Inhalation Injury is Associated with Endotheliopathy and Abnormal Fibrinolytic Phenotypes in Burn Patients: A Cohort Study.

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Abstract

Burn injury is associated with endothelial dysfunction and coagulopathy and concomitant inhalation injury increases morbidity and mortality. The aim of this work is to identify associations between inhalation injury (IHI), coagulation homeostasis, vascular endothelium, and clinical outcomes in burn patients. One-hundred and twelve patients presenting to a regional burn center were included in this retrospective cohort study. Whole blood was collected at set intervals from admission through 24 hours and underwent viscoelastic assay with rapid TEG (rTEG). Syndecan-1 (SDC-1) on admission was quantified by ELISA. Patients were grouped by the presence (n=28) or absence (n=84) of concomitant IHI and rTEG parameters, fibrinolytic phenotypes, SDC-1, and clinical outcomes were compared. Of the 112 thermally injured patients, 28 (25%) had IHI. Most patients were male (68.8%) with a median age of 40 (IQR, 29-57) years. Patients with IHI had higher overall mortality (42.68% vs. 8.3%; p<0.0001). rTEG LY30 was lower in patients with IHI at hours 4 and 12 (p<0.05). There was a pattern of increased abnormal fibrinolytic phenotypes among IHI patients. There was a greater proportion of IHI patients with endotheliopathy (SDC-1 > 34 ng/mL) (64.7% vs. 26.4%; p=0.008). There was a pattern of increased mortality among patients with inhalation injury and endotheliopathy (0% vs. 72.7%; p=0.004). Significant differences between patients with and without IHI were found in measures assessing fibrinolytic potential and endotheliopathy. Mortality was associated with abnormal fibrinolysis, endotheliopathy, and inhalation injury. However, the extent to which IHI associated dysfunction is independent of TBSA burn size remains to be elucidated.

Key Words: Burns; Inhalation Injury; Endothelial Dysfunction; Coagulopathy; Fibrinolysis
Introduction

Burn injury affects approximately 1% of the United States population annually resulting in 486,000 patients seeking medical treatment and 40,000 hospital admissions\(^1\)\(^-\)\(^3\). Concomitant inhalation injury complicates 10-20% of burn patient admissions and is associated with significant morbidity and mortality\(^4\)\(^-\)\(^5\). Advances in burn care including early excision and grafting, infection control, and increasing referral rates to centers that provide specialized critical care, wound dressings, and outpatient management have decreased mortality and improved patient outcomes\(^6\). Despite these advances, diagnostic and therapeutic approaches for inhalation injury have lagged; inhalation injury remains a predominant cause of patient morbidity and mortality and challenges burn care providers\(^3\)\(^,\)\(^5\)\(^,\)\(^7\). The pathophysiology of inhalation injury is heterogenous. Transmission of thermal energy mostly occurs in the supraglottic airway, while chemical irritants in smoke affect the lower airways and lung parenchyma\(^4\)\(^,\)\(^7\).

Regardless of etiology, destruction of the respiratory tract epithelium incites inflammatory cascades and results in loss of barrier functions\(^4\). Inhalation injury causes local pulmonary hypercoagulability that is characterized by increased thrombin generation and decreased fibrinolytic activity\(^8\)\(^,\)\(^9\). Several studies have demonstrated high levels of pro-inflammatory, procoagulant, and anti-fibrinolytic biomarkers in bronchoalveolar lavage fluid from the respiratory tracts of patients with inhalation injury\(^4\)\(^,\)\(^8\)\(^,\)\(^10\)\(^-\)\(^12\). Inhalation injury has also been shown to induce systemically measurable effects. Davis et al. (2013) showed that inflammatory plasma cytokines were present early after injury and correlate with injury severity and mortality\(^13\). The coagulation of transudated plasma and deposition of fibrin casts within the tracheobronchial tree are elements of inhalation injury pathophysiology for which treatments such as nebulized heparin have shown benefit\(^14\). More recently, studies have demonstrated that the inflammatory and procoagulant cascades resulting from thermal and
smoke-damaged respiratory endothelium extend beyond the pulmonary system. One study demonstrated that levels of systemic inflammatory mediators are increased in patients with inhalation injury in a severity-dependent manner\textsuperscript{13}. The connection between inflammation and coagulation is well established\textsuperscript{9,15}. Burn injury induces systemic coagulopathy\textsuperscript{16}. Inhalation injury clearly exacerbates the homeostatic disturbances induced by burns; however, little is known about potential systemic impacts on the vascular endothelium, hemostasis, and fibrinolysis.

