CE 1.5 ANCC Contact Hours

Accelerated Biologic Aging, Chronic Stress, and Risk for Sepsis and Organ Failure Following Trauma

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ABSTRACT

Chronic stress and accelerated aging have been shown to impact the inflammatory response and related outcomes like sepsis and organ failure, but data are lacking in the trauma literature. The purpose of this study was to investigate potential relationships between pretrauma stress and posttrauma outcomes. The hypothesis was that pretrauma chronic stress accelerates aging, which increases susceptibility to posttrauma sepsis and organ failure. In this prospective, correlational study, chronic stress and accelerated biologic aging were compared to the occurrence of systemic inflammatory response syndrome, sepsis, and organ failure in trauma patients aged 18–44 years. Results supported the hypothesis with significant overall associations between susceptibility to sepsis and accelerated biologic aging ($n = 142$). There were also significant negative associations between mean cytokine levels and chronic stress. The strongest association was found between mean interleukin-1β (IL-1β) and human telomerase reverse transcriptase (hTERT), $r(101) = -0.28$), $p = .004$. Significant negative associations were found between mean cytokine levels, IL-12p70, $r(108) = -0.20$, $p = .034$; and tumor necrosis factor-α (TNF-α), $r(108) = -0.20$, $p = .033$, and positive life events via the behavioral measure of chronic stress. Results may help identify individuals at increased risk for poor outcomes of trauma and inform interventions that may reduce the risk for sepsis and organ failure.

Key Words

Aging, Inflammation, Sepsis, Stress, Trauma

Trauma, defined as acute, life-threatening injuries, is the leading cause of morbidity and mortality for persons aged 18–44 years (Centers for Disease Control and Prevention, 2017). Sepsis and organ failure are the leading causes of inhospital trauma morbidity and mortality, although significant gaps in the literature exist regarding why some patients, especially those within this younger age group, may be more vulnerable to these deadly complications.

Chronic stress may be a factor. Research in psychoneuroimmunology shows that chronic stress can result in cumulative physiologic "wear and tear" (known as allostatic load) on immune system function (Juster, McEwen, & Lupien, 2010), a key contributing factor to susceptibility to sepsis and organ failure (Delano & Ward, 2016). National experts supported these concepts as potential significant factors associated with trauma morbidity and mortality and recommended further study (National Institutes of Health, 2003).

Stress activates biologic pathways that trigger the release of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (TNF-α) (Calcagni & Elenkov, 2006; Heffner, 2011; Ranjit et al., 2007), and chronic activation of these pathways can result in immune dysfunction (Tian, Hou, Li, & Yuan, 2014). These changes are similar to those seen in the elderly, a population known to be increased risk for sepsis and organ failure following trauma. Sustained elevations in inflammatory cytokines have been reported as contributing factors to organ failure in nontrauma patients (Boekholdt et al., 2004; Calcagni & Elenkov, 2006; Keller et al., 2007), and evidence shows that otherwise healthy individuals—like those within the 18–44 year age group in general—who

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E.G.N. conceived, designed, and implemented the study (NIH principle investigator), in consultation with all other coauthors (NIH subinvestigators). E.G.N., R.S.M., and S.B.H. recruited, screened, and consented participants, and collected data. H.Z. and Y.D. completed cytokine, and telomerase assessments, and S.W.L. analyzed the data. E.G.N., S.W.L., and H.Z. wrote the manuscript, while all others reviewed and edited.

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have high levels of IL-6, IL-8, and TNF-α are more susceptible to organ dysfunction, particularly cardiac and renal disease (Chen et al., 2018). This is significant because these organ systems must be healthy prior to trauma in order for the patient to have the best chance of survival following trauma. Research within the trauma population supports these findings, as elevated levels of IL-6 and IL-10 have been shown to correlate with organ failure in these patients (Sapan et al., 2016).

