Inhalation Injury Is Associated With Endotheliopathy and Abnormal Fibrinolytic Phenotypes in Burn Patients: A Cohort Study

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Burn injury is associated with endothelial dysfunction and coagulopathy and concomitant inhalation injury (IHI) increases morbidity and mortality. The aim of this work is to identify associations between 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 thromboelastography (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 (interquartile range, 29–57) years. Patients with IHI had higher overall mortality (42.68% vs 8.3%; P < .0001). rTEG LY30 was lower in patients with IHI at hours 4 and 12 (P < .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 = .008). There was a pattern of increased mortality among patients with IHI and endotheliopathy (0% vs 72.7%; P = .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 IHI. However, the extent to which IHI-associated dysfunction is independent of TBSA burn size remains to be elucidated.

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Burn injury affects approximately 1% of the U.S. population annually resulting in 486,000 patients seeking medical treatment and 40,000 hospital admissions.[1–3] Concomitant inhalation injury (IHI) complicates 10 to 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 IHI have lagged; IHI remains a predominant cause of patient morbidity and mortality and challenges burn care providers.[3,5,7] The pathophysiology of IHI is heterogenous. Transmission of thermal energy mostly occurs in the supraglottic airway, whereas 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] IHI causes local pulmonary hypercoagulability that is characterized by increased thrombin generation and decreased fibrinolytic activity.[8,9] Several studies have demonstrated high levels of proinflammatory, procoagulant, and antifibrinolytic biomarkers in bronchoalveolar lavage fluid from the respiratory tracts of patients with IHI.[4,8,10–12] IHI has also been shown to induce systemically measurable effects. Davis et al 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 IHI 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 IHI in a severity-dependent manner.[13] The connection between inflammation and coagulation is well established.[9,15] Burn injury induces systemic coagulopathy.[16] IHI 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.[17] Abnormal fibrinolysis is associated with poor outcomes and mortality in burn and nonburn trauma.[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 nonburn trauma patients with high admission SDC-1 levels experience increased morbidity and mortality.[20,21] Concomitant IHI probably contributes to the presence and severity of endotheliopathy and coagulopathy in burns. The objective of this study was to examine the association between IHI, 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. These data are presented according to the STROBE guidelines.[22] This study was conducted as part of the larger multicenter Systems Biology Coagulopathy of Trauma (SYSCOT) Research Program.[23]

Study Population

The Institutional Review Board of MedStar Health Research Institute and the Human Research Protections Office of the U.S. 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 preexisting 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 (Figure 1).

Clinical Patient Data

Demographic information, injury characteristics, and treatment information were prospectively collected from the medical record. Most patients with IHI 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.[24] 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.[23] TEG was performed with the TEG 5000 thromboelastograph using the rapidTEG reagent (Haemonetics, Boston, MA). Activated clotting time and reaction time (R time), α-angle, maximum amplitude, 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.

SDC-1 Measurements

Baseline admission blood samples were collected from patients within 4 hours of the injury into SCAT-144 tubes[23] (Haematologic Technologies, Essex Junction, Vermont). Platelet poor plasma was isolated.[23] 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 IHI. Descriptive statistics characterized the demographics, injuries, and coagulopathy of the patients.

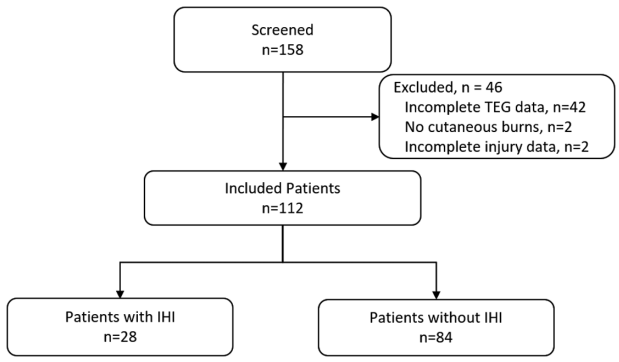

Figure 1. Flowchart of patients included in the present analysis. Patients with incomplete rTEG data were excluded. A total of 112 patients were analyzed and there were 28 patients with inhalation injury and 84 patients without. rTEG, rapid thromboelastography; *LY30*, clot lysis at 30 min; *IHI*, inhalation injury.