Thromboelastography (TEG) is a viscoelastic hemostatic assay that provides a dynamic assessment of coagulation homeostasis at the point-of-care. The use of TEG parameters in treatment algorithms to identify trauma patients with functional deficits in blood hemostasis and fibrinolysis has improved outcomes\textsuperscript{17}. Abnormal fibrinolysis is associated with poor outcomes and mortality in burn and non-burn trauma\textsuperscript{18,19}. Syndecan-1 (SDC-1) is a transmembrane proteoglycan constituent of the vascular endothelium that is shed into the plasma in response to injury. SDC-1 serves as a biomarker for endothelial dysfunction, or endotheliopathy. Previous studies have shown that burn and non-burn trauma patients with high admission SDC-1 levels experience increased morbidity and mortality\textsuperscript{20,21}. Concomitant inhalation injury likely contributes to the presence and severity of endotheliopathy and coagulopathy in burns. The objective of this study is to examine the association between inhalation injury, endothelial dysfunction, coagulation homeostasis, and clinical outcomes.
Methods

Setting

This is a retrospective cohort study of prospectively collected data from burn patients presenting to an American Burn Association-verified regional burn center. This data is presented according to the STROBE guidelines\textsuperscript{22}. This study was conducted as part of the larger multicenter Systems Biology Coagulopathy of Trauma (SYSCOT) Research Program\textsuperscript{23}.

Study Population

The Institutional Review Board of MedStar Health Research Institute and the Human Research Protections Office of the US Army Medical Research and Development Command approved this research. Between October 2012 and March 2017, patients presenting within 4 hours of burn injury were screened for enrollment. Patients with a pre-existing history of coagulopathy or anticoagulant use, pregnant women, minors, chemically-injured patients, and patients not fluent in English or Spanish were excluded. TEG assays were run by a hospital clinical laboratory. Some TEG assays were not run, or not completed due to logistic constraints as assays related to clinical care were prioritized over research samples. Of 158 thermally injured patients in this cohort, 112 patients had complete TEG data (including LY30) and were included in this analysis (Fig. 1).
Clinical Patient Data

Demographic information, injury characteristics, and treatment information were prospectively collected from the medical record. Most patients with inhalation injury were diagnosed by bronchoscopy, the remaining patients were diagnosed based on the clinical impression of the treating provider. The Baux score was calculated by taking the sum of a patients age and %TBSA burned\(^2\). Time from point of injury was estimated by responding emergency medical providers using information obtained at the scene and/or dispatch information.

Thromboelastography

Blood samples for TEG analysis were collected in 3.2% citrate tubes on arrival to the burn center arrival and sequentially at predetermined timepoints through 24 hours. Detailed sampling and other procedures have been previously described\(^2\). TEG was performed with the TEG® 5000 thromboelastograph® using the rapidTEG™ reagent (Haemonetics, Boston, MA). Activated clotting time (ACT) and reaction time (R time), \(\alpha\)-angle, maximum amplitude (MA), and clot lysis at 30 minutes (LY30) were measured. These parameters reflect speed of clot initiation, rate of development, maximum strength, and degree of fibrinolysis respectively.