It is from this context that the research question for this study had its genesis. If chronic stress in younger individuals is associated with immune dysfunction like that which is seen in the elderly, then could chronic stress, when it occurs in younger individuals, make the immune system function as if it were like that of the elderly? If so, would that translate to heretofore unrecognized increased vulnerability to sepsis and organ failure in persons 18–44 years of age who experience chronic stress prior to trauma? Though some risk factors for sepsis and organ failure have been well-described in the literature (Shankar-Hari et al., 2016; Singer et al., 2016), risks associated with accelerated biologic aging related to chronic stress and subsequent immune dysfunction in the inflammatory response following trauma have not. The relevance of this question for the clinician is that if the answer is "yes," then practice changes may be warranted to identify biomarkers of chronic stress early in the trauma care episode, and then consequently increase surveillance for sepsis and organ failure in those affected for earlier prevention, intervention, and treatment.

The purpose of this research therefore was to answer the question proposed above via the following hypothesis, developed by the Trauma Interdisciplinary Group for Research [TIGR] (NeSmith et al., 2013). Accelerated biologic aging, defined by the telomerase biomarker human telomerase reverse transcriptase (hTERT), contributes to susceptibility to sepsis and organ failure after trauma, and chronic stress contributes to increased baseline inflammation and decreased magnitude of the inflammatory response to trauma. Specifically, the TIGR anticipated that reduced hTERT expression would correlate with increased susceptibility to sepsis, indicated by an abnormal (1) overall response and (2) peak magnitude of inflammatory cytokines IL-1β, IL-6, IL-8, IL-10, TNF-α. It was also hypothesized that telomerase measures would correlate with increased susceptibility to organ failure, indicated by increased baseline inflammation.

METHODS

Following approval from the local institutional review board, a prospective, correlational study was conducted to accomplish the proposal aims. A brief flow chart outlining the study procedures is provided in Figure 1, and a more detailed narrative description is provided below.

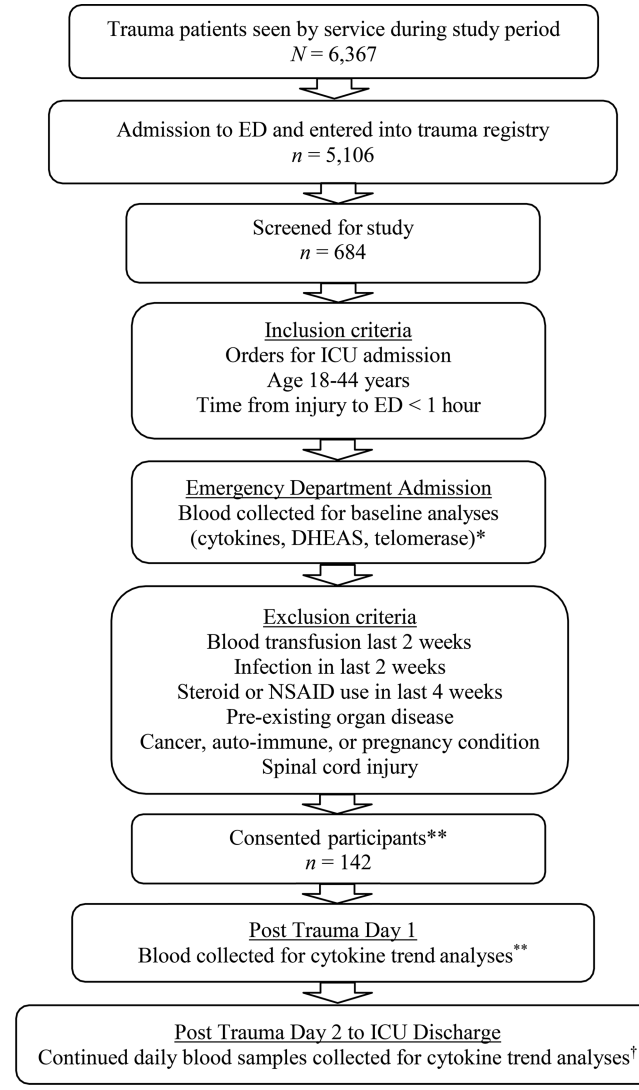

Figure 1. Procedural flow chart. *Blood collected as part of routine care that would have otherwise been discarded; **≤24 hr. postemergency department admission; †daily samples were collected by ICU nurses during a.m. laboratory collection times.

