BURNS 50 (2024) 569–577

Available online at www.sciencedirect.com

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Thromboembolic events in burn patients: An analysis of risk factors and different anticoagulants

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ARTICLE INFO

Article history:
Accepted 25 December 2023

Keywords:
Thromboembolic event
Thrombosis
Burns
Thromboprophylaxis

ABSTRACT

Background: Burn patients are in a state of activated coagulation, putting them at risk for thromboembolic events. Additionally, certain patient-related factors are associated with an increased risk of thrombus formation. This study aimed to evaluate the incidence of thromboembolic events and identify potential risk factors, including patient characteristics, surgical treatment, anticoagulation strategies, and laboratory parameters.

Methods: A single-centre retrospective cohort study was conducted on all patients with burns treated between 2002 and 2020. Medical reports of patients with and without thromboembolic events were descriptively analysed. The association of time to thromboembolic events with total body surface area (TBSA) was assessed by cause-specific Cox models adjusted for different covariates. The association of time to thromboembolic events with type and dosage of anticoagulants was assessed using a cause-specific Cox proportional hazards model with time-dependent covariates, applied to a matched subset of patients.

Results: The incidence of thromboembolic events was 8.1% in a cohort of 642 patients. We found a statistically significant increase in the hazard for thromboembolic events by a factor of 1.02 (95% CI 1.00 to 1.03; $P \leq 0.05$) per percent increase in TBSA. We identified former alcohol abuse (HR=2.54, CI 1.33 to 4.84, $P = 0.005$) and higher body mass index (HR=1.06, 95% CI 1.00 to 1.12, $P = 0.046$) as potential risk factors for the development of thromboembolic events. We further noted inadequate median anti-Factor-X activity levels and elevated C-reactive protein and procalcitonin levels at the time of the event.

Conclusion: Our results showed a moderate risk of thromboembolic events among burn patients, underlining the importance of close monitoring with regard to thrombus

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https://doi.org/10.1016/j.burns.2023.12.014

formation. In particular, patients with higher TBSA, alcohol abuse and BMI may be evaluated more regularly for thromboembolic events. Anti-Factor-X activity levels should be determined regularly and therapy should be adjusted if necessary.

1. Introduction

The reported incidence of thromboembolic complications among burn patients shows great variability ranging from 0.25% in retrospective studies to 23.3% in prospective studies in which ultrasound screening was performed [1–9]. It is well known that burn patients are in a state of increased inflammatory activity and activated coagulation [10]. All of which are apparent in patients following thermal injury, namely changes in blood flow rates due to prolonged immobilisation and multiple surgical interventions, endothelial injury, and hypercoagulability. The latter not only results from the inflammatory response but also from the endothelial damage caused by repeated surgical interventions and microtrauma by central catheters [3,7,9,11].

During thermal injury, tissue damage leads to the exposure of the subendothelial tissue factor, which acts as a trigger for the coagulation cascade. Furthermore, the release of cytokines, as part of the inflammatory response, causes additional activation of clotting factors [12]. Platelets are significantly activated, leading to a platelet count nadir around day 3 after burn followed by thrombocytosis with a peak at day 15 to 21 due to the consecutively high thrombopoietin levels [12–16]. Garcìa-Avello et al. showed that burn patients are hypercoagulable as well as hyperfibrinolytic on day one after the injury, given elevated levels of activated factor VII, thrombin-antithrombin-III-complex, tissue-plasminogen activator and D-Dimer, with simultaneously low levels of Antithrombin III (ATIII), protein C, plasminogen and alpha-2-antiplasmin [17,18]. All these changes lead to coagulation system dysfunction and hence elevate the risk for thromboembolic events, explaining why burn patients are generally considered amongst the highest risk group for developing thromboembolic complications. Although not all patients develop an acute coagulopathy after thermal injury, the complication has been shown to be independently associated with %TBSA, hence posing the highest risk for patients with extensive burns [19].

In addition to the aforementioned pathomechanisms, patient-related risk factors have been shown to be associated with a higher incidence of venous thromboembolic events (VTE). These include older age, high percentage of burnt total body surface area (TBSA) [3], higher body mass index (BMI), wound infections [1,8,9,20,21], male sex, smoking and alcoholism [2], with increased percentage of TBSA as the major driver of VTE risk trumping other patient-related risk factors [21]. Furthermore, multiple studies have described treatment-related risk factors such as the use of central venous catheters, long or multiple surgical operations and multiple blood transfusions (> 4) [5,20].

While the benefit of thromboprophylaxis in burn patients is undisputed, a number of studies have shown that burn patients show increased heparin resistance, meaning that higher dosages of heparin are necessary to achieve adequate prophylactic levels [22,23]. Recently, it was demonstrated that in almost 50% of burn patients, target anti-factor-X activity (aFXa) levels could not be achieved on standard prophylactic doses [22]. Beside this, side effects such as bleeding or even the development of heparin-induced thrombocytopenia (HIT) have to be considered in that patient cohort, prompting a meticulous risk-benefit analysis and close monitoring of anticoagulant activity.