Syndecan-1 Measurements

Baseline admission blood samples were collected from patients within 4 hours of the injury into SCAT-144 tubes\(^2\) (Haematologic Technologies, Essex Junction, Vermont). Platelet poor plasma was isolated\(^2\). Plasma SDC-1 was quantified by ELISA following protocols from the manufacturer (Human CD 138: Diaclone SAS, Besancon Cedex, France).
Statistical Analysis

Patients were grouped by the presence or absence of concomitant inhalation injury. Descriptive statistics characterized the demographics, injuries, and coagulopathy of the patients. Continuous variables were expressed as median and interquartile ranges (IQR) and were tested using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and were tested for association using a Chi-square test or Fisher’s exact test when appropriate. The associations between inhalation injury and fibrinolytic phenotypes on admission were examined. Fibrinolytic phenotypes were defined based on publications documenting the existence of three fibrinolytic phenotypes in non-burn trauma patients: Hypofibrinolysis, also referred to as fibrinolytic shutdown (SD), normal or physiologic (PHYS), and hyperfibrinolysis (HF)\textsuperscript{25,26}. The following definitions derived from Stettler et al. (2019), were used: SD was defined as LY30<0.6%, PHYS was defined as LY30 from 0.6% to 7.7%, and HF was defined as LY30>7.7%\textsuperscript{26}. Early sustained SD (ESSD) was defined as consecutive rTEG LY30 in the SD range at both hour 0 and hour 2. Sustained SD was defined as consecutive rTEG Ly30 in the SD range beginning at hour 0 or hour 2 and continuing through hour 12. Patients with an admission SDC1 level above 34ng/mL, a previously established cut-off associated with mortality and poor outcomes, were categorized as having endotheliopathy of burn (EoB)\textsuperscript{20}. The association between inhalation injury, EoB, and outcomes were also examined. Logistic regression (for computing the odds ratio [OR]) was used to determine the likelihood of mortality associated with inhalation injury and other clinical parameters (endothelial dysfunction and fibrinolytic phenotypes). By univariate logistic regression, we identified potential confounders influencing the likelihood of mortality with concomitant inhalation injury. Multivariate logistic regression adjusting for age, %TBSA, and GCS, was selected using the minimum AIC. In order to reduce bias from the possible confounding factors identified from the multivariate logistic model that would effect
the analysis, we used propensity scores for these covariates (age, %TBSA, and admission GCS) with radius matching method and bootstrapping with 5-time replications. Two matched groups with 26 patients with IHI and 39 patients without IHI were selected. Differences between groups in rTEG parameters in the first 24 hours were also examined. Statistical significance was determined at the 2-sided P-values <0.05. Data were analyzed using SAS, version 9.4 (SAS Institute Inc.) and GraphPad Prism 8 (Graphpad Software, San Diego, CA).

Results

Patient Characteristics

Patient demographics and injury characteristics are presented in Table 1. There were no significant differences between included and excluded patients on age, sex, race, burn size, mortality, presence of inhalation injury, or time between injury and blood draw. Patients included in the present analysis had a median age of 40 years (IQR, 29-57 years) and most were male (68.8%). Median total body surface area (TBSA) burn size was 15% (IQR, 6-30%) and time from point of injury to blood draw was 107 minutes (IQR, 78-171 mins). Patients with concomitant inhalation injury (n = 28) were older (58 vs. 37 years old; P=0.001) and had larger TBSA burns (41% vs. 11%, P<0.001), higher Baux scores [91 (IQR, 70-130) vs. 52 (IQR, 37-68); p<0.0001] and higher overall mortality. These patients were more likely to be admitted to the ICU (89.3 % vs.54.8%; P=0.001) and had longer ICU LOS in survivors [17 (IQR, 9-39.5) vs. 4 (IQR, 2-11) days; P=0.003]. When comparing all patients regardless of mortality, burn size (TBSA) was associated with shorter LOS in patients with inhalation injury and longer LOS in patients without. In patients who survived until discharge, larger burn size was associated with longer LOS in both groups. Inhalation injury survivors also had longer hospital LOS (Table 1).
Analysis of Viscoelastic Parameters

No significant differences in rTEG parameters associated with clot formation processes (ACT, alpha-angle, MA) were seen between patients with and without inhalation injury at admission or through 24 hours, with median values falling within normal ranges supplied by the manufacturer (Fig 2, A-C). In addition, LY30 values did not differ between these groups at admission, suggesting no difference in endogenous fibrinolytic activity. However, patients with inhalation injury had LY30 values that were significantly lower at hours 4 and 12 and numerically lower at 8 and 24 hours (Fig. 2D).

