mortality 2nd: association between TBSA and INR, PTT, PLT, HB on admission, determine changes of these parameters on 7th day post burn, estimate fluid resuscitation at day 2	Normal screening hematologic profile on admission Standard screening assays do not suggest the existence of ATC ATC unique to trauma patients
Mitra et al. (2013)[25]	3b	Retrospective single-center, civilian, Jul 1999 - Jun 2009, Australia	Investigate the incidence of ABIC in patients with severe burn during the acute post-burn phase and understand the value of ABIC as a prognostic predictor of 4-week survival and related risk factors	Major burn at high rate of early onset coagulopathy
Sherren et al. (2013)[26]	3b	Retrospective, single-center, civilian, Jan 2006 – Dec 2011, UK	1st: identify a clinically significant early ABIC 2nd: association between ABSI, fluid administration, mortality	In patients with major thermal injuries a clinically significant ABIC (acute burn induced coagulopathy) exists ABIC independent predictor of 28d mortality
Sherren et al. (2014)[27]	3b	Retrospective, single-center, civilian, Jan 2006 – Dec 2011, UK	The incidence and clinical impact of the lethal triad in major burns (hypothermia, acidaemia, coagulopathy) The impact of fluid resuscitation and ABSI score were also evaluated	Burn patients with the lethal triad have a high mortality rate reflecting the severity of the injury sustained
Tejiram et al. (2016)[28]	2b	Prospective cohort study, single-center, civilian, 2013-2014, USA	Develop a real-time assessment model to examine and characterize acute changes and associated risk factors in the coagulation profile of thermally injured patients Compare those changes to established routine measures of coagulation	Extensive changes not identified by INR, PTT after burn injury that may explain perturbed coagulation
Huzar et al. (2018)[29]	3b	Retrospective, single-center, Civilian, Jan 2010 – Dec 2012, USA	rTEG values at admission of burn patients for resuscitation prediction and patient outcomes	Severe thermal injuries developed a hypercoagulable state Patients who presented with hypocoagulable status had increased mortality Hypocoagulable patients on admission had a 5-fold greater risk of a supra-normal resuscitation compared with hyper / normal patients
Muthukumar V et al. (2019)[30]	2b	Prospective, single-center, India	Occurrence and outcome of patients presenting with the "triad of death" in burn population	Lethal triad is seen in the burn patients. Burn patient with lethal triad on admission had significantly higher mortality rates. Lethal triad is associated with higher TBSA, inhalational burn and full thickness burn
Kang et al. (2020)[1]	3b	Retrospective, double-center, civilian, Jan 2009 – Dec 2017, China	Incidence and clinical and prognostic significance of early phase ABIC	Incidence of ABIC associated with TBSA, lactic acid levels upon admission, post-burn admission interval 30% developed ABIC within 10post-burn hours, predicts 4-week mortality
Keita Y et al. (2020)[31]	3b	Retrospective, single-center, 2006 – Jan 2019 – Dec, Japan	Primary outcome: in hospital mortality Evaluation of coagulopathy in the early stage of burn injury, before resuscitation at its impact on in-hospital mortality	Non-survival group: increased age, TBSA, scoring systems, PT-INR, APTT, coagulopathy and lactate levels Coagulopathy group: increased TBSA, scoring systems, PT-INR, APTT, mortality Incidence of mortality independently associated with coagulopathy

DIC = disseminated intravascular coagulation; TNF = tumor necrosis factor; MA = maximal amplitude; MODS = multiple organ dysfunction syndrome; ATC = acute traumatic coagulopathy; TBSA = total body surface area; INR = international normalized ratio; APTT = partial thromboplastin time; PLT = platelets; HB = hemoglobin; ABIC = acute burn induced coagulopathy; ABSI = abbreviated burn severity index; rTEG = rapid thromboelastography

but one study[1] were single-centered.[5,23-31] Despite the variety of geographical distribution, the coagulation tests were in accordance. The eligibility criteria were clearly reported, increasing the applicability of the results.

Participant characteristics

The review included 928 patients (*Table II*). A total of 201 deaths occurred (21.7%). Participants were selected during defined dates of admission. All studies involved the adult population, apart from Sherren et al. who also included children[26,27] and Kang et al. who reduced the age limit to up to sixty years old.[1] All studies referred to burn patients apart from Park et al.[23] who used 25 burn and 33 non-burn trauma patients for the model development. Sherren et al.'s[26,27] studies seemed to refer to the same population, since similar demographics and characteristics were identified. Nevertheless, both studies were included as different outcomes were measured. The sample size ranged from 9 patients to 137 patients. The median age of patients ranged from 34.7 years to 63 years. Of the 928 patients, 618 were males (66.6%), a fact that may affect the generalizability of the evidence. For the studies with recorded data,[1,5,24-31] there were 125 coagulopathic non-survivors (*Table III*).