An understanding of possible risk factors that aggravate the course of disease and possibly increase the risk for thromboembolic events among burn patients is vital for the identification of at-risk patients, early diagnosis, and treatment of patients with thromboembolic complications. Considering the complex physiological processes and multimodal systemic therapy in patients with burns, the validity of existing studies is limited because of their restrictions on a few parameters.

The goal of this study was to evaluate the incidence of thrombotic complications and HIT syndrome in our cohort of 642 severely burned patients with a TBSA ≥ 10% and to identify risk factors among over 130 variables, including patient characteristics, surgical treatment, anticoagulation, and laboratory parameters. Although a number of studies with a similar aim have been conducted in the past years, to our knowledge, this is the first study to analyse such a broad range of variables and interrelate them.

2. Methods

A single-centre retrospective cohort study was conducted at the Department of Plastic Surgery and Hand Surgery of the University Hospital Zurich, analysing the data of severely burned patients with respect to the development of thromboembolic complications during hospital stay as well as possible risk constellations. All patients were admitted to and treated at the University Hospital Zurich between 01.01.2002 and 31.12.2020. The study was approved by the Central Ethics Committee of Zurich, Switzerland (Ethical approval Nr:2020–02897). A general consent form was obtained from all patients admitted to the University Hospital Zurich in 2016. Surrogate consent was provided by the Cantonal Ethics Committee of Zurich for patients admitted before 2016, as well as for patients who died before consent could be obtained.

All patients who were 18 years or older at the time of admission and presented with a TBSA of 10% or more were included in the study. This cut-off was chosen since the systemic effect of burns < 10% TBSA are expected to be minor. Traditionally, burns > 10% TBSA in children < 10 years and elderly > 50 years or > 20% TBSA in adults respectively are considered severe [24] and hence inflict relevant systemic response. Considering that the average age of patients included in the study was approximately 46 years, a cut-off at 10% TBSA seemed most representative. Patients with and without

coexisting inhalation injuries were included in the study. Patients who either died or were transferred within 24 h after hospital admission were excluded from the study, as were patients who suffered a thromboembolic complication before transfer to the University Hospital Zurich. If venous thrombosis was suspected, the diagnosis was confirmed by ultrasonography. In patients in whom pulmonary embolism was strongly suspected, CT imaging was the modality of choice to establish the diagnosis.

Information on over 130 variables was collected, including the following: age, sex, BMI, comorbidities, substance abuse, mechanism of burn injury, TBSA, abbreviated burn severity index (ABSI), number of operations, occurrence of thromboembolic events defined either as venous thrombosis, thromboembolism, or arterial thrombosis; occurrence of HIT syndrome, type and dosage of anticoagulant (including unfractionated heparin (UFH), low molecular weight heparin (LMWH) and phenoprocoumons, novel oral anticoagulants (NOACs), heparinoids, hirudins or argatroban, defined as "other") used as well as laboratory parameters, namely aFXa, levels of C-reactive protein (CRP) and procalcitonine (PCT), percentage of haematocrit (HC) and amount of thrombocytes at defined time points during the hospitalisation period (on admission and on days 1, 3, 7, 14, 21 after hospitalisation) as well as particular time points (48 and 24 h as well as at the time of diagnosis) prior to the occurrence of thromboembolic events. In addition, the date of the accident, hospital discharge, and/or death were obtained to account for right censoring.