Table 1. Demographic and injury characteristics

		Inhalation Injury		
	All	**Yes**	**No**	***P*-value**
Number of patients, no. (%)	112	28 (25.0)	84 (75.0)	—
Age, median (IQR), y	40 (29–57)	58 (39–67)	37 (26–50)	.001
Sex, no. (%)				.72
Male	77 (68.8)	20 (71.4)	57 (67.9)	
Female	35 (31.2)	8 (28.6)	27 (32.1)	
Race/ethnicity, no. (%)				
White	41 (36.6)	10 35.7)	31 (36.9)	.09
Black	43 (39.4)	8 (28.6)	35 (41.7)	
Hispanic	9 (8.0)	1 (3.6)	8 (9.5	
Other	19 (20.0)	9 (32.1)	10 (11.9)	
BMI, median (IQR)	27 (23–31)	26 (23–29)	27 (24–31)	.08
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 (min), median (IQR)	107 (78–171)	104 (78–192)	107 (78–162)	.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 rTEG parameters				
Angle, median (IQR)	74.0 (69.5–77.1)	76.0 (67.9–78.4)	73.4 (69.5–76.3)	.16
MA, median (IQR)	61.8 (56.3–64.9)	62.8 (57.9–67.1)	61.5 (55.6–64.4)	.32
LY30, median (IQR)	1.6 (0.3–3.3)	1.6 (0.0–3.6)	1.6 (0.4–3.3)	.50
ACT, median (IQR)	121.0 (105.0–132.0)	113.0 (97.0–121.0)	121.0 (113.0–136.0)	.11
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)	.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
LOS, median (IQR)	10.5 (3.0–19.5)	14.5 (1.0–26.5)	10.0 (3.5–18.0)	.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

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. *IQR*, interquartile ranges; *BMI*, body mass index; *POI*, point of injury; *ADM*, Admission; *GCS*, Glasgow Coma Scale; *ICU*, intensive care unit; *LOS*, length of stay; *rTEG*, rapid thromboelastography.

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 IHI and fibrinolytic phenotypes on admission were examined. Fibrinolytic phenotypes were defined based on publications documenting the existence of three fibrinolytic phenotypes in nonburn trauma patients: Hypofibrinolysis, also referred to as fibrinolytic shutdown (SD), normal or physiologic (PHYS), and hyperfibrinolysis (HF).[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%.[26] Early-sustained SD 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 SDC-1 level above 34 ng/mL, a previously established cutoff associated with mortality and poor outcomes, were categorized as having endotheliopathy of burn (EoB).[20] The association between IHI, EoB, and outcomes were also examined. Logistic regression (for computing the odds ratio) was used to determine the likelihood of mortality associated with IHI and other clinical parameters (endothelial dysfunction and fibrinolytic phenotypes). By univariate logistic regression, we identified potential confounders influencing the likelihood of mortality with concomitant IHI. Multivariate logistic regression adjusting for age, %TBSA, and Glasgow Coma Scale (GCS), was selected using the minimum Akaike information criterion. To reduce bias from the possible confounding factors identified from the multivariate logistic model that would affect the analysis, we used propensity scores for these covariates (age, %TBSA, and admission GCS) with radius matching method and bootstrapping with five-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 two-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).