Extent and type of burn injury

Total burn surface area (TBSA) ranged from 14.5%[31] to 100% (*Table III*).[24] Apart from Park et al.[23] and Kaita et al.[31] who did not specify TBSA in the inclusion criteria, all other studies had a clear cut-off point. Two studies included burn patients with a TBSA higher than 15%.[24,29] Mitra et al.[5] used as a cut-off point a TBSA greater than 20%, which was characterized as severe burn injury. On the contrary, both Lavrentieva et al.[5] and Tejiram et al.[28] included burn patients with TBSA >25%. For Sherren et al.[26,27] the threshold was 30%, whereas for Kang G. et al.[1] and Muthukumar V et al.[30] it reached 50%. Unfortunately, the lack of a clearly formulated definition of severe burn injury based on TBSA resulted in arbitrary interpretations that may affect consistency of the outcomes. Finally, seven studies gave an extensive report on full-thickness burn injuries.[1,23,26,27,29,30,31] All eleven studies included inhalation injury. Two studies didn't clarify the exact mechanism of burn injury.[23,25] Six studies included only thermal injury patients,[5,26,27-30] one study excluded patients with electrical injury,[24] Kaita et al.[31] excluded chemical and electrical injuries, whereas Kang et al.[1] included all types of burn injury.

Table III - Patient characteristics and total body surface area (TBSA)

Author & year of publication	N	Age (mean or median) in years	Male sex, n (%)	TBSA (%) (mean or median)
Lavrentieva A et al. (2008)[5]	45 burn patients 15 died	41	37 (82.2%)	46
Myung S Park et al. (2008)[23]	58 patients 25 burn patients 15 died	47 (19)	44 (76%)	3rd degree 10%, 2nd degree 22%
Lu R et al. (2013)[24]	102 patients 15 died	43.2	71 (69.6%)	36
Mitra B et al. (2013)[25]	99 patients 14 died	42.7 (16)	73 (73.7%)	35.8% (16.4)
Sherren P et al. (2013)[26]	117 patients 24 died	34.7 (22)	75 (64.1%)	49.3%
Sherren P et al. (2014)[27]	117 patients 24 died	34.7 (22)	75 (64.1%)	49.3%
Tejiram S et al. (2016)[28]	9 patients 5 died	49.4 (16.6)	8 (88.9%)	49.8%
Huzar T et al. (2018)[29]	65 patients 27 died	45	48 (73,8%)	38%
Muthukumar V et al. (2019)[30]	50 patients 17 died	42.3	28 (56%)	56.5%
Kang G et al. (2020)[1]	129 patients 25 died	42 (10.1)	108 (83.7%)	73.6%
Kaita Y et al. (2020)[31]	137 patients 20 died	63 (42-77)	51 (37%)	14.5% (8-27)
Total	928 patients 201 died (21.7%)		618 (66.6 %)	

Coagulation markers and definition of coagulopathy

Every study analyzed the coagulation profile of the participants through standard coagulation assays, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)[1,5,24,28] or newer viscoelastic coagulation assays (VCAs), such as thromboelastography (TEG).[23,29] Throughout the eleven studies, different definitions of coagulopathy were used. They are summarized in *Table IV*. Lavrentieva et al.[5] used the ISTH DIC scoring system. Eight studies preferred routine coagulation assays for the evaluation of the hemostatic status, with different cut-off points.[1,24-28,30,31] Park et al.[22] and Huzar et al.[29] used TEG and r-TEG respectively.