Participants and Setting

Investigators recruited, screened, and consented eligible participants over the 3-year award period from the Level 1 trauma center at an academic medical center in the southeastern United States. Informed consent was obtained from all participants.

Consent included permission to collect biological samples and interview data to determine chronic stress prior to injury, and its impact on accelerated biologic aging and the inflammatory response following injury. For participants who were unable to consent for themselves related

to condition or treatment, a legally authorized representative served as proxy. Inclusion criteria were (1) 18–44 years old; (2) orders for and subsequent admission to the intensive care unit (ICU); and (3) time from injury to the emergency department (ED) less than 1 hr. Individuals aged 18–44 years were chosen for the study because this is the population defined by the Centers for Disease Control and Prevention for whom trauma is the leading cause of death (Centers for Disease Control and Prevention, 2017) and for which susceptibility to posttrauma sepsis and organ failure is ill-defined in the literature, in contrast to that of the elderly population. Exclusion criteria were (1) blood transfusion within the last 2 weeks; (2) infection within 2 weeks of admission; (3) steroid, nonsteroidal anti-inflammatory drug, or salicylate use for more than 1 month prior to admission; (3) preexisting organ disease; (4) cancer, autoimmune conditions, or pregnancy; and (5) spinal cord injury.

Data Collection

Biological samples from blood that would have otherwise been discarded were collected from trauma patients on admission to the ED. Additional blood samples were collected daily upon admission to the ICU during normal daily laboratory collection times. All biological samples were prepared by the hospital clinical laboratory personnel and stored in a −80°C freezer. Descriptive, behavioral, and lifestyle data were also collected.

Study Outcomes

Study outcomes were (1) differences in susceptibility to systemic inflammatory response syndrome (SIRS), (2) sepsis and organ failure after trauma, (3) increased baseline inflammation, and (4) decreased magnitude of the inflammatory response to trauma. These were compared to accelerated biologic aging (assessed through telomerase activity, measured by the telomerase component hTERT), and chronic stress, measured by dehydroepiandrosterone sulfate (DHEAS) levels and behavioral questionnaires.

Measurements

Telomerase Component hTERT

Telomerase activity via the telomerase component hTERT was chosen as the measure for accelerated biologic aging based on the following rationale. Accelerated biologic aging and chronic stress have been linked via the biomarker telomerase (Kordinas, Ioannndis, & Chatzipanagiotou, 2016). Telomerase and its catalytic component, hTERT, have been well-studied in the cancer literature, although both are nearly nonexistent in the trauma injury literature. Responsible for telomere synthesis and lengthening, telomerase plays an important role in adaptation to physiologic stress. Telomerase and hTERT have been reported as biomarkers for cellular senescence, which declines with age (Chan & Blackburn, 2004).

Telomerase activity and hTERT expression in T cells have been positively correlated (Li et al., 2011), although hTERT may be a more sensitive biomarker in some cases (Gizard et al., 2011), thus explaining in part why telomerase activity was measured in this study versus telomere length. Both telomerase and hTERT have been linked to inflammatory stimulation (Gizard et al., 2011), elevated baseline inflammation (indicated by high levels of TNF-α), and poor inflammatory response (Damjanovic et al., 2007). Reduced hTERT expression has been reported in the presence in human immune cells exposed to the stress hormone cortisol (Choi, Fauce, & Effros, 2008). Declining levels of telomerase in advanced age (Lin et al., 2014) are also important in this context, as advanced age is a known risk factor for sepsis and organ failure following trauma (Keel & Trentz, 2005).