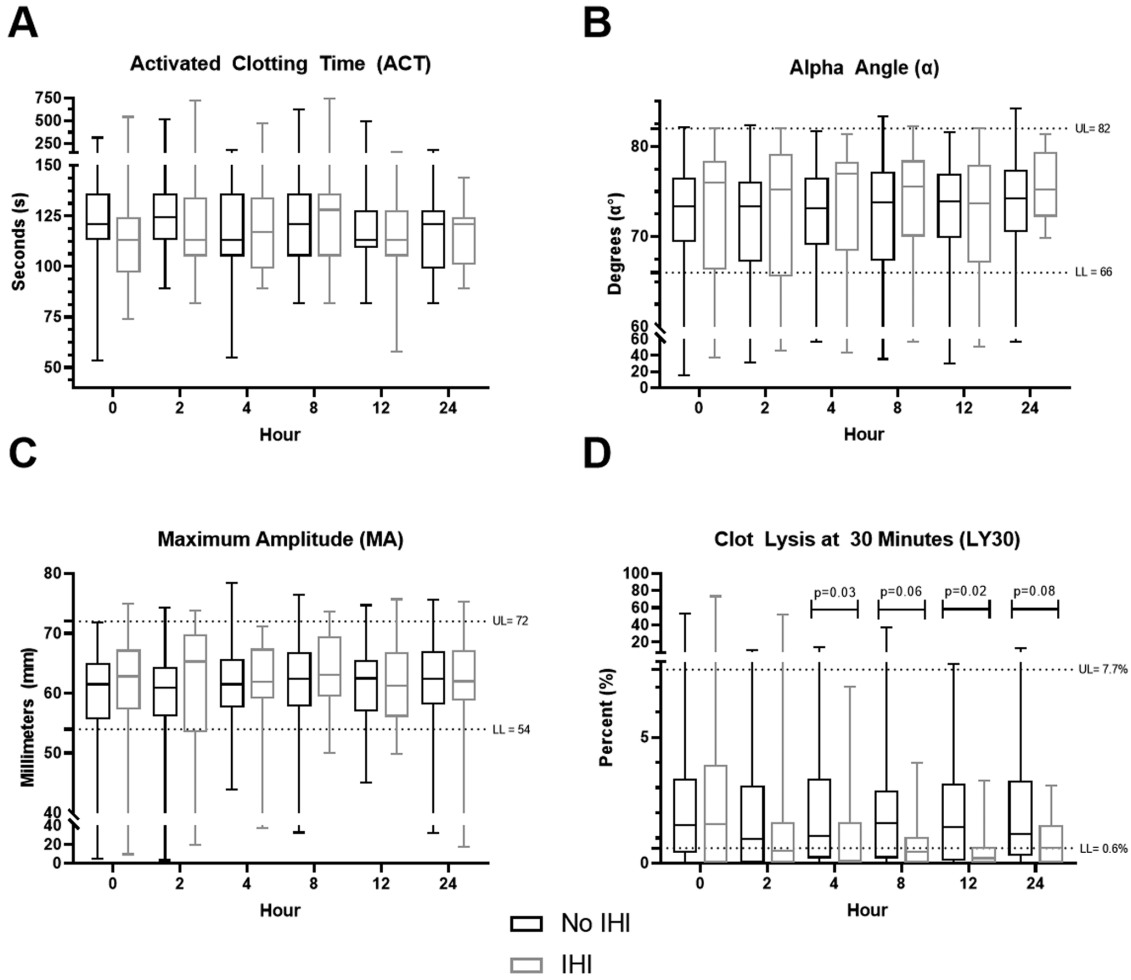

Figure 2. Patients were categorized by the presence or absence of inhalation injury and the rTEG parameters (**A**) activated clotting time, (**B**) alpha angle, (**C**) maximum amplitude, (**D**) and clot lysis at 30 minutes, were compared at predetermined timepoints (hours 0, 2, 4, 8, 12, and 24) over 24 h. Statistical analysis was performed with Mann–Whitney *U* tests. Box plots represent median, IQR, and minimum and maximum values. *IHI*, inhalation injury; *IQR*, interquartile ranges; *rTEG*, rapid thromboelastography.