All data analyses were performed using the R software (version 4.2.2) [25]. Baseline characteristics, characteristics of treatment and laboratory parameters during the first 21 days of hospital stay were descriptively analysed for patients with and without thromboembolic events. For patients with thromboembolic events, we also analysed laboratory parameters within 48 h prior to thromboembolic events. Mean and standard deviation were calculated for continuous variables with approximately normal distribution, median and interquartile range for ordinal variables or continuous variables with skewed distribution, and frequency and percentage for categorical variables. Due to a large proportion of missing values for BMI, we used multiple imputation with m= 20 imputations per missing value, as implemented in the R package mice [26]. To assess the association of TBSA with time (after hospitalisation) to thromboembolic events, we used cause-specific Cox proportional hazards models. Patients without thromboembolic events were censored at hospital discharge, and patients who died in the hospital were censored on the date of death, as death is a competing event to thromboembolic events. In addition to TBSA, we determined the most important explanatory variables: sex, age, BMI, alcohol abuse, nicotine consumption, hypertension, and diabetes mellitus. Because there were too many variables compared to the number of thromboembolic events events to fit in one model or to perform a variable selection, we decided to fit two alternative models including different sets of explanatory variables (model 1: TBSA, sex, age, and BMI; model 2: TBSA, alcohol abuse, nicotine consumption, hypertension, and diabetes mellitus). A posteriori, we fitted a third model including the three variables from models 1 and 2, which had the clearest association with thromboembolic events in these models (with $P < 0.1$). The models containing BMI (models 1 and 3) were fitted to the multiply imputed data, the results were pooled using Rubin's rules [27]. Model 2 was fitted to the original data. To assess the association of different anticoagulant therapies and their dosage with the time to thromboembolic events, a matched dataset was created, and for the patients in the matched set, detailed, time-varying data on anticoagulant therapies during hospitalisation (up to seven different prescriptions per patient) were collected. A 1:2 case-control matching was performed using the genetic matching algorithm as implemented in the R package MatchIt [28]. We matched two controls without thromboembolic events to each thromboembolic events patient based on the variables age, sex, TBSA and year of accident. The year of the accident was chosen to prevent bias due to improved case documentation. During data retrieval, a previously undetected thromboembolic events in a patient was detected, resulting in one matched triplet with two thromboembolic events and one control thromboembolic events. The matched data set was analysed using a cause-specific Cox proportional hazards model with time-dependent covariates for the type of anticoagulant (LMWH or others vs. UFH) and dosage of anticoagulant (therapeutic, subtherapeutic, highly prophylactic, or unknown vs. prophylactic). In addition, alcohol abuse was used as a patient-related covariate, which had not been accounted for in the matching process but was shown to be important in models 2 and 3.

3. Results

We included 642 burn patients who were treated between 01.01.2002 and 31.12.2020. Detailed screening and inclusion processes are shown in Fig. 1. The mechanisms of burns are as follows: explosion, implosion, fire, flame or electric arc, flow of electricity, chemical burn, or scald. Of the total of 642 patients, 52 patients (8.1%, 95% CI 6.2% to 10.5%) developed one or more thromboembolic events during their hospital stay, with 11 pulmonary embolisms, 38 venous thromboses, and 3 thromboembolisms. Seven patients (1.1%; 95% CI 0.5% to 2.3%) developed HIT. We identified 110 patients (17.1%) who died during the hospital stay. Death was related to thromboembolic events (defined as death within 48 h of TE) in 4 patients or 0.36% of the cases. The number of days to thromboembolic events varied between 2 and 68 days, with a median of 22 days.

On admission, patients with thromboembolic events were on average 47.29 ± 18.9 years old, and patients without thromboembolic events were 45.75 ± 15.24 years old (Table 1). In both groups, almost three-quarters of the patients were male (75% of patients with TE and 72.7% of patients without TE).

Non-thromboembolic event patients showed an average TBSA of 25.11 ± 16.83, while TE patients showed a considerably higher TBSA of 36.88 ± 19.62 was observed (standard mean difference, SMD=0.64). Patients with thromboembolic events on average also showed a higher ABSI score (8.40 vs. 6.75, SMD=0.7) and BMI (27.09 vs. 26.75, SMD=0.2) than non-thromboembolic event patients. Furthermore, patients with thromboembolic events suffered from diabetes more often (13.5% vs. 6.6%, SMD=0.23) and more frequently had a history of alcohol abuse (26.9% vs. 12.5%, SMD=0.37) and cocaine consumption (3.8% vs. 0%, SMD=0.28) than non-thromboembolic event patients. Patients with TE more often showed burns by flame, fire, or light arch, as well as current flow; however, they were less likely to exhibit burns by scalding or explosions. In total, 4