Samples for telomerase activity measurement were taken at baseline, following informed consent. Telomerase activity via the hTERT component was assessed using reverse transcription-polymerase chain reaction (RT-PCR). Total RNA was extracted from stored whole blood in Tempus Blood RNA tube with Trizol reagent. Single-strand cDNA was synthesized from 500 ng of total RNA using the high-capacity cDNA reverse transcription kit (Applied Biosystem, Foster City, CA). Real-time PCR amplification was used to quantify both the hTERT (Hs00972656_m1, Applied Biosystem) and GAPDH (internal quality control, Hs02758991_g1) expression using Taqman gene expression assays. Delta Ct (Ct_hTERT-CtGAPDH) represented the relative hTERT expression.

Dehydroepiandrosterone Sulfate

Chronic stress was assessed using both physiologic and behavioral measures (Robinson, Mathews, & Witek-Janusek, 2002). Dehydroepiandrosterone sulfate (DHEAS) was assessed as the physiologic measure. DHEAS values were determined by Mayo Medical Laboratories in Rochester, MN. Dehydroepiandrosterone sulfate is an established measure of functional HPA axis activity that has been shown to have inverse relationships with IL-6 and TNF-α in patients with chronic inflammation (Dowd & Goldman, 2005; Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2009; von Thiele, Lindfors, & Lundberg, 2006). Dehydroepiandrosterone sulfate was chosen as the physiologic measure following consultation with stress hormone expert William E. Rainey (Nakamura, Gang, Suzuki, Sasano, & Rainey, 2008; Rainey & Nakamura, 2008; Sirianni, Mayhew, Carr, Parker Jr., & Rainey, 2005), who advised that DHEAS is the neuroendocrine measure least affected by acute physiologic stress from trauma.

Life Events and Difficulties Schedule

The Life Events and Difficulties Schedule (LEDS) (Ackerman et al., 2003; Rojo, Conesa, Bermudez, & Livianos, 2006) was used as the behavioral measure of chronic stress. The LEDS is an instrument used for measuring chronic stress via assessment of long-term threats and threat severity (Brown & Harris, 1978). It was originally developed to measure chronic stress in mentally incapacitated patients through caregiver interviews (Brown & Harris, 1978), making it well suited for next-of-kin interviews as a proxy for incapacitated trauma ICU patients. The LEDS instrument has demonstrated an interrater reliability of at least 0.90 and has shown 79% agreement between patient and caregiver for the validity of reported life events and difficulties (Brown & Harris, 1978).

Inflammatory Cytokines

Susceptibility to sepsis was assessed using the magnitude of the inflammatory response to trauma, indicated by the (1) overall response and (2) peak magnitude of inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α) from ED admission through ICU length of stay. Baseline measures at ED admission were assessed using extra blood samples drawn in anti-coagulant-treated (EDTA) tubes as part of the routine care protocol in the ED. Subsequent samples were collected daily in the ICU.

Sepsis (SIRS Score)

Sepsis was defined by an SIRS score of 2 or more with a known or suspected source of infection. Data for a known or suspected source of infection were collected from participant history and laboratory data. Organ failure (respiratory, hepatic, renal, and cardiac) was defined from medical record data, as outlined by Lausevic, Lausevic, Trbojevic-Stankovic, Krstic, and Stojimirovic (2008).

To control for other potential interpretations, baseline data were collected for covariate analysis, including age, sex, race, socioeconomic status, smoking and substance use status, injury severity score, minutes from injury to ED admission, and length of ICU stay.

Data Analysis

Data were analyzed using various statistical methods appropriate to the measure. Canonical correlation analysis was used to determine significant overall associations between accelerated biologic aging and susceptibility to sepsis and organ failure (measured by summary measures of the cytokines IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α). Each cytokine was summarized using the peak (maximum) and overall (mean) value, calculated over all days in the ICU. The baseline value for each cytokine was also considered. The same analysis was performed to examine the association between susceptibility to sepsis and organ failure (measured by the cytokine summary measures) and chronic stress (measured by DHEAS).