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 IHI, 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 TBSA burn size was 15% (IQR, 6%–30%), and time from the point of injury to blood draw was 107 minutes (IQR, 78–171 min). Patients with concomitant IHI (n = 28) were older (58 vs 37 years old; P = .001) and had larger TBSA burns (41% vs 11%, P < .001), higher Baux scores (91 [IQR, 70–130] vs 52 [IQR, 37–68]; P < .0001), and higher overall mortality. These patients were more likely to be admitted to the ICU (89.3% vs 54.8%; P = .001) and had longer ICU LOS in survivors (17 [IQR, 9–39.5] vs 4 [IQR, 2 to 11] days; P = .003). When comparing all patients regardless of mortality, burn size (TBSA) was associated with shorter length of stay (LOS) in patients with IHI and longer LOS in patients without. In patients who survived until discharge, larger burn size was associated with longer LOS in both groups. IHI survivors also had longer hospital LOS (Table 1).

Analysis of Viscoelastic Parameters

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

Fibrinolytic Phenotypes

IHI was associated with a higher proportion of abnormal admission fibrinolytic phenotypes (57.1% vs 33.3%, P = .025; Figure 3A). IHI was associated with SD on admission (Figure

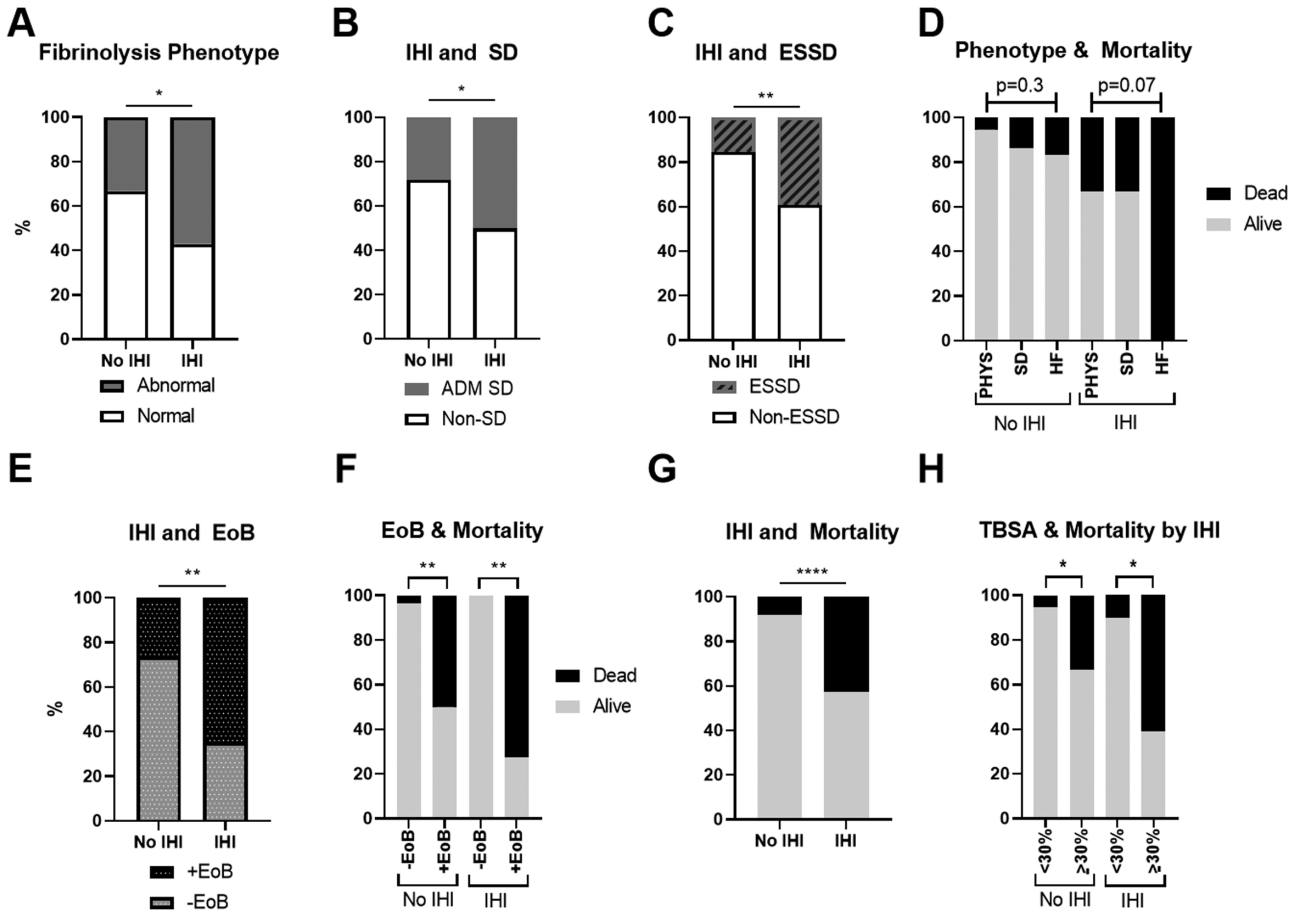

Figure 3. Patients were categorized by the presence or absence of inhalation injury, and proportions of patients exhibiting fibrinolytic phenotypes (A), fibrinolysis shutdown (B), early sustained shutdown (C), admission fibrinolytic phenotypes and mortality (D), endotheliopathy of burn (E), endotheliopathy 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.

3B, $P = .047$) and early-sustained SD (Figure 3C; $P = .008$). When examining admission fibrinolytic phenotypes, there was a trend of increasing mortality moving from PHYS to SD to HF that was amplified by IHI. Furthermore, all patients who presented with IHI and HF died (Figure 3D).

Endotheliopathy