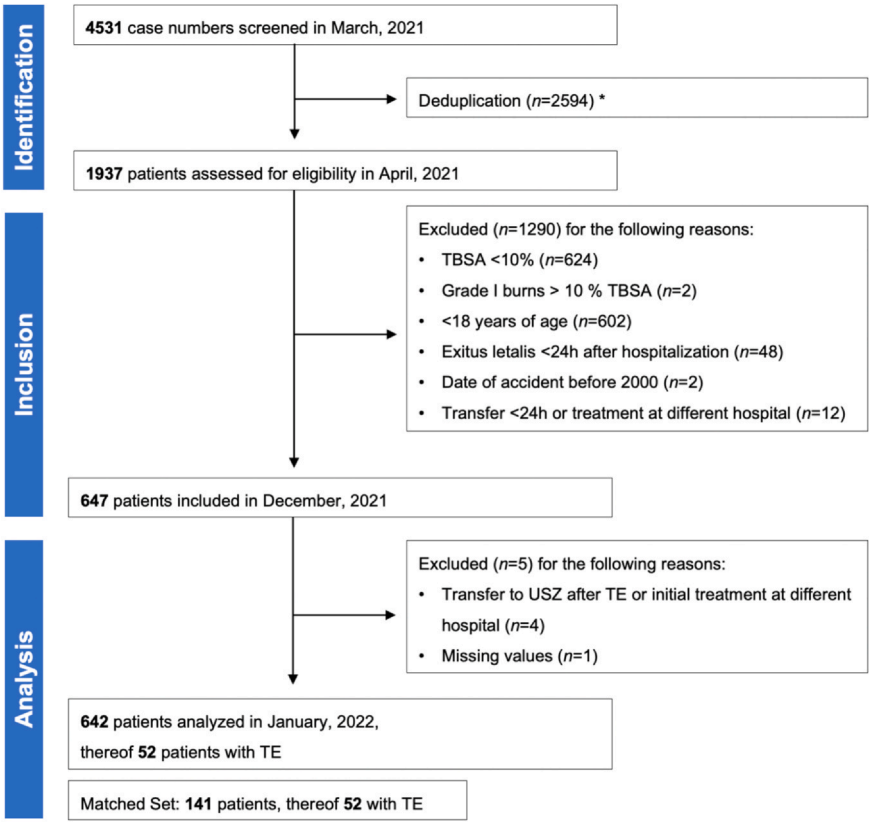

Fig. 1 – Flow-chart Diagram of the screening and inclusion process. * Some patients were displayed twice f.e. due to several case numbers per patient, multiple thromboembolic events, or thrombosis during a later hospitalisation, for example, in the course of secondary reconstruction. In total, 4531 case files were screened, and duplicate files were excluded so that each patient was represented once within the cohort. The remaining patient files were evaluated based on inclusion and exclusion criteria. All the included patients were screened for thromboembolic events.

patients suffered from thrombophilia in our study. Moreover, 8 patients suffered from malignant neoplasms and 2 from thalassaemia, both of which potentially influence coagulation function. Unfortunately, the number of patients suffering from haemophilic or hypercoagulable disorders was too small for further statistical analysis. All baseline characteristics are summarised in Table 1.

The treatment-related risk factors (accumulation after admission) are summarised in Table 2. Non-TE patients underwent a median of 2 operations [2 to 4] and thromboembolic events patients underwent a median of 6 [3 to 11] operations (SMD=0.85, Table 2). Furthermore, patients with thromboembolic events were treated less often with LMWH (SMD=0.54). The dosage of anticoagulation (prophylactic and therapeutic) was similar between patients with and without thromboembolic events (SMD < 0.2). Five patients did not receive a prophylaxis, mostly due to the presence of advanced DIC and associated high risk of bleeding. The initial dosage was determined by using a standardised formula depending on body weight and adjusted according to the aFXa level.

Approximately 50% of thromboembolic events occurred within 3 weeks of admission (median, 22 days), for which time frame data on laboratory parameters were collected. We showed that HC and TC levels were higher on admission in TE patients than in non-TE patients; however, they were relatively higher in non-thromboembolic event patients from day 3 onwards (Supplemental Digital Content Table 1). HC and TC levels remained more or less consistent within 48 h to a TE Supplemental Digital Content Table 2). PCT and CRP levels were similar in both groups on admission and showed a subsequent increase with a higher median in patients with thromboembolic events (Fig. 2 and Supplemental Digital Content Table 1). Both CRP and PCT levels were elevated at the time of the event compared to 48 and 24 h prior to the event (Fig. 3; CRP 185 mg/l from 165 mg/l, PCT 0.57 ug/l 0.45 ug/l). Thromboembolic event patients showed a slightly lower mean aFXa but a slightly higher median activity 14 days after hospitalisation, with hardly any difference in the mean aFXa, but a slightly lower median aFXa at day 21. The median aFXa level 48 h prior to TE was slightly below 0.1 IU/ml.

Three cause-specific Cox models adjusted for different sets of covariates provided moderate evidence for an association between TBSA and the hazard for TE (Table 3). The hazard ratio (HR) for TBSA (in %) was consistently estimated as 1.02 (95% CI 1.00 to 1.03, $P \leq 0.05$) by all three models, which corresponds to an increase in the hazard by a factor of 1.02 per percent increase in TBSA. We observed a significant association between the hazard for thromboembolic events and former alcohol abuse (HR=2.54, CI 1.33 to 4.84, $P = 0.005$, model 3) and higher BMI values (HR=1.06, 95% CI 1.00 to 1.12, $P = 0.046$, model 3). Associations between the hazard for

Table 1 – Baseline characteristics of burn patients in our study.