Outcomes

Clear research questions were stated to all eleven studies with relevant results responding to each of them (*Table V*). Apart from Lu et al.,[24] all other studies depicted a hypercoagulopathy in the early post-burn period. Mitra et al.[25] found no difference in mortality between coagulopathic –

Table IV - Coagulopathy among included studies

Author & year of publication	Definition of coagulopathy	Hypercoagulopathy incidence	Non survivors with coagulopathy
Lavrentieva et al. (2008)[5]	ISTH DIC score: - PLT decreased - elevated fibrin related markers - prolonged PTT - decreased plasma fibrinogen	DIC (overt/nonovert): 91.1% (41/45)	15
Park et al. (2008)[23]	- high MA on TEG		
Lu et al. (2013)[24]	ATC: - INR >1.3 - PTT ratio >1.5times mean normal - normal PLT (150-440 X 10^9/L)	0% on admission	0
Mitra et al. (2013)[25]	acute coagulopathy: - INR >1.5 - PTT >60s - early onset: first 24h post-burn	acute coagulopathy: 37%	9
Sherren et al. (2013)[26]	ABIC: PT >14.6s PTT >45s	ABIC incidence: 39.3%	18
Sherren et al. (2014)[27]	coagulopathy: INR > 1.2	ABIC incidence: 39.3%	18
Tejiram et al. (2016)[28]	abnormal coagulation: -INR >1.5 -PTT >45s	- 0% on admission - 22% after 24h	5
Huzar et al. (2017)[29]	hypercoagulable r TEG parameters: - ACT <=97sec - α-angle >=76 degrees - MA >=65mm -hypocoagulable r TEG parameters: - ACT >=128sec - k-time >=2.5min - α-angle <=60degrees - MA <=55mm - LY-30>3%	hypercoagulable: 60%	14 hypercoagulopathy 7 hypocoagulopathy
Muthukumar V et al. (2019)[30]	coagulopathy: INR > 1.2 - hypothermia: T <35.5 - acidaemia: PH <7.25	Relative risk of mortality in the presence of lethal triad: 3.896	13
Kang et al. (2020)[1]	ABIC diagnostic criteria: - INR >1.2 - PT >14.6s - aPTT >45s	-ABIC incidence: 31%	15
Kaita Y et al. (2020)[31]	Acute coagulopathy: - PT – INR >1.5 - aPTT >60s	acute coagulopathy incidence: 13.1%	11
Total			125

ISTH = International Society of Thrombosis and Hemostasis; DIC = disseminated intravascular coagulation; PLT = platelets; MA = maximal amplitude; (r)TEG = (rapid) thromboelastography; ATC = acute traumatic coagulopathy; INR = international normalized ratio; PTT = partial thromboplastin time; PT = prothrombin time; ACT = activated clotting time; ABIC = acute burn induced coagulopathy

Table V - Summary of article inclusion / exclusion criteria and findings

Author & year of publication	N	Inclusion criteria	Exclusion criteria	Follow up	Outcomes
Lavrentieva et al. (2008)[5]	45	- Enrolled during the 1st 24h after burn - Severe thermal injury (TBSA >25%)	- <18years of age - hepatic/renal failure - malignancies - associated trauma - known hematological disease affecting coagulation - early burn wound excision (7 post burn days) - patients developed infectious complications	- 28days	- Mean time between burn injury and ICU admission: 6.2 +/- 2.4h (range 3.1-7.2h), biological parameters measured within 1h of ICU admission - non-survivors died at 13.4+-4.8d - DIC (overt/non overt): 91,1% (41/45) - on admission survivors had significantly lower TBSA, ABSI score, APACHE II SCORE, SAPS score, SOFA score than non survivors - DIC, age, APACHE II, TBSA, ABSI are significantly related to mortality on day 28 - overt DIC is significantly related to mortality - antithrombin, protein S, plasminogen activator inhibitor 1, SOFA on day 3, protein C on day 5, thrombin/antithrombin complexes on day 7 revealed a good prognostic value for ICU mortality
Park et al. (2008)[23]	58	- >18 years old - admission within 24h of injury - anticipated stay >72h		- 30days	- Six independent risk factors for death: percentage 3rd degree burns, inhalation injury, TNF, MA from r TEG parameters, MODS score - high MA is indicative of hypercoagulable state and an independent contributor of mortality in the model
Lu et al. (2013)[24]	102 15 died	- >18 years old - 15-100% TBSA	- electrical injury - other traumatic injuries requiring medical attention - patients in anticoagulants before injury or during the first 7days - patients with known bleeding disorders - patients with elapsed time from injury >12h to initial blood tests	- 7days	- mean time elapsed until first sample: 2h and 30min - no ATC on admission - screening hematologic profile on admission was not influenced by burn severity. Marginal association between TBSA and INR (P=0.051) - Significant differences in all test results (INR, APTT ratio, PLT, Hgb) on admission to those at day 2 - no association with increased blood utilization and 7-day mortality
Mitra et al. (2013)[25]	99	- adults - TBSA >20%	- patients initially received/treated to other hospitals and then transferred - other tissue conditions (such as toxic epidermal necrolysis) - palliative management in the first 24h - self-presented patients - with incomplete information		- acute coagulopathy: 37% (n=37) 3 admitted coagulopathic 24 became coagulopathic within 8h 7 became coagulopathic between 8-16h - TBSA, fluid administration, inhalational injury are independent predictors of early onset coagulopathy - early onset coagulopathy was associated with higher volumes of blood and blood product administration, ICU admission and prolonged mechanical ventilation - no significant difference in mortality between coagulopathic – non-coagulopathic (p=0.051)
Sherren et al. (2013)[26]	117	- all ages - severe thermal injuries TBSA > 30%	- major trauma - admission more than 12h post burn - suspected cyanide poisoning - pre-existing bleeding diathesis / anticoagulants administration - blood product/prothrombin complex concentrate administration - non-thermal injury, medical skin loss - any missing data entries - coagulation tests not completed on admission	- 28days	- the presence of coagulopathy was associated with increased TBSA, inhalational injury, incidence of full thickness and ABSI, lower base deficit, higher lactate - correlation between PT / ABSI - correlation between serum lactate with PT and ABSI - elevated ABSI and early coagulopathy were associated with increased 28d mortality - possible mortality predictors: coagulopathy, age, sex, inhalational injury, full thickness burn, TBSA
Sherren et al. (2014)[27]	117	- all ages - severe thermal injuries TBSA > 30%	- major trauma - admission more than 12h post burn - suspected cyanide poisoning - pre-existing bleeding diathesis / anticoagulants administration - non-thermal injury, medical skin loss - any missing data entries	- 28days	- lethal triad patients tend to be older and suffered from higher ABSI, TBSA burn, incidence of inhalation injury, full thickness burns - lethal triad group was under-resuscitated according to parkland - all components of the lethal triad were each individually associated with increased mortality