Admission SDC-1 levels were significantly higher in patients with IHI (median, IQR: 42.3, 27.5–49.1 ng/mL vs 22.1, 16.1–34.2 ng/mL, $P = .003$, Table 1). There was a greater proportion of patients with endotheliopathy (SDC-1 > 34 ng/mL; EoB) among those with IHI (Figure 3E, $P = .008$). When patients were categorized by endotheliopathy, there was a pattern of increased mortality in patients with endotheliopathy that was exacerbated by IHI (Figure 3F, $P < .004$).

Mortality

A higher proportion of patients with IHI died (Table 1, Figure 3G, $P < .0001$). When burn size was stratified by TBSA ≥ 30%, IHI was associated with mortality in both small and large burns (Figure 3H; $P < .05$). Variables associated with an increased likelihood of mortality were as follows: each year increase in age (odds ratio, 1.06, 95% confidence interval = 1.03–1.10; $P = .0006$), admission GCS, each point (0.81, 0.73–0.90; $P < .0001$), burn TBSA > 30% (22.79, 6.53–79.48; $P < .0001$), IHI (8.25, 2.81–24.21; $P = .0001$), abnormal admission fibrinolysis phenotype (3.27, 1.17–9.11; $P = .024$), and SDC-1 > 34 ng/mL (55.25, 6.28–486.26; $P = .0003$). Using propensity scores matching for age, GCS, and %TBSA, concomitant IHI had a 25.1% higher average effect on mortality compared to burn patients without IHI (95% confidence interval = 11.7%–38.5%; $P = .04$; Table 2).

DISCUSSION

The data presented here demonstrate that IHI is associated with increased morbidity and mortality after burn injury. Furthermore, IHI 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 IHI 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

Table 2. Likelihood of mortality

Univariate	OR (95% CI)	*P*-value
Sex, female vs male	0.53 (0.16–1.74)	.30
Age	1.06 (1.03–1.10)	.0006
BMI, >30 vs <30	3.85 (0.83–17.78)	.08
GCS, each unit increase	0.81 (0.73–0.90)	<.0001
TBSA >30% vs. <30%	22.79 (0.53–79.48)	<.0001
Inhalation, yes vs no	8.25 (2.81–24.21)	.0001
Transport, air vs ground	1.93 (0.71–5.21)	.196
ADM LY30 phenotype		
SD vs Phys	2.26 (0.72–7.07)	.16
HF vs Phys	8.72 (2.01–37.74)	.004
HF vs SD	3.86 (0.87–17.16)	.08
Abnormal vs normal	3.27 (1.17–9.11)	.024
SDC-1, >34 vs ≤34	55.25 (6.28–486.26)	.0003
ESSD, yes vs no	1.92 (0.64–5.75)	.24
Sustained SD	3.56 (0.97–12.99)	.055
Adjusted models	IHI vs no IHI	
Model 1[a]	0.53 (0.08–3.46)	.44
Model 2, ATT (95% CI)[b]	25.1% (11.7–38.5%)	.04