	Patients without TE[a]	Patients with TE[a]	SMD[b]
n	590	52	
Female sex, *n*. (%)	161 (27.3)	13 (25.0)	0.052
Age, mean ± SD, years	47.29 ± 18.90	45.75 ± 15.24	0.090
BMI, mean ± SD, kg/m^2[c]	26.05 ± 4.58	27.09 ± 5.54	0.204
TBSA, mean ± SD, %	25.11 ± 16.83)	36.88 ± 19.62	0.644
ABSI score, mean ± SD	6.75 ± 2.37	8.40 ± 2.34	0.703
Nicotine abuse, *n* (%)	193 (32.7)	19 (36.5)	0.080
Cannabis consumption, *n* (%)	13 (2.2)	1(1.9)	0.020
Cocaine consumption, *n* (%)	0 (0.0)	2(3.8)	0.283
Alcohol abuse, *n* (%)	74 (12.5)	14 (26.9)	0.367
Arterial hypertension *n* (%)	125 (21.2)	12 (23.1)	0.046
Coronary artery disease, *n* (%)	28 (4.7)	2(3.8)	0.044
Cerebrovascular disease, *n* (%)	5 (0.8)	0(0.0)	0.131
Diabetes mellitus, *n* (%)	39 (6.6)	7 (13.5)	0.230
Polytoxicomania, *n* (%)	17 (2.9)	2(3.8)	0.054
Chronic hepatitis, *n* (%)	15 (2.5)	0(0.0)	0.228
Liver cirrhosis, *n* (%)	3 (0.5)	0(0.0)	0.101
HIV, *n* (%)	6 (1.0)	0(0.0)	0.143
Immunosuppression, *n* (%)	3 (0.5)	0(0.0)	0.101
Malignant neoplasia, *n* (%)	7 (1.2)	1(1.9)	0.060
Thrombophilia, *n* (%)	4 (0.7)	0(0.0)	0.117
Thalassaemia, *n* (%)	2 (0.3)	0(0.0)	0.082
Cause of accident, *n* (%)			
Chemical burn	6 (1.0)	0(0.0)	0.452
Current flow	23 (3.9)	4(7.7)	
Explosion	77 (13.1)	3(5.8)	
Flame / Fire / Electric arch	371 (62.9)	40(76.9)	
Implosion	1 (0.2)	0(0.0)	
Scalding	112 (19.0)	5(9.6)	

[a] Means ± SD are given for continuous variables and frequencies and percentages for categorical variables.
[b] SMD: standardised mean difference.
[c] BMI had 24.5% missing values. All other variables were available for all the patients.

Table 2 – Characteristics of treatment during hospital stay.

	Patients without TE[a]	Patients with TE[a]	SMD[b]
n	590	52	
Number of operations, median [IQR]	2 [2 to 4]	6 [3 to 11]	0.852
Anticoagulation with UFH after hospitalisation, *n* (%)[d]	374 (72.3)	38 (77.6)	0.120
Anticoagulation with LMWH after hospitalisation, *n* (%)[d]	129 (25.0)	3 (6.1)	0.538
Prophylactic anticoagulation after hospitalisation, *n* (%)[e]	487 (97.0)	39 (95.1)	0.097
Therapeutic anticoagulation after hospitalisation, *n* (%)[e]	15 (3.0)	2 (4.9)	0.097

[a]Median and interquartile range [IQR] are given for the number of surgeries, frequency, and percentage for categorical variables.
[b]SMD: standardised mean difference
[c]The variable number of surgeries had 0.8% missing values.
[d]The variables anticoagulation with UFH after hospitalisation and anticoagulation with LMWH after hospitalisation had 11.8% missing values.
[e]The variables of prophylactic anticoagulation after hospitalisation and therapeutic anticoagulation after hospitalisation had 15.4% of missing values.

thromboembolic events and sex, age, hypertension, diabetes mellitus, and nicotine were not significant.

The cause-specific Cox model fitted to the matched dataset showed no statistically significant associations between type and dosage of anticoagulant therapy and the hazard for thromboembolic events (Supplemental Digital Content Table 3).

Regarding the type of anticoagulant therapy, the cause-specific Cox model fitted to the matched dataset suggests a reduced risk for thromboembolic events when patients received LMWH (HR = 0.59, 95%CI 0.254 to 1.3617, p = 0.22), other (HR = 0.34, 95%CI 0.0398 to 2.8408, p = 0.32), or unknown (HR = 0.89, 95%CI 0.2651 to 2.9632, p = 0.84) anticoagulant substances compared to UFH (reference category).