					- early coagulopathy and admission PH were independent predictors of mortality - lethal triad was associated with increased mortality
Tejiram et al. (2016)[28]	9	- thermal injuries, TBSA >25%	- chemical burn injuries - under 18years old - actively taking anticoagulants - not fluent in English/Spanish - presented more than 4h after injury - not fit for inclusion based on preexisting conditions	- 4days	- higher Baux & FLAME scoring for mortality patients, more acidotic - within 24h of admission, all patients had normal coagulation studies, only 2 patients were abnormal after decreased antithrombin and protein C activity were seen in all patients Increased PAP, D-dimers, fibrin monomer concentrations throughout their hospital course - at admission: increased IL6, IL10, decreased IL1b, TNF - extensive changes not identified by PTT, INR - patients who died were more susceptible to the lethal triad than those who survived.
Huzar et al. (2017)[29]	65	- >18 years old - >15% TBSA - intubated - hemodynamically unstable - direct scene transport - rTEG drawn on admission	- mixed trauma-burn patients - pre-injury use of anticoagulants - non thermal burns - died within 30 min of arrival		- hypercoagulable: 60% - hypocoagulable:24% - r TEG values predicted increased 24h resuscitation volumes, plasma and platelets transfusions - controlling for age, TBSA, base deficit: admission r TEG ACT>=128sec predicted a 5-fold increased likelihood of supra-normal resuscitation - α–angle <60 predicted in-hospital mortality - admission α–angle <60 degree predicted a 100% likelihood of requiring supra-normal resuscitation
Muthukumar V et al. (2019)[30]		- 18 – 60 years - thermal / scald burn - TBSA 50-70%	- trauma other than burn - >24h admission - preexisting co morbidities - missing fluid data in referral cases	- 30days	- lethal triad is seen in burn patients - burn associated with on admission lethal triad has significantly higher mortality rates
Kang et al. (2020)[1]	129	- age between 18-60 years - all burn types, TBSA > 50% - admission within the first 10 hours post-burn	- complicated with severe trauma Concomitant severe bleeding - predisposing bleeding tendency / use of anticoagulants - treatment with concentrated clotting factor supplements before admission - suspected cyanide poisoning - history of chronic hepatitis - history of blood diseases - history of malignant tumors - missing data on the coagulation profile after admission	- 4weeks	- TBSA burn, ABIC, inhalation injury as independent risk factors 4-week mortality in patients with extensive burns - TBSA burn, post burn admission time, lactic acid level on admission as independent risk factors for ABIC development - ABIC incidence: 31%
Kaita Y et al. (2020)[31]	137	- patients transported directly to the burn center	- cardiac arrest on arrival - carbon monoxide poisoning - chemical burn - electrical burn - inhalation injury without cutaneous burn - transfer from another hospital - missing data on lab tests		- acute coagulopathy of burn patients might be present on arrival to the hospital before fluid replacement - acute coagulopathy is an independent risk factor for the in-hospital mortality