Data are presented as odds ratios (95% confidence interval) or otherwise noted. *P*-values were calculated with logistic regression. *ATT*, average effect of treatment on the treated; *ADM*, Admission; *BMI*, body mass index; *CI*, confidence interval; *ESSD*, early-sustained shutdown; *GCS*, Glasgow Coma Scale; *HF*, hyperfibrinolysis; *IHI*, inhalation injury; *LY30*, clot lysis at 30 minutes; *PHYS*, physiologic; *SD*, shutdown; *SDC-1*, syndecan-1.
[a]Model 1: Multivariate logistic regression adjusting for age, %TBSA, and GCS.
[b]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.

abnormal fibrinolysis may contribute to the increased morbidity and mortality observed in burn patients with IHI.

IHI 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 prognostic tool that estimates the likelihood of mortality using a patient's age and burn size.[24] The score has been validated and adjusted as burn care, and therefore burn survivability, has improved over time.[27] One major revision to the Baux score was the addition of IHI into the scoring system. The revised Baux score, which adds an IHI constant to the age + %TBSA sum, reflects the understanding that IHI is independently associated with a greater risk of mortality.[28] The data presented here are consistent with previous observations, as a much greater proportion of patients with IHI died (Table 1, Figure 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). Although the association between IHI 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.[29] 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.[30,31] The role of endothelial dysfunction in acute disease and traumatic injury is also a target of study.[32–34] Plasma biomarkers such as SDC-1 have been studied in burn and nonburn trauma and are used to quantify the presence and severity of endotheliopathy after injury.[20,21,35] Although the exact source(s) of cleaved, circulating SDC-1 are not known postburn 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.[36,37] IHI is associated with increased endotheliopathy in burns, and endotheliopathy is associated with poor outcomes in burn and nonburn trauma.[21] The data presented in this study demonstrate a relationship between IHI and increased circulating SDC-1 (Figure 3E). We also demonstrate that when IHI is combined with endotheliopathy, a higher proportion of patients die (Figure 3F). IHI probably exacerbates endothelial glycocalyx shedding after burn injury, which contributes to the development of burn shock and results in poor clinical outcomes.

IHI is associated with coagulopathy and inhibition of fibrinolysis in the pulmonary compartment.[8,9,12] The presence of increased procoagulant and antifibrinolytic moieties in respiratory tract isolates from patients with IHI has informed treatment modalities such as nebulized anticoagulants like heparin.[5,38] The influence of localized pulmonary coagulopathy on systemic coagulation homeostasis in cases of IHI is not well characterized. Previous work suggests that abnormal fibrinolysis is associated with poor outcomes in burn and nonburn trauma.[19,26,39–47] One potential mechanism behind abnormal systemic fibrinolysis caused by IHI 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.[48–50] When rTEG parameters were compared between burn patients with and without IHI in the first 24 hours after injury, there was a pattern of significantly lower LY30 measurements among patients with IHI at hours 4 and 12, with a similar trend at hours 8 and 24 (Figure 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 show a significant relationship between IHI and abnormal

fibrinolysis (Figure 3A–C). There is a trend toward greater mortality when IHI is combined with abnormal fibrinolysis. This is particularly true when a patient with IHI presents with HF, where a mortality rate of 100% is observed (Figure 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 heterogeneous in terms of age and burn size when compared categorized by IHI status and was skewed in numbers towards patients without IHI, which is reflective of national trends in burn epidemiology.[51] Future studies should further examine the relationship between IHI and endotheliopathy, coagulopathy, and clinical outcomes after burn injury.

CONCLUSION

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

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