4. Discussion

The results of our study showed a thromboembolic events incidence of 8.1% in burn patients with a TBSA ≥ 10% and a statistically significant association between the hazard for thromboembolic events and increased TBSA values. We further identified former alcohol abuse and higher BMI as

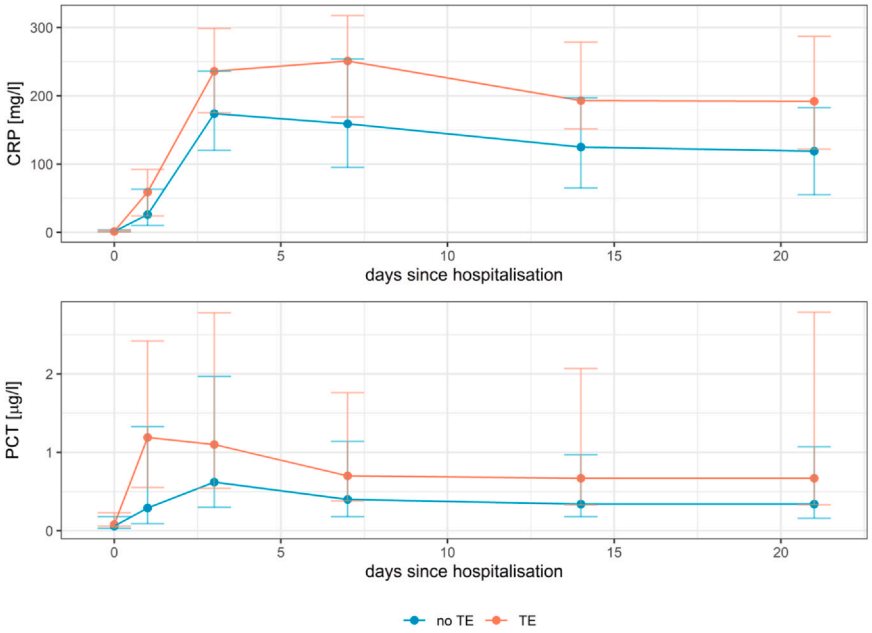

Fig. 2 – Median and IQR of CRP and PCT in TE and non-TE patients. Values for CRP are shown in the top panel and values for PCT in the bottom panel. Patients with TE are shown in red, whereas non-TE patients are shown in turquoise. The x-axis represents the time in days after hospitalisation.

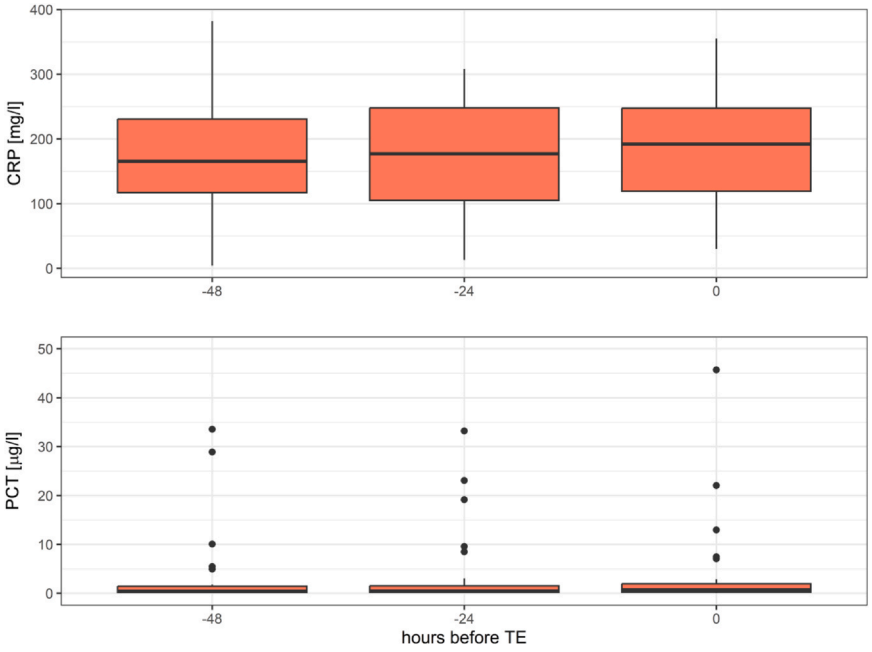

Fig. 3 – Boxplots of CRP and PCT in TE and non-TE patients prior to the TE. Values for CRP are shown in the top panel and values for PCT in the bottom panel. Patients with TE are shown in red, whereas non-TE patients are shown in turquoise. The x-axis represents the time in hours before the TE Event. Boxplots show the median (thick horizontal line), IQR (box height), and range of values (whiskers and bullets). Whiskers extend from the box to the minimum/maximum value that is still within the range of 1.5 * IQR from the box. Values outside this range (outliers) are shown in bullets. Note that one outlier for PCT (> 150 µg/l, 24 h before TE) is not shown to optimise the display of the main bulk of data.

Table 3 – HR estimates with 95% confidence intervals (CI) from three cause-specific Cox models on time to TE.