TBSA = total body surface area; ABSI = abbreviated burn severity index; APACHE II = acute physiology and chronic health evaluation II; SAPS II = simplified acute physiology score; SOFA = sequential organ failure assessment score; ISTH DIC = International Society of Thrombosis Disseminated Intravascular Coagulation; PLT = platelets; INR = international normalized ratio; PTT = partial thromboplastin time; AT = antithrombin; PC = protein C; PS = Protein S; PAI-1 = plasminogen Activator Inhibitor 1; t-PA = plasminogen activator; TAT = thrombin-antithrombin complex; PAP = plasmin/a2-antiplasmin complexes; ICU = intensive care unit; ISS = injury severity score; TNF = tumor necrosis factor; MA = maximal amplitude; (r)TEG = (rapid) Thromboelastography; TRISS = trauma injury severity score; MODS = multiple organ dysfunction syndrome; ATC = acute traumatic coagulopathy; ACT = activated clotting time; ABIC = acute burn induced coagulopathy

non-coagulopathic patients, with a marginal p (p=0.051). Eight studies concluded that coagulopathy is associated with mortality of burn patients alone, or as part of the lethal triad – acidosis, coagulopathy, hypothermia.[1,5,23,26-28,30] Other parameters that are significantly related to mortality are: age,[5,26,30,31] sex,[26] APACHE II,[5] TBSA,[1,5,26,30,31] ABSI,[5,26,30,31] percentage 3rd degree burns,[23,26,30,31] inhalation injury,[1,23,26,30] TNF,[23] MA from r TEG parameters,[23] MODS score,[23] acidosis,[27,28,30,31] hypothermia,[27,28,30] Baux score,[28,31] FLAME score[28] BI, PBI and BOBI score,[31] WBC.[31] On the contrary, Huzar et al.[29] concluded that an α–angle <60 degrees on rTEG

on admission, which stands for hypocoagulability, predicted in-hospital mortality. Predictors of coagulopathy are: TBSA,[1,25,26,31] full thickness burn injury,[26,31] fluid administration,[25] inhalational injury,[25,26,31] ABSI score,[26,31] lower base deficit,[26] higher lactate,[1,26,31] and post burn admission time.[1] Coagulation incidence ranged from 0%[24,28] to 91.1%[1] regarding mean time of measurements from admission. Early onset coagulopathy was associated with higher volumes of blood and blood product administration,[25] ICU admission[25] and prolonged mechanical ventilation.[25] Despite the fact that Lu et al.[24] did not find any relationship between coagulopathy and mortality, significant differences were noted in all test results (INR, APTT ratio, PLT, Hgb) from admission to those at day 2. Furthermore, supra-normal resuscitation was predicted from an α–angle <60 degree on admission[1] and an ACT>=128s.[29]

Meta-analysis

Coagulopathy was modeled as a risk factor for mortality. Logarithm of odds ratio and the corresponding 95% confidence intervals were calculated. The majority of the studies showed an OR for coagulopathy for non-survivors. Only one study showed negative log OR, contradicting the results of other studies. Yet this value was accompanied with patients with both hyper and hypo coagulation status, due to examination of their coagulation profile with rTEG. Other studies supported increased odds for coagulopathy. Summarized log OR under random effects model was 0,78 (95% CI=0,63-0.93). Heterogeneity based on Cochran's Q for the studies was 12,96 (p=0,02), giving an I[2] value of 22,82 (*Fig. 2*).