Fibrinolytic Phenotypes

Inhalation injury was associated with a higher proportion of abnormal admission fibrinolytic phenotypes (57.1% vs. 33.3%, p=0.025) (Fig. 3A). Inhalation injury was associated with SD on admission (Fig. 3B, p=0.047) and ESSD (Fig. 3C, p=0.008). When examining admission fibrinolytic phenotypes, there was a trend of increasing mortality moving from PHYS to SD to HF that was amplified by inhalation injury. Furthermore, all patients who presented with inhalation injury and HF died (Fig. 3D).

Endotheliopathy

Admission SDC-1 levels were significantly higher in patients with inhalation injury (median, IQR: 42.3, 27.5-49.1 ng/mL vs. 22.1, 16.1-34.2 ng/mL, p=0.003, Table 1). There was a greater proportion of patients with endotheliopathy (SDC-1 > 34 ng/mL; EoB) among those with inhalation injury (Fig. 3E, p=0.008). When patients were categorized by endotheliopathy, there was a pattern of increased mortality in patients with endotheliopathy that was exacerbated by inhalation injury (Fig. 3F, p<.004).
Mortality

A higher proportion of patients with inhalation injury died (Table 1, Fig. 3G, p<.0001). When burn size was stratified by TBSA≥30%, inhalation injury was associated with mortality in both small and large burns (Fig. 3H; p<0.05). Variables associated with an increased likelihood of mortality were as follows (OR, 95% CI): each year increase in age (1.06, 1.03-1.10; p=0.0006), admission GCS, each point (0.81, 0.73-0.90; p<.0001), burn TBSA >30% (22.79, 6.53-79.48; p<.0001), inhalation injury (8.25, 2.81-24.21; p=.0001), abnormal admission fibrinolysis phenotype (3.27, 1.17-9.11; p=0.024), and SDC-1 >34 ng/mL (55.25, 6.28-486.26; p=0.0003). Using propensity scores matching for age, GCS, and %TBSA, concomitant inhalation injury had a 25.1% higher average effect on mortality compared to burn patients without IHI (95% CI 11.7-38.5%; p=0.04) (Table 2).

Discussion

The data presented here demonstrate that inhalation injury is associated with increased morbidity and mortality after burn injury. Furthermore, inhalation injury is associated with increased endothelial dysfunction and abnormal fibrinolysis as evidenced by circulating SDC-1 and rTEG measurements respectively. There appears to be a synergistic negative effect when inhalation injury is combined with either endotheliopathy or abnormal fibrinolysis, as a higher proportion of patients presenting in this manner tended to die. This suggests that endotheliopathy and abnormal fibrinolysis may contribute to the increased morbidity and mortality observed in burn patients with inhalation injury.

Inhalation injury has long been recognized as a major contributor to morbidity and mortality in burn patients. The Baux score has been used by clinicians for decades as a...
A prognostic tool that estimates the likelihood of mortality using a patient’s age and burn size. The score has been validated and adjusted as burn care, and therefore burn survivability, has improved over time. One major revision to the Baux score was the addition of inhalation injury into the scoring system. The revised Baux score, which adds an inhalation injury constant to the age + %TBSA sum, reflects the understanding that inhalation injury is independently associated with a greater risk of mortality. The data presented here are consistent with previous observations, as a much greater proportion of patients with inhalation injury died (Table 1, Fig. 3G-H) and IHI had a significant effect on mortality in univariate analysis and after controlling for covariates in a propensity score matched model (Table 2). While the association between inhalation injury and poor clinical outcomes is known, the mechanisms that drive these outcomes require further examination.