Because many of the clinical characteristics of the participants and all of the outcome variables (sepsis, organ failure, etc.) were measured on more than 1 day for almost all patients (94%), summary measures were used in order to facilitate analysis. Because of the extreme skewness in the cytokine, telomerase, and DHEAS data, Spearman correlation was used as the measure of association any time these variables were correlated with other continuous variables.

RESULTS

During the study period, clinicians at the academic medical center where the study took place cared for 6,367 adult and pediatric patients with significant injuries. Within this cohort, 5,106 adult patients were entered into the trauma registry, and 1,394 were admitted to the ICU by the trauma service. Of these, 684 patients were screened for inclusion/exclusion criteria. The majority of patients were excluded due to age greater than our parameter of 18–44 years. Consent was received from 149 patient participants. Seven of these later withdrew from the study, for a final cohort of $n = 142$.

Participant demographics are summarized in Table 1. The majority of study participants were male, White, single/never married, smokers, employed full-time or part-time, and high school graduates. Lengths of stay in the ICU ranged from 1 to 113 days ($M = 8.5$, $SD = 13.1$; Table 2). The injury severity score ranged from 4 to 75 ($M = 18.8$, $SD = 9.7$).

More than 77% of the participants developed SIRS, and 28 of the 138 participants (20%) for whom data were available were diagnosed with sepsis on at least 1 day (Table 3).

Descriptive statistics for cytokine and telomerase summary measures are provided in Tables 4 and 5.

In the first aim, it was hypothesized that accelerated biologic aging, defined by telomerase activity and associated reduced hTERT expression, contributes to susceptibility to sepsis and organ failure after trauma. Significant overall associations were found between susceptibility to sepsis and accelerated biologic aging, as measured by the canonical correlation, regardless of the summary measure used for the cytokine values (see Supplemental Table 1, available at: http://links.lww.com/JTN/A10). The strongest association was found when the peak value was used for each cytokine, suggesting that susceptibility for sepsis increased with accelerated biologic aging. Significant negative correlations were found between cytokines and telomerase activity via hTERT. The strongest association,

TABLE 1 Descriptive Statistics for Categorical Variables at Baseline

Characteristic	Frequency	%
Gender (n = 141)		
Male	108	76.6
Race (n = 140)		
White	73	52.1
African American	65	46.4
Asian	2	1.4
Minority (n = 115)		
Yes	50	43.5
No	65	56.5
Marital status (n = 95)		
Single/never married	51	53.7
Married	28	29.5
Separated	5	5.3
Divorced	10	10.5
Member of an unmarried couple	1	1.1
Smoker (n = 77)		
Yes	51	66.2
Employment status (n = 95)		
Full-time	40	42.1
Part-time	12	12.6
Unemployed	11	11.6
Looking	20	21.1
Highest level of education (n =74)		
High school graduate	59	79.7
Associate's degree	6	8.1
Bachelor's degree	7	9.5
Master's degree	1	1.4
Other	1	1.4
Urine drug screen (n = 129)		
Negative	74	57.4
Positive	48	37.2
Not tested	7	5.4
Amphetamine urine drug screen (n = 120)		
Negative	114	95
Positive	3	2.5
Not tested	3	2.5

$r(101) = -0.28$), $p = .004$, was found between mean IL-1β and hTERT (see Supplemental Table 2, available at: http://links.lww.com/JTN/A11).

In the second aim, it was hypothesized that chronic stress contributes to increased baseline inflammation and decreased magnitude of the inflammatory response to trauma. Significant negative associations were found between mean cytokine levels (IL-12p70, TNF-α) and positive life events via the behavioral measure of chronic stress; IL-12p70, $r(108) = -0.20$, $p = .034$; and TNF-α, $r(108) = -0.20$, $p = .033$, respectively, as shown in Supplemental Table 3 (available at: http://links.lww.com/JTN/A12). There were no significant correlations between DHEAS and chronic stress.