Discussion

Burn patients in the ICU are high-risk patients with particular problems with coagulation. The up-to-date published papers are limited but needed to be reviewed before beginning a new research. The primary outcome was to summarize burn patients' characteristics and coagulation markers in the early post burn period and the secondary outcome was to
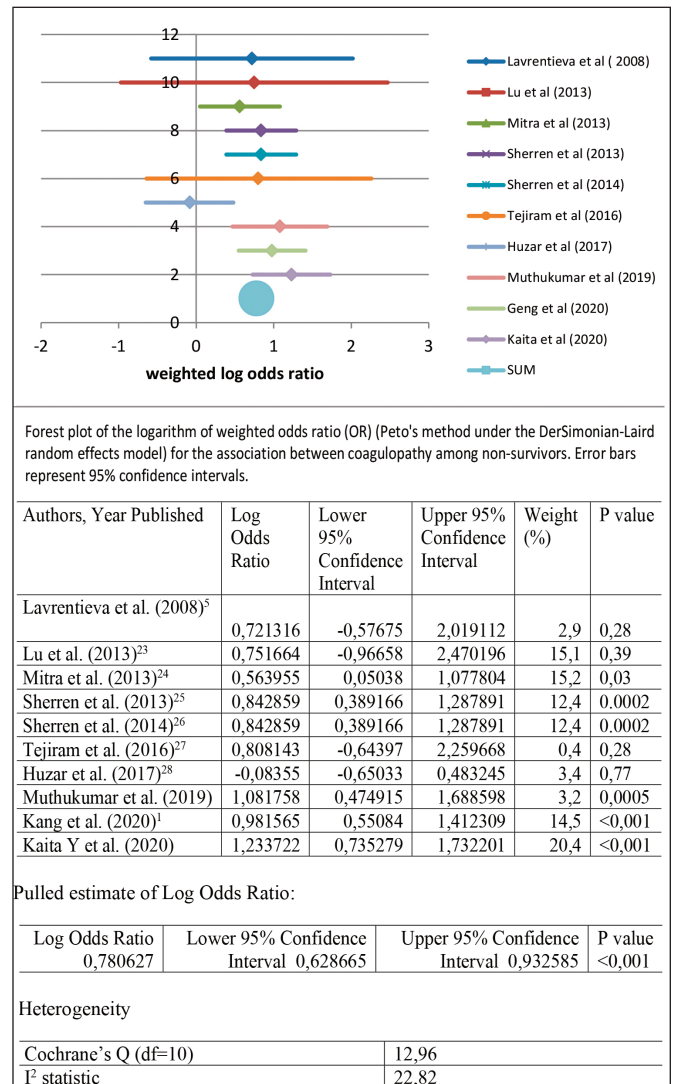

Forest plot of the logarithm of weighted odds ratio (OR) (Peto's method under the DerSimonian-Laird random effects model) for the association between coagulopathy among non-survivors. Error bars represent 95% confidence intervals.

Authors, Year Published	Log Odds Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Weight (%)	P value
Lavrentieva et al. (2008)[5]	0,721316	-0,57675	2,019112	2,9	0,28
Lu et al. (2013)[23]	0,751664	-0,96658	2,470196	15,1	0,39
Mitra et al. (2013)[24]	0,563955	0,05038	1,077804	15,2	0,03
Sherren et al. (2013)[25]	0,842859	0,389166	1,287891	12,4	0,0002
Sherren et al. (2014)[26]	0,842859	0,389166	1,287891	12,4	0,0002
Tejiram et al. (2016)[27]	0,808143	-0,64397	2,259668	0,4	0,28
Huzar et al. (2017)[28]	-0,08355	-0,65033	0,483245	3,4	0,77
Muthukumar et al. (2019)	1,081758	0,474915	1,688598	3,2	0,0005
Kang et al. (2020)[1]	0,981565	0,55084	1,412309	14,5	<0,001
Kaita Y et al. (2020)	1,233722	0,735279	1,732201	20,4	<0,001

Pulled estimate of Log Odds Ratio:

Log Odds Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	P value
0,780627	0,628665	0,932585	<0,001

Heterogeneity

Cochrane's Q (df=10)	12,96
I[2] statistic	22,82

Fig. 2 - Forest plot of data synthesis

investigate the coagulation profile of these patients in relation to mortality rates. This systematic review of the literature included eleven prospective and retrospective cohort studies. No randomized control studies were found.