	HR and 95% CI	P
Model 1		
TBSA (%)	1.02 (1.00 to 1.03)	0.05
Female vs. male sex	1.07 (0.55 to 2.08)	0.83
Age at hospital entry	1.00 (0.98 to 1.02)	0.86
BMI (kg/m^2)	1.05 (1.00 to 1.11)	0.068
Model 2		
TBSA (%)	1.02 (1.00 to 1.03)	0.013
Alcohol abuse	2.57 (1.32 to 5.02)	0.006
Nicotine abuse	0.85 (0.46 to 1.58)	0.61
Arterial hypertension	0.93 (0.45 to 1.90)	0.84
Diabetes mellitus	1.98 (0.82 to 4.79)	0.13
Model 3		
TBSA (%)	1.02 (1 to 1.03)	0.017
Alcohol abuse	2.54 (1.33 to 4.84)	0.005
BMI (kg/m^2)	1.06 (1 to 1.12)	0.046

Death was considered a competing event. Results of model 1 and 3 were pooled over 20 imputed data sets (imputing missing BMI values) using Rubin's rules. The total number of patients included in all models was 641, with 52 TE events. One patient was excluded because of a missing accident date.

patient-related risk factors for the development of thromboembolic events. No significant associations were found between therapy-related risk factors (type and dosage of anticoagulants) and the hazard for thromboembolic events, but our data suggest a decreased hazard for thromboembolic events when LMWH is administered compared to UFH.

The incidence of thromboembolic events in burn patients shows high variability in the literature, depending on the cohort size, TBSA range, definition of thromboembolic events, and study design. The incidence of thromboembolic events, including any arterial and venous thromboembolic complications, among our cohort ranks in the middle compared to the incidences reported thus far, with much higher incidences found in prospective studies. Wahl et al. found an incidence of 23.3% for deep vein thrombosis (DVT) and 3.3% for pulmonary embolism among a cohort of 30 burn patients who received either LMWH or mechanical compression devices and were screened repeatedly using duplex ultrasound [29]. In contrast, other authors reported an incidence of DVT of only 6.08% despite the absence of prophylaxis [1]. Of note, both studies described that more than half of the patients with thrombosis were asymptomatic. The reported incidence of thromboembolic events in retrospective studies is significantly lower because screening is performed only when symptoms are present. Fecher et al. found an incidence of DVT of 0.25% in 4102 patients, when screening was only performed after clinical suspicion [3]. More recently, a nationwide study in the US reported an incidence of DVT of 0.8% [7], that is similar to another study that found an incidence of thromboembolism of 0.6% among 33′637 burn patients [4]. None of the studies included arterial thromboembolic events. In line with our results, the above-mentioned studies observed a higher risk for TE in patients with higher %TBSA. Pannucci et al. observed the highest incidence in patients with 40–59% TBSA, with a lower incidence among more severely burned patients [4]. However, this most likely does not represent an actual decrease in the incidence of thromboembolic events, but is rather due to a higher mortality rate within this cohort (with death not being considered a competing event).

Half of the thromboembolic events in our study were diagnosed within three weeks of hospital admission (median, 22 days). In contrast, Wahl et al. found an average time to diagnosis of only 6.7 days when repeated screening was performed [29], while Wibbenmeyer et al. and Fecher et al. found that the average time to clinical diagnosis was 12.2 and 13.1 (median, 11) days, respectively, [1,3]. However, longer times to event are also described in the literature. Gao et al. found that most patients with thromboembolic events were diagnosed after the 20th day post-burn [8]. because of the large variance, which is also influenced by the study design, it is difficult to define a time period in which the risk is highest. Nevertheless, we conclude that if thromboembolic events is suspected within the first three weeks, diagnostics should be initiated promptly and thoroughly to rule out thrombotic complications or adjust therapy if necessary.

Concerning patient-related risk factors, we were able to show that alcohol abuse was particularly associated with an increased risk of thromboembolic events. This is consistent with the findings of Mullins et al. who identified alcoholism, in addition to male sex and smoking, as possible predisposing factors for developing DVT [2,17]. Studies found that although platelet aggregation and thromboxane A2 release were inhibited in chronic alcoholics upon hospital admission, these abnormalities tended to return to normal after 2 weeks of abstinence. Overcorrection, as observed in some cases, results in thrombocytosis and enhanced platelet aggregation and thromboxane A2 release, which increases the risk of thromboembolic events in these patients [30].

Furthermore, our results showed that patients with thromboembolic events had to undergo more surgeries during hospitalisation. Pannucci et al. found a similar relationship, with each additional operative procedure increasing the odds of VTE by 1.041 [4]. However, patients with higher TBSA typically need more operations and seem to have a higher risk for associated thromboembolic events. Consequently, the association between the number of operations and the risk of thromboembolic events could be solely due to TBSA as a common cause.

Our results suggest a higher incidence of thromboembolic events in patients who received UFH for thromboprophylaxis than in those who received LMWH alone. This finding is supported by Busche et al., who found a VTE incidence of 3.8% among patients treated with UFH, compared to 0.9% in patients who received prophylactic LMWH [31]. A possible explanation for the lower incidence of TE among patients receiving LMWH is that those patients tend to show less severe burns (on average 13.5% TBSA) and mobilisation can start earlier. The half-life of UFH is significantly shorter than that of LMWH, making UFH more controllable and favourable in the ICU setting or when multiple operations are necessary. Due to the high percentage of missing data points on thromboprophylaxis in our cohort, it was difficult to draw final conclusions.