The structure and function of the vascular endothelium and its response to disease states is an established and expanding area of research. The endothelium plays a critical role in inflammatory processes and dysfunctional endothelium has been implicated in many chronic diseases including malignancy, rheumatic disease, and atherosclerosis among others. The role of endothelial dysfunction in acute disease and traumatic injury is also a target of study. Plasma biomarkers such as SDC-1 have been studied in burn and non-burn trauma and are used to quantify the presence and severity of endotheliopathy after injury. Although the exact source(s) of cleaved, circulating SDC-1 are not known post-burn injury, the pulmonary microvasculature has been suggested as a reservoir of SDC-1 in animal studies, and the lung may be an important target for therapeutic treatment for endotheliopathy. Inhalation injury is associated with increased endotheliopathy in burns, and endotheliopathy is associated with poor outcomes in burn and non-burn trauma. The data presented in this study demonstrate a relationship between inhalation injury and increased circulating SDC-1 (Fig. 3E). We also demonstrate that when inhalation injury is
combined with endotheliopathy, a higher proportion of patients die (Fig. 3F). Inhalation injury likely exacerbates endothelial glycocalyx shedding after burn injury which contributes to the development of burn shock and results in poor clinical outcomes.

Inhalation injury is associated with coagulopathy and inhibition of fibrinolysis in the pulmonary compartment. The presence of increased procoagulant and anti-fibrinolytic moieties in respiratory tract isolates from patients with inhalation injury has informed treatment modalities such as nebulized anticoagulants like heparin. The influence of localized pulmonary coagulopathy on systemic coagulation homeostasis in cases of inhalation injury is not well characterized. Previous work suggests that abnormal fibrinolysis is associated with poor outcomes in burn and non-burn trauma. One potential mechanism behind abnormal systemic fibrinolysis caused by inhalation injury is circulating plasminogen activator inhibitor (PAI-1), the main inhibitor of fibrinolysis, that is elevated in bronchoalveolar lavage fluid as well as in the systemic circulation following acute lung injury.

When rTEG parameters were compared between burn patients with and without inhalation injury in the first 24 hours after injury, there was a pattern of significantly lower LY30 measurements among patients with inhalation injury at hours 4, and 12, with a similar trend at hours 8, and 24 (Fig. 2D). Given this signal on a functional assay of fibrinolysis, the fibrinolytic phenotypes and relationship to clinical outcomes were further investigated. The data presented here shows a significant relationship between inhalation injury and abnormal fibrinolysis (Fig. 3A-C). There is a trend towards greater mortality when inhalation injury is combined with abnormal fibrinolysis. This is particularly true when a patient with inhalation injury presents with HF, where a mortality rate of 100% is observed (Fig. 3D).

There are limitations to the current study. This is a retrospective analysis of prospectively recorded data from a single institution. Therefore, these findings are correlative and do not suggest causation. Our cohort was heterogenous in terms of age and burn size.
when compared categorized by inhalation injury status and was skewed in numbers towards patients without inhalation injury, which is reflective of national trends in burn epidemiology. Future studies should further examine of the relationship between inhalation injury and endotheliopathy, coagulopathy and clinical outcomes after burn injury.

Conclusion

Inhalation injury is associated with increased morbidity and mortality in burn patients. Poor outcomes in the setting of inhalation injury are associated with endotheliopathy and coagulopathy, but the degree to which these are mediated by burn size or inhalation injury is not determined in the present study. Our data demonstrate a higher proportion of abnormal fibrinolysis among patients with inhalation injury and greater mortality among patients with inhalation injury and endotheliopathy.
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Figure Legends

Fig. 1: Flowchart of patients included in the present analysis. Patients with incomplete rTEG data were excluded. A total of 112 patients were analyzed and there were 28 patients with inhalation injury and 84 patients without. (rTEG, rapid thromboelastography; LY30, Clot lysis at 30 minutes; IHI, Inhalation injury)