Definition of coagulopathy & mortality

In order to detect coagulation abnormalities, routine assays were used from the majority of the included studies.[1,5,24-28,30,31,32] For diagnosis of coagulopathy, several thresholds were used among them. One study referred to "disseminated intravascular coagulopathy" (DIC) in burns, according to the ISTH criteria for DIC, with an incidence of 91.1%.[5] Another study borrowed from trauma patients the term "acute traumatic coagulopathy" in

order to describe burn coagulation dysfunction.[24] The thresholds were: INR greater than 1.3, aPTT ratio >1.5 times mean normal and normal PLT (150-440 X 10⁹/L).[24] In contrast with the previous study, no patient met these criteria on admission.[24] On the other hand, Mitra et al.[25] modified the thresholds of INR>1.5 and aPTT>60s according to recent studies of acute traumatic coagulopathies.[30] The same rigorous thresholds were used by Kaita et al.[31] "Early onset" was defined as coagulopathy in the first 24h post burns injury.[25] In this study, 37% of patients developed early onset coagulopathy, 71% of them were coagulopathic within 8h and 20.6% between 8-16h post-burn. For Kaita et al. 18% were coagulopathic on admission, prior to fluid administration.[31] Sherren et al.,[26,27] Kang et al.[1] and Muthukumar et al.'s[30] studies used the same cut-off points: INR>1.2, PT>14.6s, aPTT>45s for acute burn induced coagulopathy (ABIC). These cut-off values were consistent with the International Definition of Acute Traumatic Coagulopathy (ATC) by Davenport et al.[33] The incidence was 39.3% and 31% respectively. For Tejiram et al.[28] abnormal coagulation was defined as: INR>1.5 and PTT>45s, with 0% incidence on admission, 22% after. It is obvious that different thresholds in the diagnostic criteria are responsible for the inconsistency of the results. On the contrary, rTEG analysis of whole blood sample concluded that almost a quarter of patients were hypocoagulopathic on admission, which was also associated with higher mortality rates, even though the majority of the patients developed hypercoagulable status.[29] For studies with given data, a total of 768 burn patients, 170 deaths occurred, with 124 fulfilling criteria of coagulopathy (72.9%). This means that the majority of non-survivors were coagulopathic. Despite the differences in definition of coagulopathy among the eleven studies, we cannot ignore this huge percentage of coagulopathy in non-survivors. This review is the first that gathers information on non-survivors' hematological profile and exports a significant outcome that is difficult to be ignored, dismissing the arguments on burn coagulopathy. A prospective study on burn patients, comparing the accuracy of predicting coagulopathy throughout INR/PTT and TEG/ROTEM would be of great interest.

Severity of burn injury

The severity of the burn injury played an important role in the appearance and the onset time of coagulopathy.[25,26,33] In a retrospective study of 3331 patients, 14% of whom had burns >20% of TBSA,[34] 0.1% developed DIC, whereas in a prospective study of 45 patients, DIC was diagnosed in 91.1% with TBSA >25%.[5] In another study of burn patients with TBSA >15%, no case of acute coagulopathy was found,[24] another study with mean TBSA of 14.5% had 13.1% incidence of acute coagulopathy on admission, whereas in a study of patients with TBSA >30%, 39% met the defined criteria. In addition, the timing of the onset of coagulopathy was associated with the severity of the burn.[25,26] King et al. concluded that burns greater than 6% TBSA induced a systemic hypercoagulability, whereas severe burns of TBSA over 40% induced consumptive coagulopathy.[35] In a retrospective study, patients with TBSA >30%[26] (mean TBSA 49.3%), became coagulopathic earlier than patients with lower mean TBSA of 35.8%.[25] Also, a recent prospective study of patients with a mean TBSA of 49.8% concluded that 0% of admitted patients were coagulopathic and 22% became abnormal after.[28] It is obvious that the degree of induction of coagulopathy seems to be proportional to the TBSA%.[35] Also, the post burn admission time and the time of measurements greatly differentiated the result. Finally the existence of full thickness burn area[23,26] and inhalational injury[25,26] augmented the possibility of coagulopathy and an unfavorable outcome.

Acidosis, fluid resuscitation and hypothermia

Other parameters that seemed to influence the hematological status of burn patients were acidosis[1,26,28,30,31], fluid resuscitation[25,30,31] and hypothermia.[26,28,30] Base deficit and lactate are associated with tissue damage and according to previous studies are markers of morbidity and mortality.[38,39-41] Furthermore, longer periods of acidosis and lower PH on admission are associated with activation of coagulation and mortality in burn populations.[26,28] It is undeniable that resuscitation during the first 24 h post-burn is critical since it determines survival.[36] Kaita et al.[31] investigated the existence of coagulopathy before