DISCUSSION

This study demonstrated that accelerated biologic aging, defined by a reduced telomerase activity, correlated with increased susceptibility to sepsis after trauma, results which were supported by the significant negative correlations between cytokine summary measures and telomerase variables. This study also demonstrated that chronic stress was associated with changes in the inflammatory response to trauma. To our knowledge, this is the first study to investigate and report such findings in the context of novel mechanisms to identify, explain, and ameliorate preinjury risk for sepsis in posttrauma individuals of this age group. Few studies exist within the trauma literature with which to compare these results, although results from other literature can be extrapolated.

In this study, susceptibility to sepsis in a trauma population increased in the presence of accelerated biologic aging, defined by reduced telomerase activity assessed through its component hTERT. Published results in other models of immune function appear to support this relationship. Li et al. (2011) reported similar results in 52 renal transplant patients, and Biron-Shental et al. (2013) also reported comparable results in individuals with hepatitis infection. These findings were limited, however, by a relatively small sample size (n = 30).

In similar work, Cote et al. (2012) reported that shorter telomeres, a less sensitive biomarker of aging, was likely associated with uncontrolled viremia in HIV patients aged 0–19 years. They also found that male gender, a known risk factor for sepsis following trauma, correlated with shorter telomeres, an interesting finding that warrants study in trauma. These findings were corroborated by the well-established finding that relative advanced age was also associated with shorter telomere length in this younger cohort (Cote et al., 2012)—a cohort not unlike that in trauma, which is also characterized by comparatively younger individuals. Relationships between age,

TABLE 2 Descriptive Statistics for Continuous Variables at Baseline

Variable	*n*	*M*	*SD*	*Mdn*	Minimum	Maximum	%
Injury severity score	115	18.8	9.7	17	4	75	—
ICU days	116	8.5	13.1	5	1	113	—
BAC	48	0.19	0.95	0.18	0.02	0.48	—
BAC ≥0.20	—	—	—	—	—	—	40
WBC (cells/dl)	134	14.8	7.2	12.8	3.9	42.8	—
WBC >12	—	—	—	—	—	—	55
WBC <4	—	—	—	—	—	—	1
Heart rate (beats/min)	108	96.5	21.1	96	49	169	—
RR (breaths/min)	105	19.7	5.5	18	10	40	—
RR >20	—	—	—	—	—	—	30
SIRS score	88	1.6	1.0	1.5	0	4	—
SIRS ≥2	—	—	—	—	—	—	52

Note. BAC = blood alcohol level; ICU = intensive care unit; RR = respiratory rate; SIRS = systemic inflammatory response syndrome; WBC = white blood cell count.

telomerase, and cytokine activity are further supported by reports from Jergović et al. (2014), who showed that elderly patients with low telomerase activity also had increased production of TNF-α.

The strongest cytokine–telomerase association shown in this study was a negative correlation between mean IL-1β and accelerated biologic aging defined by telomerase activity via hTERT. Miyazaki et al. (2015) also found that telomerase activation via hTERT expression was decreased in the presence of IL-1β in some types of cells in oral cancer patients (n = 46). Similarly, Zhang et al. (2010) reported that both IL-1β and TNF-α were increased (2.6 and 3-fold, respectively) in brain cells of TERT-deficient (−/−) mice. This is significant, as IL-1β and TNF-α are important early-phase cytokines in the inflammatory process, an important factor related to susceptibility to sepsis.

TABLE 3 Descriptive Statistics Per-Patient Dependent Variables

Characteristic	Frequency	%
Sepsis on at least 1 day (n = 138)	28	20.3
Pathogen present on at least 1 day (n = 142)	36	25.4
SIRS score ≥2 on at least 1 day (n = 138)	107	77.5
Cardiac failure on at least 1 day (n = 142)	5	3.5
Hepatic failure on at least 1 day (n = 142)	6	4.2
Renal failure on at least 1 day (n = 142)	2	1.4
Respiratory failure on at least 1 day (n = 142)	53	37.3

Note. SIRS = systemic inflammatory response syndrome.