Fig. 2: Patients were categorized by the presence or absence of inhalation injury and rTEG parameters were compared at predetermined timepoints (Hours 0, 2, 4, 8, 12, and 24) over 24 hours. Statistical analysis was performed with Mann-Whitney U tests. Box plots represent median, IQR, and minimum and maximum values. (IHI; Inhalation injury)

Fig 3: Patients were categorized by the presence or absence of inhalation injury and proportions of patients exhibiting fibrinolytic phenotypes (A), fibrinolysis shutdown (B), early sustained shutdown (C), admission fibrinolytic phenotypes and mortality (D), endotheliopathy of burn (E), endotheliopathy and mortality (F), mortality (G), and burn severity and mortality (H), were compared using Chi-Square or Fisher’s exact test as appropriate. (IHI, Inhalation injury; SD, shutdown; ESSD, Early sustained shutdown; PHYS, Physiologic; HF, Hyperfibrinolysis; EoB, Endotheliopathy of Burn; TBSA, Total body surface area burned).
## Table 1. Demographic and injury characteristics

|                               | All        | Inhalation Injury | P-value |
|-------------------------------|------------|-------------------|---------|
|                               | All        | Yes               | No      |         |
| No. of patients, No. (%)      | 112        | 28 (25.0)         | 84 (75.0) |         |<.001    |
| Age, Median (IQR), yr.        | 40 (29-57) | 58 (39-67)        | 37 (26-50) |         |         |
| Sex, No. (%)                  |            |                   |         |         |
| Male                          | 77 (68.8)  | 20 (71.4)         | 57 (67.9) |         |<.001    |
| Female                        | 35 (31.2)  | 8 (28.6)          | 27 (32.1) |         |         |
| Race/Ethnicity, No. (%)       |            |                   |         |         |
| White                         | 41 (36.6)  | 10 (35.7)         | 31 (36.9) |         | 0.09     |
| Black                         | 43 (39.4)  | 8 (28.6)          | 35 (41.7) |         |         |
| Hispanic                      | 9 (8.0)    | 1 (3.6)           | 8 (9.5)  |          |<.001    |
| Other                         | 19 (20.0)  | 9 (32.1)          | 10 (11.9) |         |         |
| BMI, Median (IQR)             |            |                   |         |         |
| Transport method, No. (%)     |            |                   |         |         |
| Helicopter                    | 44 (39.3)  | 18 (64.3)         | 26 (30.9) |         |<.002    |
| Ambulance                     | 68 (60.7)  | 10 (35.7)         | 58 (69.1) |         |         |
| POI to ADM blood draw (mins), median (IQR) | 107 (78-171) | 104 (78-192) | 107 (78-162) | 0.69 |
| Total %TBSA burned, median (IQR) | 15 (6-30)    | 41 (20-82)       | 11 (5-20)  |<.0001  |
| Baux score, Median (IQR)      | 60 (39-82) | 91 (70-130)       | 52 (37-68) |<.0001  |
| GCS total on ADM, median (IQR) | 15 (14-15) | 11 (3-15)        | 15 (15-15) |<.0001  |
| ADM Syndecan-1, median (IQR), n=51 | 27.5 (18.8-45.8) | 42.3 (27.5-49.1) | 22.1 (16.1-34.2) |<.003 |
| ICU, yes, No. (%)             | 71 (63.4)  | 25 (89.3)         | 46 (54.8) |         |<.001    |
| ICU days, median (IQR), n=71   | 5.0 (2.0-17.0) | 12.0 (2.0-19.0) | 4.0 (2.0 – 13.0) |      |0.21     |
| Survivors – ICU days, median (IQR), n=55 | 7.0 (2.0-17.0) | 17.0 (9.0-39.5) | 4.0 (2.0-11.0) |       |<.003    |
| Length of stay (LOS), median (QR) | 10.5 (3.0-19.5) | 14.5 (1.0-26.5) | 10.0 (3.5-18.0) | 0.29   |
| Survivors - LOS, median (IQR), n=93 | 11.0 (6.0-20.0) | 24.0 (14.5-63.0) | 10.0 (4.0-18.0) |<.0002  |
| Mortality, No. (%)            | 19 (17.0)  | 12 (42.9)         | 7 (8.3)  |         |<.0001  |

Abbreviations: TBSA, total body surface area; IQR, interquartile ranges; BMI, body mass index; POI, point of injury; ADM, Admission; GCS, Glasgow coma scale; ICU, intensive care unit.