fluid administration. They concluded that acute coagulopathy might be present before fluid replacement and it is an independent risk factor for in-hospital mortality.[31] On the contrary, over-resuscitation was associated with augmented morbidity and mortality.[36,37] Mitra et al. added to this knowledge that high volumes of crystalloid and colloid fluids were an independent predictor of early onset coagulopathy.[25] It is obvious that the existence of a marker acting as a guide for fluid administration would be of great importance. Huzar et al. using the more sensitive to coagulation disorders marker, r-TEG, concluded that hypocoagulopathic burn patients on admission are at higher demand for resuscitation and transfusion requirements.[29] Furthermore, Huzar et al. suggested that admission active clotting time (ACT) and α-angle could be the missing markers that could predict resuscitation needs since admission r TEG ACT>=128s predicted a 5-fold increased likelihood of supra-normal resuscitation and admission α–angle <60 degree predicted a 100% likelihood of requiring supra-normal resuscitation. Finally, it is well known that skin damage is associated with hypothermia leading to coagulation disorders, even from the first minutes post-burn. This hypothermia contributes to coagulopathy and as independent factor worsens acidosis.[42-44]

Surgical interventions

From escharotomies and fasciotomies for the avoidance of compartment syndrome, to debridement, excision and grafting, all types of surgical interventions affect the patient's mutable status. In order to eliminate this confounding factor, Lavrentieva et al.[5] chose to exclude patients who underwent any surgical intervention at the early post-burn period (first 7 days), whereas others chose to record them in association with blood product requirements.[23,24] For Lu et al.[24] more than half of the patients had some kind of surgery (56.8%) within the first 7 days after burn injury, and almost half of them required blood products. Unfortunately, the effect of surgery could not be depicted. As an exogenous factor of bleeding with usually high demands of blood products, surgery has a great involvement on coagulation profile, probably by altering the burn injury per se needs. A recent study measuring blood transfusion in major burn injury in the operating room

summarized that intraoperative monitoring and VCAs combined with a restricted transfusion strategy decreases by 50% transfusion needs, with no impact on morbidity–mortality compared to liberal transfusion policy, in accordance with similar studies.[45-50] Finally, Lu et al.[24] chose to include ten patients who did not receive active resuscitation and were treated with palliative measures due to their critical situation. This antidiametric to surgery "treatment" speeded up the studied population to the upper limits, clearly influencing the results.

Other coagulation markers

Apart from standard coagulation assays and viscoelastic parameters, other coagulation markers were also analyzed from two studies.[5,28] Anticoagulant activity was decreased through antithrombin and protein C in all patients. These parameters also revealed a good prognostic value for ICU mortality.[5] Furthermore, an augmentation of clot formation and fibrinolytic activity was observed throughout the patient's hospital course, since increased PAP, D-dimers, fibrin monomer concentrations were found.[27] These extensive changes were not identified by PTT, INR. It seems that these changes alter clot microstructure, leading to a weaker, fibrin clot.[51,52] A recent study measuring plasma fibrin degradation product (FDP) together with routine coagulative parameters and their relations with burn-severity concluded that the first increased significantly in burn patients, showing better and consistent correlation with burn-severity than routine coagulation parameters.[53]

Limitations and strengths of the study

No randomized controlled studies on burn patients were found. Cohort studies had clear eligibility criteria but small n-designs. Only one study used a validated control group for model development.[23] Studies also used different cut-off values and different tests, rendering the result interpretation and association difficult. Inclusion criteria differentiated between the included studies giving great heterogeneity of the studied population. From the age range, follow up time, to the burn type and the time of admission or enrollment, there were considerable deviations.

Despite the heterogeneity of the studies, important information was gained with a great clinical impact, pointing the way for future well-designed studies and the establishment of clear guidelines. Through this review we demonstrate the indubitable relationship between coagulopathy with burn injury and its significant impact on mortality.

Conclusion

Burn coagulopathy is an indisputable fact, which should be taken seriously into consideration regarding mortality from burn injury. A clear definition of this entity should be given for burn patients and recorded guidelines ought to be institutionalized for resuscitation and blood product needs. The rapid and dynamic process of coagulation makes standard coagulation assays unable to detect short-lived hemostatic changes. As a result, their use may underestimate the severity of the situation. More susceptible markers such as viscoelastic coagulation assays (VCAs) need to be applied to the daily and routine assessment of burn patients in order to obtain an overview of burn coagulopathy and standardize the gained knowledge. Additional prospective studies with clear scientific questions are necessary to clarify the bleak but intriguing field of burn coagulopathy.

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