Results from this study also showed that chronic stress was associated with changes in the inflammatory response to trauma. Specifically, results showed that when fewer positive life events were reported on the LEDS, cytokines TNF-α and IL-12 were increased. These findings are similar to recent reports by Lindqvist et al. (2014), who showed significantly increased levels of TNF-α in chronically stressed individuals assessed with posttraumatic stress disorder.

Characteristics known to identify preinjury risk for sepsis in the trauma literature include male gender, preexisting medical conditions, and chronologic age (Keel & Trentz, 2005; Wafaisade et al., 2011). Until the present study, the concept of accelerated biologic age had not been studied as a preinjury risk factor for poor outcomes of inflammatory origin in trauma. In addition to the aforementioned predictors of sepsis, the search for biomarker predictors of sepsis and sepsis risk has been elusive and sometimes controversial. Established sepsis biomarkers include cytokines such as IL-1, IL-6, IL-10, and IL-18, which can be highly influenced by systemic inflammation following trauma. Common injuries like head or abdominal trauma can also affect the biochemistry of these predictor agents

TABLE 4 Descriptive Statistics for Summary Measures for Cytokines

Measure	*n*	*M; SD*[a]	*Mdn*[a]	Minimum[a]	Maximum[a]
IL-6					
Baseline[b]	125	163.3; 493.8	36.6	4.4	4,921.0
Mean	137	115.1; 174.7	48.7	5.5	1,136.0
Peak	137	288.4; 684.7	93.0	5.5	4,988.0
IL-8					
Baseline[b]	125	36.3; 78.3	21.8	4.8	788.8
Mean	137	50.5; 216.7	22.8	7.1	2,498.0
Peak	137	89.6; 438.9	32.7	7.4	4,975.0
IL-10					
Baseline[b]	125	25.2; 48.5	10.5	0	320.1
Mean	137	22.8; 41.6	9.2	2.8	299.5
Peak	137	43.7; 152.1	13.4	4.6	1,672.0
IL-12P70					
Baseline[b]	124	10.9; 12.4	6.4	0	53.8
Mean	136	11.1; 11.4	6.7	0	43.6
Peak	136	14.8; 14.2	8.4	0	54.5
IL-1β					
Baseline[b]	125	12.5; 12.8	7.4	0	62.8
Mean	137	12.4; 12.3	7.4	0	62.8
Peak	137	15.7; 13.8	9.5	0	62.8
TNF-α					
Baseline[b]	125	12.7; 14.2	7.1	0	58.9
Mean	137	13.3; 13.1	7.1	0	52.8
Peak	137	17.4; 15.6	9.7	0	61.5

Note. IL = interleukin; TNF = tumor necrosis factor.

[a]*Reference ranges: IL-1β = 0–13 pg/ml; IL-6 = 0–8 pg/ml; IL-8 = 0-46 pg/ml; IL-10 = 0-10 pg/ml; and TNF-α = 0–7.5.*

[b]*Value obtained on Day 1 in the ICU.*

TABLE 5 Descriptive Statistics for Baseline Telomerase Variables and DHEAS

Variable	*n*	*M*	*SD*	*Mdn*	Minimum	Maximum
Relative hTERT expression (Delta Ct = Ct_hTERT-CtGAPDH)	107	13.5	1.3	13.4	10.4	16.2
hTERT expression	107	34.2	1.6	34.0	29.7	39.1
GAPDH (internal quality control for hTERT)	107	20.7	1.2	20.6	18.7	28.0
DHEAS	85	285.2	142.1	248.0	33.6	746.0

Note. Normal reference range in patients age 18-44 years is 218-286 μg/dL. DHEAS = dehydroepiandrosterone sulfate; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; hTERT = human telomerase reverse transcriptase.

(Jin et al., 2014). Most of these biomarkers co-occur with sepsis and are not indicative of the host's preinjury physiologic status and associated susceptibility to sepsis.