In patients with thromboembolic events, we found the median aFXa at the time of the event to be below the level required for adequate prophylaxis, suggesting a reduced dose-response relationship among burn patients. Several

studies have reported that target aFXa levels were not achieved with standard prophylactic doses in 50–79% of cases [22,23]. The reduced dose-response relationship of heparin in burn patients is based on the following mechanisms:

Relative hypoperfusion due to reduced cardiac output resulting from capillary leak after thermal injury, reduced bioavailability of heparin due to oedema formation, increased clearance of drugs approximately 48 h post-burn, when patients enter a hyperdynamic state [23], and lower ATIII levels [10,12,32]. In fact, Cato et al. demonstrated that 76.7% of patients showed an aFXa of < 0.2 within the first two weeks post-burn despite adequate prophylactic LMWH administration. Moreover, low ATIII levels were detected in 56.7% of patients [12]. Hence, close monitoring of anticoagulant activity is of paramount importance in patients with burns. In previous years, the debate has focused on whether routine prophylaxis is justified, considering the risk of adverse events, such as HIT or severe bleeding. However, recent studies have shown that complications from thromboprophylaxis are rare [3] with an incidence of HIT of 1.1%. Our study is comparable to the incidence of complications in burn patients receiving thromboprophylaxis, which is estimated to be 0.5–2.5% [20].

We further noted elevated CRP and PCT levels at the time of the event, as well as an increase in both parameters within the first 21 days post-burn (with a median time to thromboembolic events of 22 days) among thromboembolic events patients compared to the non-thromboembolic event group. Although a steady increase in CRP and PCT is to be expected, it is striking that inflammatory markers peak at 21 days, around which time we see an accumulation of thromboembolic events. This observation suggests that inflammatory processes play a pivotal role in thrombus formation and should be closely monitored in the clinical setting. Previous studies have shown that increasing CRP and PCT levels are associated with an increased risk of mortality, especially in the context of sepsis, and denote a poor prognosis [33]. Although not analysed in this study, it is important to keep in mind that the pathophysiologic changes induced by sepsis closely resemble those induced by thermal injuries, hence making it difficult to distinguish between a sepsis-induced and a burn-induced coagulopathy. Due to the loss of a skin barrier and hence high level of exposure as well as therapy-related risk factors such as the frequent use of indwelling catheters, a possible source of infection is present in most patients. Furthermore, there is a strong probability for burn patients to present with > 2 SIRS criteria due to the mechanism of injury and following shock, hence making the presence of a sepsis in this cohort highly likely. A high degree of suspicion and early treatment with antibiotics is indicated.

Our study has several limitations, most of which were the result of its retrospective design, with incomplete data being the most impending. Data, especially on anticoagulation practice, are lacking for patients admitted between the early 2000 s and 2010. Furthermore, the incidence of thromboembolic events in a retrospective study may be underestimated because methods such as universal screening, which may also have contributed to the statistical analysis of thromboembolic event-related risk factors, were not included. Nevertheless, this study provides new insights into specific risk factors for thromboembolic events formation.

5. Conclusions

Based on a cohort of 642 patients with burns who were treated during the last 18 years, we assessed the associations between risk factors and the risk of thromboembolic events. Thus, patients with a higher TBSA, previous alcohol abuse, and higher BMI should be monitored more closely with regard to laboratory parameters and evaluated more regularly for thromboembolic events, for example using ultrasound screening. In general, we propose strict aFXa level surveillance at least once a day in all patients with thermal injuries, with appropriate therapeutic adjustments to minimise the risk of thromboembolic events and hence reduce morbidity and mortality in this patient cohort due to thromboembolic complications.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors made substantial contributions to all of the following: (1) the conception and design of the study, analysis and interpretation of data, (2) drafting the article or revising it critically, (3) and final approval of the version.

CRediT authorship contribution statement

Claudine Schaller: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Visualization. **Anouk Petitpierre:** Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Stefanie von Felten:** Methodology, Validation, Formal analysis, Writing – original draft, Visualization, Supervision. **Daniel Rittirsch:** Conceptualization, Writing – review & editing. **Bong-Sung Kim:** Conceptualization, Writing – review & editing. **Pietro Giovanoli:** Writing – review & editing, Supervision. **Lisanne Grünherz:** Conceptualization, Methodology, Investigation, Validation, Writing – original draft, Visualization, Supervision. **Nicole Lindenblatt:** Conceptualization, Investigation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicole Lindenblatt reports a relationship with Medical Microinstruments that includes: consulting or advisory and speaking and lecture fees.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2023.12.014.

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