Data are presented as number (percentage) of patients unless otherwise indicated. P values were calculated with the use of a chi-square or Fisher’s exact test and Wilcoxon-Mann-Whitney test as appropriate.
| Univariate                                      | OR (95% CI)            | P-value |
|------------------------------------------------|------------------------|---------|
| Sex, female vs. male                           | 0.53 (0.16-1.74)       | 0.30    |
| Age                                            | 1.06 (1.03-1.10)       | 0.0006  |
| BMI, >30 vs <30                                | 3.85 (0.83-17.78)      | 0.08    |
| GCS, each unit increase                        | 0.81 (0.73-0.90)       | <.0001  |
| TBSA >30% vs <30%                              | 22.79 (5.53-79.48)     | <.0001  |
| Inhalation, yes vs no                          | 8.25 (2.81-24.21)      | 0.0001  |
| Transport, Air vs ground                       | 1.93 (0.71-5.21)       | 0.196   |
| ADM LY30 Phenotype                             |                        |         |
| SD vs Phys                                     | 2.26 (0.72-7.07)       | 0.16    |
| HF vs Phys                                     | 8.72 (2.01-37.74)      | 0.004   |
| HF vs SD                                       | 3.86 (0.87-17.16)      | 0.08    |
| Abnormal vs Normal                             | 3.27 (1.17-9.11)       | 0.024   |
| SDC-1, >34 vs ≤34                              | 55.25 (6.28-486.26)    | 0.0003  |
| ESSD, Yes vs No                                | 1.92 (0.64-5.75)       | 0.24    |
| Sustained SD                                   | 3.56 (0.97-12.99)      | 0.055   |
| Adjusted Models                                |                         |         |
| IHI vs. no IHI                                 |                        |         |
| Model 1*                                       | 0.53 (0.08-3.46)       | 0.44    |
| Model 2, ATT (95% CI)**                        | 25.1% (11.7-38.5%)     | 0.04    |

**Abbreviations:** BMI, body mass index; TBSA, total body surface area; ADM, Admission; LY30, Clot lysis at 30 minutes; SD, Shutdown; PHYS, Physiologic; HF, Hyperfibrinolysis; SDC-1, Syndecan-1; ESSD, Early sustained shutdown. IHI, inhalation injury; ATT, Average effect of treatment on the treated

Data are presented as Odds Ratios (95% Confidence Interval) or otherwise noted. P-values were calculated with logistic regression.

*Model 1: Multivariate logistic regression adjusting for age, %TBSA, and GCS

**Model 2: Propensity score using radius matching for age, %TBSA, and GCS with n=26 for IHI group and n=39 for No-IHI group.
Figure 1

Screened  
\[ n = 158 \]

Excluded, \( n = 46 \)  
- Incomplete TEG data, \( n = 42 \)  
- No cutaneous burns, \( n = 2 \)  
- Incomplete injury data, \( n = 2 \)

Included Patients  
\[ n = 112 \]

Patients with IHI  
\[ n = 28 \]

Patients without IHI  
\[ n = 84 \]
Figure 2

A. Activated Clotting Time (ACT)

B. Alpha Angle (α)

C. Maximum Amplitude (MA)

D. Clot Lysis at 30 Minutes (LY30)

Legend:
- No IHI
- IHI
Figure 3

A. Fibrinolysis Phenotype

B. IHI and SD

C. IHI and ESSD

D. Phenotype & Mortality

E. IHI and EoB

F. EoB & Mortality

G. IHI and Mortality

H. TBSA & Mortality by IHI