Telomerase as a biomarker for accelerated biologic aging is a novel methodology that has been tested in nontrauma populations, and, until this study, had not yet been translated to trauma research. This approach offers an innovative solution to the uniquely challenging issue of inflammatory cytokines as biomarker predictors of sepsis, as telomerase and related measures are insensitive to daily/hourly hormonal fluctuations, which occur during the acute stress of trauma. In the new age of epigenetic influences on health, telomerase measures like hTERT may prove to be an earlier and less variable biomarker predictor of trauma-related sepsis.

New therapies may ameliorate preinjury risk for sepsis in posttrauma individuals. Simple, low-cost interventions have been shown to increase telomerase activity. Scientists within the TIGR team have shown that supplementing with vitamin D_3 is one way to increase telomerase activity. In a population of healthy African American study participants, Zhu et al. (2012) demonstrated that vitamin D_3 supplementation (2,000 IU/day) increased telomerase activity by more than 19%, an intervention that could help to reduce accelerated biologic aging and associated declines in immune function. Others report that aspirin increases telomerase activity in bone marrow mesenchymal cells in mice, and the effect can be maintained for more than 7 days (Chen et al., 2016). Traditional biomarkers like procalcitonin are used to guide antibiotic therapies, but other therapies that do not involve antibiotic therapy would be desirable in this age of multiresistant pathogens. Although much research is still needed, newer work implies that manipulating telomerase through hTERT transfection in selected cell groups could improve sepsis survival (Chen et al., 2016).

Limitations

The major strengths of the present study include findings that support an as-yet underinvestigated mechanism to explain increased preinjury risk and postinjury vulnerability to poor outcomes of inflammatory origin in trauma, although significant limitations apply. The study population was represented by a relatively small sample size, which may have limited discovery of significant statistical relationships. This may have also explained the relatively weak associations demonstrated by the correlation analysis. The study population was unique to the geographical area and limited to trauma patients who were admitted to the ICU. It is acknowledged that some patients could have been admitted to the ICU for reasons other than trauma, although patients with comorbidities associated inflammatory pathogenic origins were excluded. Taken together, these factors could limit generalizations to other trauma populations.

Inflammatory response, as assessed by cytokine measures, is vulnerable to diurnal rhythms and associated collection times. For example, IL-6 peaks between 2:00 a.m. and 2:30 a.m. and TNF-α peaks between 7:30 a.m. and 1:30 p.m. (Briones, 2007). The TIGR team attempted to minimize these differences by collecting blood samples at the same time each day and during the same venipuncture used for collecting clinical samples. To reduce variation or errors in processing, samples were processed by the existing hospital clinical laboratory personnel and cytokine analysis was completed by experienced TIGR colleagues in basic science.

Lack of evidence that chronic stress increases baseline inflammation may be related to the necessity of collecting behavioral data from next-of-kin, instead of from the patient. This is a challenging reality for all trauma studies in the critical care setting, but one that should not discourage forward progress. Future studies could include trauma patients with and without SIRS/sepsis to extend this work.

CONCLUSIONS

Among theories that explain preinjury risk for postinjury sepsis, declines in immune function associated with accelerated biologic aging and chronic stress provide a novel and as-yet relatively unexplored framework in trauma. The present study contributes new knowledge that increases the understanding of stress and aging as potential unrecognized comorbidities for sepsis and organ failure and forms the foundation for future studies focused on prevention. This study extends work with telomerase and the inflammatory response in cancer patients and applies it to a new population in trauma. Findings complement similar work done with animal models and translates it to human research in trauma. More research is needed to confirm or deny these results and to identify best practices to guide clinicians in identifying and managing risk for sepsis and organ failure among trauma patients.

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KEY POINTS

- This study contributes new knowledge that increases the understanding of stress and aging as potential unrecognized comorbidities for sepsis and organ failure and forms the foundation for future studies focused on prevention.
- This study extends work with telomerase and the inflammatory response in cancer patients and applies it to a new population in trauma.
- Findings complement similar animal model work and translate it to human research in trauma.
- More research is needed to confirm or deny results and to identify best practices to guide clinicians in identifying and managing risk for sepsis and organ failure among trauma patients.

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